

Cutaneous Manifestations and Types of skin affection Associated with COVID-19 Infection: A simple Review Article

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Abstract

Although COVID-19 is best known for causing fever and respiratory symptoms, it has been reported to be associated also with different extra pulmonary manifestations, including dermatological signs. Whilst the COVID-19-associated cutaneous manifestations have been increasingly reported that were unexpected before their onset, their exact incidence has yet to be estimated. Furthermore, evidence is accumulating that skin manifestation associated with COVID-19 are extremely polymorphic. This review article aimed to explore the updated evidence regarding the cutaneous manifestation associated with Covid-19 infection during the pandemic. COVID-19. Associated cutaneous manifestations have an extremely polymorphic nature including (i) urticarial rash, (ii) confluent erythematous/maculopapular/morbilliform rash, (iii) papulovesicular exanthem, (iv) chilblain-like acral pattern, (v) livedo reticularis/racemosa-like pattern, (vi) purpuric “vasculitic” pattern.... etc. Skin eruptions vary in morphology, time of onset, location, and duration. The incidence of cutaneous involvement in COVID-19 varies from 1% to 20% in different reports. The exact mechanism of cutaneous involvement in COVID-19 is not precise, the role, direct or indirect, of SARS-CoV-2 in their pathogenesis, is still debated but the pathogenesis probably involves high interferon.

Keywords: Cutaneous Manifestations, Skin affection, COVID-19 Infection, Fever and respiratory symptoms

INTRODUCTION

In December 2019, a novel zoonotic RNA virus named “severe acute respiratory syndrome coronavirus 2” (SARS-CoV-2) was isolated in patients with pneumonia in Wuhan, China. Since then, the disease caused by this virus, called “coronavirus disease-19” (COVID-19), has spread throughout the world at a staggering speed becoming a pandemic emergency [1]. The virus is mainly spread by droplets, but direct contact and fecal excretions are other possible sources of infection. Vertical transmission may be possible. The primary target of SARS-CoV-2 is the upper respiratory mucosa, and angiotensin-converting enzyme 2 (ACE2) acts as a functional receptor for the viral spikes and eventually viral entry into host cells [2]. Expression of the SARS-CoV-2 cell receptor gene ACE2 has been demonstrated in several human tissues including skin and adipose tissue. One of the main reasons for pulmonary consolidation during active disease is the development of extensive pulmonary fibrosis. SARS-CoV-2 induces pulmonary fibrosis in a tumor growth factor-beta (TGF-beta)/Smad-dependent pathway. In both cutaneous and pulmonary fibrosis, trans-differentiation of adipocytes or lipofibroblasts into myofibroblasts is involved. Adipocytes can serve as a viral reservoir [3].

The incubation time of COVID-19 is up to 14 days. Typical clinical symptoms include fever, dry cough, sore throat, fatigue, diarrhea, conjunctivitis, hyposmia, and hypogeusia. Diagnosis is based on medical and travel history, contact with COVID-19 patients, and clinical symptoms. Confirmation is done by the detection of viral RNA by reverse-transcriptase polymerase chain reaction (RT-PCR) for nasopharyngeal swabs or bronchoalveolar fluid [4].

Although COVID-19 is best known for causing fever and respiratory symptoms, it has been reported to be associated also with different extrapulmonary manifestations, including

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How to cite this article: Alenazy AES, Alabdulwahab K, Alabdulwahab F, Alanazi SIS. Cutaneous Manifestations and Types of skin affection Associated with COVID-19 Infection: A simple Review Article. Arch Pharm Pract. 2022;13(2):94-8. <https://doi.org/10.51847/5HMEAOU6>

dermatological signs. Whilst the COVID-19-associated cutaneous manifestations have been increasingly reported, their exact incidence has yet to be estimated, their pathophysiological mechanisms are largely unknown, and the role, direct or indirect, of SARS-CoV-2 in their pathogenesis, is still debated. Furthermore, evidence is accumulating that skin manifestation associated with COVID-19 are extremely polymorphic [5].

Incidence

The incidence of cutaneous involvement in COVID-19 varies from 1% to 20% in different reports. Skin eruptions vary in morphology, time of onset, location, and duration [6]. Several studies have reported some COVID-19-related skin involvements that were unexpected before their onset. A systematic review found that skin lesions were present in only 0.25% of 2445 pediatric patients in 119 published studies [7]. The cutaneous manifestations of childhood COVID-19 differ from those of adults. The initial studies from Central China reported low frequencies of skin disease in COVID-19 patients. Among 1099 confirmed cases in Wuhan, only 0.2% presented with cutaneous symptoms [8]. With a closer involvement of dermatologists in the battle against the latest pandemic, the interest in cutaneous signs of SARS-CoV-2 infection increased.

The first report from Northern Italy on 88 COVID patients observed cutaneous symptoms in 18 patients (20.4%) of whom 8 patients developed cutaneous signs at the onset, and 10 patients after the hospitalization [9].

Pathophysiology

The exact mechanism of cutaneous involvement in COVID-19 is not precise, but the pathogenesis probably involves high interferon [10]. Viral infection causes the release of type I interferon, which activates the JAK-STAT signaling pathway, resulting in increased expression of genes, which inhibits viral proliferation and helps eliminate virus and immunity against viral disease [11]. Chilblain-like lesions have been reported in patients with high type I interferon. So, there is a possibility that these children had high IFN initially, which helped in the early elimination of the virus and the development of skin lesions in the convalescent phase. It is proposed that erythema multiforme type lesion in COVID-19 occurs secondary to activation of the complement pathway in a setting of prevailing procoagulant state, causing thrombogenic vasculopathy [12].

Types of Skin Affection

Acro-ischemia

Severe COVID-19 can lead to a state of hypercoagulation and disseminated intravascular coagulation with laboratory findings such as increased levels of D-dimer, fibrinogen, and fibrinogen degradation products, and prolonged prothrombin time. These critically ill patients present acro-ischemia with finger and toe cyanosis, cutaneous bullae, and dry gangrene [13]. Livedo-like features and necrosis were noted in 6% of

Spanish COVID-19 patients, mostly elderly people. These findings were associated with a mortality rate of 10%. Two more temporary cases were reported in a 47-year-old woman and a 67-year-old male from Atlanta, GA, USA [14].

Histopathological investigations of various tissues in three patients who died from COVID-19 disease revealed hyaline thrombi in micro-vessels of skin.

Urticarial Rash

It is well known that urticaria and angioedema can be triggered by viral and bacterial agents, such as cytomegalovirus, herpesvirus, Epstein-Barr virus, and mycoplasma. However, establishing a cause-effect relationship may be difficult in single cases [15]. Urticarial eruptions associated with COVID-19 have been first reported by Recalcati in his cohort of hospitalized patients, accounting for 16.7% of total skin manifestations. Urticaria-like eruptions have been subsequently described in other cohort studies. Galván Casas *et al.* [16] stated that urticarial rash occurred in 19% of their cohort, tended to appear simultaneously with systemic symptoms, lasted approximately 1 week, and was associated with medium-high severity of COVID-19. Moreover, the itch was almost always present. Freeman *et al.* [17] found a similar prevalence of urticaria (16%) in their series of 716 cases, in which urticarial lesions predominantly involved the trunk and limbs, relatively sparing the acral sites. Urticarial lesions associated with fever were reported to be early or even prodromal signs of COVID-19, in the absence of respiratory symptoms, in 3 patients [18]. Therefore, the authors of the reports suggested that isolation is needed for patients developing such skin symptoms if COVID-19 infection is suspected in order to prevent possible SARS-CoV-2 transmission. COVID-19-related urticaria occurred also in a familial cluster, involving 2 patients belonging to a Mexican family of 5 people, all infected by SARS-CoV-2 and suffering also from anosmia, ageusia, chills, and dizziness. Angioedema may accompany COVID-19-related urticaria, as evidenced by the case published in June 2020 of an elderly man presenting with urticaria, angioedema, general malaise, fatigue, fever, and pharyngodynia. Urticarial vasculitis has also been described in association with COVID-19 in 2 patients. Histopathological studies of urticarial rashes are scant. In a 60-year-old woman with persistent urticarial eruption and interstitial pneumonia who was not under any medication, Rodríguez-Jiménez *et al.* [19] found on histopathology slight vacuolar interface dermatitis with occasional necrotic keratinocytes curiously compatible with an erythema multiform-like pattern. Low-dose systemic corticosteroids are a therapeutic option for COVID-19-associated urticarial rash. Indeed, the author hypothesized that low-dose systemic corticosteroids, combined with non-sedating 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 [20].

Maculopapular Eruptions

Maculopapular eruptions accounted for 47% of all cutaneous manifestations in the cohort of Galván Casas *et al.* [21] the prevalence of erythematous rash was higher in other studies, like that published by De Giorgi *et al.* in May 2020, in which erythematous rashes accounted for 70% of total skin manifestations. The clinical picture of the eruptions may range from erythematous confluent rashes to maculopapular eruptions and morbilliform exanthems. Erythematous lesions may show a purpuric evolution or coexist from the beginning with purpuric lesions. Erythematous papules may also be arranged in a morbilliform pattern. Maculopapular eruptions including also purpuric, erythema multiform-like, pityriasis rosea-like, erythema elevatum diutinum-like, and perifollicular eruptions, morbilliform exanthems were the most frequent maculopapular pattern [22]. In most cases lesions were generalized, symmetrical, and started on the trunk with centrifugal progression. In the same subanalysis, hospital admission due to pneumonia was very frequent (80%) in patients with a morbilliform pattern. In this group, the main differential diagnoses are represented by exanthems due to viruses other than SARS-CoV-2 and drug-induced cutaneous reactions [23].

Histopathology of erythematous eruptions has shown vascular damage in all the 3 cases examined, mild superficial perivascular lymphocytic infiltrate on the histology of 4 patients, and/or dense neutrophilic infiltrates in 8 patients with late maculopapular eruptions. This could be attributable to the history of new drug assumptions.

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 deserve to be administered just in more severe and widespread presentations [24].

Chilblain-Like Eruption

Chilblain-like edematous and erythematous eruptions have been observed in milder cases of COVID-19 and in particular in youngsters and young adults, which disappear after the infection without leaving scars [25]. Caucasians seem to be significantly more affected than other ethnic groups. Chilblain-like acral lesions were the second most frequent cutaneous manifestation ($n = 46/159$; 28.9%) in the multicenter Italian study. Chilblain-like eruptions are mostly asymmetrically distributed. Among 375 COVID-19 patients in Spain, 19% presented with “pseudo-chilblains.” They may be associated with itch or pain and disappear on average after 2 weeks. Chilblain-like lesions in pediatric dermatological outpatients (mean age 14 years) have been noted in 25 children in Spain. None of these children had the typical symptoms of COVID-19, except one who suffered from diarrhea. The lesions disappeared within 2 weeks without treatment [26]. The frequent occurrence of chilblain-like lesions in the absence of cold exposure and the involvement of patients without evident COVID-19-related symptoms raised the question of whether these manifestations were

associated with SARS-CoV-2 infection. Chilblain-like lesions share many histopathological features with idiopathic and autoimmunity-related chilblains, including epidermal necrotic keratinocytes, dermal edema, and perivascular and perieccrine sweat gland lymphocytic inflammation. Vascular changes such as endothelins and microthrombi may be found. 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 [27].

Papulovesicular Exanthem

COVID-19-associated papulovesicular exanthem was first extensively reported in a multicenter Italian case series of 22 patients published in April 2020. The exact prevalence of papulovesicular exanthems is variable. Indeed, in a cohort of 375 patients with COVID-19-associated cutaneous manifestations [28], patients with papulovesicular exanthem were 34 (9%), 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 by Askin *et al.*, Recalcati and De Giorgi *et al.* [29], respectively. In the Italian multicentric study, papulovesicular rash accounted for 18.2% of skin manifestations. Furthermore, even if papulovesicular exanthem tends to involve more frequently the adult population, with a median age of 60 years in the study by Marzano *et al.* [30], also children may be affected. Galván Casas *et al.* [31] reported that vesicular lesions generally involved middle-aged patients, before systemic symptoms' onset in 15% of cases, and were associated with intermediate COVID-19 severity. Two different morphological patterns were found: a widespread polymorphic pattern, more common and consisting of small papules, vesicles, and pustules of different sizes, and a localized pattern, less frequent and consisting of monomorphic lesions, usually involving the mid-chest/upper abdominal region or the back.

Histological pattern of skin lesions showed prominent acantholysis and dyskeratosis associated with the presence of a unilocular intraepidermal vesicle in a suprabasal location. Based on these histopathological findings, the authors refused the term “varicella-like rash” and proposed a term that was more suitable in their view: “COVID-19-associated acantholytic rash.” Histopathological findings of another case of papulovesicular eruption revealed extensive epidermal necrosis with acantholysis and swelling of keratinocytes, ballooning degeneration of keratinocytes, and signs of endothelins in the dermal vessels [32]. No standardized treatments for COVID-19-related papulovesicular exanthem are available, also given that it is self-healing within a short time frame. Thus, a “wait-and-see” strategy may be recommended.

Livedo Reticularis

Livedo reticularis or racemosa is defined by a mottled, lace- or net-like vascular pattern of erythematous to violaceous discoloration associated with ischemia of the cutaneous capillaries. Compared with other cutaneous findings in

COVID-19, livedo reticularis seems less common (2.3%) but associated with more severe disease and possibly greater mortality [33].

Sacral Ulcers

Sacral “ulcers” represent a peculiar finding in COVID-19 that require heightened awareness among medical providers, as they are distinct from sacral decubitus ulcers. Risk factors for the development of sacral decubitus ulcers include immobility and prolonged bed rest, incontinence, poor nutrition, diabetes, and vascular disease [34]. Similar to other institutions, we have noted cases of sacral lesions and ulcerations in patients with critically ill, multi-organ system COVID-19 disease. Sacral ulcerations may present with purpuric lesions, violaceous induration, livedoid plaques, and eschars [35]. The pathogenesis is hypothesized to be multifactorial including a combination of systemic coagulopathy, cutaneous ischemia, and pressure-induced deep tissue injury. Wound care consultation is warranted in these cases as some sacral ulcerative lesions require local debridement and removal of devitalized tissue. Specialized care must be taken to ensure that patients do not develop subsequent bacterial infection leading to sepsis [36, 37].

Retiform Purpura

Retiform purpura is classified as a more severe cutaneous finding in COVID-19 [38, 39]. Published findings from the AAD COVID-19 Registry noted that all patients with retiform purpura were hospitalized and 82% had ARDS due to SARS-CoV-2. Painful, retiform purpura with hemorrhagic blistering and evidence of small vessel thrombi and complement activation was observed in the setting of progressive thrombocytopenia with acute SARS-CoV-2 infection [40, 41]. Retiform purpura with concomitant acral livedo racemosa has also been noted. Histopathology shows complement deposits suggesting complement pathway activation involved in coagulopathic-driven thrombi [42, 43]. Furthermore, a pauci-inflammatory vascular thrombosis with extensive complement deposits and detection of SARS-CoV-2 protein localized to endothelial cells have been found [44, 45].

CONCLUSION

COVID-19-associated cutaneous manifestations have a polymorphic nature including urticarial rash, confluent erythematous/maculopapular/morbilliform rash, papulovesicular exanthem, (iv) chilblain-like acral pattern, livedo reticularis/racemosa-like pattern, purpuric “vasculitic” pattern... etc. The exact mechanism of cutaneous involvement in COVID-19 is not precise, but the pathogenesis probably involves high interferon.

ACKNOWLEDGMENTS: Many thanks to everybody give us continuous help, support and encouragement to complete this work.

CONFLICT OF INTEREST: None

FINANCIAL SUPPORT: None

ETHICS STATEMENT: None

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