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DELAYED CUTANEOUS MANIFESTATIONS IN PATIENTS WITH COVID-19 CAUSED BY SARS-COV-2. CLINICAL OBSERVATIONS IN THE RUSSIAN FAR EAST

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ABSTRACT — Chung M. K., Zidar D. A., Bristow M. R., et al. (2021) warn that a historic pandemic due to the coronavirus disease, COVID-19, could have negative potential consequences for the cardiovascular system for millions of survivors worldwide [1]. At the present stage, mechanisms of the long-term consequences of COVID-19 disease caused by SARS-COV-2 are not studied well; any assumptions regarding to the consequences of SARS-Cov-2 are hypothetical. Therefore, long-term effects require in-depth research in the dynamics of recovery process after severe infections and rehabilitation of survivors. This will facilitate and increase the effectiveness of the treatment protocol for this disease and its complications [2]. The duration of the incubation period of the disease, the presence of sometimes not expressed or absent symptoms makes identification of the disease caused by SARS-CoV-2, COVID-19 infection, in some cases, too complicated [3]. The duration of the rehabilitation time, the complexity of pathogenetically based treatment do not yet have comprehensive information, therefore, it is difficult to resolve the issue of the timing of vaccination of patients who have recovered from COVID-19 infection. All the data obtained for each case of the disease, depending on age, the presence of concomitant diseases and individual terms of health recovery with the characteristics of complications in the late periods after recovery, has high relevance and great importance [4]. According to Wu Y., Guo C., Tang L., (2020), the excretions of recovered patients remains dangerous for others around 5 weeks after clinical recovery [5]. At the moment, there is practically no exact information about the duration and intensity of immunity in an infection caused by SARS-CoV-2 [6]. To develop protocols of COVID-19 treatment, principles and paradigms for the development of alternative effective vaccines for the prevention COVID-19 affects the health of consumers of the vaccine, which requires long-term monitoring in the post-recovery.

KEYWORDS — COVID-19, SARS-COV-2, SARS-COV-2 complications; skin rashes, endothelial dysfunction, thrombosis, fibrosis of the lung tissue, cognitive abilities, asthenia, "Covid nails".

INTRODUCTION

The analysis of the long-term consequences of COVID-19 infection in patients of the Primorsky Territory (Russian Far East) with a severe form caused by SARS-COV-2 has been performed. The late and long-term consequences of the disease in recovered patients with COVID-19 were evaluated. It was found that some patients has got complications in the function of the organ of vision, increased blood clotting. Vesicular skin rashes are observed that developed after 6 months and persist for a year. On the skin of the extremities, small blood vessels are visible, as a manifestation of dermatological disorders, which are characterized as a looped vasculature due to the capillary damage. There are complaints of problems with the cardiovascular system in the form of a rapid pulse, tachycardia. Most patients with COVID-19 have had minor or mild neurological symptoms. Some patients complained of headaches, memory impairment, increased weakness and rapid fatigue. MRI studies have shown that not all patients got recovery of lung tissue, some of them shown persistent fibrosis. In the presence of a clinical picture of lesions of the skin vessels, a clinical blood test is required to prevent thrombosis and ischemia. Obtained data expand the understanding of the pathogenesis and skin complications of COVID-19, which is necessary to improve the skills of young dermatologists and infectious disease doctors. The data can serve as a platform for the development of pathogenetically based prevention of complications of COVID-19 infection caused by SARS-COV-2.

Aim of research

The purpose of our investigation was to study and analyze COVID-19 infection complications on the

skin caused by SARS-COV-2 in a long-term period after the illness.

METHODS

The study was carried out in the dynamics of patient observation (10 men and 9 women) of older age groups receiving treatment at infectious diseases hospitals in Vladivostok, Primorsky Territory, in strict accordance with the provisions of the Helsinki Declaration (2000–2013) based on informed consent of patients. The study includes analysis of the dynamics of distant clinical manifestations development in the skin, obtained after discharge from the hospital and in the process of rehabilitation measures. The patients were on outpatient observation with monitoring of clinical complaints for 1 year after the disease. We focused on skin clinical symptoms during the development of the acute stage of infection and distant post-infectious manifestations using clinical and biochemical blood tests both in the disease dynamics and during the rehabilitation period. We further examined the data of female and male patients, according to the time of the onset of clinical symptoms after the disease, the severity of the infection. The exclusion criterion was cases of COVID-19 without complications in the form of skin symptoms, both during the acute period of infection and in the long-term period after the illness. The exclusion group included patients who had pathology of the skin and its appendages before infection with SARS-COV-2. The distribution of patients by age group is shown in Table 1.

Table 1.

Age groups (years)	Number of patients examined (absolute number)	
	Women	Men
20–39	3	3
40–59	3	3
60 and more	3	4
Total	9	10
Total number of examined patients	19	

RESULTS

As a result of patients observation admitted to a hospital in a serious condition with diagnosed pneumonia and confirmation of SARS-COV-2 etiology, complications in the form of developed local skin lesions of the upper and lower extremities were established. The ratio of the number of hemoglobin molecules to the total number of molecules in conjunction with oxygen — saturation in the acute period dropped to 80%, which corresponded to respiratory failure of the 2nd degree. In addition to complex anti-inflammatory treatment, non-invasive mechanical ventilation, oxygen therapy, and anticoagulant therapy were used.

We found that in the acute period of the disease and the long-term period after the infection, patients of older age groups with a severe level of illness (with the use of artificial lung ventilation (ALV), there were complications in the form of skin rashes. Rashes resembling herpes, on the inner surface of the palms, were observed both during the disease and in 1 year after discharge from the hospital, (Fig. 1).

In addition, on the lower extremities, local manifestations of complications were characterized by small vessels with signs of circulatory disorders. The legs usually had blue, purple (more commonly) or red linear and arborizing telangiectasias (Fig. 2).

Subcutaneous thin telangiectasias were located both protruding above the skin surface and in depth, while they were expanded by more than 0.1 and 0.2–0.3 mm. The sizes correspond to the present disruptions in all structures of the microvasculature, both in capillaries, in arterioles and venules. We also observed polymorphism of telangiectasias: arachnids - with a clearly defined center and vascular rays radiating from it (common arterial); dendritic — with a branching, tree-like structure and linear, parallel-directed vessels.

Usually there are manifestations of reticular varicose veins, but they may also indicate about changes of the hormonal (mainly estrogenic) background. The same stars and nets can be on the hands, but much less often. With such clinical manifestations, it should be borne in mind that any systemic disease can disrupt the blood circulation in the microvasculature of the skin, which can subsequently manifest itself in the form of transient anomalies in their structure and appearance.

In the group of patients during observation, there were no signs of severe lesions of the skin and its appendages, such as *cob-like nails*. Rashes similar to skin diseases of unclear etiology were not detected.

DISCUSSION

Some of the pathological manifestations could be considered the side effects of exposure to ultraviolet radiation after treatment with glucocorticoids. Perhaps, the appearance of spotted or stellate telangiectasias is a consequence of ultraviolet intolerance (photodermatitis), after the use of dexamethasone.

In contrast to the symptoms of skin pathology upon admission to the hospital COVID-19, which may result from the use of drugs for the treatment of

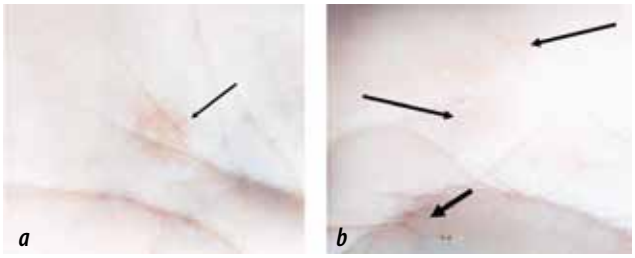

Fig. 1. 65-year-old female patient after complications of COVID-19 infection caused by SARS-COV-2 12 months after the illness.
a), b) vesicular rashes on the skin of the palms

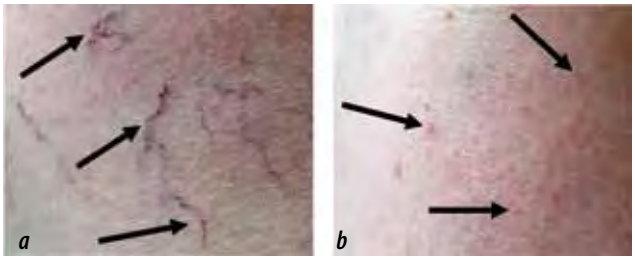

Fig. 2. 65-year-old female patient with complications of COVID-19 infection caused by SARS-COV-2 12 months after the disease.
a) capillaries of the skin of the outer surface of the thigh, telangiectasia in the form of branch-like reticules; b) the skin of the anterior surface of the leg, telangiectasia in the form of stellate mesh.

infection caused by SARS-COV-2, clinical signs of skin abnormalities in the patients appear after a few months or a year. This reflects the true state of the immune system and blood vessels of the skin, displayed without the use of medications.

Canedo-Marroquín G., Saavedra F., Andrade C. A., et al. (2020) argue that clinical symptoms may result from the migration of immune cells to the affected organs with an increased release of pro-inflammatory mediators that contribute to the development of the disease and make the immune response a major player during the development of pathological manifestations in the skin with COVID-19 [7].

Bernard I., Limonta D., Mahal L.K., Hobman T.C. (2020) note that despite the fact that COVID-19 is primarily a respiratory disease, extrapulmonary manifestations of COVID-19 include gastrointestinal, cardiovascular, renal and neurological pathology [8]. Recent studies have shown that endothelial dysfunction in COVID-19 can aggravate these deleterious phenomena, provoking inflammatory and microvascular thrombotic processes in the skin.

There is evidence that SARS-CoV-2 can infect endothelial cells by binding to the cell receptor for angiotensin converting enzyme 2 (ACE2) using the viral spike protein [9]. Accordingly, it is necessary to investigate the parameters that not only lead to severe illness in patients with COVID-19, but also to analyze how direct infection of endothelial cells with SARS-CoV-2 can further contribute to the process of circulatory disorders in various organs and skin [10, 11].

CONCLUSION

Due to the ongoing pandemic, new symptoms of multiple organ damage, including skin lesions, are emerging in the clinical symptoms of COVID-19. Monitoring studies and analysis of complications in recovered patients after infection with SARS-CoV-2 are needed, aimed at a better understanding of the epidemiology, the mechanisms of pathogenesis of COVID-19 infection caused by SARS-CoV-2. These screening studies will provide an understanding of the key issues of the pandemic impact, aimed at containing the outbreak of the disease and developing a timetable for effective preventive vaccination in recovered patients.

REFERENCES

1. **Chung M.K., Zidar D.A., Bristow M.R., et al.** COVID-19 and Cardiovascular Disease: From Bench to Bedside. Circ Res. 2021;128(8):1214–1236. doi:10.1161/CIRCRESAHA.121.31799.
2. **Halboub E.., Al-Maweri S..A., Alanazi R.H., Qaid N.M., Abdulrab S.** Orofacial manifestations of COVID-19: a brief review of the published literature.//Braz Oral Res. 2020 Oct 30;34:e124. doi: 10.1590/1807-3107bor-2020.vol34.0124.
3. **Alamri A., Oriez C., Bouilloud F., Dupuy O., Ben Hamou A.** Sudden onset anosmia and dysgeusia in two patients: An early sign of SARS-CoV-2 infection.//Presse Med. 2020 Apr;49(1):104027. doi: 10.1016/j.lpm.2020.104027.
4. **Day C.J., Bailly B., Guillon P., et al.** Multidisciplinary Approaches Identify Compounds that Bind to Human ACE2 or SARS-CoV-2 Spike Protein as Candidates to Block SARS-CoV-2-ACE2 Receptor Interactions. mBio. 2021;12(2):e03681–20. Published 2021 Mar 30. doi:10.1128/mBio.03681-20
5. **Wu Y., Guo C., Tang L., Hong Z., Zhou J., Dong X., et al.** Prolonged presence of SARS-CoV-2 viral RNA in faecal samples. Lancet Gastroenterol Hepatol (2020) 1253:20–1. 10.1016/S2468-1253(20)30083-2
6. **Prescott H.C., Rice T.W.** Corticosteroids in COVID-19 ARDS: evidence and hope during the pandemic. JAMA. 2020;324:1292–1295.

7. **Canedo-Marroquín G., Saavedra F., Andrade C.A., et al.** SARS-CoV-2: Immune Response Elicited by Infection and Development of Vaccines and Treatments. Front Immunol. 2020;11:569760. Published 2020 Dec 11. doi:10.3389/fimmu.2020.569760

8. **Bernard I., Limonta D., Mahal L.K., Hobman T.C.** Endothelium Infection and Dysregulation by SARS-CoV-2: Evidence and Caveats in COVID-19. Viruses. 2020;13(1):29. Published 2020 Dec 26. doi:10.3390/v13010029

9. **Chung J.Y., Thone M.N., Kwon Y.J.** COVID-19 vaccines: The status and perspectives in delivery points of view. Adv Drug Deliv Rev. 2021;170:1–25. doi:10.1016/j.addr.2020.12.011

10. **Recalcati S.** Cutaneous manifestations in COVID-19: a first perspective J. Eur. Acad.Dermatol. Venereol. . 2020 May;34(5):e212–e213. doi: 10.1111/jdv.16387. DOI: 10.1111/jdv.16387

11. **Fernandez-Nieto D., Ortega-Quijano D., Segurado-Miravalles G., Pindado-Ortega C., Prieto-Barrios M., Jimenez-Cauhe J.** Comment on: Cutaneous manifestations in COVID-19: a first perspective. Safety concerns of clinical images and skin biopsies.//J Eur Acad Dermatol Venereol. 2020 Jun;34(6):e252–e254. doi: 10.1111/jdv.16470.