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COVID-19: Important Updates and Developments
 Edited by Franco Rongioletti, MD, and Leonard J Hoenig, MD

Clinicopathologic correlations of COVID-19–related cutaneous manifestations with special emphasis on histopathologic patterns



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Abstract Skin is one of target organs affected by the novel coronavirus SARS-CoV-2, and in response to the current COVID-19 pandemic, a fast body of literature has emerged on related cutaneous manifestations. Current perspective is that the skin is not only a bystander of the general cytokines storm with thrombophilic multiorgan injury, but it is directly affected by the epithelial tropism of the virus, as confirmed by the detection of SARS-CoV-2 in endothelial cells and epithelial cells of epidermis and eccrine glands. In contrast with the abundance of epidemiologic and clinical reports, histopathologic characterization of skin manifestations is limited. Without an adequate clinicopathologic correlation, nosology of clinically similar conditions is confusing, and effective association with COVID-19 remains presumptive. Several patients with different types of skin lesions, including the most specific acral chilblains-like lesions, showed negative results at SARS-CoV-2 nasopharyngeal and serologic sampling. The aim of this review is to provide an overview of what has currently been reported worldwide, with a particular emphasis on microscopic patterns of the skin manifestations in patients exposed to or affected by COVID-19. Substantial breakthroughs may occur in the near future from more skin biopsies, improvement of immunohistochemistry studies, RNA detection of SARS-CoV-2 strain by real-time polymerase chain reaction-based assay, and electron microscopic studies.

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Introduction

Global public health has been severely affected by the spread of the novel corona virus 2019 (SARS-CoV-2), be-

ginning in December 2019, from Wuhan, China, then rapidly becoming a pandemic.¹⁻³ Respiratory tract manifestations are the most common findings, conditioning COVID-19 outcome. Many cutaneous manifestations have been increasingly described in association with SARS-CoV-2 infection. A recent systematic review indicates a worldwide incidence of skin involvement around 1% to 2%, whereas the preva-

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lence ranges from 0.2% in a cohort of Chinese patients to 20.4% in an Italian study.⁴⁻⁶ Some cutaneous manifestations arise before the onset of respiratory signs and clinical manifestations, suggesting their role in diagnosis and prognosis. According to the recent classification,⁷ based on a Spanish prospective nationwide consensus study of 375 cases, the most characteristic presentations are chilblain-like lesions, ischemic-livedoid/necrotic lesions, and varicelliform-like/vesicular eruptions. Although less specific manifestations are more frequent, there are erythematous, urticarial, purpuric, and maculopapular eruptions, followed by an increasing list of anecdotal and unusual manifestations.⁸⁻¹¹

In contrast with the abundance of epidemiologic and clinical reports, histopathologic characterization of skin eruptions related to COVID-19 has been limited. A plausible explanation is that in view of the greater severity of lung and multiorgan involvement, invasive skin assessment has often been postponed. Dermatopathology may be crucial to differentiate clinically similar lesions and deepen the comprehension of pathogenetic mechanisms effectively associated with COVID-19. For these reasons, we have gathered emerging data from the literature and personal observations to provide an analysis of the clinicopathologic correlation of the skin manifestations emphasizing the associated histopathologic patterns (Table 1).

Methods

A search in the electronic databases PubMed, Scopus, and Web of Science was performed up to July 31, 2020, using the term “COVID-19” and “SARS-CoV-2” in combination with “dermatology,” “skin,” “cutaneous manifestations,” “histopathology,” and “pathology” to collect papers describing cutaneous manifestations in affected patients. A search was also conducted using the terms “multisystem inflammatory syndrome” and “COVID-19” in combination with “dermatology” or “skin.” We screened 942 contributions, including all of the related clinicopathologic reports, most of which concerned anecdotal cases or small case series. We screened the presentations based primarily on the title and abstract. Full texts were then carefully examined to evaluate the content. Papers from the references cited in the retrieved papers were also manually searched when appropriate. We gave specific attention to those contributions that included histopathologic studies. The histopathologic features were reviewed in greater detail, and the main microscopic patterns were then highlighted.

Results

From the initial 942 contributions, 262 papers were collected, but further screening excluded 178 of them, because the histopathologic features were not addressed or only marginally studied. Of the 84 contributions accepted

for our analysis,⁴⁻⁸⁷ 10 were extensive reviews about the skin manifestations related to COVID-19, where “dermatopathology” and “pathology and skin” were specifically discussed or highlighted.^{4,6-14} Six reports dealing with a “multisystem inflammatory syndrome” related to COVID-19 and including histopathologic findings were also retained.¹⁵⁻²¹

Clinicopathologic classification

Skin manifestations related to COVID-19 can be divided into five groups, based on the pathologic findings using the Spanish clinical classification⁷ or the case series from the international registry developed by the American Academy of Dermatology and International League of Dermatologic Societies⁹:

1. Chilblain-like lesions (pernio-like)
2. (Acro)Ischemic/livedoid/necrotic lesions
3. Exanthematous eruptions, including
 - a. Varicelliform-like/vesicular
 - b. Confluent erythematous/maculopapular/morbilliform
 - c. Urticarial
 - d. Erythema multiforme-like
 - e. Purpuric/petechial
4. Skin manifestations of multisystem inflammatory syndrome (atypical Kawasaki disease)
5. Miscellaneous
 - a. Pityriasis rosea-like eruption
 - b. Digitate papulosquamous
 - c. Transient livedo reticularis
 - d. Erythema nodosum/sweet's (SDRIFE-like lesions)

Chilblain-like lesions

Clinical presentation

Chilblain-like lesions are considered one of the most specific manifestations of COVID-19, occurring in 19% of the Spanish series⁷ and 18% of the American Academy of Dermatology and International League of Dermatologic Societies registry.⁹ They closely resemble chilblains but characteristically affect young adults, as well as children, in a higher percentage not previously reported before the outbreak of COVID-19. Lesions appear late in the disease course in milder cases, lasting from 10 to 14 days and sometimes persisting for a few months, but the prognosis is good.^{22,23}

Two prevalent patterns have been recognized involving the dorsal aspect of the toes (COVID-19 toe):

- The lateral and plantar aspects of the feet and less frequently the fingers: Dusky erythematous and edematous macules or plaques, sometimes with a purpuric hue (Figure 1A); or blisters formation. Distribution is usually asymmetric, and lesions may be asymptomatic, pruritic, or painful.

Table 1 Clinicopathologic characterization of current COVID-19–associated skin manifestations

Skin manifestation	Clinical presentation	Histopathology	COVID-19 course
Pernio-like eruption (pseudo-chilblain)	Acral: Dorsal aspect of the toes (COVID-19 toe), lateral sides of the feet, soles and less frequently fingers Variable clinical manifestations; i.e.itching, pain, etc.	<ul style="list-style-type: none"> • Superficial and deep dermal perivascular lymphocytic infiltrate with perieccrine extension and intramural lymphocytes with thickening and enlargement of endothelium (lymphocytic vasculitis) • Vacuolar interface dermatitis with scattered necrotic (apoptotic) keratinocytes • No evidence of thrombosis or leukocytoclastic vasculitis • Sometimes, microthrombi in superficial capillaries and epidermal necrosis in acral lesions overlapping with livedoid/ischemic/necrotic lesions • Direct immunofluorescence negative 	Children/young person: Asymptomatic or mild disease Older adults: Often associated with ischemic lesions, more severe disease
Ischemic/livedoid/necrotic lesions	Acral acute painful lesions; often bullae; possible progression to dry gangrene	<ul style="list-style-type: none"> • Epidermal necrosis • Thrombotic vasculopathy of small and medium vessels (venules and small-medium arteries) in superficial and deep dermis • Sweat gland necrosis • Slight perivascular lymphocytic infiltrate • No sign of leukocytoclastic vasculitis • Complement deposition in vessel walls 	Severe disease; 10% mortality in the Spanish survey
Vesicle/varicella-like eruption	Diffuse, constant trunk involvement Itching	<p>Earlier lesions:</p> <ul style="list-style-type: none"> • Vacuolar degeneration of basal layer • Multinucleate, hyperchromatic keratinocytes with many dyskeratotic (apoptotic) cells • Paucity to absent inflammatory infiltrate <p>Well-established lesion:</p> <ul style="list-style-type: none"> • Intra-epidermal vesicle containing multinucleated and ballooned keratinocytes, with acantholytic and dyskeratotic cells (similar to herpetic lesions or pseudo-herpetic Grover disease) 	Unpredictable Severe pulmonary disease in 42% of Spanish patients; 13.6% fatal outcome in an Italian survey
Confluent erythematous/maculopapular/morbilliform eruptions	Widespread Spare palmoplantar surfaces and mucosae	<p>Variable features consistent with viral exanthem:</p> <ul style="list-style-type: none"> • Spongiosis, basal cell vacuolization, perivascular lymphocytic infiltrate with some neutrophils and eosinophils in early lesions • Interstitial histiocytes in late lesions • Lymphocytic vasculitis • Grover-disease–like feature • Microthrombi (rarely) 	Early symptomatic disease, usually severe course Adults
Urticarial eruptions	Widespread small or larger wheals (giant)	<ul style="list-style-type: none"> • From spongiotic with perivascular infiltrate to interface dermatitis (two cases) to small vessels vasculitis (urticarial vasculitis) • Variable tissue eosinophilia 	Usually severe disease; presence of eosinophils suggested as sign of a better prognosis

(continued on next page)

Table 1 (continued)

Skin manifestation	Clinical presentation	Histopathology	COVID-19 course
Erythema multiforme-like eruptions	Variable: Acral in young persons and children Generalized in older adults	Acral type in youngsters: • Reminiscent of pernio-like lesions with a superficial and deep perivascular CD3+ lymphocytic infiltrate with perieccrine involvement and some vasculopathic changes • Positivity of the SARS-CoV/SARS-CoV-2 spike protein in endothelial cells and epithelial cells of eccrine glands with immunohistochemistry Diffuse type in adults: • Consistent with erythema multiforme, although not typical • Normal epidermis or spongiosis, exocytosis, variable degrees of interface dermatitis, absent or a few necrotic keratinocytes • Absence of fibrinoid necrosis, thrombosis, eosinophils	Mild disease in young Symptomatic disease with variable outcome in adults
Petechial/purpuric rash	Variable: Periflexural onset Limited to lower limb Generalized	Two different patterns from few biopsies: • Superficial perivascular lymphocytic infiltrate with hemorrhages, papillary edema, and some dyskeratotic cells in the absence of vasculopathy • Leukocytoclastic vasculitis	Symptomatic disease with benign outcome
Skin manifestations of multisystem inflammatory syndrome, atypical Kawasaki disease	Variable morphology suggestive of erythema multiforme, maculopapular, rashes, and/or vasculitis	Two different patterns from few biopsies: • Leukocytoclastic vasculitis • Erythema multiforme-like	Multiorgan signs and clinical manifestations in children Nasopharyngeal swab often negative, 1 case in adult
Miscellaneous • Pityriasis rosea-like • Digitate papulosquamous • Livedo reticularis • Skin mottling (neonate) • Atypical Sweet syndrome • Intertriginous and flexural exanthema	Anecdotal reports with specific morphology	Usually not biopsy. In the digitate papulosquamous: • Epidermal spongiosis, with spongiotic vesicles containing lymphocytes, and Langerhans cells • Mild papillary edema, and a superficial lymphohistiocytic infiltrate • In the typical Sweet syndrome • Superficial and deep neutrophilic dermatosis	Associated with symptomatic disease, but benign course Only 1 fatal outcome (digitate papulosquamous eruption)

- An additional type of lesions in children,²⁴ usually mixed with chilblain-like ones, is referred as erythema multiforme-like, although histopathology is similar to chilblains (see also Erythema multiforme-like eruption section).

Although highly suspect, several patients with acral chilblain-like lesions were found to be negative for SARS-CoV-2 polymerase chain reaction (PCR) and serology.^{21,25-27} A prospective study in Spain found only 14.8% of the patients to be positive.²⁸

Histopathology

Microscopic features of long-lasting chilblain-like lesions in true COVID-19-positive patients have been collected from small case series but are reproducible.²⁹ The prevalent pattern simulates idiopathic chilblains or chilblain lupus erythematosus,³⁰ showing a superficial and deep perivascular lymphocytic infiltrate with perieccrine accentuation (Figure 1B and C). The dermal infiltrate tightly cuffs the vessel walls (“lymphocytic vasculitis”) with endothelium thickening and no occlusion (Figure 1D), although small thrombi may occasionally be present in the superficial por-

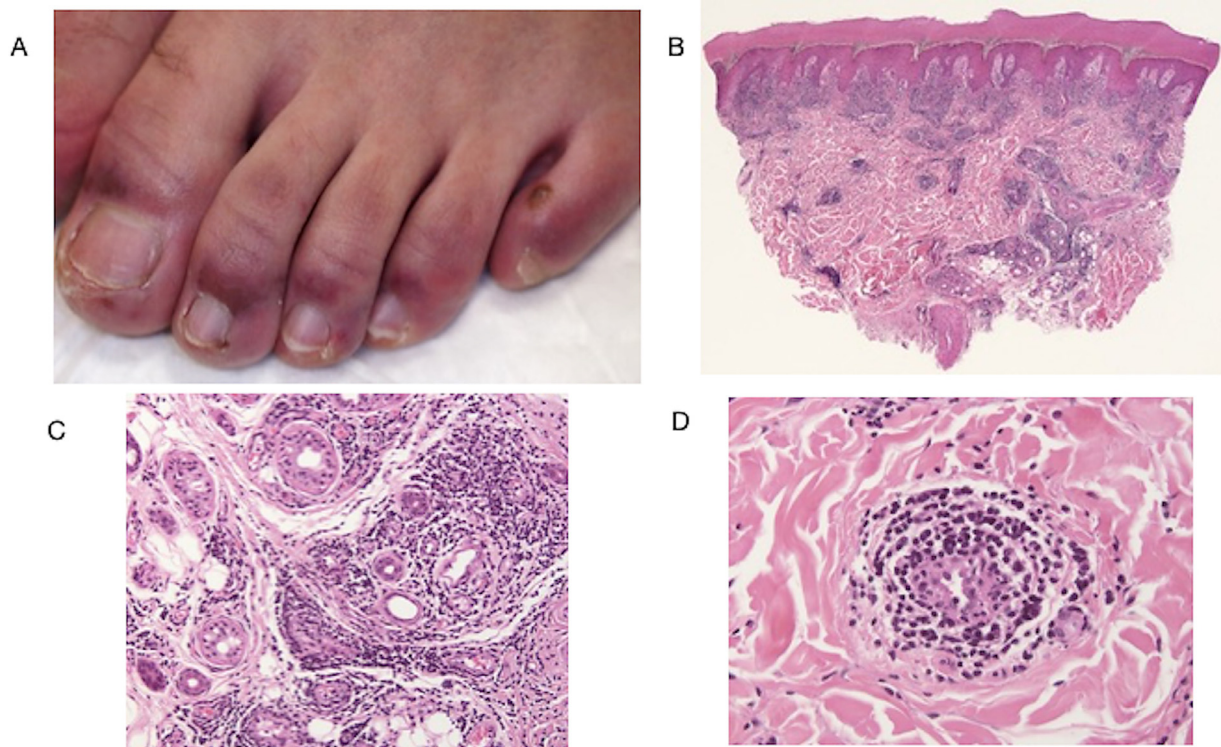


Fig. 1 (A) Chilblain-like lesions of the dorsal aspect of the toes (COVID-19 toe) having dusky erythematous edematous macules or plaques with a purpuric hue. (B) Superficial and deep perivascular lymphocytic infiltrate with perieccrine accentuation (hematoxylin & eosin [HE], 40 \times). (C) Perieccrine extension of the lymphocytic infiltrate (HE, 200 \times). (D) The dermal infiltrate tightly cuffs the vessels walls (“lymphocytic vasculitis”) with endothelium thickening without true thrombosis (HE, 200 \times).

tion of the dermis. Epidermal necrosis is usually absent, but scattered necrotic (apoptotic) keratinocytes and smudging of the basement membrane may be found.³¹ Dermal and perieccrine mucin deposition may also be a feature.³² Direct immunofluorescence is usually negative.^{22,33,34}

In a recent study in Madrid, seven children with chilblains were found to be SARS-CoV-2 immunohistochemistry positive in endothelial cells and epithelial cells of eccrine glands.³⁵ Electron microscopy showed coronavirus particles in the cytoplasm of endothelial cells. In the same patients, SARS-CoV-2 PCR was negative in both nasopharyngeal and oropharyngeal swabs.³⁵

Pathogenetic mechanisms

An interesting theory suggests that the innate immune system is implicated through an early interferon (IFN) type I–mediated response of the host, muting early SARS-CoV-2 replication but producing a peripheral microangiopathy, clinically visible as chilblain-like lesions.³⁰ The adaptive immune system does not intervene, explaining the lack of specific antibodies in most patients. Effective host innate response also explains the otherwise indolent course of the infection in the majority of young patients, who were mostly asymptomatic or having negative COVID-19 nasopharyngeal swabs. Conversely, as IFN type I levels are known to increase with age, in older persons an excessive

IFN-pathway activation can be deleterious, that is, “cytokine storm,” characteristic of symptomatic COVID-19 patients.³⁶ A delayed immune-mediated reaction to the virus in genetically predisposed patients has also been proposed²³; however, some authors have suggested that lifestyle changes, consequent to the lockdown measures and quarantine, might be themselves responsible for the chilblains occurrence. Several risk factors for chilblains development were reported in the Belgian survey, including reduced physical activity, a more sedentary lifestyle, and walking either barefoot or wearing only socks.²⁷

Acro-ischemic/livedoid/necrotic lesions (acral livedo racemose, retiform purpura)

Clinical presentation

Acro-ischemic/livedoid/necrotic lesions are characterized by an acute and painful presentation, including purplish retiform and roundish dusky patches, some with angled edges, mostly on the feet and toes and less frequently on the fingers and hands.³⁷ Progression to bullous formation and dry gangrene is frequent (Figure 2A). A continuum spectrum has been postulated, ranging from mild chilblain-like manifestations to dry gangrene.³⁸ The first cases were reported in severely ill Chinese patients (median age of 59 years),³⁹ and then in 6% of the Spanish COVID-19 patients⁷ and in 3 U.S.

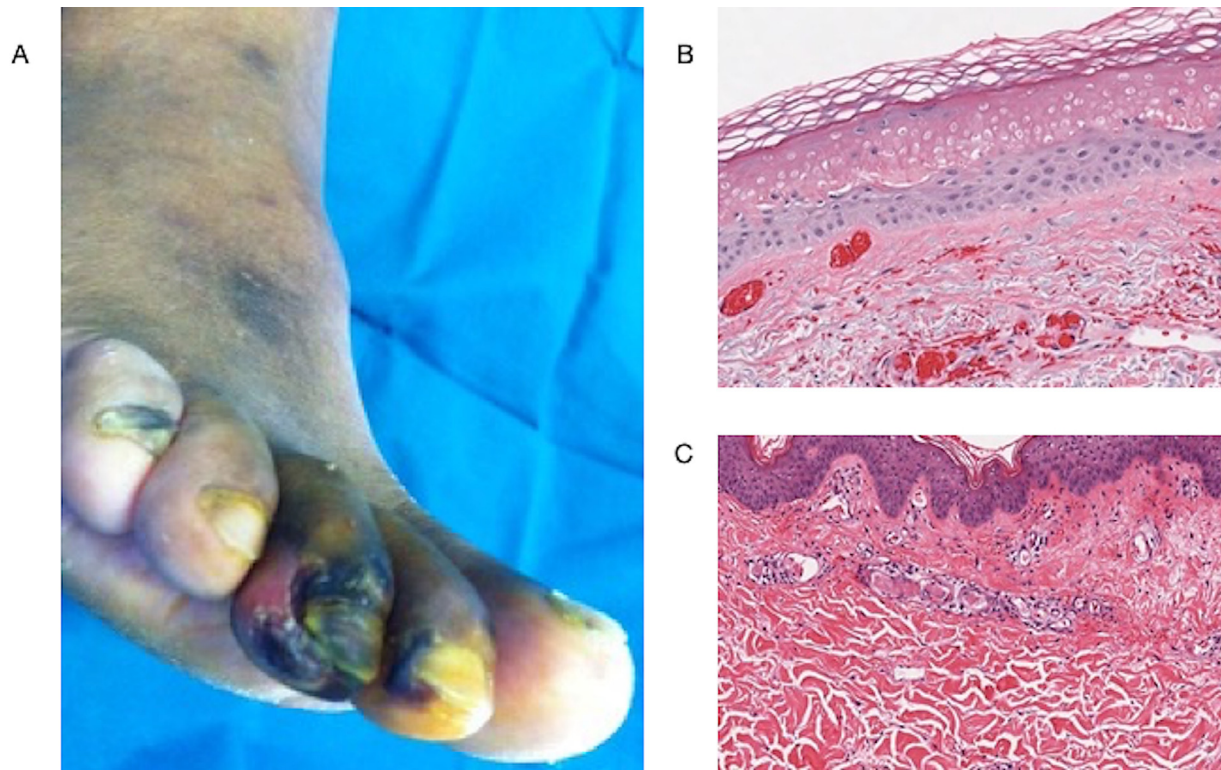


Fig. 2 (A) Acro-ischemic/livedoid/necrotic lesions of the toe with dry gangrene. (B) Epidermal necrosis and thrombotic vasculopathy, involving the superficial vessels (hematoxylin & eosin [HE], 200 ×). (C) Thrombotic vasculopathy with most of the superficial small vessels filled with hyaline thrombi and pauci perivascular inflammatory infiltrate. No signs of leukocytoclastic vasculitis are seen (HE, 200 ×).

patients, presenting with a diffuse purpuric, livedo racemose-like eruption involving the chest, buttocks, and extremities.⁴⁰ The prognosis of acro-ischemic lesions is serious, being associated with a hypercoagulation state.⁴⁰⁻⁴⁴ Elevated levels of D-Dimer, fibrinogen, and fibrinogen degradation products are usually found, along with a prolonged prothrombin time in the setting of disseminated intravascular coagulation.⁴¹ In the Spanish survey, the mortality rate was approximately 10%,⁷ whereas median time from acro-ischemia onset to death in the Chinese study was 12 days.⁴¹ An anecdotal report of a COVID-19-positive 74-year-old woman with acral necrotic lesions noted that she recovered completely without systemic implications.⁴²

Histopathology

Livedoid ischemic lesions in severely ill patients are characterized by epidermal necrosis with features of thrombotic vasculopathy, involving the superficial and deep vessels, most of them filled with hyaline thrombi^{37,41,43} (Figure 2B and C). Perivascular infiltrate is usually mild, mainly lymphocytic or neutrophilic.⁴⁴ Sweat gland necrosis, more evident in the secretory portion of the eccrine sweat coil, with preserved eccrine ducts is a peculiar finding. In some areas, arterioles at the dermo-hypodermal junction showed focal fibrinoid necrosis surrounded by a scarce neutrophilic infil-

trate, but no findings of leukocytoclastic vasculitis have been observed. One report described a pauci-inflammatory thrombotic vasculopathy,⁴⁰ with deposition of C5 b-9 and C4 d in both grossly involved and normally appearing skin. The microscopic features were similar to those observed in the lungs of three patients who had died from severe pneumonitis due to SARS-CoV-2.

Pathogenetic mechanisms

Acro-ischemic/necrotic lesions are related to the activated coagulation system due to SARS-CoV-2,^{41,43} involving both alternative and lectin-based complement pathways. These may cause microvascular injury, although the pathophysiology is still unclear.

Exanthematous eruptions

Morphology of skin eruptions associated with COVID-19 outbreak is very polymorphic, and classification is limited by the subjectivity of the description in various reports.⁴⁶ A recent subanalysis of the cross-sectional Spanish study noted the impossibility of defining the cause-effect relationship with SARS-CoV-2 infection⁴⁷; however, some histopathology findings support a subclassification with at least five patterns.

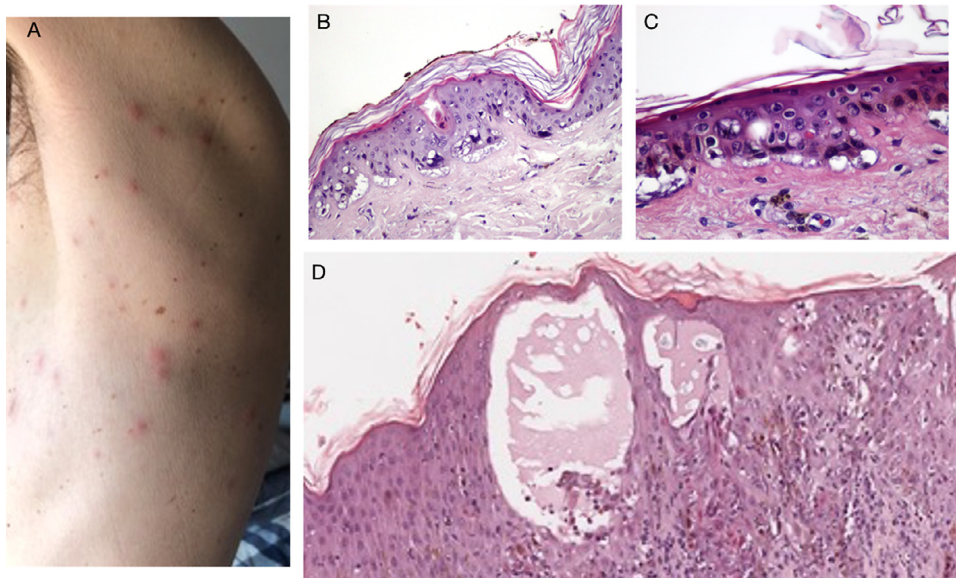


Fig. 3 (A) Varicella-like/vesicular eruption with small, scattered vesicles, and erythematous papules of the trunk involvement. (B, C) Slightly atrophic epidermis, vacuolar degeneration of the basal layer, and multinucleate, hyperchromatic keratinocytes with dyskeratotic (apoptotic) cells associated with minimal to absent inflammatory infiltrate in early lesions (hematoxylin & eosin [HE], 200 ×). (D) Later findings include intra-epidermal unilocular vesicles, exocytosis, reticular degeneration of the epidermis, acantholytic cells, and scattered dyskeratotic keratinocytes similar to herpetic lesions (HE, 200 ×).

Varicella-like/vesicular eruption

Clinical presentation

The varicella-like/vesicular eruption is considered the most specific COVID-19–associated diffuse cutaneous eruption. This was initially described in a case series of 22 Italian COVID-19–positive patients¹² and up to 9% of middle-aged Spanish patients.⁷ A systematic review confirmed a prevalence ranging from 11% to 18% among COVID-19 patients.⁴ Prognostic significance is variable, as 42% of the Spanish patients developed pneumonia, and 13.6% of the Italian patients died of COVID-19.¹²

The eruption is characterized by small, scattered monomorphic vesicles, very similar to chicken pox, with constant trunk involvement and mild to absent pruritus (Figure 3A), occurring 3 days after systemic findings have developed and disappearing in about 8 days and without scarring.^{12,48} In addition to this typical vesicular eruption, a more polymorphic pattern that includes papules and pustules has been recently described.⁴⁸ In some patients the eruption was reminiscent of Grover disease or herpes-like lesions.⁴⁹

Histopathology

In the few patients in whom skin biopsies have been performed, cytopathic changes consistent with a viral exanthem were found. In early lesions,¹² a slightly atrophic epidermis was described with vacuolar degeneration of the basal layer and multinucleate, hyperchromatic keratinocytes with dyskeratotic (apoptotic) cells associated with minimal to absent inflammatory infiltrate (Figure 3B and C). Later findings

included intra-epidermal unilocular vesicles, reticular degeneration of the epidermis, multinucleated and ballooned keratinocytes, and acantholytic cells, some of them with dyskeratotic features similar to herpetic lesions (Figure 3D) or pseudo-herpetic Grover disease.⁴⁹ Prominent dyskeratosis, with pomegranate-like aspects due to suspected nuclear viral inclusions in multinucleated cells, has also been described.⁵⁰ Direct immunofluorescence and SARS-CoV-2 PCR tests of the vesicles were negative.⁵⁰ The differential diagnosis with true chickenpox is difficult, but typical microscopic findings have not been outlined, such as nuclear atypia, large multinucleated cells, and acantholysis secondary to ballooning.⁵⁰ Grover disease presents with a distinct clinical context, but the prevalence of dyskeratosis and acantholytic changes has suggested that this entity be termed “COVID-19–associated acantholytic rash.”⁵⁰

Pathogenesis

Histopathologic findings and reproducible timing from COVID-19 manifestations onset support a direct viral effect. Identification of angiotensin-converting enzyme 2,⁵¹ the receptor for SARS-CoV-2 spike protein, expressed in the basal cell layer keratinocytes support this hypothesis. Viral interaction with the ACE-2 seems able to induce acantholysis and dyskeratosis.

Confluent erythematous/maculopapular/morbilliform eruption

Clinical presentation

A slightly itching widespread erythematous eruption is the most frequent cutaneous manifestation associated with

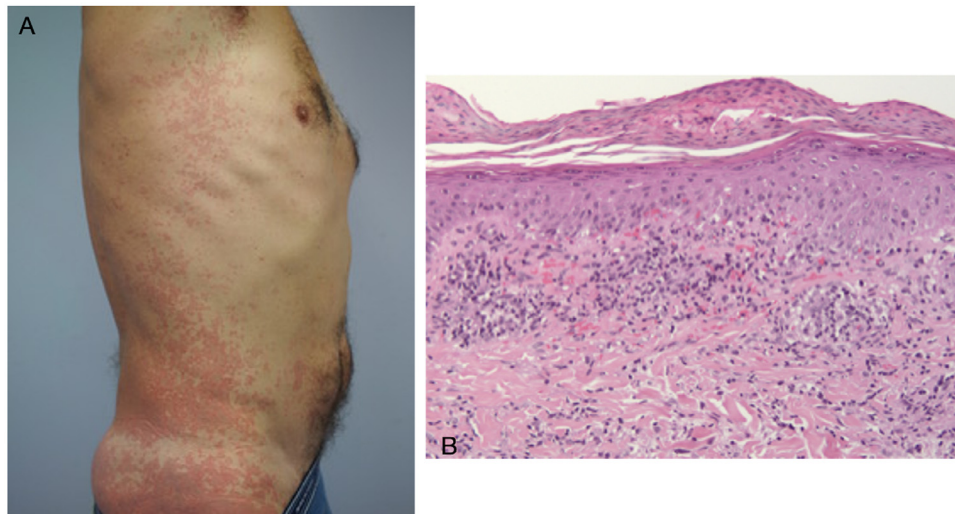


Fig. 4 (A) Maculopapular eruption of the trunk in a COVID-19 symptomatic man. (B) Parakeratosis, slight spongiosis, and vacuolar degeneration of basal cell layer, and perivascular and interstitial infiltrate made by lymphocytes, histiocytes, and some neutrophils with red blood cell extravasation (hematoxylin & eosin, 200 \times).

COVID-19, although less specific. The first Italian study reported its occurrence in 16% of patients,²² whereas two Spanish studies reported a prevalence ranging from 30%⁵² to 47%.⁷ A systematic review assessed a prevalence of 44%⁸; however, in most of the papers, terminology is variable,^{46,47} going from erythematous eruption to maculopapular (Figure 4A) or morbilliform eruption. The eruption spares the palmoplantar skin and mucosae. Characteristically, it appears at a late stage of the disease,⁴ lasts for about 9 days, and seems to be associated with a more severe course.^{7,47} It is uncommon among COVID-19-positive children.⁵²

Histopathology

Although infrequently performed, histopathology shows variable features of spongiotic dermatitis, slight vacuolar degeneration with a superficial perivascular and mixed inflammatory infiltrate (Figure 4B).^{22,52-54} Some authors consider these histopathologic findings as consistent with a viral exanthem. Timing of the biopsy might be crucial, as early-onset cases showed epidermal spongiosis and a perivascular lymphocytic infiltrate with eosinophils, whereas the delayed lesions showed perivascular lymphocytic infiltrate and histiocytes among collagen fibers. In a series of eight patients with COVID-19 pneumonia who developed a late-onset maculopapular exanthem, histopathology revealed a spongiotic dermatitis with a neutrophilic infiltrate and sign of vascular injury due to small microthrombi in dermal capillaries without vasculitis.⁵⁵ Subcorneal pustules were also present. In three elderly patients from Milan, Italy,⁵⁶ microscopic findings were variable, going from a superficial perivascular dermatitis with mild spongiosis to a lymphocytic vasculitis with rare microthrombi and extravasated red blood cells. In one of these cases, histopathologic features overlap with those of the varicelliform eruption (see above)

showing dyskeratotic, ballooning, and necrotic keratinocytes with lymphocytic exocytosis and Grover-like features. Nests of Langerhans cells within the epidermis were also observed.

Pathogenesis

From the few information recovered, it can be postulated that viral particles circulating in the blood of patients with COVID-19 infection reach the skin vessels, where they set off a lymphocytic vasculitis.⁵⁴ Immune complexes deposition and activated cytokines might produce alterations similar to what happens in thrombophilic arteritis. Keratinocytes may be a secondary target, after Langerhans cells activation, thus inducing a spectrum of different clinical and pathologic manifestations, going from simple vasodilation and spongiosis to lymphocytic vasculitis and microthrombi formation.

Urticarial eruption

Clinical presentation

Acute urticaria, although nonspecific, has been reported as a prodromal clinical finding among adult COVID-19 patients, with a variable timing: Some lesions appeared before onset of fever, whereas others in combination with pyrexia and cough.⁵⁸⁻⁶⁰ Presentation is not different from idiopathic urticaria (Figure 5A), with small or larger itching wheals. In the Spanish cohort of COVID-19-positive patients, 19% of them presented an urticarial eruption lasting a mean time of 6.8 days, and carrying a quite severe prognosis with a mortality rate of 2%.⁷ Concomitant systemic eosinophilia has been suggested to be predictor of a better outcome.⁶¹

Histopathology

The prevalent pattern is reminiscent of idiopathic urticaria, with a perivascular lymphocytes infiltrate, some eosinophils

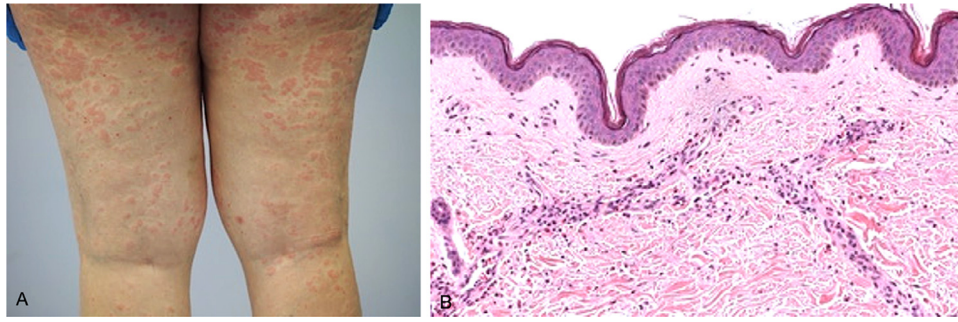


Fig. 5 (A) Figurate urticarial eruption of the extremities in a COVID-19 symptomatic woman. (B) Normal epidermis and a superficial perivascular infiltrate with eosinophils and some neutrophils with slight edema (hematoxylin & eosin, 100 ×).

and upper dermal edema (Figure 5B), without virally induced cytopathic alterations or intranuclear inclusions.⁶² Urticarial vasculitis has also been documented in two patients with persistent urticarial plaques and residual purpura, showing a small vessel leukocytoclastic vasculitis, with red blood cell extravasation, perivascular infiltrate of neutrophils and karyorrhexis, endothelial swelling, and fibrinoid necrosis.⁶³ Finally, a superficial perivascular lymphocytic infiltrate without eosinophils, accompanied by a lichenoid and vacuolar interface dermatitis with occasional dyskeratotic keratinocytes in the basal layer, has been described in a 39-year-old man with a widespread erythematous and edematous, nonpruritic urticarial-like eruption.⁶⁴

Pathogenesis

SARS-CoV-2 might directly and/or indirectly induce mast cell and basophil activation, although not yet showed.⁶⁵ Late-onset persistent lesions are probably related to the general immune system activation, confirmed by the association with vasculitis and absence of eosinophils in the infiltrate, with spongiotic or lichenoid interface dermatitis.^{63,64}

Erythema multiforme-like eruption

Clinical presentation

The occurrence of erythema multiforme (EM) lesions is reported both in young patients, with good prognosis,^{7,22} and in older persons, associated with severe COVID-19 findings.⁶⁶ In youngsters, the lesions vary from target (three rings) to targetoid (two rings) confluent macules, papules, and plaques, some with hemorrhages and central crusts and associated with chilblain-like lesions on acral sites such as palms, elbows, and knees. Lesions recover spontaneously within 1 to 3 weeks, whereas in older patients (mean age 67 years) the eruption is widespread, with palatal macules and petechiae, sparing palms, and soles and is associated with mild alterations of the coagulation system.⁶⁶ In one patient the skin eruption occurred concomitantly to COVID-19 clinical manifestations, whereas three additional patients presented with EM-like eruption after the discharge for disease recovery, thus causing a new hospitalization.

Histopathology

Microscopic features confirm different patterns: Acral lesions in adolescents with chilblain-like showed a superficial and deep perivascular lymphocytic infiltrate with perieccrine involvement and some vasculopathic changes, reminiscent of what is observed in chilblain-like lesions.²⁴ The infiltrate was composed of CD3+ T cells, with a mix of CD4+ and CD8+ lymphocytes. Immunohistochemical stain with the antibody against the SARS-CoV/SARS-CoV-2 spike protein in two cases showed granular positivity in the endothelial cells and epithelial cells of eccrine glands. In the diffuse form involving adults,⁶⁶ histopathology was consistent with true EM, showing spongiosis, lymphocytic exocytosis, and variable degrees of interface dermatitis and focal necrotic keratinocytes.

Pathogenesis

It is likely that the acral EM-like lesions in children are a clinical variant of chilblain-like lesions,²⁴ whereas the more generalized adult EM-like eruption with enanthem corresponds to EM related to a late response to SARS-CoV-2, as the majority of patients recovered from COVID-19 at the onset of skin lesions. An adverse drug reaction could not be ruled out, due to the relative multidrug intake, as well as other possible triggers.⁶⁶

Petechial/purpuric eruption

A petechial/purpuric eruption should be considered the herald of symptomatic COVID-19 in aged patients, carrying a benign course with complete recovery. Lesion distribution is variable, from symmetric periflexural confluent erythematous macules, papules, and petechiae in a 48-year-old patient⁶⁷ to a more generalized petechial eruption in a 59-year-old man (Figure 6A),⁶⁸ as well as being limited to the legs in a 61-year-old woman.⁶⁹

The petechial eruption can be a misleading feature in tropical countries, where Dengue fever is endemic, and overlapping signs and clinical manifestations would make the diagnosis and treatment difficult.⁷⁰ From the first case reported from Thailand,⁷¹ a general alert has been sounded, and the

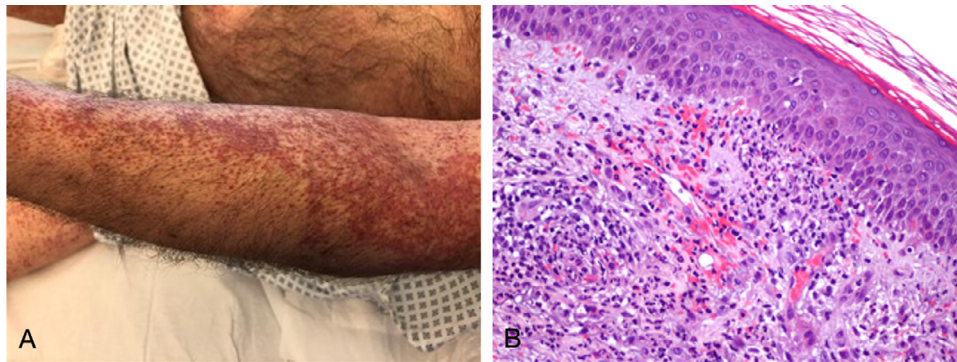


Fig. 6 (A) Petechial/purpuric eruption in a 59-year-old symptomatic COVID-19 man. (B) Histopathologic findings showing a typical leukocytoclastic vasculitis of small vessels with red blood cell extravasation (hematoxylin & eosin, 200 ×).

presence of high Dengue antibodies can give false-negative testing for SARS-CoV-2. In this setting, only reverse transcription PCR (RT-PCR) testing is resolute.⁷²

Histopathology

Results from the few histopathologic studies are again variable. One survey showed a superficial perivascular lymphocytic infiltrate with hemorrhages and papillary edema along with some dyskeratotic epidermal cells in the absence of vasculopathy.⁶⁷ Two other reports found a leukocytoclastic vasculitis of small vessels (Figure 6B).^{68,69} No viral cytopathic changes were observed.

Pathogenesis

Purpuric lesions with features of leukocytoclastic vasculitis may represent an immune complex hypersensitivity reaction to antigens of SARS-CoV-2^{68,69}; however, an immune-mediated reaction to drugs cannot be ruled out.

Skin manifestations of multisystem inflammatory syndrome (atypical Kawasaki disease)

Numerous pediatric cases of a severe hyperinflammatory condition, with features reminiscent of atypical Kawasaki disease or toxic shock syndrome, were recently associated with COVID-19 and named “multisystem inflammatory syndrome in children” (MIS-C). This syndrome was described with unrelenting fever, conjunctivitis, and abdominal pain, progressing to hemodynamic shock and severe myocardial involvement.¹⁵ An Italian survey reported a 30-time increase in the rate of Kawasaki-like presentation during the COVID-19 pandemic among children.¹⁶ The nasopharyngeal swabs taken from these children were negative, once again putting into discussion a direct responsibility of SARS-CoV-2 infection.

The skin morphology has been poorly characterized, mostly suggestive of erythema multiforme but also of maculopapular or morbilliform eruptions, and vasculitis.¹⁷⁻¹⁹

Recently, MIS occurrence in an adult with SARS-CoV-2 infection has been reported, and dermatologic findings were also described as erythema multiforme-like lesions.²⁰

Histopathology

Microscopic findings from a few biopsies identify at least two different patterns: The former is consistent with typical leukocytoclastic vasculitis,²¹ whereas the latter is characterized by erythema multiforme-like changes, showing a nonspecific sparse inflammatory infiltrate with few intra-epidermal neutrophils and necrotic keratinocytes.¹⁷

Pathogenetic mechanisms

Exaggerated innate immunologic activation is implicated in MIS, with similar pathologic abnormalities in affected internal organs and the skin, rather than direct viral injury. Direct immunofluorescence examination has revealed the presence of IgA- and complement in the vessel walls, which might be a key factor of the vasculitis.²⁰

Miscellany

A widespread pityriasis rosea-like eruption in a 27-year-old COVID-19–positive patient occurred 3 days after mild systemic clinical manifestations had developed that included low-grade fever, fatigue, anorexia, and gastroenteritis.⁷³ No biopsy was taken. The patient recovered completely.

A similar papule-squamous eruption, but with a peculiar digitate morphology, presented in a hospitalized elderly diabetic man.⁷⁴ The patient died from COVID-19–related complications, although the eruption had spontaneously resolved in 1 week. A skin biopsy revealed diffuse spongiosis with vesicles containing lymphocytes and Langerhans cells. The dermis showed mild papillary edema, and a superficial lymphohistiocytic infiltrate. The real-time PCR for SARS-CoV-2 in the fresh tissue resulted negative.

Manifestations suggestive of livedo reticularis in COVID-19–positive adults have been reported.^{75,76} The dusky, non-blanching lace-like network, forming annular patches around a pale center, may be unilateral and transitory or symmetric or more generalized without signs of vasculitis. A biopsy was not performed.

Similar to transient livedo, skin mottling developed in an Iranian neonate,⁷⁷ with a positive history of COVID-19 in

the mother. Fever, sepsis signs, and positive SARS-CoV-2 testing confirmed the disease in the child, but the course was benign, with discharge within 2 days. No skin biopsies were performed.

An atypical Sweet syndrome, characterized by erythema nodosum-like indurated painful nodules, occurred in a 61-year-old Turkish woman, with a one-week history of fever, fatigue, arthralgia, and oral ulcers.⁷⁸ Histopathologic study showed a superficial and deep neutrophilic dermatosis. SARS-CoV-2 testing was initially negative but became positive during hospitalization. The skin lesions regressed after COVID-19 treatment.

An intertriginous and flexural exanthema, similar to the symmetric drug-related intertriginous and flexural exanthema (SDRIFE), developed in a 64-year-old diabetic woman 4 days after the onset of COVID-19 clinical manifestations.⁷⁹ A biopsy was not performed.

Discussion

Understanding COVID-19 pathogenesis is a great challenge and, actually, it is difficult to categorize what is directly related to the viral pathogenicity, and the effect of the exaggerate host response, unleashing a devastating “cytokine storm.”¹⁻³ The skin mirrors this complexity, producing a plethora of polymorphous cutaneous lesions.⁴⁻¹⁴ Only three patterns are considered specifically related to COVID-19 with a consistent degree of reliability, because they have occurred in many patients in the course of the pandemic, and they have been described by independent investigators. They include chilblain-like lesions, acro-ischemic/livedoid necrotic lesions and varicelliform-like/vesicular eruptions.^{12,22-50} Clinicopathologic correlation provides more insights on these conditions. A superficial and deep perivascular lymphocytic infiltrate with perieccrine extension and microthrombi formation similar to idiopathic chilblains is found in chilblain-like lesions, and although a continuum spectrum toward acral ischemia has been postulated,³⁸ microscopic findings support a distinct pathogenesis. Fore-runners’ reports have documented in chilblains a positive immunohistochemical staining with the antibody against the SARS-CoV/SARS-CoV-2 spike protein in endothelial cells and epithelial cells of eccrine glands.^{24,35,80-83} Chilblain-like lesions are otherwise associated with negative results of nasopharyngeal swabs and serology,²⁵⁻²⁷ which have been explained with a limited involvement of the adaptive immunity in asymptomatic or mild disease in young patients.¹¹ On the contrary, histopathologic findings of the ischemic/livedoid necrotic skin are superimposable to the severe internal organ injury of COVID-19, showing thrombosis and fibrin deposition into dermal blood vessels.^{36,37,41} Blood examinations usually confirm the hypercoagulability state. Age appears as a limiting factor, as severe coagulopathy is unlikely to develop in young otherwise healthy patients, and the host response against the viral spread

is more effective.¹¹ Advanced age, together with comorbidities, unleashes an exaggerate innate immune response, named “macrophage activation syndrome associated with a more severe prognosis.”^{1-3,11,65}

Between the two-prognostic opposite, varicelliform-like/vesicular eruption seems to be related to the skin tropism of the virus, as documented by microscopic cytopathic changes.⁴⁸⁻⁵¹ As for the other exanthematous eruptions, histopathologic findings are less reliable, because the mixed perivascular infiltrate might be secondary to a direct endothelial cell damage mediated by SARS-CoV-2, as well as by circulating cytokines, unleashing tissue factors expression, vasodilation, spongiosis, and variable interface dermatitis.

Differential diagnosis remains a big challenge. With the exception of chilblain-like and acro-ischemic-necrotic lesions, the SARS-CoV-2 association with exanthematous eruptions remains presumptive, because many viral infections develop similar eruptions. Epstein-Barr virus, human herpes virus (HHV) 6 and 7, cytomegalovirus, herpes simplex, and varicella-zoster may reactivate in course of systemic disease, or as effect of the treatments to contrast COVID-19. Differential with dengue fever is an emergent problem in tropical countries, where both diseases are prevalent.⁷⁰⁻⁷² Bacterial infections have been suspected to co-associate with COVID-19, especially *Mycoplasma pneumoniae*, which may trigger erythema multiforme.⁸⁴ The main differential diagnosis involves adverse drug reactions^{85,86} whose histopathology includes a wide range of microscopic patterns,⁸⁷ from spongiotic or perivascular mixed infiltrate to interface dermatitis or vasculitis. Temporal correlation with drug administration, as well as the spectrum of reactions associated with a specific drug,⁸⁶ together with main histologic features may help distinguish COVID-19 lesions from drug-related ones. For instance, pustular eruptions such as acute generalized exanthematous pustulosis are more frequently associated with hydroxychloroquine and macrolides than to viral infections.⁸⁸

Conclusions

A great heterogeneity of cutaneous manifestations is increasingly associated with SARS-CoV-2 infection. It has become necessary to distinguish among pathognomonic signs, and not specific consequences of the COVID-19 systemic involvement or management, including adverse drug reactions. Clinicopathologic correlation provides insights into possible mechanisms and the course of the disease. Chilblain-like lesions are associated with a paucity or asymptomatic course, whereas acro-ischemic/livedoid necrotic manifestations alert about the severe thrombotic vasculopathy in progress. Although the varicelliform-like/vesicular eruptions are associated with a variable outcome, they represent the most specific manifestation of the viral direct cytopathic interaction with the skin.

From all information collected, clinicopathologic correlation confirms its crucial role in distinguishing coincidence from causal correlation to COVID-19, but more skin biopsies are warranted. Improvement of accessibility to immunohistochemical staining with antibodies to the SARS-CoV/SARS-CoV-2 spike protein on paraffin-embedded specimens, RNA detection of SARS-CoV-2 strain by real-time PCR-based assay, and electron microscopy studies would make the final difference, especially in patients with negative nasopharyngeal swab and serology.

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