

Cutaneous manifestations of coronavirus disease 2019 – review of literature and case reports

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Adv Dermatol Allergol 2021; XXXVIII (6): 943–947

DOI: <https://doi.org/10.5114/ada.2020.95958>

Abstract

Primary clinical manifestations of coronavirus disease are respiratory tract infections, ranging from an asymptomatic carrier state to severe interstitial pneumonia. The most common symptoms are fever, dry cough, fatigue, nausea, diarrhea, and loss of smell or taste. Recent reports indicate the possibility of several nonspecific dermatological symptoms. These include urticaria, maculopapular lesions, vascular lesions involving petechiae, purpura and livedo reticularis. The onset of cutaneous lesions may precede full-blown COVID-19 or remain the only manifestation of the disease (especially in young patients). Focusing on dermatological symptoms may be crucial for preventing the spread of SARS-CoV-2. However, unambiguous assessment of cutaneous manifestations of COVID-19 requires more research and case studies conducted by dermatologists.

Key words: COVID-19, skin manifestations, pseudo-chilblain, SARS-CoV-2, coronavirus, cutaneous manifestations.

Introduction

The first cases of pneumonia caused by the new SARS-CoV-2 coronavirus appeared in December 2019 in Wuhan, China [1, 2]. Due to the rapid spread of the virus, on March 11th the World Health Organization (WHO) designated COVID-19 outbreak a pandemic [3]. The primary clinical manifestations of coronavirus disease 2019 (COVID-19) include a large spectrum of respiratory tract infections, ranging from an asymptomatic carrier state (15.5–20% of patients) [4] and mild influenza-like illness to severe interstitial pneumonia and acute respiratory distress syndrome [5–7]. The most common symptoms of the infection include fever, dry cough, dyspnea, nasal congestion, smell and taste disorders, general weakness and gastrointestinal disorders [8–11]. In severe cases the patients may develop coagulation dysfunction, acute respiratory distress syndrome (ARDS), arrhythmia and septic shock [4, 12]. There are numerous new publications concerning neurological disorders associated with COVID-19 (e.g. ischemic strokes) [13], as well as clotting disorders posing a risk of thromboembolism [14, 15].

Recent studies indicate the possibility of several nonspecific dermatological symptoms which may be the only manifestation of the infection. In our study we con-

ducted a systematic literature review, aiming to analyze and summarize current data and case reports of patients with cutaneous lesions in order to outline the profile and prevalence of various dermatoses in the course of coronavirus disease.

Cutaneous lesions in the course of COVID-19

One of the first research papers concerning the prevalence of various symptoms in the course of COVID-19 was published by Guan *et al.* [16]. Based on the analysis of medical records of 1099 patients (with laboratory-confirmed COVID-19) hospitalized in 552 Chinese hospitals, the authors concluded that cutaneous lesions occurred in only 2 patients.

Moreover, Zhang *et al.* in their study also described the prevalence of various symptoms in the course of SARS-COV-2 infection. The research was conducted on 140 patients treated for COVID-19 in Hospital No. 7 in Wuhan, China [11]. On admission, the condition of 52 of them was considered to be critical. The mean age was 57 years (ranging from 25 to 97 years) and the majority of patients (70%) were aged 50 years or older. A similar number of male ($n = 71$) and female ($n = 69$) patients

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Received: 12.05.2020, **accepted:** 20.05.2020.

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was enrolled in the study. The most common symptoms among the reported cases included fever (91.6%), cough (75%) and fatigue (75%). The authors found that only 1.9% of patients developed urticaria-like cutaneous lesions.

Recalcati with a group of dermatologists from Lecco Hospital, Lombardy, Italy, assessed the prevalence and profile of dermatoses in the course of COVID-19 [17]. Out of the 88 patients enrolled in the study, 18 (20.4%) developed cutaneous lesions including erythematous rash (14 patients, 15.9%), diffuse urticaria (3 patients, 3.4%) and varicella-like vesicular lesions (1 patient, 1.1%). Moreover, the authors concluded that skin lesions most often occurred on the trunk, associated with little or no pruritus and uncorrelated with the severity of the clinical course of COVID-19.

Galvan Casas *et al.* proposed a classification of cutaneous lesions associated with coronavirus disease [18]. Three hundred and seventy-five cases of patients hospitalized in Spanish hospitals were analyzed in the study. The authors evaluated the percentage represented by each dermatosis as well as their duration, correlation with age, comorbidities and the course of the underlying disease. According to the authors, several types of lesions can be distinguished, including pseudo-frostbite (19% of lesions in COVID-19), other vesicular lesions (9%), urticarial lesions (19%), maculopapular lesions (47%) and livedo-like/necrotic lesions (6%) [18].

Vascular lesions in the course of COVID-19

Clinical features of cutaneous vascular lesions in the course of COVID-19 may be diverse. Such lesions may be present both in asymptomatic/oligosymptomatic patients and those hospitalized in intensive care units [16, 18, 19]. There are case reports of petechiae and purpura, often limited to distal extremities only (pseudo-frostbite, chilblains) [20, 21], as well as livedo reticularis [22].

These lesions are probably related to coagulation abnormalities and microemboli formation, which may manifest by exerting a negative impact on the cardiopulmonary system or lead to disseminated intravascular coagulation (DIC) in severe cases [23, 24].

In their study, Galvan Casas *et al.* [18] concluded that vascular lesions including livedo reticularis or necrotic lesions occur more often in patients with a severe course of COVID-19 (mortality rate about 10%).

However, this subgroup of patients also included individuals with transient livedo reticularis, who did not require hospitalization [22].

Acro-ischemic lesions

The first reports of acro-ischemic lesions affecting the distal lower extremities in the course of COVID-19 come from a single center in Wuhan, China [19]. Seven patients (4 male and 3 female) with a mean age of 59 years were described in a retrospective study. Three of them reported comorbidities. On admission to the intensive care

unit they were found to have developed fever, cough, dyspnea and diarrhea. All patients had acro-ischemia presentations including finger/toe cyanosis, skin bulla and dry gangrene. Laboratory findings revealed markers of thrombosis, and 4 patients were diagnosed with disseminated intravascular coagulation.

Unfortunately, 5 out of 7 patients died. The mean time from the onset of cutaneous symptoms to death was 12 days [19].

Pseudo-chilblains

In their study, Mazzotta *et al.* [20] noted an increased prevalence of acro-ischemia (mainly affecting the toes) observed in asymptomatic children and adolescents during the COVID-19 pandemic.

The authors presented a case of a 13-year-old hitherto healthy boy who suddenly developed erythematoviolet, rounded lesions with blurred limits on the plantar surface of the 1st right toe and on the dorsal surface of the 2nd toe both on the right and left foot.

After 2 days general symptoms appeared, including fever, headache and myalgia, as well as pruritus and a burning sensation on the affected skin. On the 2nd toe of the left foot appeared a tense bulla, followed by erosion covered with a scab. All skin lesions located on the toes became purpuric. A few days later the skin lesions gradually subsided along with pain and pruritus [20].

Transient livedo reticularis

Livedo reticularis is probably caused by clotting abnormalities leading to intravascular coagulation and a decrease in blood flow through small venous plexuses [25].

Manalo *et al.* [22] presented two clinical cases of patients with a diagnosis of mild coronavirus disease (confirmed with RT-PCR tests) who developed transient livedo reticularis.

The authors described a clinical case of a 67-year-old man who presented with a 10-day history of low fever, nasal congestion, post-nasal drip, and cough without dyspnea. On the 7th day of general symptoms, the patient developed reticulated blanching affecting the right thigh. The lesions were not pruritic and completely subsided within 19 h. Interestingly, the patient reported fatigue and transient hematuria as the cutaneous lesions appeared.

In the other clinical case described by Manalo *et al.* [22], a 47-year-old woman was found to have mild headache, sinus pain, anosmia and subfebrile temperature. The patient had a history of celiac disease, Hashimoto's thyroiditis and portal vein thrombosis (which occurred in 2017, during treatment with oral contraceptives and after a long-haul flight). Livedo reticularis located on the right lower extremity appeared after the general symptoms had subsided, within 20–30 min after exposure of both lower extremities to sunlight. The lesions completely resolved within 20 min and did not relapse after subsequent sunlight exposure on the following day.

Urticarial lesions

Lu *et al.* [26] presented a case of a patient who was admitted to the Dermatology Ward of the Affiliated Chencun Hospital of Shunde Hospital, China, due to generalized urticarial lesions. The patient had no medical history of comorbidities (including asthma and urticaria), but reported a mild, dry cough over the previous week. Only cutaneous lesions were present on admission. Based on the epidemiological interview (reported contact with individuals from areas of frequent occurrence of COVID-19) and results of additional imaging tests, a diagnosis of coronavirus disease was made. After treatment with ribavirin, interferon and antiallergic agents, a significant reduction of skin lesions and radiographic improvement of lung lesions was achieved [26].

In the above-mentioned study by Racalcati, urticarial lesions of one patient had appeared prior to the onset of fever and respiratory symptoms [17].

A similar clinical case was described by Henry *et al.* [27]. A 27-year-old female patient with no medical history of comorbidities presented to the hospital with odynophagia, arthralgia and urticaria-like cutaneous lesions affecting the face and the distal extremities. Treatment with antihistamines led to gradual improvement of skin lesions. Forty-eight hours later the patient developed chest pain, fever and chills. RT-PCR test confirmed the presence of SARS-CoV-2.

In the majority of the described cases, presence of hives and pruritus in the course of COVID-19 affects mostly adolescents/young adults.

Fernandez-Nieto *et al.* [28] presented a case of a 32-year-old female patient hospitalized due to COVID-19 in whom urticarial skin lesions appeared 6 days after the onset of the first symptoms of the disease (dry cough, nasal congestion, fatigue, myalgia, arthralgia) and 4 days after treatment with azithromycin and hydroxychloroquine had begun. Furthermore, histopathological examination of a biopsy taken from the cutaneous lesion was conducted, which revealed perivascular infiltrate of lymphocytes, eosinophils and upper derma edema. Therapy with oral antihistamine drugs was initiated, leading to clinical improvement within 5 days. In their study, the authors indicate the significance of histopathological examination for precise identification of characteristic cutaneous lesions in the course of COVID-19 [28].

Maculopapular lesions

Another type of skin lesions observed in COVID-19 patients is maculopapular lesions.

Hunt *et al.* [29] described a case of a 20-year-old male who initially reported fever and rash, had been earlier diagnosed with viral upper respiratory infection and received symptomatic treatment in outpatient care. After 6 days the patient developed high fever, tachycardia, tachypnea, hypotension and decreased oxygen saturation (91%).

A chest radiograph revealed bilateral infiltrates consistent with multifocal pneumonia. Physical examination of the skin revealed diffuse, maculopapular, measles-like lesions located on the trunk and the extremities, with no face involvement. The patient was confirmed to be infected with SARS-CoV-2. Due to general symptoms, the patient was hospitalized for 6 days in an intensive care unit.

The above case presented by Hunt *et al.* indicates that the course of COVID-19 in young people may be rapid, despite initial manifestations limited to cutaneous lesions and mild general symptoms [29].

Erythema elevatum, persistent erythema, shooting target lesions and pseudo-vesicular lesions located on the dorsal surface of hands belong to the broad spectrum of cutaneous lesions as well [18, 30]. They usually occur as the general symptoms develop, often in patients with a severe course of the underlying disease (2% mortality rate according to Galván Casas *et al.*) [18].

Different types of cutaneous lesions

Apart from the above-mentioned cutaneous lesions found in patients with COVID-19, in whom their etiology is usually related to the disease or the systemic response to SARS-CoV-2 infection, there is a large number of less distinctive dermatoses.

Mahe *et al.* [31] described a case of a 64-year-old woman with a history of type 2 diabetes who was tested positive for SARS-CoV-2 and presented with fatigue and fever up to 40°C. After 4 days of treatment with oral paracetamol, the patient developed an erythematous rash/diffuse erythematous lesions on the anterior surface of elbow flexures with subsequent spread to the skin of the trunk and the axillae. The rash subsided on the 9th day of the disease, despite persistence of other symptoms and taking paracetamol.

According to the authors, the observed skin lesions may be associated with symmetrical drug-related intertriginous and flexural exanthema (SDRIFE), a dermatosis frequently caused by treatment with paracetamol. Nevertheless, cases of SDRIFE secondary to viral infections have also been observed [32, 33].

A similar case was presented in a publication by Jimenez-Cauhe *et al.* [30]. An 84-year-old woman with a history of hypertension and dyslipidemia was hospitalized due to bilateral pneumonia in the course of COVID-19. Three days after initiation of treatment with hydroxychloroquine and lopinavir/ritonavir the patient developed small, bluish, erythematous papules with a tendency to merge, which affected mostly the lateral surface of the chest and the groin. The lesions were slightly pruritic.

The above examples show that determining the etiology of skin lesions may be challenging, especially considering the limited availability of diagnostic examinations (i.e. histopathological examinations) in the time of the coronavirus pandemic. Accurate anamnesis including

detailed medication history as well as information on the onset and the duration of symptoms of COVID-19 may be crucial for differential diagnosis.

Conclusions

In the literature, there is a growing number of reports on cutaneous lesions in patients infected with SARS-CoV-2. It seems that certain dermatoses may be a systemic response to the infection and can constitute a crucial diagnostic element as well as providing prognostic information on the course of the disease. In numerous cases the onset of cutaneous lesions preceded full-blown COVID-19 or remained the only manifestations of the disease (especially in children and young adults); therefore meticulous examination of patients and focusing on dermatological symptoms may be crucial for preventing the spread of SARS-CoV-2.

Unfortunately, due to exceptional circumstances during the COVID-19 pandemic there is a lack of clinical studies involving large groups of patients conducted by dermatologists able to perform complete clinical and laboratory evaluation of cutaneous lesions in the course of COVID-19.

Conflict of interest

The authors declare no conflict of interest.

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