

Clinical cases of extrapulmonary manifestations in patients with coronavirus disease (COVID-19)

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The aim of the work – to provide variants of extrapulmonary manifestations of coronavirus disease (COVID-19) based on the analysis of the relevant course of the disease in adults.

Results. The paper presents two clinical cases of coronavirus disease (COVID-19) with the manifestation of extrapulmonary symptoms, which required some individualization of therapy.

The first clinical observation showed that in a 56-year-old patient with moderate COVID-19, the development of oxygen dependence on the 8th day of the disease was combined with the manifestation of extrapulmonary symptoms in the form of cutaneous manifestations. Individualization of glucocorticosteroid therapy and endothelioprotective therapy has been shown to be effective in regressing both oxygen dependence and cutaneous vasculitis.

The second clinical observation showed that in a 35-year-old patient, moderate COVID-19 without oxygen dependence was accompanied by the development of extrapulmonary manifestations, namely short-lasting diarrheal syndrome, which manifested in the onset of the disease and of the development of orchiepididymitis on the 9th day of illness, which required the appointment of anti-inflammatory therapy.

Conclusions. The abovementioned clinical observations of COVID-19 cases show relatively rare cases of SARS-CoV-2-associated extrapulmonary manifestations in patients with moderate disease, but their development necessitated individualization of treatment.

Ключові слова:

коронавірусна хвороба COVID-19, вірусна інфекція, позалегенові прояви, лікування.

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Клінічні випадки позалегенових проявів у хворих на коронавірусну хворобу (COVID-19)

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Мета роботи – описати варіанти позалегенових проявів коронавірусної хвороби (COVID-19) на підставі здійсненого аналізу відповідного перебігу хвороби у дорослих.

Результати. В роботі наведено два клінічних випадки коронавірусної хвороби (COVID-19) з маніфестацією позалегенової симптоматики, що потребувала певної індивідуалізації терапії.

Перше клінічне спостереження показало, що в пацієнтки віком 56 років із середньотяжким перебігом COVID-19 виникнення кисневої залежності на 8 добу хвороби поєднувалося з маніфестацією позалегенової симптоматики – шкірними проявами. Виявили, що індивідуалізація лікування з призначенням глюкокортикостероїдів та ендотеліопротективної терапії виявилась ефективною щодо регресу і кисневої залежності, і шкірних проявів васкуліту.

У другому клінічному випадку показано, як у пацієнта віком 35 років середньотяжкий перебіг COVID-19 без кисневої залежності супроводжувався виникненням позалегенових проявів: ураженням кишечника, що проявилось короточасним діарейним синдромом у дебюті захворювання, та розвитком орхоепідидиміту на 9 день хвороби, яке потребувало призначення протизапальної терапії.

Висновки. Клінічні спостереження випадків COVID-19, що описали, показують відносно рідкісні випадки виникнення SARS-CoV-2-асоційованих позалегенових проявів, які виникли у пацієнтів із середньотяжким перебігом хвороби, проте їх розвиток зумовив необхідність індивідуалізації лікування.

An essential feature of the clinical course of coronavirus disease (COVID-19) is the development of extrapulmonary symptoms, which may be combined with pulmonary ones, or in cases of mild and moderate course of the disease even dominate, which can lead to late diagnosis [1]. The presence of extrapulmonary symptoms in COVID-19 is due to the presence of angiotensin-converting enzyme receptor 2 (ACE2), which uses SARS-CoV-2 to penetrate the target cell [2], not only on lung cells, but also on vascular endothelial cells, epithelial cells of the intestine,

kidneys, endocrine system, etc. [3]. It is believed that all cells in which ACE2 expression exceeds 1 % may be a target for SARS-CoV-2 virus [2]. It is assumed that certain extrapulmonary manifestations are most characteristic for non-severe COVID-19, in particular at the nervous system (anosmia, dysgeusia) [4], gastrointestinal tract (diarrhea) [5], skin manifestations [6]. Therefore, understanding by physicians of different specialties of the features of the clinical manifestation of mild COVID-19 will improve diagnostics of new coronavirus disease.

Aim

To provide variants of extrapulmonary manifestations of coronavirus disease (COVID-19) based on the analysis of the relevant course of the disease in adults.

Materials and methods

Two clinical cases of self-monitoring of mild coronavirus disease (COVID-19) with extrapulmonary manifestations were analyzed: in patient B., 56 years old and patient G., 35 years old, who were treated at the Municipal Non-Profit Enterprise "Regional Infectious Diseases Clinical Hospital" of Zaporizhzhia Regional Council (MNP "RIDCH" ZRC) in 2020 and 2021.

The diagnosis of coronavirus disease (COVID-19) was laboratory confirmed by the isolation of RNA-SARS-CoV-2 in nasopharyngeal mucus by polymerase chain reaction. The patients were treated according to the Protocol for the provision of medical care for the treatment of coronavirus disease (COVID-19) [7].

Results

Clinical observation 1. Patient B., 56 years old (inpatient card No. 62) was admitted to MNP "RIDCH" ZRC on January 11, 2021 (on the 6th day of illness) with complaints of weakness, dry cough, fever up to 37.5 °C.

From the anamnesis of the disease it became known that she fell ill on January 6, 2021 with a rise of the body temperature to 37.5 °C, the appearance of general weakness and headache. She received symptomatic treatment on the advice of a family doctor. The results of computed tomography of the chest of January 8, 2021, showed signs of bilateral polysegmental pneumonia, probably COVID one, with lung damage of 25–30 %. PCR testing of nasopharyngeal mucus for RNA-SARS-CoV-2 was performed and taking into account the positive result on January 09, 2021 (No. 817) the patient was sent to the infectious hospital.

From the anamnesis of life it became known that in November 2020 the family had patients with COVID-19. At that time, the patient was examined by contact and the result of PCR testing of nasopharyngeal mucus for RNA-SARS-CoV-2 appeared positive on Nov 22, 2020 (No. 16835), but at that time there were no clinical symptoms, indicating on the development of asymptomatic COVID-19. After 10 days, at the control, PCR test was negative. The patient was not vaccinated against COVID-19. She had grade II hypertension, for which she took antihypertensive drugs as prescribed by a cardiologist. Grade I obesity (body mass index 31.25 kg/m²) also occurred.

At hospitalization on January 11, 2021 (on the 6th day of illness) the patient's condition was moderate, body temperature was 37.4 °C, heart rate was 90 per minute, blood pressure was 130/80 mm Hg, respiratory rate was 18 per minute, oxygen saturation 98 % without oxygen support. Auscultatory areas of crepitation were heard in the lower lobes of both lungs. The laboratory examination showed no signs of absolute lymphopenia, but there were already signs of hypercoagulation, as evidenced

by an increase in fibrinogen levels at normal levels of prothrombin index (PTI) and the international normalized ratio (MNS). The presence of hyperinflammation was confirmed by an increase in the level of C-reactive protein (CRP) in 9.2 times above the upper limit of the reference value at the level of procalcitonin 0.1 ng/ml. The results of laboratory data are shown in the *Table 1*. Symptomatic drug treatment and low molecular weight heparin in a prophylactic dose were prescribed.

However, against the background of the prescribed treatment for two days of observation, negative clinical and laboratory dynamics was noted due to the increase in body temperature to 39.5 °C, increased intensity of dry cough, auscultatory increase in crepitation, shortness of breath up to 22–24 times per minute and reduction of oxygen saturation to 93–92 % on January 13, 2021 (8th day of illness), which was corrected by oxygen support with the use of oxygen concentrator at an oxygen flow of 4 l/minute to 96 %. However, according to the results of the coagulogram of January 15, 2021, progression of signs of hypercoagulation was revealed, as prothrombin index, hyperfibrinogenemia and a decrease in INR. During this period of the disease (10th day of illness) the appearance of cutaneous manifestations of vasculitis in the form of feathery rashes on the skin of the lower extremities was detected, the number of which increased the next day (*Fig. 1*). The abovementioned sign was the reason for doubling the dose of enoxiparin and the appointment of dexamethasone at a dose of 12 mg/day, the appointment of antibacterial therapy with ceftriaxone at a dose of 1.0 grams twice a day. L-arginine was also administered orally for endothelioprotection.

Against the background of the ongoing treatment, a clear positive clinical and laboratory dynamics was observed for three days, which persisted in the future. Namely, the body temperature gradually decreased with normalization on January 18, 2021 (13th day of illness), at the same time oxygen dependence disappeared, and skin signs of vasculitis began to regress. The results of biochemical studies at discharge showed normalization of coagulogram parameters, a significant reduction in CRP (*Table 1*). The patient was discharged for outpatient treatment with recommendations for continued anticoagulant therapy with enoxiparin in a prophylactic dose for two weeks.

As one can see from the above clinical example, a 56-year-old patient had coronavirus disease (COVID-19) on the background of concomitant pathology (hypertension II, obesity I) and had a moderate course with oxygen dependence on the 8th day of illness. A feature of the clinical course of COVID-19 in this patient was the appearance of cutaneous manifestations of vasculitis in the form of feathery rashes on the skin of the lower extremities with the appearance of oxygen dependence. The application of glucocorticosteroids and endothelioprotective therapy has been shown to be effective in regressing both oxygen dependence and cutaneous manifestations of vasculitis.

Clinical observation 2. Patient G., 35 years old (inpatient card No. 4395) was admitted to MNP "RIDCH" ZRC on December 3, 2020 (9th day of illness) with complaints of fever up to 39.0 °C with chills, severe weakness, dry cough, pain in the right testicle.



Fig. 1. Cutaneous manifestations of vasculitis in the form of feathery rash in an oxygen-dependent patient with COVID-19 (A – when the rash appeared; B – after a week of treatment).

Table 1. The main laboratory parameters of patient B., 56 years old in the dynamics of COVID-19

Index	Laboratory parameters of patient B., 56 years old		
	at hospitalization	at the condition worsens	at discharge
Erythrocytes	$3.9 \times 10^{12}/l$	$4.1 \times 10^{12}/l$	$4.1 \times 10^{12}/l$
Hemoglobin	110 g/l	114 g/l	113 g/l
Leukocytes	$6.7 \times 10^9/l$	$7.7 \times 10^9/l$	$9.7 \times 10^9/l$
Bands	5 %	3 %	2 %
Segments	71 %	65 %	57 %
Lymphocytes	20 %	29 %	38 %
Lymphocytes	$1.3 \times 10^9/l$	$2.2 \times 10^9/l$	$3.7 \times 10^9/l$
Monocytes	4 %	2 %	2 %
Thrombocytes	$200 \times 10^9/l$	$250 \times 10^9/l$	$292 \times 10^9/l$
ESR	26 mm/hour	27 mm/hour	29 mm/hour
Prothrombin index	109.2 %	166.8 %	104.9 %
INR	0.93	0.71	0.93
Fibrinogen	5.35 g/l	6.1 g/l	4.1 g/l
D-dimer	0.5 ng/ml	0.5 ng/ml	0.3 ng/ml
CRP	46.1 mg/l	48.2 mg/l	9.2 mg/l
AIAT activity	91.8 U	94.5 U	59.9 U
Creatinine	89.3 mmol/l	88.7 mmol/l	81.0 mmol/l
Urea	5.1 mmol/l	5.0 mmol/l	3.6 mmol/l
Glucose	4.4 mmol/l	4.8 mmol/l	5.4 mmol/l

From the anamnesis of the disease it became known that he fell ill on November 25, 2020 with a rise in body temperature to 39.0–40.0 °C, which was periodically accompanied by chills and it persisted despite taking paracetamol. In the first days of the disease, the patient noted a weakness of bowel up to 3–4 times a day without pathological impurities. Since November 27, 2020 there was a dry cough, when examined in the nasopharyngeal mucus was detected RNA-SARS-CoV-2 via PCR test (No. 1968). The family doctor prescribed ceftriaxone antibacterial therapy, but it showed no effect. Since December 03, 2020, computed tomography of the chest revealed signs of bilateral polysegmental pneumonia with a lesion of approximately 10 % of the lung parenchyma. On the same day, December 3, 2020, there was pain

in the right testicle. Due to the lack of effect from outpatient treatment, the patient was sent to hospital. In the anamnesis there are no data on the presence of concomitant pathology, body mass index 24.6 kg/m².

At the time of hospitalization to MNP "RIDCH" ZRC the patient's condition was moderate, body temperature 38.0 °C after taking antipyretics, respiratory rate – 20 per minute, oxygen saturation without oxygen support – 98 %, hemodynamics was stable. Auscultatory examination showed weakening of breathing in the lower parts of both lungs, crepitation is heard. Hyperemia of the scrotal skin, moderate enlargement and soreness of the right testicle were noted. On December 3, 2020, the patient was consulted by a surgeon, the development of right-sided orchiepididymitis was confirmed. The results of laboratory blood tests of December 03, 2020 were as follows. In the general analysis of blood the tendency to lymphopenia and the presence of thrombocytopenia. Signs of hypercoagulation were noted, as evidenced by increased prothrombin index and fibrinogen, decreased INR. Functional tests of the kidneys showed an increase in creatinine at a normal glomerular filtration rate – 69 ml/min. Acute phase indicators indicated the presence of inflammation: an increase in CRP by 6.2 times, ferritin by 1.7 times. At a normal level of procalcitonin 0.19 ng/ml. The results of the main laboratory parameters of the patient are shown in Table 2. Taking into account the established features of clinical and laboratory manifestations of COVID-19, in addition to symptomatic drug treatment, the patient was prescribed enoxiparin in a prophylactic dose, dexamethasone 16 mg per day with gradual dose reduction for a total course of 7 days, antibacterial therapy for 5 days, probiotics.

Against the background of treatment, there was a clear positive dynamics, namely during the day the level of fever decreased to subfebrile, pain in the right testicle decreased, and since December 06, 2020 (12th day of the disease) stable normothermia, no pain in the right testicle, reducing its edema and reducing the severity of hyperemia of the scrotum were recorded. Complete regression of clinical manifestations of right-sided

orchiepididymitis occurred within a week of the treatment. The results of laboratory blood tests from December 10, 2020 were as follows: recorded recovery of the absolute number of lymphocytes and thrombocytes of blood, normalization of blood creatinine, a significant reduction in CRP (Table 2). During the X-ray examination of December 11, 2020, the signs of bilateral polysegmental pneumonia with a certain positive dynamics in relation to the regression of these manifestations were preserved. The patient was discharged with improvement for outpatient treatment.

As one can be see from the abovementioned clinical example, a 35-year-old patient with coronavirus disease (COVID-19) had a moderate course with the development of bilateral polysegmental pneumonia without oxygen dependence. However, the clinical course was accompanied by the development of extrapulmonary manifestations, namely intestinal lesions, manifested by short-term diarrheal syndrome in the onset of clinical manifestations and the development of orchiepididymitis on the 9th day of illness, requiring anti-inflammatory therapy.

Discussion

To date, the direct role of the virus in the formation of skin manifestations has been proven by the detection of RNA-SARS-CoV-2 in skin cells and is explained by the expression of ACE2 receptors on cells of the basal layer of the skin [8]. Clarification of the frequency of skin manifestations, the nature of skin elements and their clinical and prognostic significance continues. References show that the frequency of registration of cutaneous manifestations vary from detection in 20.4 % of patients with COVID-19 [9] to description of individual cases [10]. And data on the nature of the rash indicate a wide range of these changes [9,11].

Our clinical observation is based on the rarity in clinical practice of cutaneous manifestations that were clearly associated with SARS-CoV-2 infection and had the appearance of feathery changes. At the same time skin manifestations appeared in moderate COVID-19 in the second week of the disease with oxygen dependence, and regression of these manifestations occurred when receiving the dynamics of regression of respiratory failure, which in our opinion was also some confirmation of their relationship with COVID-19.

Spanish study [12], which analyzed 375 cases of COVID-19 with cutaneous extrapulmonary manifestations, also confirms that the appearance of pernio-like skin changes more often, namely in 59 % of patients, appears late after the manifestation of all respiratory manifestations of the disease. The pernioid skin changes detected in our clinical observation are considered to be the most natural cutaneous extrapulmonary manifestation of COVID-19 [13]. Pathogenetic explanation of the appearance of SARS-CoV-2-associated pernio-like skin changes are tissue damage caused by the deposition of immune complexes in the walls of blood vessels, peripheral thrombotic microangiopathy due to the transmission of type 1 interferon signals and secondary ischemia due to vascular damage [14]. This is confirmed

Table 2. The main laboratory parameters of patient G., 35 years in the dynamics of COVID-19

Index	Laboratory parameters of patient G., 35 years old	
	at hospitalization	at discharge
Erythrocytes	$5.1 \times 10^{12}/l$	$5.0 \times 10^{12}/l$
Hemoglobin	151 g/l	148 g/l
Leukocytes	$5.2 \times 10^9/l$	$4.8 \times 10^9/l$
Bands	2 %	5 %
Segments	71 %	46 %
Lymphocytes	22 %	40 %
Lymphocytes	$1.1 \times 10^9/l$	$1.9 \times 10^9/l$
Monocytes	5 %	8 %
Thrombocytes	$146 \times 10^9/l$	$165 \times 10^9/l$
ESR	9 mm/hour	11 mm/hour
Prothrombin index	143.2 %	115.1 %
INR	0.79	0.89
Fibrinogen	4.1 g/l	4.0 g/l
Ferritin	423 ng/ml	–
CRP	31.1 mg/l	7.5 mg/l
Alat activity	33.3 U	–
Creatinine	139.0 mmol/l	96.0 mmol/l
Urea	7.6 mmol/l	5.6 mmol/l
Glucose	5.5 mmol/l	5.9 mmol/l

by histopathological data, namely the presence of perivascular lymphocytic infiltrate mainly CD3+/CD4+ T-cells, papillary edema, necrosis/apoptosis of epidermal keratinocytes, epidermal thrombosis and fibrin deposition [15,16].

According to the literature [17], endothelial damage is an independent predictor of unfavorable prognosis in many diseases, which necessitates timely medical correction. In clinical practice, the effectiveness of endothelioprotector based on L-arginine in the treatment of vasculitis has been proven. The L-arginine-NO pathway is thought to play a major role in maintaining normal endothelial function, inflammatory response, apoptosis, and protection against free radical damage. However, in inflammatory processes, in particular in infectious diseases, endogenous synthesis of L-arginine does not provide physiological needs [18]. Therefore, in the pathogenetic treatment of various pathological conditions accompanied by endothelial lesions, the use of L-arginine (α -amino- δ -guanidinovaleric acid) – a relatively essential amino acid, especially in pathological conditions, which is the only substrate for NO synthesis [18,19]. According to our clinical observations, individualization of pathogenetic treatment by additional administration of L-arginine to a patient with COVID-19-associated vasculitis was effective in regressing skin manifestations.

To date, there are clear reports in the references that receptor expression ACE2 is much more represented in the cells of the reproductive system of men than women [20–22]. Yes, low receptor expression of ACE2 was found on ciliated and endothelial cells of the fallopian tube, endometrium, ovaries, cervix and vagina [20,21]. However, a high level of receptor expression ACE2 on Leydig and Sertoli cells has been noted, as well as moderate expression on glandular testicular cells [20,22]. Studies [23,24] demonstrated the presence of functional changes in the male reproductive system, which was

manifested by a decrease in the amount of testosterone in combination with an increase in luteinizing hormone in both severe and moderate COVID-19 cases.

It is believed that viruses that can infect the male reproductive system can cause orchitis, in particular during the SARS-CoV epidemic orchitis has been described in severe coronavirus infection [25]. With the deepening of knowledge about the extrapulmonary manifestations of COVID-19, studies have emerged that show the presence of discomfort in the scrotum in 19 % of patients, the intensity of which resembled orchitis [26]. Even an atypical course of COVID-19 in a 42-year-old patient with a predominance of weakness, abdominal and scrotal pain without respiratory symptoms has been described [27]. In this case, the predominance of extrapulmonary symptoms led to hospitalization of the patient in a non-infectious department, but the examination confirmed COVID-19 and computed tomography revealed signs of pneumonia with the presence of foci of infiltration type "frosted glass", and the phenomenon of colitis of the sigmoid colon and descending colon was not excluded [27]. In the described clinical case, a patient with moderate COVID-19 who was not accompanied by oxygen dependence, but in the second week of the disease developed extrapulmonary symptoms, namely orchiepididymitis, which required hospitalization and appropriate individualization of therapy. The references present a small number of pathomorphological results of autopsy of gonadal tissues in deaths due to COVID-19, and their results confirm the connection with infection. In the study [28] on the basis of pathomorphological examination of testicular tissue in 12 deceased damage to the seminal tubules, a significant decrease in the number of Leydig cells and the presence of signs of mild lymphocytic inflammation with the presence of T-lymphocytes in infiltrates was noted.

Conclusions

1. These clinical observations of COVID-19 cases show relatively rare cases of SARS-CoV2-associated extrapulmonary manifestations in patients with moderate disease, but their development necessitated individualization of treatment.

2. Expanding knowledge about the features of the clinical manifestation of extrapulmonary manifestations of COVID-19 will allow general practitioners to improve diagnostics of the disease and timely individualization of treatment.

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