

## CUTANEOUS MANIFESTATIONS IN COVID-19: PATHOGENETIC MECHANISMS AND CHALLENGES IN DIAGNOSTICS

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### Summary

Coronavirus disease (COVID-19) is a viral infection which traditionally presents with fever, dyspnea, cough, malaise, anosmia, and, recently, an increasing number of reports of skin damage related to Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2). Skin lesions may provide suspicion of COVID-19 and a rational basis to test patients for SARS-CoV-2. The direct links between SARS-CoV-2 and cutaneous manifestations remain unclear, but the involvement of the virus in the cascade of events leading to various skin lesions is highly likely. Individuals with otherwise unexplained skin lesions and an epidemiologic or clinical suspicion of SARS-CoV-2 infection should be treated as potential COVID-19 patients regardless of their PCR test results. A frequently negative polymerase chain reaction (PCR) result should not exclude the diagnosis COVID-19. We need to acquire a comprehensive understanding of the skin manifestations and clear pathogenesis of this disease in order to recognize potential COVID-19 patients in a timely manner and be able to treat the disease appropriately. The purpose of this review was to review the most recent literature on cutaneous manifestations associated with COVID-19, analyze systematic reviews of a large cohort of case reports, and present the most specific skin lesions: erythematous, maculopapular, vesicular, ischemic, urticarial, and pseudochilblains.

### Introduction

Coronavirus disease (COVID-19) is an infectious illness caused by the SARS-CoV-2 (Severe Acute Respiratory Syndrome-Coronavirus-2). The typical clinical manifestations of COVID-19 are fever, respiratory symptoms (cough, shortness of breath), and malaise [1]. Neurological (anosmia,

dysgeusia) and gastrointestinal (diarrhoea, constipation) symptoms are also reported, although less frequently [2]. The number of case reports regarding cutaneous manifestations in COVID-19 patients is rapidly increasing. According to previous studies, the prevalence of skin lesions in Coronavirus patients varies from 0.5 to 20% worldwide. The vast majority of clinical cases with cutaneous symptoms are reported in Europe and the United States of America (USA), with the fewest ones in Asia [3,4]. In patients infected with SARS-CoV-2 skin lesions are important as they can help to suspect the disease before the onset of respiratory or other symptoms; this encourages healthcare professionals to test patients earlier, thus contributing to the management of the COVID-19 pandemic.

**The aim** of the article was to review and discuss the most recent literature regarding cutaneous manifestations associated with COVID-19.

### Materials and methods

The literature review was performed using the data from Medline (PubMed) and Science Direct data bases. The research was conducted on articles published before the 1st of February 2022.

### Research results

**The spectrum of cutaneous manifestations in patients of COVID-19.** The variety of cutaneous manifestations in COVID-19 patients is wide, ranging from simple erythema to severe ischemic lesions. Currently, there is no uniform classification of these lesions; it is merely observed that some of them are more frequent than others. The most characteristic presentations in adult patients are maculopapular exanthema, erythema, urticaria, pseudochilblains, vascular, ischemic, and vesicular lesions [3–5]. These skin symptoms are accompanied by pruritus in up to 70% of the patients [5,6]. The vesicular rash tends to occur in the early stages, pseudochilblains – in later stages, while other lesions may

become present simultaneously with other symptoms of COVID-19 [3,4]. It is important to note that the great heterogeneity of SARS-CoV-2-related skin manifestations makes this infection unique, as it is not particularly common for one virus to cause such a variety of different skin symptoms [4].

**Erythematous and maculopapular rash.** The largest and most common group of skin lesions is the erythematous and maculopapular rash. The frequency of these lesions ranges from 27 to 47% [4,7–9]. Maculopapular rashes may present as multiple, irregular pink patches typically localized on the torso [9]. This lesion may resemble a drug-induced allergic reaction or measles, hence it is sometimes referred to as a morbilliform (“measles-like”) rash. Erythema and/or papules typically develop in the active stage of the disease when patients are already receiving treatment, making it particularly difficult to distinguish from drug-induced allergies [9,10]. Català (2020) conducted analysis of 375 cutaneous COVID-19 patients (45.5% of which were maculopapular) and noticed the main symptom for these patients was itching [7]. Maculopapular rash is associated with a more severe disease course. The average duration of this rash is 7-9 days [7,10,11]. Cazzato (2021) reported cases of COVID-19-related maculopapular rash that revealed the presence of virions in the endothelial cells by electron microscopy, which may indicate direct involvement of SARS-CoV-2 virus in the pathogenesis of the lesion [12]. Histologic findings display epidermal spongiosis, dilated dermal capillaries, perivascular lymphocytic and minor neutrophilic infiltration (in the early stages), erythrocyte extravasation, histiocytes (in later stages), and an appearance similar to Grover’s disease [9–11,13]. Although erythematous and maculopapular rashes are the most frequently reported, they are also the least specific for SARS-CoV-2, resulting in low diagnostic and prognostic value [5].

**Pseudochilblains.** The most specific skin manifestations in COVID-19 patients are pseudochilblains (also called chilblain-like acral lesions, COVID toes, pseudoperniosis). They manifest as skin lesions resembling chilblains, typically localized on the lower extremities and toes, and are usually asymmetric [6,10,13]. Pseudochilblains are more common in younger patients and are generally associated with a milder disease course and better prognosis [5,8,10]. It is important to distinguish them from chilblains, which can be primary (idiopathic) and secondary (due to frostbite, connective tissue disease, anorexia, cryoglobulinemia, etc.). The latter tend to occur more frequently in older patients [14]. However, the individuals who develop pseudochilblains during the COVID-19 pandemic usually do not have any comorbidities or exposure to cold temperatures and are more often younger (children and adolescents) [15]. The frequency of this

type of skin manifestation varies from 11 to 27% [13,16]. In a study conducted in the USA, 716 clinical cases from 31 different countries were analyzed, and the incidence of pseudochilblains was reported to be 18% [6]. However, the true incidence is likely to be higher for several reasons. First, this type of skin lesion may occur in otherwise asymptomatic patients, therefore, several individuals infected with SARS-CoV-2 may remain undiagnosed [3]. In addition, darker skin color (Fitzpatrick scale – IV-VI) makes these lesions very subtle and challenging to detect [6]. Due to the relatively high specificity of pseudochilblains for COVID-19 infection, researchers consider a direct involvement of SARS-CoV-2 in the development of these lesions; however, the relationship between the two remains controversial [3]. A widely discussed hypothesis regarding the pathogenesis of this lesion is explained by the intense viral response to interferon-1 (IFN-1), which inhibits the replication of SARS-CoV-2 but may promote the development of peripheral microangiopathy itself [9,10,17]. Hübiche (2021) conducted a study in France and revealed that patients with suspected COVID-19 who developed pseudochilblains had increased IFN-1 production, which is known as viral interferonopathy type I [16]. Currently, the vast majority of case reports of COVID-19 related chilblains have been described in Caucasian individuals. Maiti (2020) explained this racial disparity with the *IFIH-1* gene: Caucasians have the T allele in this gene, which is associated with higher IFN production [18]. Regardless, it cannot be excluded that pseudochilblains simply remain less pronounced in other skin types. Histologically, these skin lesions resemble those of regular chilblains: lymphocytic vasculitis (dermal perivascular lymphocytic infiltration) without evidence of thrombosis and vacuolar dermatitis with few apoptotic or necrotic keratinocytes as well as dermal edema [10,16]. Direct immunofluorescence is typically negative for immune deposits (immunoglobulins or complement) [10]. When pseudochilblains co-occur with ischemic lesions, microthrombi in the superficial capillaries and epidermal necrosis in the extremities, as well as sporadic bullous lesions have been observed [10,16].

It is clinically relevant to discuss some discrepancy between positive polymerase chain reaction (PCR) test results and clinical manifestation of pseudochilblains. The incidence of chilblain-like lesions has dramatically increased during the pandemic, leading to the suggestion that it may be a manifestation of SARS-CoV-2. However, a substantial number of patients receive negative PCR results, even the individuals who present with strong clinical and/or epidemiological suspicion of COVID-19. A systematic literature review by Matar (2020) has presented the rate of positive PCR tests to be only 15% in patients with pseudochilblains [5].

A study previously conducted by Hubiche (2021) analyzed 40 suspected COVID-19 patients with pseudo-chilblains and noticed 12 of them have been positive for serology although none of them were positive for SARS-CoV-2 [16]. Colmenero (2020) performed immunohistochemical examinations for SARS-CoV-2 spike protein on skin biopsies of 7 pediatric patients with pseudo-chilblains, which were all positive and “coronavirus particles were found in the cytoplasm of endothelial cells on electron microscopy”. Moreover, these patients have been negative by PCR [11]. The detection of SARS-CoV-2 virus in damaged skin tissue was also mentioned in several other case reports [12,19,20]. The PCR negativity could be potentially explained by two main factors: the timing of taking PCR samples (viral shedding period) and the milder course of the disease, as well as lack of extensive upper respiratory damage. The observed duration of these lesions was longer than that of other COVID-related skin manifestations – the average duration of pseudo-chilblains was 14 days, although it may extend to several months [5,8,12]. These lesions usually occur in the later stages of the disease than other forms of skin manifestations, with some authors suggesting a period of 1-5 weeks after epidemiological or clinical suspicion of COVID-19 or asymptomatic/pauci-symptomatic infection in younger patients [15]. By that time, viral load in the nasopharyngeal specimen is often no longer detectable by PCR [16]. Freeman (2021) conducted an international registry of suspected COVID-19 patients with cutaneous manifestations, which revealed that PCR positivity occurred 8 days after symptoms and negativity – 14 days later in individuals with pseudo-chilblains [21]. For clinicians, this further emphasizes the importance of understanding PCR timing and not relying solely on one test to diagnose COVID-19. Overall, the value of recognizing pseudo-chilblains appears to be more epidemiologic in nature, as it may help identify otherwise asymptomatic and PCR-negative individuals, but not those patients who are actively spreading the virus.

**Vesicular rash.** The vesicular rash manifests as small monomorphic vesicles with surrounding erythema, typically localized on the trunk [8,10]. The frequency of these lesions is 9-15%, and the duration ranges from 10 to 12 days [6,11,22]. In vesicular rash, the timing of skin biopsy is very important as it affects the histological findings: early lesions show vacuolar degeneration of the basal layer, multinucleated hyperchromic keratinocytes, multiple apoptotic cells, and little to no inflammatory infiltration; in later lesions, histologic features include intraepidermal vesicles with multinucleated balloon keratinocytes, acantholysis, dyskeratosis [10]. Based on the histological findings above, it is hypothesized that this type of rash results from direct

exposure to the virus. The detection of ACE-2 receptors in keratinocytes supports this hypothesis. Viral interactions with these receptors can cause previously mentioned acantholysis and dyskeratosis [10]. The vesicular rash is reminiscent of a lesion caused by other viruses, such as *Varicella zoster* or *Herpes simplex*. Therefore, it is important to distinguish whether the rash is a clinical manifestation of SARS-CoV-2 or a reactivation of a pre-existing viral disease [23].

**Urticaria.** The third most common (11-19%) skin manifestation in COVID-19 patients is urticaria [9,10]. It presents as a well-demarcated, prominent edematous papule that resolves spontaneously within 24 hours [9]. Urticaria typically occurs at the onset of infection and lasts on average 6-8 days [9,12]. Approximately 10% of COVID-19 patients develop this lesion prior to the “classic symptoms” [24]. If the lesion develops later, it could perhaps be considered to be an allergic reaction to the drug rather than a viral rash [3]. Wei Tan (2021) observed that urticaria is more prevalent in women [9]. Histological features range from spongiosis with perivascular infiltration to urticarial vasculitis with eosinophilia [9,10]. The pathogenesis of COVID-19-induced urticaria was attempted to be explained by the hypothesis of SARS-CoV-2 entering cells via ACE-2 receptors: immune complexes activate the complement system, mast cells degranulate and release bradykinin, which in turn leads to dilatation of arterioles and venous constriction [9]. As a result, capillary pressure and permeability increase [25]. This hypothesis was confirmed by the simultaneous detection of SARS-CoV-2 glycoproteins and complement components in cutaneous blood [9]. Eosinophilia was present in several patients and was associated with a more favorable disease course [26]. It was found that urticaria was associated with a better prognosis in COVID-19 patients, and hospitalization was rarely necessary [6,23].

**Vascular lesions.** Vascular lesions account for a smaller but very significant proportion of skin lesions in SARS-CoV-2 infected patients. This group of symptoms includes livedo racemosa, livedo reticularis, petechiae, purpura, ischemia, and necrosis [23]. The overall incidence of such lesions is about 6% [10]. Each lesion differs in its expression – livedo racemosa and livedo reticularis are transient or persistent pinkish-blue discolorations forming an interrupted and irregular pattern. Livedo reticularis is considered benign, whereas livedo racemosa is always pathologic and is often associated with antiphospholipid syndrome [27]. Purpura and petechiae are clinical manifestations of vasculitis. Vascular lesions can occur at any stage of the disease, and are generally associated with a more severe course [28]. Several researchers refer to COVID-19 as “an endothelial disease” because of endothelial cell damage being one of the key

pathophysiological features [28,29]. Endothelial cells are affected by the excessive production of inflammatory cytokines (e.g. Interleukin-1 (IL-1), IL-6, tumor necrosis factor  $\alpha$  (TNF- $\alpha$ )). Their hyperproduction results in an imbalance between fibrinolytic and coagulation function, producing even more IL-1, which stimulates the expression of its own and other inflammatory cytokine genes. All described processes lead to a syndrome called “cytokine storm”. IL-1 also stimulates the production of chemokines, which increases capillary permeability and disrupts normal microcirculation. In addition, when endothelial cells are stimulated by proinflammatory cytokines, they might express and exert tissue factor activity, which activates the coagulation system and leads to hypercoagulable state [30]. As a result, microthrombi may form in small vessels and vascular lesions develop. Histologic features include epidermal necrosis, thrombotic vasculopathy of small and medium vessels in the superficial and deep layers of the dermis (hyaline thrombi), necrosis of the epithelium of the eccrine glands, minor perivascular lymphocytic infiltration and complement deposition in the vessel walls [10].

Acral ischemia and necrosis are the most severe vascular lesions. They are characterized by painful purple or bluish, well-defined ischemic patches, more frequently localized to the feet and toes and less common on the hands. Progression to bullous formations or dry gangrene can be expected [10,13]. The exact pathogenesis of these lesions remains unclear, but most recent hypotheses are related to a COVID-19 linked hypercoagulable state in which the coagulation system is activated by both alternative and lectin pathways of the complement system [17,29]. Vasculitis and acral ischemia occur more frequently in the elderly and are associated with a worse prognosis (survival rate 78.9% according to Wei Tan (2021)). Patients with these lesions are at higher risk of severe pneumonia and disseminated intravascular coagulation and are therefore more likely to require treatment in the intensive care unit [9,10,23]. It is important to distinguish ischemic lesions from pseudochilblains – typically both involve the limbs, and the early appearance may be very similar. In addition, one lesion may transform into another as the disease progresses. Therefore, it is necessary to consistently assess the condition of the skin to avoid ischemic complications [6]. Since ischemic lesions have a much worse prognosis, Wei Tan (2021) suggested that vascular lesions could be a potential marker for severe COVID-19 disease [9].

### Conclusions

1. Currently, the direct involvement of the SARS-CoV-2 in cutaneous manifestations remains controversial, because only few studies have been able to demonstrate the particles

of the virus in the lesions. It is more likely that the virus plays an important role in the cascade of events leading to the skin damage discussed in this article.

2. Cutaneous lesions may be overlooked by clinicians because they are not considered “classic” symptoms of SARS-CoV-2. Pathologic findings show endothelial damage in cutaneous vessels, which may indicate similar processes in other internal organs occurring simultaneously.

3. Skin lesions may raise suspicion of COVID-19 and provide a rational basis for screening patients for SARS-CoV-2. Clinicians need to be aware of the importance of PCR timing, as a single negative PCR result does not exclude COVID-19.

4. To obtain an accurate diagnosis, potential COVID-19 patients with otherwise unexplained cutaneous lesions should be evaluated for signs of viral infection in the blood. Repeated PCR and serology testing could be the next diagnostic step for PCR-negative patients.

5. Hospitalized patients must receive appropriate thromboembolic prophylaxis or anticoagulant therapy and early endothelial protection with antiaggregants to ensure a better prognosis in moderately severe cases of COVID-19. Consistent reassessment of skin condition is important to prevent additional damage. Further research is needed to determine the relationships between SARS-CoV-2-related skin lesions and effects on other organ systems.

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**COVID-19 IŠRAIŠKOS ODOJE: PATOGENETINAI  
MECHANIZMAI IR DIAGNOSTIKOS IŠŠŪKIAI**  
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Raktažodžiai: SARS-CoV-2, COVID-19, odos išraiškos.

#### Santrauka

Koronavirusinė liga (COVID-19) yra virusinė infekcija, įprastai pasireiškianti karščiavimu, dusuliu, kosuliu, bendru negalavimu, anosmija. Pastaruoju metu daugėja pranešimų apie odos pažeidimus, siejamus su SARS-CoV-2 virusu. Įvairios odos išraiškos gali padėti įtarti COVID-19 ir suteikti pagrindą tirti pacientą dėl šios ligos. Tiesioginis ryšys tarp SARS-CoV-2 ir odos pažeidimų ne visiškai aiškus, tačiau viruso įsitraukimas į pažeidimo vystymosi procesus yra labai tikėtinas. Pacientai su nepaaiškinamais odos pokyčiais ir epidemiologiniu ar klinikiu COVID-19 įtarimu turėtų būti vertinami kaip potencialiai infekuoti, nepriklausomai nuo jų PGR rezultato. Neretai neigiamas PGR atsakymas neturėtų atmesti COVID-19 diagnozės. Labai svarbu suprasti galimas odos išraiškas bei jų patogenezę, siekiant adekvačiai gydyti šią infekcinę ligą. Darbo tikslas yra apžvelgti naujausią literatūrą apie COVID-19 išraiškas odoje, išanalizuoti sisteminės apžvalgas bei pristatyti pačius dažniausius pažeidimus: eritemą, makulopapulinį, pūslelinį, išeminį bėrimus, dilgėlinę ir pseudonušalimus.

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