



POLISH SCIENCE JOURNAL

INTERNATIONAL SCIENCE JOURNAL

Issue 1(46)



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ISSUE 1(46)

INTERNATIONAL SCIENCE JOURNAL

WARSAW, POLAND
Wydawnictwo Naukowe "iScience"
2022

ISBN 978-83-949403-4-8

POLISH SCIENCE JOURNAL (ISSUE 1(46), 2022) - Warsaw: Sp. z o. o. "iScience", 2022. – 193 p.

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ISBN 978-83-949403-4-8

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CHARACTERISTICS OF CUTANEOUS MANIFESTATIONS AND HEMATOLOGICAL PARAMETERS IN CORONAVIRUS INFECTION

Abstract. *The review is devoted to skin manifestations in a new coronavirus infection, information on which are continuously updated and supplemented. However, until now the available data were not systematized. The purpose of this review is to analyze dermatological manifestations with a new coronavirus infection. On average, 12.5-20.4% of patients with confirmed COVID-19 has developed cutaneous manifestations. The question of whether skin symptoms are secondary due to a respiratory infection or a primary infection of the skin itself, at this time the cop remains open. The probable mechanisms of the development of skin lesions and the role of diseases of the complement system and the state of blood hypercoagulation in the pathogenesis of their development. The review also provides clinical examples of the involvement of the skin in infectious diseases. process in COVID-19. As COVID-19 tends to be asymptomatic within 14 days after infection, skin manifestations can serve as an indicator of infection contributing to timely diagnosis.*

Key words: COVID-19, skin manifestations, complement system, infectious DIC.

During the pandemic, a number of cases were recorded COVID-19, who have reported cutaneous manifestations of infection. The purpose of this article is to review the literature for various skin manifestations in COVID-19. Familiarization with them is important not only for dermatologists, but also for a wider circle of doctors of general family / medical practice (AFP) of the polyclinic / outpatient level of medical care, because it is they who are in contact with patients more often, incl. with COVID-19 infection.

Dermatological manifestations of COVID-19, along with with general clinical signs including fever, dry cough, shortness of breath, myalgia, and fatigue, observed in relatively large-scale clinical studies of patients with COVID-pneumonia, were quite rare. Most a well-known study on the cutaneous manifestations of COVID-19, published by Recalcati S. et al. (2020) from Italy, includes 88 patients. In this study, 20.4% of confirmed COVID-19 (18/88) patients developed cutaneous manifestations. It was found that the majority of cutaneous manifestations were erythematous rash (77.8%, or 14/18) with rare cases of urticaria (16.7%, or 3/18) and the formation of vesicles (5.6%, or 1/18). A similar distribution of cutaneous manifestations was noted in another review: in a study, conducted by a group of scientists from Israel, Canada and Italy, which analyzed 72 cases of COVID-19 with dermatological manifestations, described by different authors during the pandemic COVID-19 (table). The

average age of the patients was 53.6 years, and the age of the patients was from 15 days to 84 years. In terms of diagnosis of COVID-19 2.8% of patients were suspected cases, and 97.2% - confirmed cases. Generalized macular or maculopapular exanthema (measles) was found to be the most common cutaneous manifestation in COVID-19 patients. was recorded in 36.1% (26/72) of patients. Papulo-vesicular rash (vesicles) was seen in 34.7% (25/72) patients. Urticaria occurred in 9.7% (7/72) confirmed patients and painful acral reddish-purple papules with or without vesicles was observed in 15.3% (11/72) patients in general. Finally, in 2.8% (2/72) of patients lesions in the form of reticulated livedo were found, and 1 patient (1.4%) had petechiae. Of 72 cases, localization of the lesion was recorded in 67 patients, with the majority of lesions being found on the torso, arms and legs. In general, 69.4% (50/72) of patients, skin manifestations on the trunk were observed. In addition, 19.4% (14/72) of patients had skin manifestations on the hands and feet. Timing the development of skin lesions varied in different patients from developmental 3 days prior to diagnosis of COVID-19 to 13 days after diagnosis¹.

In the cases examined, 12.5% (9/72) of patients had cutaneous manifestations at diagnosis or symptoms of COVID-19, while 69.4% (50/72) of patients, skin manifestations occurred after onset of respiratory symptoms or staging diagnosis of COVID-19. Of the 49 patients who developed lesions after the onset of respiratory symptoms or the diagnosis of COVID-19, 74.0% (37/50) had a skin abnormality within 7 days, and 6.0% (3/50) reported rashes after 7 days. Out of 50 cases with a reported healing time of 100% of patients reported healing of skin lesions, with the healing time reached 10 days. Healed within 7 days 48.0% (24/50) of skin manifestations, 50.0% (25/50) dermatological manifestations healed after 7 days, with the healing time not determined for one case (2.0%). It was also reported about a possible connection between COVID-19 and the severity of skin lesions in 23 patients. Of these, in 21 patients (91.3%), the severity of skin lesions was unlikely or did not correlate with the severity of COVID-19. On the contrary, in 2 separate posts Mahé A. and Estébanez A. COVID-19 and the severity of skin lesions were associated in 2 patients (8.7%). Skin manifestations have arisen she had after clinical recovery and manifested itself as a maculopapular itchy rash on the trunk, reminiscent of Grover's disease. The second case was presented by 77-year-old a woman who has developed skin manifestations at the very beginning of the disease - on the first day of hospitalization, skin rashes were represented by maculopapular (measles-like) exanthema on the trunk, and during the following days in the patient there was a patchy-hemorrhagic rash on the skin of the legs. The third case was presented by a 72-year-old woman. Skin rashes have occurred in the patient on the 4th day of illness in the form of papulo-vesicular itchy rashes in the area of the fold under the breast, on the trunk and thighs. All patients was confirmed by COVID-19.

Consultation with a hematologist: skin rashes are regarded as probable manifestations in COVID-19. Consultation with a dermatologist: hemorrhagic angitis of the skin, of an infectious-allergic nature, possibly associated with SARS-CoV-2. Systemic administration of glucocorticosteroids is recommended (prednisone at a dosage of 1.2 mg per 1 kg of body weight). Primary diagnosis: coronavirus infection caused by COVID-19 virus, virus identified

¹ Zhang Y., Cao W., Xiao M., Li Y.J. Clinical and coagulation characteristics of 7 patients with critical COVID-2019 pneumonia and acro-ischemia. *Za Zhi.*, 2020, 41 (0), E006.

(PCR analysis). Bilateral community-acquired polysigmented pneumonia of moderate severity, respiratory failure 1-2. Hemorrhagic angitis skin, common form. Against the background of systemic hormonal therapy (prednisolone 90 mg per day), the patient experienced a rapid regression of the skin pathological process. Some authors propose to distinguish 7 groups skin manifestations in COVID-19: angitis, papullo-vesicular rashes, papullo-squamous rashes and lichen rosacea, measles-like rashes, toxidermias, urticaria and artificial lesions (trophic changes in facial tissues).

The main mechanisms of the occurrence of skin disorders in COVID-19 are not yet sufficiently understood but some generally accepted theories are already widely discussed. It is believed that viral particles present in the blood vessels of the skin in patients with COVID-19 infection can lead to lymphocytic vasculitis similar to that observed with thrombophilic arteritis induced circulating immune complexes and activating cytokines. Keratinocytes can be a secondary target after activation of Langerhans cells, inducing a spectrum of different clinical manifestations. The virus is not supposed to be targeting on keratinocytes, but rather the immune response to infection leads to the activation of Langerhans cells, which leads to a state of vasodilation and spongiosis. Other theories suggest that the manifestations of livedo reticularis may be caused by microthrombosis, which leads to a decrease in blood flow to the cutaneous system. microcirculatory vessels. The same way low disseminated intravascular coagulation and hypoxia-related accumulation deoxygenated blood in the venous plexuses can additionally explain such manifestations².

In addition, Magro C. et al reported on inflammatory thrombogenic vasculopathy with deposition C5b-9- and C4d-components of complement as strongly involved and unchanged skin (Fig. 10). Also, in two examined patients, there was an association of COVID-19 glycoproteins (S or spike) with C4d- and C5b-9- complement components in the interalveolar septa of the lungs and vessels of the microvasculature skin. In conclusion, the authors suggest that the catastrophic damage to the microvasculature in COVID-19 is mediated by the activation alternative and lectin complement pathways and concomitant activation of the hemocoagulation cascade a person with the development of an infectious-mediated DIC syndrome. These data are the basis for further study of the pathophysiological role of complement in COVID-19 infection and in the future may help develop a specific intervention protocol for the treatment of COVID-19

Tang N. At all studied in detail the state of the hemostasis system in 283 patients with severe forms of coronavirus pneumonia. The overall mortality rate among the surveyed was 11.5%. Dying patients have high rates D-dimer and fibrin degradation products (PDP), prolongation of prothrombin time (PT) and activated partial thrombin time (APTT).

During hospitalization 71.4% of deaths and 0.6% survivors met ICE criteria. Should pay attention to the fact that the deceased compared with the recovered complications more often occurred, such as acute respiratory distress syndrome (89.9% versus 7.6%, $\chi = 148.105$, $P < 0.001$), acute heart damage (59.6% versus 0.8%, $\chi = 93.222$, $P < 0.001$), acute kidney injury (18.3% versus 0, $\chi = 23.257$, $P < 0.001$), shock (11.9% versus 0, $\chi = 14.618$, $P < 0.001$) and ICE

² Henry D., Ackerman M., Sancelme E., Finon A., Esteve E. Urticarial eruption in COVID-19 infection. J. Eur. Acad. Dermatol. Venereol. 2020 (April 15).

(6.4% versus 0, $\chi = 7.655$, $P = 0.006$). There is no doubt that in all of these conditions, hypercoagulation was observed, and in many cases and thrombosis leading to acute heart failure and other complications. In work published by Tang N. At all, retrospectively analyzed the results therapy with low molecular weight heparins (LMWH) in 449 patients with severe COVID-19. Established that mortality in groups of patients with a high level of D-dimer (6 times higher than normal) was lower among patients on LMWH therapy (32.8% versus 52.4%, $P = 0.017$), as well as patients with sepsis-induced DIC (40.0% versus 64.2%, $P = 0.029$) compared with those who did not receive LMWH. It was concluded that the use of anticoagulant therapy is associated with better disease prognosis in severe COVID-19 patients with the presence of sepsis-induced coagulopathy and a high content of D-dimer.

The main purpose of the proposed therapy is prevent the development of thrombosis, multiple organ failure, thrombotic microangiopathy, and disseminated intravascular coagulation. In the case of the development of these complications must be immediately introduced plasminogen activator (t-PA) or its recombinant analogue (APSAC). In this case, the dose should be adjusted strictly individually, based on the severity of the pathological process. Researchers from Japan Kandeel M. and Al-Nazawi M. suggest that viral subunits (compartments) of COVID-19 are able to interact with fibrin and, changing the structure of the latter, lead to the development microthrombovasculitis in the pool of terminal / subterminal pulmonary arteries.

All this in the background interstitial inflammation and the development of severe autoimmune alveolitis provokes manifestation rapidly progressive fibrosing alveolitis with an outcome in pulmonary fibrosis and acute respiratory failure (ARF). This is why researchers suggest that early use of tissue plasminogen activator (t-PA) along with LMWH will prevent or delay the onset of pulmonary fibrosis and have a positive effect on pulmonary microcirculation and gas exchange. At the same time, the combination of LMWH and t-PA can in some cases lead to the development of hemorrhagic syndrome, and therefore the doses of drugs must be carefully selected.

This requires constant laboratory monitoring of hemocoagulation and fibrinolysis.

Whether the skin symptoms are a secondary consequence of a respiratory infection or a primary infection of the skin itself remains open at this time.

Dermatovenerologists have a unique opportunity to study the cutaneous manifestations of COVID-19 during this pandemic, so new data is very important and illustrative images of skin lesions. It is generally accepted that we cannot disagree with the well-known principle: "the more you see, the more you know; and the more you know, the more you see", which becomes now more than relevant.

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