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КОЖНЫЕ ПРОЯВЛЕНИЯ ПРИ КОРОНАВИРУСНОЙ БОЛЕЗНИ 2019 ГОДА (COVID-19)

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The Dermatological Manifestations in the Coronavirus Infection COVID-19

Резюме

В статье обсуждается разнообразие кожных проявлений у пациентов с новой коронавирусной инфекцией COVID-19, характеристики которых аналогичны возникающим при обычных вирусных инфекциях, а частота встречаемости определятся сопутствующей патологии и особенностей медикаментозного лечения. Выделяют несколько групп кожных проявлений в зависимости от причины и механизма развития: ангииты кожи; папуло-сквамозные сыпи и розовый лишай; кореподобная сыпь и инфекционные эритемы; папуло-везикулезные высыпания; токсидермии; уртикарные высыпания и артифициальные поражения. Многообразие клинической картины кожных проявлений коронавирусной инфекции требует глубокого анализа для правильной интерпретации и дифференциальной диагностики поражений кожного покрова при COVID-19 с другими инфекционными экзантемами и дерматозами.

Ключевые слова: *коронавирусная инфекция, COVID-19, кожные проявления, экзантема*

Конфликт интересов

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Abstract

The variety of dermatological manifestations in patients with the novel coronavirus infection COVID-19, the incidence of which depends on concomitant pathology and the characteristics of drug treatment, and their characteristics are similar to those that occur with conventional viral infections is discussed. At the present time it is proposed to distinguish several groups depending on the cause and mechanism of development: angiitis of the skin; papulo-squamous rash and pink lichen; measles rash and infectious erythema; papulo-vesicular rash; toxidermia; urticarial eruptions and artifical

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lesions. The variety of the clinical picture of the skin manifestations of coronavirus infection requires in-depth analysis in order to interpret correctly the skin lesions and other infectious exanthema and dermatoses in patients with COVID-19.

Key words: *coronavirus infection, COVID-19, dermatological manifestations, rash*

Conflict of interests

The authors declare that this study, its theme, subject and content do not affect competing interests

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Coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) spread quickly in most countries of the world and led to a pandemic [1].

A probable (clinically confirmed) case of COVID-19 includes clinical manifestations of acute respiratory infection, including the following: elevated body temperature of more than 37.5 °C and one or more symptoms (cough, shortness of breath, feeling of stuffiness in chest, sore throat, signs of nasal congestion or rhinitis, impairment or loss of smell, taste (dysgeusia), conjunctivitis, general weakness and myalgia, headache) in the presence of at least one of the following epidemiological signs: 1) return from a foreign trip 14 days before the onset of symptoms; 2) close contact over the past 14 days with a person who was monitored for COVID-19 and fell ill subsequently; 3) close contact over the past 14 days with a person with laboratory-confirmed COVID-19; 4) professional contact with persons who have suspected or confirmed COVID-19 [2].

Coronavirus is transmitted via respiratory droplets upon contact with infected people, during coughing, sneezing and talking, as well as by droplets on the surface, for example, on bedding or bathroom equipment [3].

There are now ample scientific papers describing skin manifestations associated with COVID-19. Algorithms for diagnosing dermatological symptoms have been proposed [4–6].

The variety of the clinical presentation of skin manifestations of coronavirus disease requires thorough analysis for the correct interpretation and differential diagnosis of skin lesions in cases of COVID-19 and other infectious exanthems and dermatoses. Timely identification of skin manifestations in patients with symptoms of acute respiratory diseases can make diagnostic search significantly easier [7].

Dermatological Symptoms of COVID-19

Dermatological symptoms in patients with COVID-19 are very diverse; their incidence depends on age, comorbidities and drug treatment of patients.

Recalcati S. (2020) observed skin manifestations in 18 (20.4%) of 88 hospitalized patients in northern Italy. He focuses on the fact that 60 (40.5%) out of 148 patients with a positive COVID-19 test who had already taken medications in the previous 15 days were excluded from the study beforehand [8]. Eight (44%) out of 18 patients developed exanthema with the onset of the first clinical symptoms of COVID-19, the rest – after discharge from hospital. Skin manifestations included mainly erythematous rash (14 patients); in three patients, it was in the form of generalized urticaria and vesicles similar to the signs of chickenpox. Overall, skin manifestations were most often located on the torso and were accompanied by slight itching; they disappeared within several days and had no correlation with disease severity. The authors suggested that the abovementioned symptoms were similar to those that develop in cases of conventional viral infections.

Marzona A.V. et al. (2020) described a rash similar to chickenpox rash in 12 (54.6%) of 22 patients with COVID-19. All seven patients who underwent skin biopsy showed histological results that corresponded to viral infection [9].

Other Italian authors suggested that exanthema similar to chickenpox was a rare but specific skin manifestation associated with PCR-confirmed coronavirus disease. The authors described a rash that appeared three days after the onset of specific clinical symptoms of COVID-19; it was spread across the torso, of small size, with no itching, and disappeared without scarring after eight days [10].

One also described petechial and reticular rash in patients with COVID-19: almost asymptomatic, accidentally found elements on the mucosa of cheeks, gums, in the vestibule of the oral cavity, on the mucosa of lips. Rash in the form of spots of opal-like color and small, slightly elevated papules with striae on their surface (*Wickham striae*). Rash similar to livedo, in the form of a tree branch or a fern leaf on hyperemic mucosa [7, 9, 11].

Acro-ischemia: cyanosis of fingers and toes, skin blisters and dry gangrene were described in a number of patients from the Chinese city of Wuhan with severe COVID-19 [12].

Some authors reported the development of symptoms resembling frostbite in connection with coronavirus disease ("COVID toes") [13].

Preliminary results of a systematic meta-analysis based on publications from PubMed/MEDLINE and medRxiv databases using the keywords «COVID-19», «2019-nCoV» and «coronavirus» published during the period from December 31, 2019 to May 03, 2020 revealed the following: 46 articles with a total of 998 patients from nine countries met the inclusion criteria declared in these works (confirmed novel coronavirus disease (COVID-19), skin symptoms appeared several days after the first symptoms of COVID-19). A smaller part of these articles (9) contained information on skin manifestations of COVID-19 in more than five patients in the sample. The most common skin findings were frostbite-like lesions (n = 402, 40.2%), maculopapular lesions (n = 227, 22.7%), urticaria (n = 89, 8.9%), vesicular elements (n = 64, 6.4%), livedoid and necrotic lesions (n = 28, 2.8%), and other undescribed skin elements and lesions (n = 192, 19.8%). Pain and burning were reported in at least 85 (8.5%) cases, and itching – in 256 (25.6%) patients. The prevalence of skin manifestations of COVID-19 ranged from 0.19 to 20.45% [14].

Skin manifestations of coronavirus disease are shown in Fig. 1 [15].

Like other countries, Russia has accumulated data on the prevalence and features of skin signs of COVID-19. These signs have been divided into

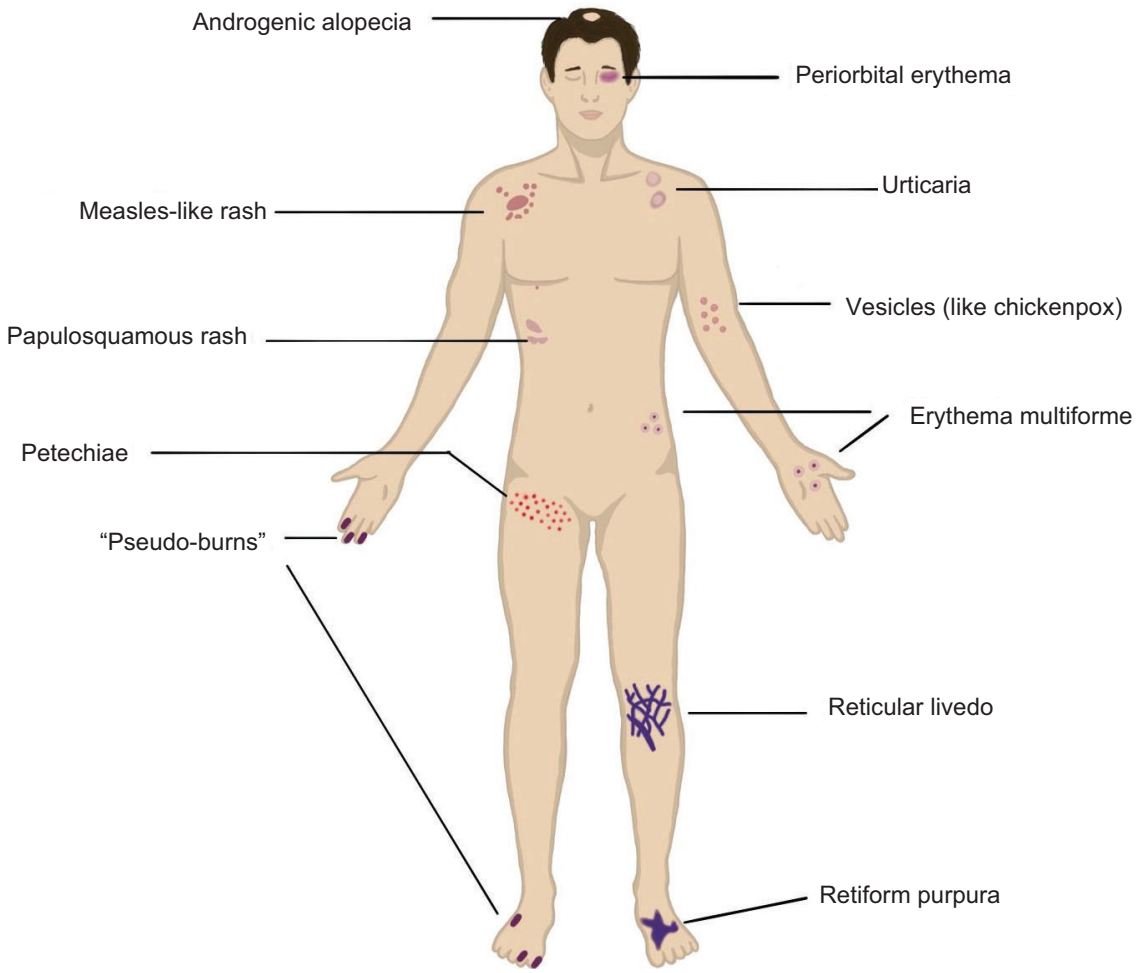

Figure 1. *Skin signs of coronavirus disease (COVID-19)*

several groups depending on their cause and mechanism of development [2]:
- skin angiites;
- papulosquamous rash and pityriasis rosea;
- measles-like rash and infectious erythems;
- papulovesicular rash;
- urticarial rash and artificial lesions;
- toxidermias.

Skin Angiites

Skin angiites, in most cases, are of infectious and allergic origin; they usually manifest in the form of acute erythema nodosum in connection with acute respiratory viral infection (ARVI). In cases of coronavirus disease, small skin vessels are also involved in the pathological process due to the deposition of circulating immune complexes in the form of deposits with viral antigens. Endothelial dysfunction, especially in older people and individuals with atherosclerotic diseases of the cardiovascular system, can aggravate the deposition process since smooth muscle cells of the middle lining of the vascular wall can produce interleukin-6, a key cytokine for the development of inflammation and cytokine storm syndrome [16]. Also, hypoxia accompanying severe disease can contribute to the development of distal angiitis – rash on distal phalanges, distal parts of the body (ears, nose, fingers), i.e., the so-called acral rash or acro-dermatitis. Such localization of rash is typically characterized by a benign course and rapid reverse development (within 2-3 weeks).
Infection-associated thrombotic and ischemic skin lesions may be caused by a direct vascular invasion of an infectious agent, vascular occlusion, or disseminated intravascular coagulation.
Casas Galvan C. et al. (2020) identified asymmetric distal erythema and swelling with vesicles or pustules that were described as of ***«pseudo-frostbite»*** type in 71 (19%) of 375 patients with COVID-19 [17].
Mazzotta F., Troccoli T. (2020) described purple erythematous lesions on the toes of a 13-year-old boy with COVID-19 that disappeared within a short period of time. The authors suggested that such skin lesions can be caused by acro-ischemia due to endothelial damage and microthrombosis caused by a viral invasion [18].
Kolivras A. et al. (2020) presented their own observation of "pseudo-frostbite" caused by COVID-19 in a patient with psoriasis [19]. These skin manifestations (purpura, reticular livedo and thrombotic and ischemic lesions) confirm the hypothesis about hypercoagulation significantly contributing to the high mortality rate in patients with COVID-19.

Papulosquamous Rash, Maculopapular Rash and Pityriasis Rosea

Dursun R. and Temiz S.A. (2020) describe an increase in the number of cases of papulosquamous rash or annular erythema during the COVID-19 pandemic; this was represented by papules and small plaques located on the shoulders, upper chest and back, less often – on the face, scalp. The rash tends to be confluent and is characterized by the absence of a "herald patch". The rash usually disappears without scars, with foci of hypopigmentation with telangiectasias or, in some cases, superficial cicatricial atrophy [20]. The authors do not exclude the contribution of the reactivation of Human Herpes Virus 6 (HHV-6) and focus on two diseases with etiopathogenesis influenced by HHV-6: Kawasaki disease and pityriasis rosea.
Many infectious diseases (infectious mononucleosis, measles, scarlet fever, herpes, hepatitis B and C, infections caused by Zika, Ebola and HIV) can be accompanied by maculopapular rash [21]. Casas Galvan C. et al. (2020) reported that maculopapular rash was observed in 18 (47%) of 375 patients diagnosed with COVID-19. Several patients showed signs of perivascular inflammation, while some had rash similar to pityriasis rosea. The authors reported that in several cases, there were infiltrating papular lesions resembling erythema multiforme [17]. Recalcati S. et al. (2020) found maculopapular rash in 14 (77.8%) of 18 patients with COVID-19, while Hedou M. et al. (2020) reported a similar rash in two patients [8, 22]. Jones V.G. et al. (2020) reported a case of Kawasaki disease in a six-month-old female patient with a positive COVID-19 test. Clinical presentation with fever, conjunctivitis, enlarged papilla of the tongue, dry and cracked lips, polymorphic maculopapular rash and swelling of limbs met the criteria for Kawasaki disease [23].

Measles-like rash and infectious erythems are similar to rash in cases of measles and other infections, which indicates common pathogenetic mechanisms of viral exanthems. A causative agent with tropism for skin and lymphatic tissue epithelium appears on the skin epithelium and in lymph nodes, and viremia usually results in exanthema [24].

Papulovesicular Rash

Skin rash can be a manifestation of bacterial (staphylococcal skin infections, gonococcal bacteremia) and viral infections (enterovirus infections, herpes simplex, herpes zoster, chickenpox, HIV, parvovirus B19). In this case, vesiculobullous and papulovesicular rash can be observed; it can be local or generalized. Extensive skin lesions characterize papulovesicular rash in patients in subfebrile condition with excessive sweating lasting many days in connection with COVID-19. Herpes simplex and herpes zoster are usually manifested by limited lesions; chickenpox usually causes a more generalized papulovesicular rash [21].

Casas Galvan C. et al. (2020) described small monomorphic vesicles located on the torso in 34 (9%) of 375 patients with COVID-19 included in the study. The authors reported that the vesicular rash did not resemble polymorphic vesicles typical of varicella [17]. On the other hand, Hedou M. et al. (2020) described the manifestations of oral herpes in an intubated patient, and Tammaro A. et al. (2020) reported herpes-related vesicular lesions localized on the torso in three patients [22, 25].

Urticarial Rash

Urticarial rash may be a premonitory symptom of COVID-19 or may appear with the first symptoms of the disease. Besides, urticaria develops with drug intolerance and can be considered a variant of toxidermia. Acral blisters in cases of COVID-19 are considered a specific symptom.

In one of the largest studies of skin manifestations of COVID-19, Casas Galvan C. et al. (2020) reported that in 71 (19%) of 375 patients, urticaria was observed, mainly on the torso; in several patients, rash was localized on the palms [17]. Recalcati S. et al. (2020) demonstrated that skin lesions were observed in 18 (20.4%) of 88 patients with COVID-19, and urticaria was found in three of them. Skin rash was localized mainly on the torso, while urticaria severity was not associated with disease severity [8]. Hedou M. et al. (2020) observed urticaria in 2 (1.9%) of 103 patients with COVID-19. One of these patients developed rash at the prodromal stage of infection [22].

Henry D. et al. (2020) found urticaria in a 27-year-old female patient with a positive COVID-19 test and with no fever; she had rash localized on the face and limbs [11]. In contrast, van Damme C. et al. (2020) reported two patients with urticarial rash spread all over the torso, with fever; these manifestations were actually the first symptoms of COVID-19 [26].

Therefore, it is obvious that urticaria can be a fairly common skin manifestation of viral infection. In this regard, during the pandemic, patients with urticaria should be carefully examined for COVID-19.

Other Causes of Dermatological Symptoms During the COVID-19 Pandemic

Lifestyle changes, including extended contact with personal protective equipment and excessive adherence to personal hygiene rules, can also cause skin lesions, for example, skin injury due to the pressure of protective equipment on the skin. It may result in contact dermatitis or urticaria [27–29]. Exacerbations of existing skin diseases such as seborrheic dermatitis, atopic dermatitis and acne are often observed.

Artificial lesions (trophic changes in facial tissues) are due to patients lying in a prone position for prolonged periods in order to improve lung ventilation. Medical workers often have skin lesions of the nose, hands, cheeks and forehead. Frequent use of hand hygiene products is associated with a higher incidence of hand dermatitis. Increased risk of Goldman-Fox syndrome is reported – «green nails» infected with pseudomonas in medical professionals with the possibility of transmitting pseudomonads to the patients [29].

Antimalarial drugs, in particular, chloroquine and hydroxychloroquine, can aggravate the severity of the manifestations of previously diagnosed psoriasis, or cause other skin reactions (onychodystrophy, discoloration of hair and skin, photosensitivity, dermatitis) [30].

Treatment of patients with COVID-19 and a history of autoimmune and chronic inflammatory diseases (especially patients with psoriasis, atopic dermatitis, connective tissue diseases and purulent hydradenitis) taking biological agents or immunosuppressants is a challenge [31].

The European Dermatology Working Group published its recommendations to continue treatment with immunomodulators for patients with COVID-19, including immunosuppressive therapy, since the exacerbation of underlying diseases in such patients can adversely affect the state of their immune system [32]. The authors of these recommendations believe that several conventional systemic immunomodulatory drugs, such as cyclosporine, can affect antiviral

immunity mechanisms. However, they warn that it is not yet known how SARS-CoV-2 affects the course of atopic dermatitis, especially in patients receiving treatment with immunomodulating agents.
The possibility of concomitant infections in the ICU should also be considered, in particular, secondary *Candida auris* [33]. Like SARS-CoV-2, *Candida auris* can be viable on surfaces made of plastic, stainless steel, copper and cardboard [34].

Toxidermias

Every year, many people worldwide develop undesirable skin reactions in response to drug treatment. Drug toxidermias are not only the most common undesirable skin reactions; they are hard to diagnose, especially at the early stages.
Toxidermia is an acute inflammatory disease of the skin and/or mucosae caused by the hematogenous spread of an allergen that enters the body by oral, inhalational, intravenous, subcutaneous, intramuscular or intravaginal routes [35].
The development and active implementation of new drugs, uncontrolled self-medication of patients, repeated courses of the same drugs – all currently observed in connection with the COVID-19 pandemic – contribute to increased drug toxidermias. Differential diagnosis of skin manifestations in cases of coronavirus disease with toxidermias in senile patients requires a thorough analysis [36]. In this regard, physicians should focus their attention on considering the possible development of undesirable skin reactions in different clinical manifestations at any time after taking a drug, or in the case of simultaneous prescription of several drugs. A physician prescribing drug treatment should consider risk factors for the development of undesirable skin reactions, including elderly age, multiple comorbidity and polypharmacy – to assess the benefit/risk ratio of previously taken and currently prescribed drugs.

Mixed Infections in Patients with COVID-19 and Exanthems

Bibliographic search by keywords «mixed infection», «Covid-19», «exanthema» in the PubMed database returned information about one clinical observation made by researchers from France and the UK [37].
A clinical case of a female patient, 18, with confirmed Dengue fever (positive laboratory result for NS1 virus antigen) and COVID-19 (PCR – gene E, RdRP gene, N gene positive) was presented. Along with intoxication, respiratory symptoms and cervical lymphadenopathy, there was a roseola-like maculopapular exanthema on the patient's torso, limbs and face that quickly developed into scarlatiniform rash. There were no areas of healthy skin, but there was a rash described as «white islands in a sea of red». No lesions of the mucosa, hands or feet were found. Itching stopped by day 10 from disease onset; there were no scratches.
Clinical symptoms of Dengue fever and COVID-19 have much in common, which makes them difficult to diagnose. The abovementioned patient had a prolonged fever, facial hyperemia, skin erythema, generalized acne, myalgia, arthralgia, retroorbital pain, photophobia, scarlatiniform exanthema and headache. Some of these symptoms are similar to those of COVID-19. Thrombocytopenia and increased liver enzymes were reported both for Dengue fever and COVID-19. Immune-mediated damage or direct cytotoxicity due to active virus replication in hepatocytes may be associated with liver damage in both Dengue fever and COVID-19. Clinical presentation may be caused by hypoxic hepatitis due to anoxia or drug-induced damage of the liver (for example, paracetamol, antiviral drugs, etc.) [38].
As for skin rash, the authors lean towards the theory that it developed due to Dengue fever since rash described as «white islands in a sea of red» is typical for this disease.
Analysis of available literature sources on the study of the relationship of exanthemas and increased immunoglobulin E level in blood serum in patients with COVID-19 revealed nothing. Only one study by C. Lucas et al. (2020), where the immune status of 113 patients with a moderate and severe course COVID-19 was analyzed, demonstrated that severe COVID-19 was accompanied by increased levels of interleukins 5, 13, immunoglobulin E and eosinophils. No information on exanthems in these patients was provided [39].
In cases of COVID-19, not only the respiratory but also the gastrointestinal tract is involved in the pathological process – and it can also be the «site of entry» for infection [40]. High expression of angiotensin-converting enzyme 2 receptors in COVID-19 was observed not only in type II alveolocytes but also in endothelial cells of arteries and veins, smooth muscles of the arterial wall, immune cells, glandular epithelial cells of the stomach, duodenum and rectum. This may cause gastrointestinal symptoms [41].

These data indicate the multifactorial nature of COVID-19, including the specific features of innate immune response and the state of hypercoagulation, damage to lung tissue, nervous and cardiovascular system, gastrointestinal tract, and syndrome of monocytes/ macrophages activation culminating in increased secretion of cytokines, leading to the exacerbation of the disease course and mortality. These general symptoms may cause skin lesions that have a polymorphic manifestation and require further study.

Conclusion

Analysis of the currently available literature revealed a limited number of studies on the association of various skin lesions with both COVID-19 and viral infections in general. However, timely detection and accurate diagnosis of skin manifestations in cases of COVID-19 can play a key role in the early diagnosis and treatment of this disease.

The American Academy of Dermatology, one of the largest dermatological organizations in the world, recently launched the much-needed COVID-19 patient registry to track skin manifestations. Careful documentation and reliable reporting of skin lesions associated with COVID-19 are necessary to improve our understanding of the epidemiology and mechanisms of manifestation of this disease. Timely diagnosis of skin manifestations, comorbidities and improvement of treatment methods will increase the level of high-quality medical care.

Author Contribution:

All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication

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