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Review

Clinical and morphological specifics, pathogenetic ways of skin manifestations in SARS-CoV-2 infection

Lyubov O. Severgina, Olga Yu. Olisova, Daria M. Martynenko, Tatiana A. Demura

I.M. Sechenov First Moscow State Medical University (Sechenov University), Moscow, Russia

ABSTRACT

To date, the most studied clinical and morphological changes characteristic of SARS-CoV-2 virus are its pulmonary manifestations and cardiovascular involvement. However, the evaluation of COVID-associated skin changes and the analysis of their mechanisms are also important for us, because the skin manifestations of the infection can change the patient's appearance for the worse, i.e. affect the aesthetic sphere and significantly reduce the quality of life. The study of not only skin manifestations of COVID-19, but also their morphological substrate and pathogenetic basis allows us to apply the most effective methods of treatment and provide adequate management of patients even in the post-coital status.

According to the information collected to date, the most frequently reported skin manifestations of SARS-CoV-2 are pseudo-frostbite, maculopapular and vesicular lesions, urticaria, lividoid and necrotic lesions, hemorrhagic purpura (vasculitis), and conditions from the group of other unclassified skin lesions. Despite the variety of clinical variants of SARS-CoV-2-associated skin changes, morphological stigmas are often stencil-like: these are areas of lymphohistiocytic infiltration of perivascular localization, the presence of fibrinoid necrosis foci in the vessel walls, the formation of occlusive thrombi, erythrocyte extravasation. Mechanisms of damage to epidermis and dermis within COVID-19 infection may be due to the influence of complement components, activation of cytotoxic lymphocytes and NK-cells, excessive synthesis of proinflammatory cytokines, in particular, interleukin 6, as well as interferons, hyperergic reactions. In addition to routine morphological, immunohistochemical examination of skin biopsy specimens from patients with different forms of skin manifestations of SARS-CoV-2 infection is an important tool in the diagnostic confirmation of COVID-associated dermatologic pathology, especially in patients with a suspected history of this disease or with problematic laboratory results.

Keywords: SARS-CoV-2 infection; COVID-19; skin manifestations; morphological characteristics.

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Научный обзор

Клинико-морфологические и патогенетические особенности кожных проявлений при инфекции SARS-CoV-2

Л.О. Севергина, О.Ю. Олисова, Д.М. Мартыненко, Т.А. Демура

Первый Московский государственный медицинский университет имени И.М. Сеченова (Сеченовский Университет), Москва, Россия

АННОТАЦИЯ

К настоящему времени наиболее изученными клиническими и морфологическими проявлениями, характерными для вируса SARS-CoV-2, являются лёгочные изменения, а также поражение сердечно-сосудистой системы. Однако оценка COVID-ассоциированных изменений кожи и анализ механизмов их возникновения также представляются нам важными, поскольку часто именно кожные проявления инфекции способны изменить внешность пациента в худшую сторону, так как затрагивают эстетическую сферу и существенно снижают качество жизни. Изучение не только кожных проявлений, характерных для COVID-19, но и их морфологического субстрата и патогенетического базиса, позволяет применить наиболее эффективные методы лечения и обеспечить грамотное ведение пациента в постковидном статусе.

Согласно собранной на сегодняшний день информации, наиболее часто регистрируемыми кожными проявлениями SARS-CoV-2 являются псевдообморожения, макулопапулёзные и везикулярные поражения, крапивница, ливедоидные и некротические поражения, геморрагическая пурпура (васкулиты) и состояния из группы других неклассифицированных поражений кожи. Невзирая на многообразие клинических вариантов SARS-CoV-2-ассоциированных изменений кожи, морфологические стигмы часто бывают трафаретными: это участки лимфогистиоцитарной инфильтрации периваскулярной локализации, наличие фокусов фибриноидного некроза в стенках сосудов, формирование окклюзирующих тромбов, экстравазация эритроцитов. Механизмы повреждения структур эпидермиса и дермы в рамках инфекции COVID-19 могут быть обусловлены воздействием белков комплемента, активацией цитотоксических лимфоцитов и NK-клеток, избыточным синтезом интерферонов и провоспалительных цитокинов, в частности интерлейкина 6, а также реакциями гиперчувствительности. Иммуногистохимический анализ биоптатов кожи у пациентов с различными формами кожных проявлений при SARS-CoV-2, помимо рутинного морфологического исследования, представляет собой важный инструмент в достоверной диагностике COVID-ассоциированной дерматологической патологии, особенно у пациентов с подозрением на перенесённое заболевание в анамнезе и с сомнительными результатами лабораторных показателей.

Ключевые слова: инфекция SARS-CoV-2; COVID-19; кожные проявления; морфологическая характеристика.

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ЭКО•ВЕКТОР

INTRODUCTION

Since the COVID-19 pandemic started up to the present time, various manifestations of SARS-CoV-2 infection have been of interest to physicians of various specialties, and morphologic examination of biopsy specimens from affected organs is crucial in understanding the pathogenesis and clinical manifestations of this infection. Additionally, a morphologic basis provides a foundation for the development of effective therapies, which may facilitate the discovery of personalized treatment strategies and ensure adequate management of patients even in the post-COVID-19 status.

This literature review focused on studies wherein a complete morphological analysis was presented, along with the description of the dermatological manifestations of COVID-19.

CLINICAL, MORPHOLOGICAL, AND PATHOGENETIC FEATURES OF SKIN MANIFESTATIONS IN SARS-COV-2 INFECTION: A LITERATURE REVIEW

To date, the most studied clinical and morphological manifestations characteristic of SARS-CoV-2 infection are pulmonary changes and cardiovascular system damage. However, the evaluation of COVID-19-associated skin changes and analysis of their mechanisms is crucial, because it is often the skin manifestations of infection that can change the patient's appearance for the worse, as they affect the aesthetic sphere and significantly reduce the quality of life. The American Academy of Dermatology COVID-19 Task Force launched an international COVID-19[1] dermatologic registry wherein clinical cases of skin lesions with coronavirus infection can be reported.

According to data collected to date, the most frequently reported skin manifestations of SARS-CoV-2 are pseudo-frostbite, maculopapular and vesicular lesions, urticaria, and livedoid and necrotic lesions, as well as other unclassified skin lesions [1]. Rubio-Muniz et al. [2] analyzed the clinical and morphological features of skin manifestations of COVID-19 in 34 patients. The most common forms were maculopapular exanthemums (10 cases) and pseudo-frostbite (9 cases), followed by target-like lesions characteristic of erythema multiforme (5 cases), palpable purpura (4 cases), acute urticaria (3 cases), and vesicular rashes (2 cases), and one case accounted for mesh livedo, urticaria rashes, and itching. Moreover, maculopapular exanthemums appeared more often at a later stage of COVID-19 [2].

Considering the variety of skin manifestations of SARS-CoV-2, some studies have recommended the use of a special classification based on their pathogenetic mechanisms of development. In severe cases of COVID-19, this classifier includes thrombotic vascular damage mediated by complement, including alternative and lectin pathways of activation of the complement system (as a factor in the activity of innate immunity), as well as contributing to the synthesis of cytokines, particularly interleukin 6 (IL-6), vascular endothelium; persistent (persistent) inflammatory process caused by T cells and type I interferon; with mild to moderate severity of COVID-19 — skin vasculitis (humoral immunity and immune complex) [3].

Based on a summary of publications analyzing clinical and morphological data of 997 patients from 9 countries, Kubanov et al. [4] revealed that the most common and frequently occurring morphologic features of skin lesions in coronavirus infection are perivascular lymphocytic infiltrate and edema of the upper dermis and the presence of thrombi in small skin vessels. The authors noted the correlation between the results of morphological analysis of skin biopsies and autopsy data when the peripheral parts of the lungs were studied, which indicated the similarity of the pathogenetic mechanisms of their damage. Morphological changes are associated with the SARS-CoV-2 infection and damage to endothelial cells, which leads to the development of diffuse vasculitis and the formation of disseminated intravascular thrombi accompanied by perivascular lymphocytic infiltration [4]. In a study of lung and skin biopsy samples obtained from five patients with severe COVID-19 and pronounced skin manifestations, it was found that the characteristic feature in all the samples was generalized microvascular damage with thrombus formation. According to the study, this pathology, which affects the microcirculation vessels of the lungs and skin, is mediated by the activation of certain complement fractions. This was confirmed by the detection of damage to the capillaries of the interalveolar septa in the lung tissue of two patients with pronounced deposition of complement fractions C5b-9, C4d, and MASP2. Simultaneous with the described changes in the skin, thrombi were found in the microvascular vessels, the formation of which is due to an insufficient amount of complement. In three cases of retiform purpura, deposition of C5b-9 and C4d complement fractions was detected in biopsies taken from the area of skin lesions and externally unchanged skin. Additionally, the conjugated expression and localization of SARS-CoV-2 spike glycoproteins with C4d and C5b-9 complement fractions were found in the capillaries of the interalveolar septa and in the microvascular vessels of the dermis. The results of the study indicate that severe and therapy-resistant COVID-19 may be associated with catastrophic damage to the microvascular vessels (catastrophic microvascular injury syndrome), which develops due to the activation of certain complement fractions, and the associated procoagulant condition [5].

[1] American Academy of Dermatology Association [Internet]. COVID-19 dermatology registry. Available at: https://www.aad.org/member/clinical-quality/clinical-care/covid-19/registry.

Gianotti et al. [6] described the clinical and morphological features of patients with various skin manifestations of COVID-19: a 59-year-old woman with widespread spots on her arms, trunk, and lower extremities; an 89-year-old woman with exanthema on the trunk and arms; and a 57-year-old man with an acute itchy rash in the form of erythematous spots and papules. The morphological picture in the first two cases corresponded to viral exanthema, as a dermal lymphocytic perivascular infiltrate was detected. Interestingly, blood clots in small vessels of the dermis were found in the skin biopsy of the first patient, and microthrombi were absent in the skin sample of the second patient; however, signs characteristic of lymphocytic vasculitis were noted, namely, cuffs of lymphocytes surrounding small blood vessels (vasculitis phenomena) and hemorrhages in the middle part of the dermis. The skin biopsy of the third patient revealed morphological signs of transient acantholytic dermatosis (Grover's disease) with the presence of multinucleated cells combined with the presence of dyskeratosis in the epidermis, suprabasal slits similar to acantholytic ones, and the presence of balloon herpes-like dystrophy and a small number of Langerhans cells and single necrotized keratinocytes; a dense lymphocytic infiltrate with an insignificant number of eosinophils was detected in the dermis. According to the authors, such superficial dermatitis with necrosis of individual keratinocytes surrounded by lymphocytes may be caused by activation of cytotoxic lymphocytes and NK-cells that damage keratinocytes and subsequent cascade synthesis of pro-inflammatory cytokines [6].

Herrero-Moyano et al. presented data of eight patients (four men and four women, with an average age of 72.2 years) with exanthema that developed following COVID-19 infection [7]. In most patients, rashes ranged from indistinctly outlined spots to a merging spotted papular rash, and some of the formations had a purple center. On the trunk, a high concentration of rashes was noted in the back and natural folds of the body. One of the patients had pustular elements and peeling. Histological examination of biopsies taken from the rash zone in three patients revealed characteristic signs of vascular damage with microthrombi in the capillaries of the dermis and extravasation of erythrocytes; however, no fibrinoid necrosis of the vessel walls was observed. The formation of blood clots in the microvascular vessels of the dermis may be associated with endothelial damage and dysfunction that developed against the background of SARS-CoV-2 infection. Interestingly, a greater severity of morphological changes, in particular a thicker perivascular inflammatory infiltrate, was found with a longer duration of COVID-19 in the material of those patients whose biopsies were performed later. Similar morphological changes were noted in other studies, when, as part of a histological study of maculopapular rashes induced by COVID-19 (18 observations), in all cases of skin biopsy (4 patients), a moderately pronounced lymphocytic infiltrate located perivascularly in the superficial parts of the dermis was detected [8].

Among the skin manifestations in COVID-19, acral pseudo-frostbite are of particular interest, as these changes usually develop in young patients. One study described four cases of so-called COVID fingers, or pseudo-frostbite, in children and adolescents who also had skin lesions similar to erythema multiforme [9]. Skin biopsy specimens from two patients showed morphologic features not characteristic of erythema multiforme, such as marked perivascular and perieccrine infiltrate in the deep parts of the dermis in the absence of keratinocyte necrosis. Immunohistochemical examination of both biopsy samples showed granular expression of the SARS-CoV-2 spike protein in the vascular endothelium and epithelial cells of the eccrine glands. The authors highlighted the combination of erythema multiforme and pseudo-frostbite that developed against the background of COVID-19 and the positive result of immunohistochemical studies on spike protein, indicating a direct pathogenetic relationship between erythema-like skin lesions and SARS-CoV-2 infection [9].

Ambiguous data were presented in a study by Mahieu et al. [10], which evaluated the clinical cases of 10 young patients (average age: 27 years) with acral pseudo-frostbites of the skin characteristic of COVID-19. Morphological analysis of skin biopsies in all the patients revealed perivascular lymphohistiocytic infiltrate in the superficial and deep layers of the dermis; in one case, fibrinoid necrosis of the arteriole wall of the deep layer of the dermis was detected. These changes are characteristic of COVID-associated skin lesions. Notably, in all cases, the results of polymerase chain reaction (PCR) on SARS-CoV-2 from nasopharyngeal discharge and skin samples were negative; additionally, specific antibodies (IgA and IgG) to SARS-CoV-2 were not detected. Owing to such unusual results, the author hypothesized that the skin symptoms is not induced by the virus itself, but by cytotoxic CD8+ T cells activated during inflammation, which are capable of damaging infected keratinocytes and endothelial cells [10].

Regarding the pathogenetic mechanisms of the development of pseudo-frostbites, some studies hypothesized on the immune genesis of this phenomenon. Inadequate immune activity (by the type of hyperergic reaction) associated with a cytokine storm and excessive synthesis of interferon-1a explains negative serological and PCR tests, as in this case, rapid elimination of the virus is possible without the production of antibodies detectable during tests [11].

Despite the fact that pseudo-frostbite is common in young patients, some studies reported its incidence in elderly patients. Skin manifestations similar to frostbite of the fingers, which developed as part of a PCR-confirmed COVID-19 infection, were described in an 80-year-old patient. Morphological examination of skin biopsy sample revealed weakly expressed lymphohistiocytic perivascular infiltrates in the dermis, including diffuse ones. Fibrin-like thrombi were noted in some small vessels of the dermis. SARS-CoV-2

spike protein expression was detected in a skin biopsy using fluorescent immunohistochemistry [12].

A study presented the clinical case of an 81-year-old man who had severe bilateral pneumonia with negative COVID-19 smears, but had petechial rashes on his fingers and toes (pseudo-frostbite-like) that developed into hemorrhagic blisters and necrosis after a few days. Skin biopsy revealed partial necrosis of the superficial part of the epidermis; weakly expressed inflammatory infiltrate in the papillary layer of the dermis, consisting mainly of neutrophils; extravasation of erythrocytes; and focal infiltration of the walls of blood vessels by neutrophils, which morphologically corresponds to vasculitis with damage to small vessels. No typical COVID-associated morphological changes were found in the biopsies: there were no blood clots in the vascular lumen and no lymphoid perivascular infiltrate in the deep layers of the dermis. A later test for COVID-19 showed a positive result; 17 days after the development of skin manifestations, the patient died of pulmonary complications [13].

Regarding the phenomenon of pseudo-frostbite, it is crucial to mention a study by Magro et al. [3], wherein they analyzed data from a large number of patients with COVID-19 (n = 55). All patients had skin signs that developed against the background of thrombosis of large subcutaneous arterial vessels, which was due to a generalized procoagulant condition confirmed by laboratory tests. Minimally pronounced signs of inflammation were considered to be a characteristic morphological feature of all studied skin biopsies: signs of thrombogenic vasculopathy associated with a weakly inflammatory perivascular reaction were observed [3].

It is crucial to separately highlight the cases of COVID-induced dermatologic changes, when the phenomenon of clinical mimicry was observed, with skin manifestations corresponding to a certain nosology, which was not confirmed by morphologic examination of skin biopsy. Such an observation was presented by a group of researchers led by Rodríguez-Jiménez [14], who described skin lesions resembling urticaria in a 60-year-old patient with COVID-19. The patient underwent skin biopsy, which revealed mild vacuole dermatitis of a superficial nature with rarely occurring necrotic keratinocytes and the absence of eosinophils in the inflammatory infiltrate. These morphological changes are more characteristic of erythema multiforme. Additionally, two cases of urticular vasculitis have been described in patients with asymptomatic COVID-19 infection. The clinical manifestations of the disease were similar to those of urticaria; however, morphological analysis of skin biopsies in both cases revealed an inflammatory infiltrate of perivascular localization in the form of clusters of neutrophils and leukocytoclasia, i.e., signs of leukocytoclastic vasculitis. Moreover, an immunohistochemical study revealed the presence of SARS-CoV-2 nucleocapsid in the epithelium of sweat glands, keratinocytes of the epidermis, and endothelium of small blood vessels [15].

A special group of COVID-associated skin diseases consists of patients with the clinical picture of hemorrhagic cutaneous vasculitis (hemorrhagic purpura). Notably, all the described clinical observations were morphologically confirmed leukocytoclastic vasculitis. One of the cases was presented in a study by Caputo et al. [16]: a seriously ill patient with a positive PCR test for COVID-19 was diagnosed with generalized purpura with morphological signs of leukocytoclastic vasculitis. When a skin biopsy in the superficial and deep layer of the dermis was examined, an inflammatory perivascular infiltrate consisting of neutrophils was detected, and fibrinoid necrosis of the vessel walls with extravasation of erythrocytes was noted. These changes are typical for leukocytoclastic vasculitis.

A bullous form of hemorrhagic vasculitis, which developed in an elderly 79-year-old patient against the background of COVID-19 infection, was described by Negrini et al. [17]. Interestingly, during the initial testing of a nasopharyngeal smear for COVID-19, the PCR results were negative, and only 15 days after hospitalization, after an increase in characteristic pulmonary symptoms, a positive PCR result confirmed SARS-CoV-2 infection. Ten days after the start of complex therapy, including glucocorticoids, the patient developed numerous bullous rashes on the neck and back of the hands, with no itching. Various laboratory tests were performed to rule out cystic dermatoses; all the results were normal. The accurate diagnosis was made only after a morphological analysis of a skin biopsy, which revealed a typical picture of leukocytoclastic vasculitis. Based on the results, it was hypothesized that inflammatory damage to the walls of blood vessels is one of the main pathogenetic mechanisms in the development of cutaneous manifestations of SARS-CoV-2 infection [17].

A similar case was described in an 83-year-old woman with lesions of small skin vessels in the form of palpable purple papules and blisters with serous hemorrhagic contents localized on both shins, feet, and toes and whose PCR test for SARS-CoV-2 showed a negative result. A later serological rapid test for SARS-CoV-2 antibodies (IgM and IgG) was positive. According to the results of histological examination of the skin biopsy, leukocytoclastic vasculitis was revealed with its characteristic morphological stigmas in the form of perivascular neutrophil infiltration, foci of fibrinoid necrosis in the walls of blood vessels, extravasation of erythrocytes, and necrosis of the basal layer of the epidermis. The study demonstrated that the vasculitis of small vessels of the skin found in the patient is a consequence of an immune reaction to the deposition of viral antigen; it may also be associated with damage to the endothelium as a result of the negative action of the pro-inflammatory cytokine IL-6, which is actively synthesized at the height of COVID-19 disease and activates autoimmune reactions [18].

Another study analyzed the development of hyperinflammatory shock syndrome in children with COVID-19 infection — fever associated with skin rashes, conjunctivitis,

abdominal pain, and development of hemodynamic shock with severe myocardial damage. The authors noted that in many cases, the PCR test for COVID-19 from the nasopharynx of children was negative, which made it difficult to establish the etiology of skin rashes. Moreover, they presented a detailed analysis of the clinical case of a teenager with hyperinflammatory shock syndrome, accompanied by skin lesions of the scalp in the form of moderately edematous and erythematous plaques with rapid progression to multiple-organ failure. Interestingly, repeated PCR tests for SARS-CoV-2 samples of nasopharynx, feces, and bronchoalveolar lavage were negative; however, two serological tests for IgG SARS-CoV-2 showed a positive result. Morphological examination of the skin biopsy revealed characteristic signs of leukocytoclastic vasculitis: necrosis of the epidermis and most of the dermis, perivascular neutrophil infiltration with elements of leukoclasia, extravasation of erythrocytes, and fibrin thrombi in the capillaries of the dermis. Direct immunofluorescence showed deposits of the C3b fraction of complement and IgA in the walls of arterioles in the deep parts of the dermis. Given that PCR tests for SARS-CoV-2 were negative, in this case, we can talk about the immuno-mediated pathogenesis of hyperinflammatory shock syndrome (by the type of hyperergic reaction), and not about the direct action of the pathogen itself [19].

In a previous study, Zengarini et al. investigated the morphological changes in SARS-CoV-2-induced skin rash [20]. They emphasized that in skin biopsies, the morphological picture did not fundamentally differ from that of rashes of a different viral etiology, with the exception of excessively dilated vessels of the dermis. According to the authors, this morphological feature can be considered as one of the characteristic skin manifestations of COVID-19 infection [20]. Other studies have discussed the lack of specific distinguishing features in the morphologic examination of different variations of COVID-19-associated skin rashes. A clinical case series of 28 patients with confirmed COVID-19 and various skin manifestations without specific morphological features were described. When examining skin biopsies, changes such as epidermal edema (spongiosis) with vacuolization of basal cells and perivascular lymphohistiocytic infiltrate with an admixture of neutrophils and eosinophils in the superficial parts of the dermis were found. These morphological changes can be considered typical for SARS-CoV-2-associated skin manifestations [21].

In addition to studying the morphological features of skin manifestations caused by the SARS-CoV-2 virus, studies aimed at verifying the particles of the culprit of the disease itself—the SARS-CoV-2 spike protein—including in cases wherein the PCR test was negative during the initial examination of patients. Welsh et al. [22] presented data of three patients with COVID-associated skin manifestations in the form of rashes resembling papillary rash, with a negative PCR test and negative serologic tests for SARS-CoV-2. Morphologically, in the skin biopsies of all three patients, signs that are generally characteristic of skin lesions induced by COVID-19 were found, namely, perivascular lymphocytic infiltrate in the surface layer of the dermis and erythrocyte extravasates. Immunohistochemical study detected the expression of the SARS-CoV-2 spike protein in the skin biopsies of all three patients, which confirmed the presence of a pathogenetic relationship between this infection and the development of dermatological pathology [22].

Interesting results were obtained by Liu et al. [23] when they examined autopsy skin fragments from five patients who died from COVID-19. Immunohistochemical examination revealed the expression of SARS-CoV-2 spike proteins in the vascular endothelium and in epithelial cells of sweat glands, as well as in areas of lymphocytic infiltration in the subepidermal zone and near the eccrine glands of the dermis. In addition to the defeat of the sweat glands and their ducts by the SARS-CoV-2 virus, its effect on small vessels of the dermis in the form of vasculitis with pronounced perivascular infiltration by lymphocytes and swelling of endothelial cells was determined, which is a characteristic morphological sign of COVID-associated skin diseases [23].

A study has presented an immunohistochemical assessment of the presence of SARS-CoV-2 capsid proteins in 12 skin samples of patients who died from COVID-19. In this study, it was found that a viral spike protein without viral RNA, the so-called pseudovirion, was localized in ACE2+ cells of the dermal and subcutaneous fat (hypoderm) of the microvascular network. Moreover, the expression of spike protein was detected in visually affected and visually intact skin and in the endothelium of the capillaries of the brain. Morphological examination of samples of various tissues taken during autopsy of patients who died from COVID-19 (kidney, brain, heart, skin, and liver) revealed signs of thrombosis of vessels of various diameters associated with endothelial damage, in the absence of perivascular inflammatory infiltration. The authors emphasized that, as in the case of immunohistochemical examination, damage to the microvasculature was observed not only in the areas of rashes, but also in areas where the skin looked normal [24].

Several scientific studies focused on the manifestation and exacerbation of the course of such chronic dermatoses as psoriasis, Devergy's disease, bullous dermatoses, scleroderma, and lupus erythematosus [25, 26]. However, pathomorphological examination of skin changes was not performed in all cases, and during its conduct, no specific morphological changes characteristic of viral pathology were detected. Furthermore, none of the studies performed an examination of the obtained biopsy specimens for the presence or absence of spike protein SARS-CoV-2. Conducting an immunohistochemical study in patients with chronic dermatoses against the background of SARs-CoV-2 infection should be considered as a prerequisite for determining the cause or exacerbation of skin diseases and in developing personalized approaches to the treatment of such patients.

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CONCLUSION

Based on the analysis of clinical features and morphological characteristics of skin manifestations associated with SARS-CoV-2 infection, it can be argued that patients with this pathology exhibit certain patterns of skin changes associated with damage to the endothelium of microvascular vessels and the phenomenon of coagulopathy and virus-induced activity of immunocompetent cells, primarily cytotoxic lymphocytes and NK-cells that, in some cases, cause necrotic changes in the cells of the epidermis and endothelium of the vessels of the dermis. According to various studies, severe cases of COVID-19 infection may be associated with the catastrophic damage to microvascular vessels (catastrophic microvascular injury syndrome), which developed after activation of certain complement fractions, and the associated procoagulant condition. Additionally, it should be considered that microthrombus formation during coagulopathy has a systemic character, owing to a conjugated lesion of dermal microvessels and capillaries of the interalveolar septa of the lungs, which is the target organ in SARS-CoV-2.

Detection of viral particles in the endothelium of blood vessels of skin and pulmonary capillaries in patients with COVID-19 at immunohistochemical examination confirms systematic and pattern-like morphologic changes. Thus, immunohistochemical examination of skin biopsies in patients with various forms of skin manifestations and SARS-CoV-2 infection is crucial in the diagnosis of COVID-associated dermatological pathology, especially in patients with a history of the disease and with controversial laboratory results. As for chronic dermatoses that develop against the background of SARS-CoV-2 infection, no studies that morphologically confirm the association of the skin process with the viral infection were found.

ADDITIONAL INFORMATION

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AUTHORS' INFO

*** Daria M. Martynenko;**
address: 8-2 Trubetskaya street, 119991 Moscow, Russia;
ORCID: 0000-0002-5123-6473;
eLibrary SPIN: 7402-2532;
e-mail: dariamart19@mail.ru

Lyubov O. Severgina, MD, Dr. Sci. (Medicine), Professor;
ORCID: 0000-0002-4393-8707;
eLibrary SPIN: 3343-1752;
e-mail: severgina_l_o@staff.sechenov.ru

Olga Yu. Olisova, MD, Dr. Sci. (Medicine), Professor, Corresponding member of the Russian Academy of Sciences;
ORCID: 0000-0003-2482-1754;
eLibrary SPIN: 2500-7989;
e-mail: olisovaolga@mail.ru

Tatiana A. Demura, MD, Dr. Sci. (Medicine), Professor;
ORCID: 0000-0002-6946-6146;
eLibrary SPIN: 2198-5765;
e-mail: demura_t_a@staff.sechenov.ru

* Corresponding author / Автор, ответственный за переписку

ОБ АВТОРАХ

*** Мартыненко Дарья Марковна;**
адрес: Россия, 119991, Москва, ул. Трубецкая, д. 8, стр. 2;
ORCID: 0000-0002-5123-6473;
eLibrary SPIN: 7402-2532;
e-mail: dariamart19@mail.ru

Севергина Любовь Олеговна, д-р мед. наук, профессор;
ORCID: 0000-0002-4393-8707;
eLibrary SPIN: 3343-1752;
e-mail: severgina_l_o@staff.sechenov.ru

Олисова Ольга Юрьевна, д-р мед. наук, профессор, чл.-корр. РАН;
ORCID: 0000-0003-2482-1754;
eLibrary SPIN: 2500-7989;
e-mail: olisovaolga@mail.ru

Демура Татьяна Александровна, д-р мед. наук, профессор;
ORCID: 0000-0002-6946-6146;
eLibrary SPIN: 2198-5765;
e-mail: demura_t_a@staff.sechenov.ru