

SKIN LESIONS THAT COULD BE CONSIDERED SYMPTOMS OF COVID-19

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Abstract: COVID-19, the respiratory syndrome caused by the “new” coronavirus, also known as SARS-CoV-2, started in Wuhan, China, in 2019. The rapid spread of the virus around the world led to the pandemic. Several symptoms have been observed in infected people, such as involvement of the respiratory, cardiovascular, renal and neurological systems, and skin lesions. Studies have shown that cutaneous manifestations can be indicative of COVID-19 infection and help in early diagnosis. However, some physicians do not have the necessary knowledge for this correlation. Therefore, in this qualitative and descriptive review, we present studies published in the last two years, related to possible skin lesions related to COVID-19, association with the severity of the infection, and the mechanisms associated with the lesions. The Scielo, MedLine and PubMed database platforms were used for the search, and 18 articles were selected. Studies show that skin lesions can be considered for predicting the diagnosis of COVID-19, provided they are well evaluated, associated with other symptoms and confirmed by specific tests. The most commonly reported skin manifestations were: acral erythema, urticaria, erythematous rash, maculopapular rash, pruritus, and erythema multiforme. Acral injuries were associated with lower severity of SARS-CoV-2. Antiviral treatment and virus infection were associated with skin lesions. Different mechanisms involved in the lesions were mentioned, such as vasodilation and thrombotic events. The studies addressed in this review are important for physicians to understand the possible skin lesions associated with COVID-19 and thus relate them to other methods for early diagnosis of the infection.

Keywords: Skin lesions, SARS-CoV-2, pseudo-chilblains, dermatological manifestations, diagnosis.

INTRODUCTION

COVID-19, also called novel “coronavirus” or severe acute respiratory syndrome (SARS-CoV-2), was discovered in December 2019 in the city of Wuhan, China. After the discovery, it spread to different regions of the world, becoming a pandemic and a case of Emergency and International Public Health Concern by the World Health Organization (WHO). Since then, this virus has become a major challenge for health professionals around the world (Guan et al., 2020; Yurasseck & Brandão, 2021).

The manifestations most commonly identified in people infected with SARS-CoV-2 are: involvement of the respiratory, cardiovascular, renal and neurological systems. Non-specific skin lesions have also been reported as concomitant conditions with COVID-19 infection (Yurasseck & Brandão, 2021). Therefore, COVID-19 is a multisystem disease and requires a multidisciplinary approach involving specialists from all areas and levels of care.

The pathophysiology of cutaneous involvement of patients with COVID-19 is uncertain and thus, other etiologies such as herpesvirus co-infections, reactivations and drug reactions cannot be ruled out (Conforti et al., 2020). Therefore, a difference in prognosis cannot be predicted based on cutaneous manifestations alone. However, according to Gisondi et al. (2020), dermatologists can play a relevant role in the early recognition of skin lesions suggestive of SARS-CoV-2. Skin lesions may represent a relevant feature for COVID-19, but they are still poorly understood due to the lack of routine dermatological consultations during the pandemic. Only patients with severe respiratory symptoms are screened.

There are several skin lesions related to COVID-19, the most commonly documented being morbilliform eruptions, urticaria,

vesicular eruptions, acral lesions (also called pseudochilblains) and livedoid eruptions. Some of these lesions may appear before the signs and symptoms most commonly associated with COVID-19, suggesting contamination, as well as being correlated with the severity of the infection (Young & Fernandez, 2020).

However, the cutaneous manifestations related to the coronavirus are poorly characterized. Thus, the objective of this review article was to describe the possible cutaneous manifestations associated with COVID-19, to relate them to the severity of the infection and to other clinical findings, as well as to explain the factors and mechanisms associated with the lesions.

METHODS

The proposed work is a systematic literature review, consisting of a qualitative and descriptive study. In the study, publications in Portuguese, English and Spanish were selected from the Scielo, MedLine and PubMed database platforms, according to the following descriptors: “*cutaneous lesions*” AND “*symptoms*” AND “COVID-19”. Publications were selected in the period related to the COVID-19 pandemic, from 2020 to 2022. Articles outside the mentioned period, duplicates, unavailable in full and not corresponding to the proposed theme were excluded.

In the present systematic review, applying the inclusion criteria, 323 articles were found. After excluding duplicate articles among the database platforms used, a total of 151 articles was reached for reading the abstracts. After reading the abstracts, 58 articles were excluded because they did not present one or some of the descriptors previously selected and mentioned in the item “Methodology”. After reading, 75 articles were excluded because they did not present the descriptors in the

title, reaching a total of 18 articles included in the review.

RESULTS

In this review work, applying the inclusion and exclusion criteria, a total of 18 articles were selected from 2020 to 2022. The articles address studies that relate skin lesions as a possible symptom of COVID-19 (Table 1).

DISCUSSION

CUTANEOUS MANIFESTATIONS AND COVID-19

The contamination of COVID-19 has been declared a public health emergency by the World Health Organization (WHO), which has been showing great challenges for health professionals. The main site of infection for COVID-19 is the lungs, with symptoms ranging from mild to potentially lethal respiratory illnesses. However, other manifestations can be important and help for the timely diagnosis of coronavirus, such as skin lesions (Galván Casas et al., 2020).

COVID-19 infection may not produce symptoms for up to 14 days after infection, and therefore, as with other infectious diseases (measles, e/scarlet fever and meningococemia), cutaneous manifestations can aid in early diagnosis. Studies show that different skin lesions may be related to the manifestations of COVID-19 infection, indicating patient isolation and for biosafety procedures to be followed in dermatology clinics.

Sachdeva et al. (2020) verified, through studies and case reports, that different cutaneous manifestations have been observed in patients infected by COVID-19 in Milan, Italy. The study showed that the skin manifestation most commonly related to the coronavirus was maculopapular rash (36.1% of patients), also known as morbilliform. Skin lesions such as papulovesicular rash (34.7%),

painful purple papules (15.3%), urticaria (9.7%), livedo reticularis (2.8%) and petechiae (1.4%) were also reported. identified in infected patients. In addition, about 67% of the lesions were located on the trunk and occurred before the onset of respiratory symptoms and diagnosis of COVID-19.

Data obtained by de Almeida Sousa & Antelo (2020) showed the clinical polymorphism related to the cutaneous manifestations of patients infected by COVID-19, emphasizing the importance of clinical suspicion by the dermatologist in the treatment of suspected cases in the current pandemic scenario. The study was carried out in Brazil, with patients infected with the coronavirus and who had skin lesions. Clinical and epidemiological characteristics of each case were described, demonstrating the polymorphism of the cutaneous manifestations and correlating with the systemic symptoms presented. The skin lesions most commonly observed during, after and before symptoms were: urticaria, erythematous rash, maculopapular rash, pruritus, erythema multiforme, dyshidrotic eczema, acral erythematous lesions.

Rodriguez-Cerdeira et al. (2021) also documented the main skin lesions found in patients with COVID-19. Dermatologic manifestations associated with COVID-19 included: maculopapular rash (16.10%), urticaria (26.80%), pseudochilblains (22.60%), petechiae/purpura (6.50%), distal ischemia, and necrosis (6.50%), livedo racemosa (12.90%) and others (9.70%). About 83.90% were confirmed cases by qRT-PCR, 6.50% by serology and 9.7% were suspected due to previous contact with positive patients. Therefore, the findings indicate that a febrile or afebrile rash in the early stages of the disease may be the only clinical manifestation of COVID-19.

In addition to being an indication of contamination by COVID-19, skin lesions are

Author/Year	Causal	Clinical features
Sachdeva et al. (2020)	Overview of cutaneous manifestations in patients with COVID-19 through studies and case reports, in Milan, Italy.	Cutaneous manifestations most commonly related to coronavirus: maculopapular or morbilliform rash (36.1%), papulovesicular rash (34.7%), painful purple papules (15.3%), urticaria (9.7%), livedo reticularis (2.8%) and petechiae (1.4%). Lesions often located on the trunk. There was no correlation between skin lesions and the severity of COVID-19.
de Almeida Sousa & Antelo (2020)	Study carried out in Brazil, with patients infected with COVID-19 who had cutaneous manifestations.	Clinical and epidemiological characteristics demonstrated the polymorphism of the cutaneous manifestations and were correlated with the systemic symptoms presented. Most commonly seen skin lesions: urticaria, erythematous rash, maculopapular rash, pruritus, erythema multiforme, dyshidrotic eczema, acral erythematous.
Rodriguez-Cerdeira et al. (2021)	Retrospective study of patients diagnosed with COVID-19 and multiple skin lesions from five countries (Argentina, Dominican Republic, India, Mexico and Spain).	Dermatological manifestations: maculopapular eruptions (16.10%), urticaria (26.80%), pseudochilblains (22.60%), petechiae/purpura (6.50%), distal ischemia and necrosis (6.50%), livedo racemosa (12.90%) and others (9.70%). About 83.90% were confirmed cases by qRT-PCR, 6.50% by serology and 9.7% were suspected due to previous contact with positive patients. Findings indicate that a febrile or afebrile rash in the early stages of the disease may be the only clinical manifestation of COVID-19.
Genovese et al. (2021)	Study of current knowledge about the cutaneous manifestations associated with COVID-19: clinical characteristics, therapeutic management, hypotheses and pathophysiological mechanisms of these conditions.	Association of skin lesions with medium to high severity of COVID-19. Polymorphic classification of lesions: (1) urticarial rash, (2) confluent erythematous/maculopapular/morbilliform rash, (3) papulovesicular rash, (4) acral (chilblain) pattern, (5) livedo reticularis (racemose pattern), (6) purpuric "vasculitic" pattern.
Askin et al. (2020)	Prospective observational study evaluating patients diagnosed with COVID-19 and hospitalized in Istanbul, Turkey, during April 2020.	Findings: erythematous squamous rash (32.7%), maculopapular rash (23%), urticarial lesions (13.5%), petechial purpuric rash (7.7%), necrosis (7.7%), enanthema and aphthous stomatitis (5.8%), vesicular eruption (5.8%), pernio (1.9%) and pruritus (1.9%). The antiviral drugs used and the infection caused by the virus may be associated with rashes, more commonly found in hospitalized patients. The age group from 55 to 74 years old presented more intense cutaneous manifestations compared to the others. Patients admitted to the intensive care unit tended to have cutaneous manifestations.
Galván Casas et al. (2020)	Survey of data and images of Spanish patients with COVID-19 with cutaneous manifestations.	Classification of lesions: acral areas of erythema with vesicles or pustules (pseudochills) (19%), vesicular eruptions (9%), urticaria (19%), maculopapular eruptions (47%) and livedo or necrosis (6%). Vesicular eruptions appeared before other symptoms, while pseudochilblains appeared later. The other lesions appeared with other symptoms of COVID-19. Acral and vesicular lesions are the main indicators of coronavirus infection and correspond to less serious infections of COVID-19.
Vezzoli et al. (2021)	Data from Italian dermatology units provided demographic, clinical and histopathological data of patients with cutaneous manifestations associated with COVID-19.	Acral lesions, similar to chilblains, were more frequent in younger asymptomatic COVID-19 patients and were less severe. Patients with confluent erythematous/maculopapular/morbilliform phenotype skin manifestations were associated with more severe COVID-19.
Visconti et al. (2021)	To assess the cutaneous manifestations of SARS-CoV-2 infection in the UK and investigate its duration in relation to other symptoms. The COVID app <i>Symptom Stud</i> and an online survey were used to assess diagnoses.	They compiled and publicly available a catalog of images of the most common cutaneous manifestations of COVID-19. About 17% of COVID-19 positive cases reported rash as the first symptom, while 21% of cases as the only clinical sign of infection.

Table 1 Studies linking skin lesions and COVID-19.

also important so that hospitalized patients are not neglected in dermatological care. In these patients, skin lesions are more evident and may be related to the severity of the infection, as shown in studies carried out by Genovese et al. (2021), Askin et al. (2020), Galván Casas et al. (2020) and Vezzoli et al. (2021).

Genovese et al. (2021) showed that case studies associated skin lesions with a 1-week durability with the medium to severe severity of COVID-19 (Galván Casas et al., 2020). In addition, they classified the polymorphic nature of coronavirus-associated skin lesions into 6 main clinical patterns: (a) urticarial rash, (b) confluent erythematous/maculopapular/morbilloform rash, (c) papulovesicular rash, (d) acral-type rash chilblains, (e) livedo reticularis/racemosa-like pattern, (f) purpuric “vasculitic” pattern.

Askin et al. (2020) analyzed possible cutaneous manifestations in 210 hospitalized patients. The findings were observed in 52 of the patients analyzed and were classified as: squamous erythematous exanthema (32.7%), maculopapular exanthema (23%), urticarial lesions (13.5%), petechial purpuric exanthema (7.7%), necrosis (7.7%), enanthema and aphthous stomatitis (5.8%), vesicular eruption (5.8%), pernio (1.9%) and pruritus (1.9%). As demonstrated in the study, scaly erythematous rash was the most commonly observed lesion in patients with COVID-19. The antiviral drugs used in the treatment and even the infection caused by the virus can be associated with this type of skin lesion. The study also showed that the age groups from 55 to 74 years old presented the most cutaneous manifestations compared to the others and there was no significant difference between male and female patients. In addition, patients admitted to the intensive care unit were at greater risk of cutaneous manifestations due to coronavirus infection.

A survey of data and images of patients with COVID-19 and with cutaneous manifestations, carried out in Spain by Galván Casas et al. (2020), allowed the description of clinical patterns, patient demographics, time to symptoms, severity and prognosis. The study classified the lesions as: acral areas of erythema with vesicles or pustules (pseudochills) (19%), vesicular eruptions (9%), urticaria (19%), maculopapular eruptions (47%), and livedo or necrosis (6%). Vesicular eruptions appeared early in the course of the disease, even before other symptoms, whereas pseudochilblains manifested later. The remaining lesions tended to appear along with other symptoms of COVID-19 infection. Regarding severity, patients with less severe infections more commonly developed acral lesions (pseudochills), while the other manifestations correlated with medium to high severity of infection. The authors concluded that patterns of acral and vesicular lesions are the main indicators of coronavirus infection. Acral injuries were also correlated with mild severity in the study by Vezzoli et al. (2021), with Italian patients infected with COVID-19 who had skin lesions. Most of these lesions were found more frequently in young patients. In addition, the study showed that lesions such as erythematous/maculopapular/confluent morbilliform phenotype were associated with moderate/severe severity of COVID-19.

In order to assist physicians in recognizing cutaneous manifestations and relating them to the early diagnosis of COVID-19, Visconti et al. (2021) together with the British Association of Dermatologists, have compiled and publicly available a catalog of images of the most common cutaneous manifestations of COVID-19 (<https://covidskinsigns.com>). Furthermore, Visconti et al. (2021) investigated the duration and timing of cutaneous manifestations in relation to other symptoms of COVID-19, through images,

application (COVID *Symptom Study*) and an online survey of UK patients. The study showed that 17% of COVID-19 positive cases reported a rash as the first symptom, while 21% of cases as the only clinical sign of the infection. Therefore, rashes can cluster with other symptoms of COVID-19, are predictive of a positive swab test, and occur in a significant number of cases, either alone or as an initial symptom.

FACTORS AND MECHANISMS ASSOCIATED WITH THE CUTANEOUS MANIFESTATIONS OF COVID-19

It is not yet fully understood which factors are associated with cutaneous manifestations in patients with COVID-19, but it is believed that the combination of the primary infection of the skin itself and the secondary consequence of respiratory infection is responsible for these lesions. According to Carrascosa et al. (2020), skin lesions related to COVID-19 may reflect activation of pathogenic pathways by the virus or a response to inflammatory processes, vascular or systemic complications, and even antiviral treatments administered. Therefore, knowledge of the cutaneous manifestations of COVID-19 can enable diagnosis and help guide prognosis.

Studies describe different mechanisms involved in the skin lesions associated with SARS-CoV-2. The study carried out by Sachdeva et al. (2020) suggests that viral particles present in the cutaneous blood vessels of people infected with the coronavirus can cause lymphocytic vasculitis, a phenomenon similar to what occurs in thrombophilic arteritis, induced by blood immune complexes, which activate cytokines. According to Gianotti (2020) and Gianotti, Zerbi & Dodiuk-Gad (2020), keratinocytes can be secondary targets of the coronavirus, after activation of Langerhans cells, leading

to vasodilation and spongiosis, and inducing different cutaneous manifestations.

Other studies suggest that livedo-like manifestations, similar to reticular lesions, may occur due to reduced blood flow to the cutaneous microvasculature system, due to the accumulation of microthrombosis originating from various organs of the body (Manalo et al., 2020). On the other hand, Magro et al. (2020) report that patients infected with coronavirus and with the presence of skin lesions were associated with thrombotic or microangiopathic events. These data were obtained by performing the biopsy of patients infected with COVID-19 and who developed purpura retiforme or livedo racemosa. These lesions were associated with high levels of D-dimer and clinical findings such as pauci-inflammatory thrombogenic culopathy and deposition of C5b-9 and C4d glycoproteins. Furthermore, these mechanisms may be associated with procoagulant states in other organs.

CONCLUSION

The studies addressed in this literature review describe the main cutaneous manifestations associated with COVID-19. In addition, they relate these manifestations to other typical symptoms and the severity of the infection. The possible factors and mechanisms involved in the development of these skin lesions were also addressed. The main clinical findings were: maculopapular/morbilloform rash, papulovesicular rash, urticaria, livedo reticularis/necrosis, erythematous acral/pseudochiliform lesions and petechiae/purpura. Studies have shown that in some cases the only obvious symptom of COVID-19 infection is the skin lesion. Also, a correlation between the types of skin lesions and the severity of the infection. Acral (pseudochiliform) lesions were considered indicative of mild SARS-CoV-2 infections,

while maculopapular/morbilliform rash-type lesions indicated moderate to severe severity of COVID-19. The mechanisms involved in the aforementioned lesions may be related to different factors, among them, the antiviral treatments administered. Skin lesions were most commonly associated with vasodilation and thrombotic events. Thus, this review contributes to the knowledge of the cutaneous manifestations of COVID-19, allowing the diagnosis in patients with few symptoms and guiding the prognosis. In the future, cutaneous manifestations may serve as important clinical features in the diagnosis, treatment and knowledge of the sequelae caused by COVID-19.

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