

COVID-19 and cutaneous manifestations: Two cases and a review of the literature

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Abstract

COVID-19 can affect multiple organs, including skin. A wide range of skin manifestations have been reported in literature. Six main phenotypes have been identified: i) urticarial rash, ii) confluent erythematous/maculopapular/morbilliform rash, iii)

papulovesicular exanthem, iv) a chilblain-like acral pattern, v) a livedo reticularis/racemosa-like pattern, and vi) a purpuric vasculitic pattern. The pathogenetic mechanism is still not completely clear, but a role of hyperactive immune response, complement activation and microvascular injury have been postulated. The only correlation between the cutaneous phenotype and the severity of COVID-19 has been observed in the case of chilblain-like acral lesions, that is generally associated with the benign/subclinical course of COVID-19. Herein, we report two cases of SARS-CoV-2 infection in patients who developed cutaneous manifestations that completely solved with systemic steroids and antihistamines. The first case is a female patient not vaccinated for SARS-CoV-2 with COVID-19 associated pneumonia, while the second case is a vaccinated female patient with only skin manifestations.

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Highlights

- Skin rash can be an extrapulmonary manifestation of COVID-19.
- COVID-19 cutaneous lesions can be classified in six main clinical patterns: i) urticarial rash, ii) confluent erythematous/maculopapular/morbilliform rash, iii) papulovesicular exanthem, iv) a chilblain-like acral pattern, v) a livedo reticularis/racemosa-like pattern, and vi) a purpuric vasculitic pattern.
- The pathogenesis is not completely clear, but a role of hyperactive immune response, complement activation and microvascular injury have been postulated.
- Therapy is based on topical or systemic corticosteroids with or without antihistamines, or a "wait-and-see" strategy, depending on the clinical pattern.

Case Reports

Case 1 is an 87-year-old woman who was hospitalized in our Emergency Department (ED) for COVID-19 pneumonia with acute respiratory failure requiring oxygen therapy via nasal cannulas. High-resolution chest CT scan showed a diffuse interstitial pattern with subpleural bilateral consolidations with an estimated visual score of 25%. She had not been vaccinated for Sars-CoV-2 and her past medical history consisted in hypertension, diabetes mellitus type 2, overweight, and a previous femoral fracture. Therapeutic management included dexamethasone 6 mg iv daily, low molecular weight heparin at prophylaxis dose, remdesivir 200 mg iv the first day and 100 mg daily for the next four days, and subcutaneous insulin to control plasmatic glucose levels. On day 2, she developed red macular slightly itching patches (wheals) on the skin of her abdomen and thighs (Figure 1) that increased in size in the next 2 days and progressively disappeared after a week. The

patient was discharged after 10 days of recovery in good clinical condition without oxygen need.

Case 2 is a 65-year-old woman with an asymptomatic SARS-CoV-2 infection, who was admitted to our ED for acute onset of facial oedema with pruritus, treated by her general practitioner with dexamethasone 4 mg im and chlorphenamine 10 mg im with partial benefit. She was vaccinated with 3 doses of tozinameran, with no adverse reactions. She denied dyspnea or fever. She had a history of alpha 1 antitrypsin deficiency with chronic obstructive pulmonary disease, rheumatoid arthritis, and hypercholesterolemia. Her medications included alpha-1 antitrypsin, adalimumab and vitamin D. She was allergic to pollen with cough and rhinitis. During the observation in the emergency room, she developed urticarial rash of the trunks and lower limbs with itch and facial angioedema in absence of respiratory symptoms (Figure 2). Chest CT scan excluded interstitial pneumoniae, confirming panacinar emphysema and bronchiectasis. Blood analysis was normal, including procalcitonin, C-reactive protein and erythrocyte rate sedimentation. IL-6 resulted increased (28.21 pg/mL, normal value < 6.4). She was treated with systemic corticosteroids (methylprednisolone 40 mg bid) and antihistamines (chlorphenamine 10 mg daily) with progressive improvement of the cutaneous lesions, which completely solved after 7 days. She did not develop respiratory failure during the recovery, and she was completely asymptomatic at discharge with a negative RT-PCR nasopharyngeal swab.

Discussion

Since the first case of COVID-19 in December 2020, clinicians have learned that the most common clinical manifestations of this disease are flu-like symptoms, such as cough, fever and fatigue, and respiratory symptoms ranging from exertional dyspnea to acute respiratory distress syndrome. With the worldwide spread of the SARS-CoV-2, new symptoms are emerging, and an increasing number of reports are documenting extrapulmonary manifestations of COVID-19, including dermatological signs. It is well-known that most viruses can cause skin manifestations acting as foreign particles in the skin^{1,2} through an inflammatory process,³ and COVID-19 associated skin rashes can be a manifestation of viremia,⁴ as firstly reported by Recalcati *et al.* in a case series of 18 COVID-19 patients.⁵ Since 2020 an increasing number of reports regarding COVID-19 associated cutaneous manifestations has been published,⁵⁻¹⁰ but the real incidence of the COVID-19 associated cutaneous manifestations has yet to be estimated due to their heterogeneous spectrum of presentation. A difficulty in determining the actual prevalence has been mostly linked to the fact that in some countries only patients with pneumoniae or requiring hospitalization are screened. In a binational Chinese-Italian cohort of 678 hospitalized adults with laboratory confirmed disease, the prevalence was 7.8%, but cutaneous lesions are likely to have been underestimated for many other reasons, including the paucity of dermatology consultations.¹¹ Moreover, cutaneous lesions may be neglected as their duration can be very short and local symptoms can be minimal or absent. The first large clinical study of 375

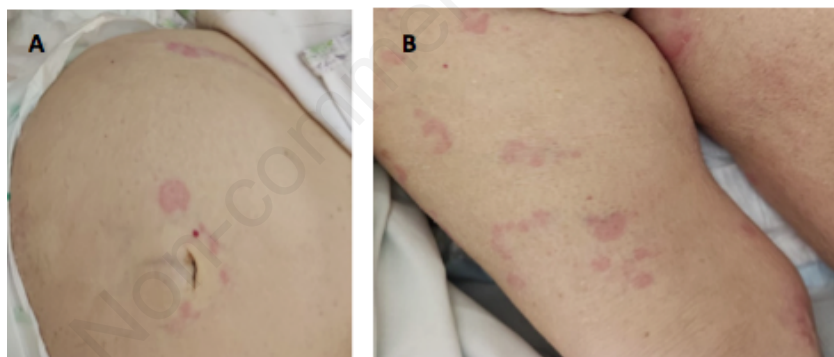


Figure 1. Urticarial rash involving the abdomen (A) and the thighs (B).

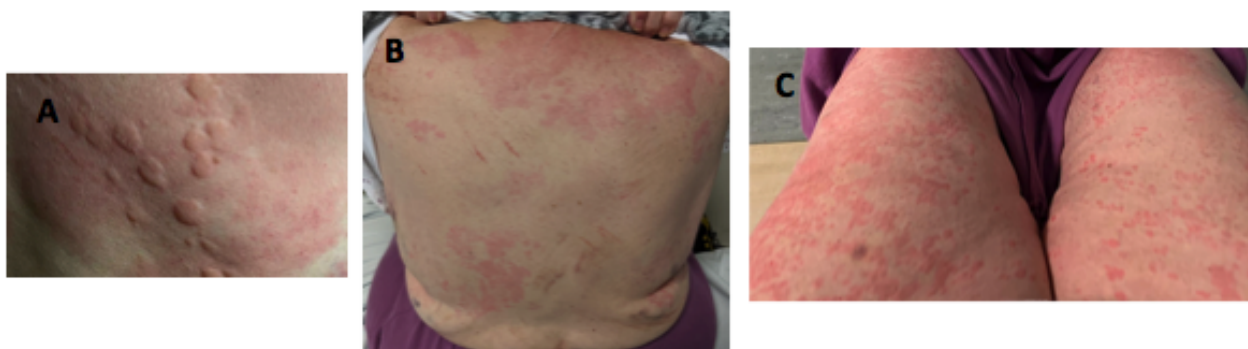


Figure 2. Urticarial rash (A) of the trunk (B) and lower limbs (C).

patients with COVID-19 associated skin manifestations has been published in 2020 by Galvan Casas *et al.*¹² The authors recognized five clinical patterns of presentation, as follows: i) acral areas of erythema with vesicles or pustules (pseudo-chilblains) (19%), ii) other vesicular eruptions (9%), iii) urticarial lesions (19%), iv) maculopapular eruptions (47%), and v) livedo or necrosis (6%). Vesicular eruptions were found to appear early in the course of the disease (before other symptoms in 15% of cases), chilblain-like lesions frequently appear late over the disease course, whereas the remaining patterns tend to develop during the illness phase. Chilblain-like lesions also tend to have a longer duration as compared to the other forms. A gradient of severity of COVID-19 could be observed ranging from less severe disease in acral lesions to most severe in the case of livedo.¹² Subsequently, Marzano *et al.* identified 6 main phenotypes on the basis of the available literature and direct clinical experience, including: i) urticarial rash, ii) confluent erythematous/maculopapular/morbilloform rash, iii) papulovesicular exanthem, iv) a chilblain-like acral pattern, v) a livedo reticularis/racemosa-like pattern, and vi) a purpuric vasculitic pattern.¹³ In addition, case series of a miscellany of other cutaneous presentations that cannot be included in this classification, such as erythema multiforme like,¹⁴ pityriasis rosea like,¹⁵ and Grover disease like manifestations¹⁶ have been published. Considering the pathophysiological mechanisms, these six patterns can be assigned to two broader categories: i) inflammatory/exanthematous eruptions, including urticarial rash, confluent erythematous/maculopapular/morbilloform rash and papulovesicular exanthem, and ii) vasculopathic/vasculitic lesions, including chilblain-like acral pattern, livedo reticularis/racemosa-like pattern and purpuric “vasculitic” pattern. The most frequent cutaneous phenotypes are confluent erythematous/maculopapular/morbilloform

rash and a chilblain-like acral pattern, whereas the least frequent is a livedo reticularis-like/racemosa-like pattern. Mucous membrane lesions have very rarely been reported in COVID-19 patients. The median latency between the onset of the cutaneous manifestations and systemic symptoms is 14 days, varying from 4 days in the case of papulovesicular exanthem to 24.5 days in the case of a livedo reticularis-like/racemosa-like pattern, and the median duration of the cutaneous manifestations is 12 days, ranging from 8 days in the case of urticarial rash to 22 days in the case of a chilblain-like acral pattern. Only chilblain-like acral phenotype is significantly associated with the benign/subclinical course of COVID-19. Chilblain-like acral phenotype is also associated with a younger age, whereas the livedo-like/vasculitic and maculopapular phenotypes are associated with an older age.¹³

Here we report the main characteristics for each phenotype (Table 1).

Inflammatory/exanthematous eruptions

Urticarial rash and angioedema

Estimated incidence of urticarial eruptions associated with COVID-19 varies from 16.7% to 19% of total skin manifestations.^{5,12} Familial clusters have been reported.¹⁷ The rash tends to appear simultaneously with systemic symptoms, involving predominantly the trunk and limbs, and relatively sparing the acral sites.¹⁸ Itch is generally, as reported in the case 1. The rash lasts approximately 1 week, and it is associated with medium high severity of COVID-19.¹² Angioedema can accompany the urticarial rash, as reported in the case 2 and by Najafzadeh *et al.*¹⁹ Histopathological studies are poor.²⁰ Amatore *et al.* documented the presence of lichenoid and vacuolar interface dermatitis, associated with mild spongiosis, dyskeratotic basal keratinocytes and

Table 1. The six main COVID-19 related cutaneous manifestations.

	Type	Clinical features	Body involvement	Therapy
Inflammatory/ Exanthematous eruptions	Urticarial rash	Itching urticarial rash lasting 1 week +/- angioedema	Trunk and limbs	Low-dose systemic corticosteroids + non-sedating antihistamines
	Confluent erythematous / maculopapular / morbilloform rash	Symmetrical itchy maculopapular eruption after COVID-19 systemic symptoms' onset. Evolution in morbilloform rash.	Trunk and limbs with centrifugal progression	Topical steroids. Parenteral route for severe and widespread cases
	Papulovesicular exanthem	“Varicella-like”: i) widespread pattern: small papules, vesicles, and pustules of different sizes; ii) localized pattern: monomorphic papulovesicular lesions	i) Widespread; ii) Mid chest, upper abdominal region or the back	Wait and see
Vasculopathic/ Vasculitic lesions	Chilblain-like acral pattern	Erythematous-violaceous patches or plaques + pain/burning sensation + pruritus	Feet and hands, rarely auricular region	Wait and see
	Livedo reticularis / racemosa-like pattern	i) Livedo reticularis: tight, symmetrical, lace-like, dusky patches forming complete rings surrounding a pale center. ii) Livedo racemosa: larger, irregular, and asymmetrical rings. Possible microthrombotic vasculopathy and severe coagulopathy.	Not specific	Wait and see
	Purpuric vasculitic pattern	Purpuric lesions with possible evolution in haemorrhagic blisters and necrotic-ulcerative lesions	Acral distribution or intertriginous regions	Topical corticosteroids for mild cases. Systemic corticosteroids for ulcerative lesions and widespread presentation

superficial perivascular lymphocytic infiltrate.²¹ Rodríguez-Jiménez *et al.* found a vacuolar interface dermatitis with occasional necrotic keratinocytes compatible with an erythema multiforme-like pattern in a 60-year-old woman with persistent urticarial eruption and interstitial pneumonia who was not under any medication.²²

Low-dose systemic corticosteroids combined with non-sedating antihistamines have been suggested as therapeutic option,²³ based on the hypothesis of hyperactivity of the immune system in COVID-19 patients.

Confluent erythematous/maculopapular/morbilliform rash

The clinical picture of this group may range from erythematous confluent rashes to maculopapular eruptions and morbilliform exanthems, similar to non-specific rashes observed in common viral infections. The most commonly reported skin manifestations are maculopapular eruptions,¹² which appear generalized, symmetrical, itchy, and predominantly localized on the trunk and limbs with centrifugal progression,²⁴ more frequently after COVID-19 systemic symptoms' onset.²⁵ Erythematous lesions can progress to a purpuric evolution²⁵ or coexist with purpuric lesions.²⁶ Maculopapular eruptions can change in a morbilliform pattern.²⁷

Histopathological studies were possible only in a few patients. Gianotti *et al.* described a vascular damage in all the 3 cases investigated,²⁸ while Reymundo *et al.* documented a mild superficial perivascular lymphocytic infiltrate.²⁹

The main differential diagnoses are drug-induced cutaneous reactions and viral exanthems.

The therapeutic management consists in corticosteroids according to the severity of the rash: topical steroids can be used successfully in most cases, reserving the parenteral route to severe and widespread cases.²⁷

Papulovesicular exanthem

COVID-19-associated papulovesicular exanthem was firstly described as "varicella-like" in an Italian multicentre case series of 22 patients.³⁰ As reported by Marzano *et al.*²⁰ this exanthem is a rare, but specific COVID-19 skin manifestation, that resembles that observed in true varicella, but with a different pattern, as follows: a frequent trunk involvement, usually scattered distribution, and mild/absent pruritus. Lesions generally appear 3 days after systemic symptoms and disappear after 8 days without leaving scarring, and they are associated with intermediate COVID-19 severity.²⁰ This rash is more common in adult patients,³⁰ but also children can be affected.³¹ Two different presentation patterns have been reported: i) a more common widespread polymorphic pattern consisting of small papules, vesicles, and pustules of different sizes, and ii) a localized pattern, less frequent and consisting of monomorphic lesions, usually involving the mid chest/upper abdominal region or the back.³² The prevalence is extremely variable. Indeed, in a cohort of 375 patients with COVID-19-associated cutaneous manifestations patients with papulovesicular exanthem were 34 (9%),¹² while they were 3 out of 52 (5.8%), 1 out of 18 (5.5%) and 2 out of 53 (4%) in the cohorts published respectively by Askin *et al.*,³³ Recalcati,⁵ and De Giorgi *et al.*¹¹

Histopathological studies showed epidermal necrosis with acantholysis, dyskeratosis and signs of endotheliitis in the dermal vessels.^{20,34,35} Immunohistochemical analysis has demonstrated the presence of SARS-CoV-2 in the endothelial cells of damaged skin.³² In all the published studies PCR assays failed to detect the presence of SARS-CoV-2 inside the vesicles. However, as reported by Magro *et al.* a small viral load can result in false negative results, and PCR assays in skin samples are not standardized.³²

The differential diagnosis with infections caused by the Herpes viridae family can be difficult and in some cases Herpes Zoster can complicate the course of COVID-19.³⁶ The current opinion is to consider herpes viruses as a mere superinfection in patients with dysfunctional immune response associated with COVID-19.³⁷

Given the self-limiting course, a "wait-and-see" strategy is the most recommend therapeutic option.

Vasculopathic/vasculitic lesions

Chilblain-like acral pattern

Chilblain-like acral lesions associated with COVID-19 are peculiar cutaneous manifestations, more common in Caucasians,^{38,39} that appear as erythematous-violaceous patches or plaques predominantly involving the feet and hands,^{40,41} and rarely other acral sites, such as the auricular region.⁴² The lesions frequently appear late over the disease course and tend to have a longer duration. In a large Italian study by Marzano *et al.* the chilblain-like acral phenotype was significantly associated with less severe COVID-19.¹³ The acral eruption is frequently characterized by erythematous-violaceous papules and macules, with possible bullous evolution, or digital swelling. Pain/burning sensation, as well as pruritus, are commonly reported symptoms. Dermoscopy revealed the presence of an indicative pattern represented by a red background area with purpuric globules.⁴³ Young patients confined at home, in the absence of cold exposure, comorbidities or other potential triggers, and without systemic symptoms seem to be mostly affected.^{12,44}

The pathogenesis is not completely clear. Different hypotheses have been proposed, including increased interferon release induced by COVID-19 and consequent cytokine-mediated inflammatory response, and virus-induced endothelial damage with obliterative microangiopathy and coagulation abnormalities.⁴⁵ Data on the relationship between the SARS-CoV-2 infection and these clinical manifestations are controversial. In most cases laboratory confirmation of the infection was not performed or gave negative results. Colmenero *et al.* demonstrated the presence of SARS CoV-2 in endothelial cells of skin biopsies of 7 children with chilblain-like acral lesions by immunohistochemistry and electron microscopy, suggesting that virus-induced vascular damage and secondary ischemia could explain the pathophysiology of these lesions.⁴⁶

Chilblain-like lesions share many histopathological features with idiopathic and autoimmunity-related chilblains, including epidermal necrotic keratinocytes, dermal edema, perivascular and perieccrine sweat gland lymphocytic inflammation.

In the absence of significant therapeutic options and given the tendency of these cutaneous lesions to spontaneously heal, a "wait and see" strategy is recommended.

Livedo reticularis/racemosa-like pattern

Livedo appears as a reticulate pattern of slow blood flow, with consequent desaturation of blood and bluish cutaneous discoloration. It can be classified in 2 types, as follows: i) livedo reticularis, which develops as tight, symmetrical, lace-like, dusky patches forming complete rings surrounding a pale center, and ii) livedo racemosa, characterized by larger, irregular, and asymmetrical rings.⁴⁷

In a large cases series of 716 patients by Freeman *et al.* livedo reticularis-like lesions and livedo racemosa-like lesions accounted for 3.5% and 0.6% of all cutaneous manifestations, respectively.¹⁸ Therefore, livedo reticularis and racemosa-like lesions have been suggested to occur in elderly patients with severe systemic symptoms and were pronounced and/or persistent.¹² The basis of

the pathogenetic mechanisms is an occlusive/microthrombotic vasculopathic aetiology¹³ with a mechanism not completely understood, but probably due to several mechanisms including neurogenic, microthrombotic and immune-complex mediated processes.⁴⁸ The histopathology of these lesions has been described by Magro *et al.* who documented the presence of thrombotic microvascular damage in the lung and/or skin of five critical COVID-19 patients.⁴⁹ The authors demonstrated that in 3 patients with severe COVID-19, purpuric/livenoid skin lesions were characterized by a pauci-inflammatory microthrombotic vasculopathy, associated with a minimal interferon response, that cause an increased viral replication with the release of viral proteins, that localize into the endothelium inducing widespread complement activation. The same authors suggested that severe COVID-19 may induce a catastrophic generalized microvascular injury syndrome mediated by intense activation of the alternative and lectin complement pathways and an associated procoagulant state.

Therefore, Chinese authors reported the development of severe acro-ischemia in a few intensive care unit patients in Wuhan, manifesting as finger/toe cyanosis, skin blisters and dry gangrene, resulting from a hypercoagulable status or confirmed disseminated intravascular coagulation.⁵⁰

In general, livedo reticularis-like lesions are frequently mild, transient, and not associated with thromboembolic complications.^{51,52} On the contrary, livedo racemosa-like lesions and retiform purpura have often been described in patients with severe coagulopathy.^{53,54}

In absence of a targeted therapy, a “wait-and-see” approach is suggested with the recommendation to always assess and monitor platelet count, coagulation times, and fibrin degradation products.

Purpuric “vasculitic” pattern

The purpuric “vasculitic” pattern is the expression of a “true” vasculitic process due to the direct damage of the endothelial cells by the virus, or dysregulated host inflammatory responses induced by COVID-19. It is very rare, more frequent in elderly patients with severe COVID-19 and always associated with high-mortality.¹² The first case has been reported in March 2020 by Joob and Wiwanitkit, who described a petechial rash misdiagnosed as dengue in a COVID-19 patient.⁸ In a case series Freeman *et al.* reported 1.8% and 1.6% of patients with purpura and dengue-like eruption, respectively.¹⁸ Purpuric lesions can be generalized or localized in the intertriginous regions or arranged in an acral distribution.⁵⁵⁻⁵⁷ Del Giudice *et al.* described a case of an 83-year-old man affected by obesity and distal arteriopathy, who developed a catastrophic acute bilateral lower limbs and foot necrosis associated with COVID-19 as a likely consequence of a malignant synergy of the vasculitis and severe coagulopathy.⁵⁸

When performed, histopathology showed leukocytoclastic vasculitis,⁵⁵ severe neutrophilic infiltrate within the small vessel walls, intense lymphocytic perivascular infiltrates, presence of fibrin and endothelial swelling.^{57,59}

Topical corticosteroids have been successfully used for treating mild cases of purpuric lesions.⁵⁶ Patients with necrotic-ulcerative lesions and widespread presentation can be treated with systemic corticosteroids.

Other unclassifiable COVID-19 skin lesions

Rare COVID-19-related cutaneous manifestations, that cannot be pigeonholed in the classification proposed by Marzano *et al.*,¹³ include the erythema multiforme-like eruption,⁶⁰ pityriasis rosea-like rash,¹⁵ multi-system inflammatory syndrome in children,⁶¹ anagen effluvium,⁶² and a pseudo herpetic variant of Grover dis-

ease.¹⁶ Pityriasis rosea like and erythema multiforme like patterns are the most frequently reported skin manifestations falling outside the classification, but it is still debated whether the former is directly mediated by SARS-CoV-2 or caused by COVID-19-related immune system dysfunction leading to human herpes virus 6/7 reactivation⁵, and whether the latter is triggered by SARS-CoV-2 or other viruses.

Conclusions

Cutaneous manifestations in COVID-19 patients are still an emerging issue as documented by the current literature. It is evident that the spectrum of COVID-19-associated skin manifestations is still incomplete, and it is expected that new skin lesions will be described. Dermatologists play a central role in the diagnosis and the treatment strategy. The presence of cutaneous findings can lead to suspect COVID-19 and identify potentially contagious cases with indolent course. The role of COVID-19-associated skin manifestations as prognostic markers needs to be further investigated. When possible, histological analysis and detection of SARS-CoV-2 in the content of the skin lesions should be performed both to clarify the pathophysiological process at the basis of COVID-19 associated cutaneous manifestations, and to design a tailored therapy for each patient.

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