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## **Cutaneous manifestations associated with COVID-19: summary of current knowledge**

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## **ABSTRACT:**

**Introduction and purpose:** Coronavirus disease (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), had been spreading rapidly throughout the world, mainly affecting respiratory system. Except pulmonary symptoms, skin lesions might also occur. The precise percentage of patients with confirmed COVID-19 who presented cutaneous manifestations is still unknown (0.2% - 20.4%). Part of the skin lesions might be drug-induced.

**Brief description of the state of knowledge:** Cutaneous manifestations in the course of the coronavirus disease could be divided into six main groups: maculopapular rash, urticarial lesions, chilblain-like lesions, vesicular eruptions, petechial/purpuric lesions and livedoid lesions. The most common skin lesions are maculopapular eruptions (47%). Trunk is the most affected location, whereas pruritus is the most frequent additional symptom among patients with skin lesions associated with coronavirus disease. These lesions appear mainly in elderly patients except pseudo chilblains which are present among children and young adults with SARS-Cov-2 infection. The majority of cutaneous manifestations occur after COVID-19 systemic symptoms, but the appearance of vesicular lesions before the respiratory signs was also reported. Cutaneous manifestations resolved spontaneously at different times, ranging from a few days to 2-4 weeks. Moreover, patients with severe course of COVID-19 with maculopapular rash have better prognosis (2% mortality rate) in comparison to patients who developed livedoid lesions in course of the coronavirus disease (10% mortality rate).

**Summary:** Pseudo-chilblains and vesicular lesions are the most specific cutaneous manifestations of coronavirus disease. Healthcare professionals should pay attention

to patients who present skin symptoms in the course of COVID-19. Cutaneous manifestations can facilitate the doctor the diagnosis and even estimate the severity of coronavirus disease.

**Keywords:** COVID-19; skin manifestations of COVID-19; cutaneous manifestations of COVID-19; COVID-19 skin lesions.

## **INTRODUCTION AND PURPOSE:**

Coronavirus disease (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The virus was first reported in China in December 2019 and spread rapidly across the world through human-to-human transmission [1]. In March 2020, World Health Organization declared COVID-19 a pandemic [2]. As of December 24, 2023, the total number of confirmed coronavirus disease cases worldwide had been 773 119 173 with 6 990 067 deaths [3]. Infection of SARS-CoV-2 differs in degree of severity - from asymptomatic form to multiple organ failure in the severe course of the disease. Moreover, the clinical manifestations of the disease include signs from many organs [4]. The most frequent symptoms of coronavirus disease, like fever, fatigue, myalgia and cough, are nonspecific. In addition, anosmia, ageusia, headache and diarrhea can also occur.

Skin, being the body's largest organ, can also present visible features of SARS-CoV-2 infection. It may be linked to the interaction of the virus with angiotensin-converting enzyme-2 (ACE2) receptors found in the skin epithelial cells and dermal blood vessels [5].

According to research, the frequency of skin lesions in course of COVID-19 are ranging from 0.2% to 20.4%, and it depends on the study and as well as on the population. In the Chinese study, at the beginning of the pandemic, a prevalence of 0.2% of skin manifestations (2/1099 cases) with confirmed coronavirus disease, has been reported [6].

At that time, cutaneous changes associated with COVID-19 were rarely described in the literature due to lack of dermatological care in this group of patients. Subsequently, 20.4% patients according to Italian study, developed cutaneous lesions in the course of SARS-CoV-2 infection [7].

It is worth mentioning that the medications commonly used in COVID-19 treatment, such as antiviral agents, can induce skin lesions [8]. It is extremely hard to distinguish if appearance of cutaneous findings were due to SARS-CoV-2 infection or applied treatment.

The aim of the article is to categorize and provide an overview of the clinical features of cutaneous manifestations associated with COVID-19 and their relation with severity of the disease.

## **DESCRIPTION OF THE STATE OF KNOWLEDGE:**

According to research, skin manifestations of COVID-19 are polymorphic and often were misdiagnosed as other disorders, like dengue, urticaria or Kawasaki disease [9] [10] [11].

Numerous studies showed that the most frequent types of dermatological patterns associated with COVID-19 are maculopapular rash, urticarial lesions, chilblain-like lesions, vesicular eruptions, petechial/purpuric lesions and livedoid lesions. There are also rare cutaneous manifestations related with coronavirus disease which vary widely and do not match the classification above.

In this section, we describe the morphological features, prevalence, duration and histopathological changes of skin lesions associated with COVID-19.

### **Maculopapular rash**

Maculopapular rash, also described as morbiliform eruption or erythematous plaques, was present in 47% of patients with SARS-CoV-2 infection [12]. These skin lesions were observed in middle-aged patients, mainly located on the trunk and the extremities [12] [13] [14] [15]. It was reported that itching was present in 56% of patients with maculopapular lesions [12]. A Spanish study reported the simultaneous onset of the lesions and COVID-19 systemic symptoms [12], while other works noted a delayed onset of these cutaneous manifestations [13] [14] [15]

[16]. The duration of these skin eruptions was relatively short, and varied depending on the studies - ranging from 8.6 to 11.6 days [12] [13]. The majority of patients witnessed spontaneous resolution of the rash, although one study mentioned the use of intravenous corticosteroids and antihistamines [17]. In some cases, a few patients experienced rash worsening or secondary changes such as scaling of the skin [17].

Research show that maculopapular rash was more frequent in patients in the severe course of SARS-CoV-2 infection. According to the Spanish study, the mortality was 2% [12]. Moreover, the medications such as chloroquine, hydroxychloroquine, and lopinavir /ritonavir, used in COVID-19 treatment, are known to cause maculopapular rash [8]. It is worth mentioning that patients in the severe course of COVID-19 have consequently received more medication [12]. However, maculopapular eruptions also occurred in patients who had not taken any medications, suggesting that these lesions may not be exclusively drug-induced [13] [14] [16] [17].

Skin biopsies of patients diagnosed with COVID-19 and presenting a maculopapular rash revealed perivascular lymphocytic infiltrate, papillary dermal edema and epidermal spongiosis with eosinophils in dermis [18] [19] [20].

### **Urticarial lesions**

Urticarial lesions have been observed in the course of SARS-CoV-2 infection, manifesting as hives or erythematous rash [21]. The prevalence of these skin lesions vary from 9.7% to 19% [7] [12]. Urticarial lesions can be localized on the trunk, the limbs or present as a generalized rash across the entire body [12] [13] [15] [22]. Pruritus was reported in even 92% of patients with these lesions [12]. It was observed that urticarial lesions occur simultaneously with other systemic symptoms of COVID-19 or afterwards [12] [16]. The average duration of urticarial lesions is around 6.8 days [12]. The urticaria rash disappeared spontaneously without any specific treatment or was treated through the administration of antihistamines [23].

Urticarial lesions in COVID-19 have been linked with the severe course of the disease [12]. However, anti-COVID-19 medications such as chloroquine, hydroxychloroquine, lopinavir/ritonavir, corticosteroids, baricitinib, intravenous

immunoglobulins (IVIg) and checkpoint inhibitors can also induce urticarial lesions as adverse drug reaction [8].

Histological examinations of patients' skin with confirmed COVID-19 and presenting an urticarial rash revealed perivascular lymphocytic infiltrate accompanied by eosinophils, along with edema in the upper dermal layer [23].

### **Chilblain-like lesions**

Chilblain-like lesions, also known as pernio-like lesions or pseudo chilblains, were described as erythematous to violaceous papules or plaques on the distal parts of the extremities [12] [24] [26] [27]. These manifestations are often accompanied by pruritus, pain and burning sensation [12] [25] [26]. The precise mechanism behind these lesions remains incompletely understood, as their presentation is not linked to cold exposure. The prevalence of the lesions varies across studies, ranging from 14.3% to 72% [12] [22] [24] [25] [26]. The rise in the number of pernio-like lesions has resulted in the term "COVID toes." According to research, pseudo chilblains were commonly observed in children and young adults [12] [24] [26] [27]. These lesions were also frequently reported in asymptomatic patients or those with mild coronavirus disease [12] [24]. It is worth mentioning that pseudo chilblains typically appeared after COVID-19 systemic symptoms and lasted from a few days to 2-4 weeks [12] [24]. These lesions disappeared spontaneously without leaving scars [26]. However, the use of topical corticosteroids for accompanying pruritus or progression to firm plaques was also reported [26] [28].

Skin specimens of these lesions revealed vacuolar alterations in the epidermis, superficial and deep dermal lymphocytic infiltrates arranged in a perivascular pattern and dermal edema. Features of vasculitis and vasculopathy were also seen [24] [26] [27].

### **Vesicular lesions**

Vesicular lesions, described as varicella-like lesions, chickenpox-like vesicles, isolated herpetiform lesions or oral vesiculobullous eruption, were present in 4% to 9% of patients with confirmed coronavirus disease [12] [29] [30] [31] [32]. These manifestations were mainly observed on the trunk, less commonly on the extremities and occasionally on the oral mucosa [12] [22] [29] [33]. Vesicular lesions

were typically found in middle-aged patients with intermediate severity of COVID-19 [12] [29] [33]. Mild pruritus was often reported in association with these lesions [12] [29].

Vesicular eruption occurred the most frequently after the other COVID-19 symptoms, but the appearance of these lesions before or coincidentally with COVID-19 systemic signs was also observed [12] [33]. The duration of the vesicular lesions was between 8 and 10.4 days [12] [29]. In majority of patients, spontaneous disappearance of these lesions was reported [29]. However, in one study, patients with vesicular lesions on the oral mucosa were treated using antiseptic mouthwash, hyaluronic acid or valacyclovir [32].

It is worth mentioning that vesicular lesions associated with COVID-19 seem to be unrelated to drug adverse reactions [33]. Moreover, these lesions were described as the most specific cutaneous manifestation of COVID-19 [12] [29].

Histopathological examination of skin samples revealed characteristics such as basket-wave hyperkeratosis, a mildly atrophic epidermis, vacuolar degenerations in the basal layer, and the presence of multinucleate, hyperchromatic keratinocytes and dyskeratotic cells [29] [33].

### **Petechial/purpuric lesions**

Petechial and purpuric lesions were present in only 3% patients with COVID-19 [22]. These manifestations were localized on the trunk and extremities [30]. Petechial and purpuric lesions occurred mainly among middle-aged patients with severe course of coronavirus disease [30]. It was also reported that administration of intravenous immunoglobulin (IVIg) can cause petechial eruption [8]. It is unknown whether these lesions are associated with COVID-19 or are drug-induced.

Skin biopsies of patients diagnosed with COVID-19 and presenting petechial and purpuric lesions revealed pauci-inflammatory vascular thrombosis with endothelial cell injury [34]. There was also a significant degree of interstitial and perivascular neutrophilia with leukocytoclasia [34].

### **Livedoid lesions**

Livedoid lesions were present in 6% of patients with confirmed coronavirus disease [12]. These eruptions were mainly localized on the trunk, forearms and dorsal surface of hands and feet [12] [35]. It was observed that these lesions

coincided with the onset of other COVID-19 symptoms and were more prevalent among elderly patients with the severe course of the disease [12]. The average duration of livedoid lesions was reported to be 9.4 days [12]. It is worth mentioning that the mortality rate in patients with COVID-19 and livedoid lesions was reported to be the highest of all cutaneous manifestations, reaching 10% [12].

Histological examinations of patients' skin with confirmed COVID-19 and presenting livedoid lesions revealed perivascular lymphocytic inflammation, increased superficial dermal mucin and necrotic keratinocytes [36].

### **The other rare skin manifestations**

The other cutaneous manifestations associated with COVID-19 reported in the literature include erythema multiforme-like eruption and periorbital dyschromia [37] [38] [39]. It should be emphasized that two patients who developed periorbital dyschromia two days prior to the onset of COVID-19 systemic symptoms [39].

### **SUMMARY:**

The aim of this review article was to outline the most frequent types of cutaneous manifestations associated with COVID-19. These skin lesions appear at various stages of the disease and differ in duration. The dermatological patterns are also linked to different severity of coronavirus disease. The precise pathomechanisms of these skin lesions remain unknown.

According to research, the urticarial and maculopapular manifestations might not offer significant diagnostic value, as these lesions can be multifactorial. Patients with urticarial and maculopapular eruption tended to have more severe course of COVID-19 and received a greater number of drugs [12].

Numerous studies have shown that livedoid and petechial/purpuric lesions were relatively infrequent, appearing mainly in elderly patients with severe course of COVID-19 [12] [30]. These skin manifestations, occurring late in the course of coronavirus disease, are likely unhelpful for early diagnosis.

It is worth mentioning that pseudo-chilblains and vesicular lesions may be more informative for suspicion of COVID-19. Chilblain-like lesions commonly appear later than the other COVID-19 symptoms and are associated with mild

course of the disease [12] [24]. Moreover, these manifestations occur mainly in children and young adults [12] [24].

It should be emphasized that vesicular lesions appear more frequently than the other dermatological patterns before COVID-19 systemic symptoms and are not drug-induced [12] [33].

We believe that this review article can be helpful to healthcare professionals in dealing with patients with the suspicion of coronavirus disease. Skin symptoms can facilitate diagnosis and even estimate the severity of COVID-19. However, further research is needed to provide the diagnostic utility of cutaneous manifestations associated with coronavirus disease.

### **Disclosure:**

The authors declare that they have no financial or non-financial conflicts of interest that could be perceived as influencing the interpretation of the research findings or the content of this manuscript. This work was conducted independently without any external funding or support.

### **Author's contribution**

Conceptualization: Magdalena Jung, Kinga Woźniak; methodology: Magdalena Jung, Maximilian Jung; software: Oliwia Sysło; check: Patryk Hedesz; formal analysis: Monika Gardian-Baj; investigation: Alicja Szczerbiak; resources: Aleksandra Żuk-Łapan; data curation: Aleksandra Doroń; writing – rough preparation: Magdalena Jung, Kinga Woźniak; writing – review and editing: Maximilian Jung, Patryk Hedesz, Krystian Jędrał; visualization: Krystian Jędrał; supervision: Oliwia Sysło; project administration: Magdalena Jung; receiving funding: Not applicable  
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## **Institutional Review Board Statement**

Not applicable

## **Informed Consent Statement**

Our work did not involve direct human subject research or obtaining their consent for participation in the study

## **Data Availability Statement**

As a review paper, our work does not present new data or analyses. Therefore, there are no specific databases or data availability to report. The information and findings presented in this review are based on previously published studies, which can be accessed through their respective sources as cited in the reference section.

## **Conflicts of Interest Statement**

The authors declare that there are no significant conflicts of interest associated with this research work.

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