

Skin diseases accompanying COVID-19 infection

– literature review

Dermatozy skórne towarzyszące zakażeniu COVID-19
– przegląd piśmiennictwa

INTRODUCTION

The basic clinical manifestations of SARS-CoV-2 infection come from the respiratory system. Along with the spread of the virus and in more and more patients, symptoms of the digestive system, smell and taste disturbances and skin lesions, which are characterized by a rather dynamic course, were also noticed. They gradually disappear as viral load decreases. The problem

of skin lesions in patients infected with coronavirus may have many causes and is related to the severity of SARS-CoV-2 (*severe acute respiratory syndrome CoV-2*) infection. Dermatoses take various forms - from vesicular lesions, urticaria, maculopapular rash to covid fingers (*pseudo-frostbite lesions*) or net cyanosis.

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ABSTRACT

Coronavirus disease 2019 (COVID-19) is a new disease entity caused by SARS-CoV-2 coronavirus. It was first diagnosed in Wuhan, China. Its high rate of infectivity, low virulence, and asymptomatic transmission have caused it to spread rapidly beyond geographic boundaries, leading to a pandemic. The COVID-19 outbreak was identified as a public health emergency of international concern following a declared global pandemic. SARS-CoV-2 is an enveloped virus composed of single-stranded RNA and belongs to the coronavirus family. The virus enters cells through the angiotensin-converting enzyme receptor 2 (ACE2) on the surface of the cells. The lungs are the main site of COVID-19 infection, with symptoms ranging from mild flu-like, to fulminant pneumonia in patients. Patients have also been diagnosed with multiple cutaneous manifestations during the course of COVID-19.

The aim of the article was to present, based on the available literature, selected skin disorders in patients with COVID-19. The basis of these changes is not fully understood and requires further research.

STRESZCZENIE

Choroba koronawirusowa COVID-19 to nowa jednostka chorobowa wywołana przez koronawirusa SARS-CoV-2. Po raz pierwszy została zdiagnozowana w Wuhan w Chinach. Wysoka zakaźność, niska wirulencja i bezobjawowe przenoszenie spowodowało szybkie rozprzestrzenienie się poza granice geograficzne prowadząc do pandemii. Wybuch COVID-19 został uznany za stan zagrożenia zdrowia publicznego o zasięgu międzynarodowym, a w następstwie ogłoszony jako pandemia o zasięgu światowym. SARS-CoV-2 to wirus otoczkowy złożony z jednoniciowego RNA, należy do rodziny koronawirusów. Wirus wnika do komórek poprzez znajdujący się na powierzchni komórek receptor enzymu konwertującego angiotensynę 2 (ACE2). Płuca są głównym miejscem zakażenia COVID-19, wśród pacjentów objawy zaliczane są od łagodnych grypopodobnych, po ostre zapalenie płuc. Podczas przebiegu COVID-19 zdiagnozowano również wiele objawów skórnych.

Celem artykułu było przedstawienie na podstawie dostępnej literatury wybranych dermatoz skórnych u pacjentów z COVID-19. Podłoże tych zmian nie jest do końca poznane i wymaga dalszych badań.

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THE INFLAMMATORY PROCESS IN THE COURSE OF COVID-19

Fever, dry cough, shortness of breath, muscle aches, fatigue, a tendency to leukopenia and radiological symptoms of progressive pneumonia that may cause multi-organ failure are symptoms observed in COVID-19 (coronavirus disease 2019), SARS-CoV (severe acute respiratory syndrome CoV-2) and MERS (Middle East respiratory syndrome coronavirus). The pathogenesis of these diseases seems to be similar [1]. In the course of COVID-19, very high levels of ferritin and D-dimers in the serum are observed, disproportionate to the severity of the infection, as well as the ability to monocytosis and small amounts of NK cells (Natural Killers) and cytotoxic T lymphocytes. Spikes composed of glycoproteins on the surface of the virus belong to the most immunogenic parts of coronaviruses and have the ability to bind to angiotensin-converting enzyme-2 ACE-2 (Angiotensin-converting enzyme 2) receptors to enter the host cell. A similarity has been demonstrated between SARS-CoV and SARS-CoV-2 spike glycoproteins. The distribution of ACE-2 receptor expression on the surface of type II follicular epithelial cells, heart, kidney, intestine and endothelial cells is consistent with target organs and the clinical picture in COVID-19 infected [1, 2]. SARS-CoV-2 is spread mainly through direct contact with saliva or secretions from the respiratory tract, when an infected person sneezes or coughs [3]. After binding to ACE-2 receptors on the cell surface through a glycoprotein spike, the virus enters the cytoplasm of the cell, releases the RNA and replicates, resulting in the formation of new viral particles. As a result, the cell breaks down and the virus spreads to other cells. When the immune system recognizes the antigens, they are presented to NK cells and CD8 + cytotoxic T cells. This presentation activates both innate and acquired immunity, provoking the production of large amounts of pro-inflammatory cytokines and chemokines. After binding to ACE-2 receptors on the cell surface through a glycoprotein spike, the virus enters the cytoplasm of the cell, releases the RNA genome and replicates, resulting in the formation of new viral particles. As a result, the cell breaks down and the virus spreads to other cells. When the immune system recognizes the antigens, they are presented to NK cells and CD8 + cytotoxic T cells. This presentation activates both innate and acquired immunity, provoking the production of large amounts of pro-inflammatory cytokines and chemokines. PRR receptors identify PAMP molecular patterns mainly in the extracellular environment and to a lesser extent in the intracellular environment. A signaling system is triggered that leads to the expression of pro-inflammatory transcription factors inducing cytokines such as NF- κ B and interferon regulatory factors that mediate the type I interferon-mediated antiviral response [9, 10]. Another pathogen recognition system is in the cytosol and involves the NLRP1, NLRP3, NLRP7, NLRC4 family of leucine-rich

proteins NLR (NOD-like receptors) responsible for the detection of DAMPs (Damage-associated molecular patterns) that are expressed inside cells. Binding of DAMP activates NRLs, causing a cascade of processes leading to the formation of protein complexes called inflammasomes, which convert procaspase-1 to caspase-1 (Fig. 1). As a result of these events, IL-1 β is activated [9, 11]. If the signaling activation processes are controlled, they are used to fight viruses and maintain the body's homeostasis. Under normal conditions, virus-infected cells are destroyed by NK cells and CD8 + cytolytic T cells. Recognition is followed by apoptosis of the antigen presenting cells and the corresponding cytotoxic T cells in order to avoid unnecessary antigenic activity. With acquired diseases, a defect in the cytolytic activity of lymphocytes may occur. NK cells and CD8 + T cells become unable to lyse infected and activated antigen presenting cells. Interactions between innate and adaptive immune cells take longer and many pro-inflammatory cytokines, including TNF (Tumor necrosis factor), interferon γ , IL-1, IL-6, IL-18 and IL-33, are continuously secreted. The entire pathological process, starting with defects in the cytolytic activity of lymphocytes, through the increased activity of macrophages and the activation of the entire immune system, provokes a continuous release of cytokines. It may lead to multi-organ failure [4, 12, 13]. This life-threatening condition is one of the leading causes of death in COVID-19 patients.

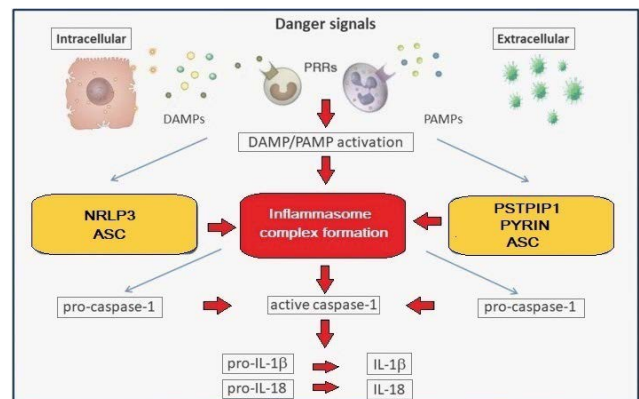


Fig. 1 A cascade of pro-inflammatory events following virus entry.
PRR – Pattern recognition receptor, **DAMP** – Damage-associated molecular pattern,
PAMP – Pathogen-associated molecular pattern, **ASC** – Apoptosis-associated speck-like protein containing a CARD, **CARD** – Caspase Activation and Recruitment Domain,
NLRP3 – NLR family pyrin domain containing 3 (NLRP3),
PSTPIP1 – Proline-serine-threonine phosphatase-interacting protein 1
 Source: [13]

SKIN DERMATOSES ACCOMPANYING COVID-19

Skin changes in COVID-19 are related to the body's ongoing process of fighting the virus. The best known case stages of cutaneous COVID-19 symptoms as published by Recalcati et al., in Lombardy, Italy, included 88 patients. This study reported 20.4% of confirmed COVID-19 cases, of which 19 had skin symptoms. It was shown that most of the skin lesions were manifested by an erythematous rash (77.8%). There were also several cases of urticaria (16.7%)

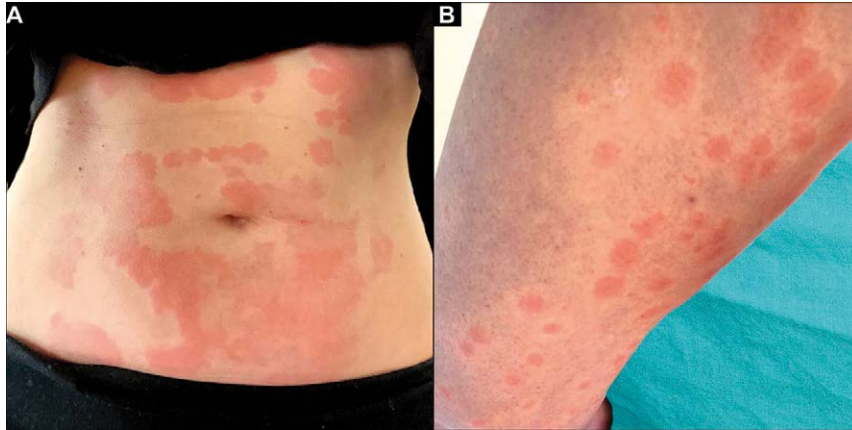


Fig. 2 A 39-year-old female with hives on the abdomen and thigh. The hives started the day before the fever appeared. Shortly thereafter, she was diagnosed with Covid-19 positive Source: [15]



Fig. 3 Pseudo-frostbite changes, the so-called "covid fingers" Source: [16]

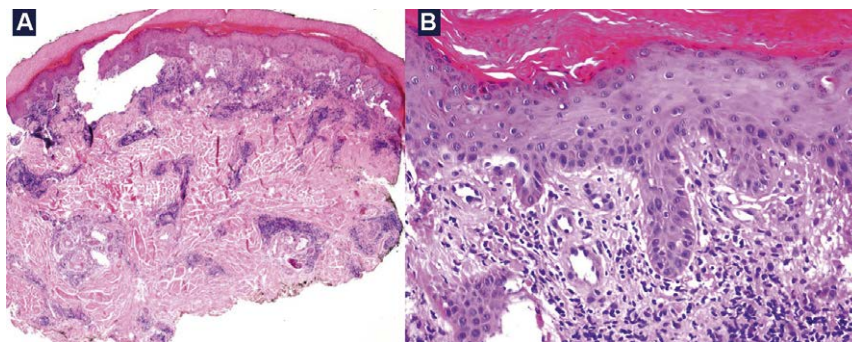


Fig. 4 Histopathological and pseudo-frostbite changes as a result of COVID-19 infection. a) visible deep lymphoplasmic infiltrate, b) image with visible necrotic keratinocytes Source: [16]

maculopapular rash (15.3%) and the formation of vesicular lesions on the skin (34.7%). The time of development of skin lesions among patients varied, ranging from 3 days before COVID-19 diagnosis to 13 days after diagnosis. The article describes a few selected dermatoses associated with coronavirus infection in the world [14].

• Vesicular lesions

They are characterized by the occurrence of small vesicles located mainly in the area of the trunk, subcutaneous folds and legs, and they mainly affect middle-aged people. The vesicular lesions accompanying COVID-19 are of medium to high intensity. The duration of the rash is 8 to 10 days. Recalcati et al., in Lombardy reported vesicular lesions in 34.7% of patients with a positive COVID-19 result [14].

• Urticaria lesions

Urticaria-like lesions are less common and last about 7 days. According to Recalcati et al., urticaria occurred in 9.7% of the reported patients (Fig. 2). The accompanying symptom of urticaria, which occurs mainly on the buttocks and around the lower extremities, is itching [14].

• Maculopapular rash

According to Italian scientists, the manifestation accompanying COVID-19 infection was observed in 15.3% of patients. It lasts about 8 days, 60% of it may be pruritic. It occurs in both children and adults. It is characterized by infiltrating papular changes [14, 15].

• Covid fingers

Experts say that they are increasingly noticing characteristic pseudo-frostbite changes called covid fingers in people infected with COVID-19. Changes located asymmetrically on the fingers and toes, accompanied by slight swelling (Fig. 3). Patients have discoloration on the hands and fingers, on which painful blisters and ulcers appear. Noticeable changes are painful red-purple bumps that tend to be on the tips of the fingers or toes. The blue discoloration of the fingers may be indicated by small blockages in the vessels, as COVID-19 is believed to cause an increased tendency to blood clots [14, 15]. The obtained histopathological image of the altered sites showed that there were pseudofreezing lesions (chilblains) with visible single, necrotic keratinocytes and a deep lymphoplasmic infiltrate (Fig. 4) [16].

• Reticular sinus (Lat. *Livedo reticularis*)

This is a blood vessel disorder. These are characteristic lesions forming a network of red-blue, marbled, mosaic-like lesions on the patient's skin. Vessels in COVID-19 infected patients can lead to lymphocytic vasculitis, similar symptoms are observed in thrombosis [14, 15].

SUMMARY

The underlying cause of skin lesions accompanying COVID-19 is not fully recognized and requires further research. The efficiency of the immune system determines the course of SARS-CoV-2 infection, and dermatological treatment in many cases is immunosuppressive, which may result in a potentially more severe course of COVID-19. In such case, if the patient has been diagnosed with COVID-19 disease, immunosuppressive treatment should be discontinued. As the pandemic unfolds and the number of cases increases, the number of studies showing the association of COVID-19 infection with skin lesions is also growing. Early detection of the disease, especially in asymptomatic, poorly symptomatic people or with atypical symptoms, may help to inhibit the spread of the virus, therefore disturbing, atypical skin lesions cannot be underestimated. As COVID-19 may be asymptomatic for 14 days after infection, skin symptoms can be used as an indicator of infection to aid prompt diagnosis.

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