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Patient with Jaundice, Dyspnea and Hyperferritinemia after COVID-19

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The aim: to highlight the importance of considering hemophagocytic lymphohistiocytosis in patients with jaundice of unclear origin and systemic inflammatory manifestations after coronavirus infection.

Key points. A 64-y.o. patient was admitted to the hospital with jaundice, pruritus, fatigue, weight loss. The complaints occurred 2 weeks after discharge from the hospital for treatment of patients with coronavirus infection. Laboratory tests revealed signs of hepatic insufficiency, markers of cholestasis and inflammation persisted in time. Upon instrumental examination no signs of hepatosplenomegaly, biliary tree changes, intra- and extrahepatic obstruction were found. S. aureus was identified in blood cultures, CT scan of the facial skull bones showcased the focus of infection in the area of the roots of teeth 2.4 and 2.5. Therefore, antibiotics were prescribed. Subsequently, the patient's condition was complicated by the development of two episodes of acute respiratory distress syndrome, which occurred during the withdrawal of glucocorticosteroid therapy. Liver biopsy was performed, morphological study revealed signs of "vanishing bile duct" syndrome, excessive activation of macrophages and hemosiderosis of sinusoidal cells. Identified lesions can be found in hemophagocytic lymphohistiocytosis (HLH), a life-threatening complication of coronavirus infection. Glucocorticosteroids therapy, transfusions of human immunoglobulin, albumin, and parenteral nutrition have led to patient's condition improvement.

Conclusion. COVID-19 provokes the development of secondary HLH 10 times more often than other respiratory viral infections. The possibility of hemophagocytic syndrome development should be considered, including cases of overlap syndrome with sepsis, in patients with unresolved jaundice, hyperferritinemia after coronavirus infection. Routinely used scales and criteria for diagnosis of HLH (H-score, HLH 2004) in such cases lacks sensitivity, therefore, careful analysis of clinical picture and exclusion of other causes of jaundice are required.

Keywords: COVID-19, SARS-CoV-2 infection, hemophagocytic lymphohistiocytosis, HLH, H-score, HLH 2004, "vanishing bile duct" syndrome

Conflict of Interest: the authors declare no conflict of interest.

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Желтуха, одышка и гиперферритинемия у пациентки, перенесшей COVID-19

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Цель представленного клинического наблюдения: продемонстрировать необходимость включения в круг дифференциального диагноза гемофагоцитарного лимфогистиоцитоза у пациентов с желтухой неясного генеза и системными воспалительными проявлениями после перенесенной коронавирусной инфекции.

Основные положения. Пациентка обратилась в клинику с жалобами на желтуху, интенсивный кожный зуд, выраженную общую слабость, потерю веса. Жалобы возникли через 2 недели после выписки из стационара для лечения пациентов с коронавирусной инфекцией. Лабораторно выявлены признаки печеночной недостаточности, в динамике отмечалось персистирование маркеров холестаза и воспаления. По данным инструментального обследования признаков гепатоспленомегалии, изменений билиарного дерева, внутри- и внепеченочной обструкции не выявлено. При посеве крови выявлен *S. aureus*, по данным КТ костей лицевого черепа — очаг инфекции в области корней зубов 2.4 и 2.5, что послужило основанием для назначения антибактериальной терапии. В дальнейшем состояние пациентки осложнилось развитием двух эпизодов острого респираторного дистресс-синдрома на фоне отмены терапии глюкокортикостероидами. Проводилась биопсия печени, при которой выявлены признаки синдрома «исчезающих желчных протоков», чрезмерной активации макрофагов и гемосидероза клеток синусоидов. Подобная картина характерна для гемофагоцитарного лимфогистиоцитоза (ГЛГ), грозного осложнения коронавирусной инфекции. Терапия глюкокорти

костероидами, трансфузии человеческого иммуноглобулина, альбумина, парентеральное питание привели к улучшению состояния пациентки.
Заключение. COVID-19 в 10 раз чаще других респираторных вирусных инфекций провоцирует развитие вторичного ГЛГ. Следует помнить о возможности развития гемофагоцитарного синдрома, в том числе в составе синдрома перекреста с сепсисом, у пациентов с неразрешающейся желтухой, гиперферритинемией после перенесенной коронавирусной инфекции. Рутинно применяемые шкалы и критерии диагностики ГЛГ (H-score, HLH 2004) в ситуации после перенесенной коронавирусной инфекции не обладают достаточной чувствительностью, в связи с чем необходим тщательный анализ клинической картины, исключение других причин желтухи.
Ключевые слова: COVID-19, инфекция SARS-CoV-2, гемофагоцитарный лимфогистиоцитоз, ГЛГ, H-score, HLH 2004, синдром «исчезающих желчных протоков»
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A 64-y.o. female patient was admitted to the Department of Hepatology of the Clinic of Internal Medicine, Gastroenterology and Hepatology of Seche-nov University. Her main complaints were jaundice (yellowing of the skin and sclerae), intense pruritus that disturbs sleep, fatigue, 11 kg weight loss for the last 3 months. According to patient's medical history, she was hospitalized with COVID-19 infection, which proceeded with the development of bilateral multisegmental viral pneumonia of moderate severity (CT-2) and a "cytokine storm". In accordance with the temporary guidelines for the prevention, diagnosis, and treatment of coronavirus infection, glucocorticosteroid therapy (dexamethasone 20 mg intravenously daily with gradual reduction to 4 mg), anticoagulants (apixaban 2.5 mg twice a day), and biological therapy with IL-6 blocker (olokizumab 128 mg intravenous once a day) were prescribed. As soon as clinical improvement was achieved, patient was discharged from the hospital and glucocorticosteroids therapy was continued (prednisolone 10 mg orally with a reduction in the dose by 5 mg per week). In two weeks, patient's skin and sclerae suddenly turned yellow, her urine became darker and her stools -lighter, pruritus occurred and she was admitted to the hospital. Her blood tests revealed conjugated hyperbilirubinemia (total bilirubin 308 umol/l, direct bilirubin 226 umol/l), elevated cholestasis (ALT 705 u/l, GGTP 737 u/l, total cholesterol 13 mmol/l) and cystolysis (ALT 306 units/l, AST 146 units/l) markers. Further examinations excluded viral hepatitis (markers of HCV, HBV, HAV, HEV were not found), HIV-infection, autoimmune liver diseases, CA 19-9, AFP, REA, CA 125 — their values were within the reference interval. According to the results of instrumental examination (abdominal ultrasound, contrast enhanced CT scan of abdomen) no signs of organomegaly, neoplasms, dilation of intra- and extrahepatic bile ducts, extrahepatic biliary obstruction were found.

Detoxification therapy (thioctic acid, reamberine), therapy with glucocorticosteroids (dexamethasone 20 mg intravenously with gradual reduction to 4 mg) were conducted. Despite the therapy, the patient's condition deteriorated and she was transferred to another hospital for further examination and plasmapheresis: According to abdominal MRI with CT-scan there were signs of diffuse changes of liver parenchyma, polyp of gallbladder. No changes of bile ducts, signs of biliary hypertension were revealed. At the same time, laboratory signs of cholestasis and cytolysis kept on increasing. The patient's condition was regarded as nonspecific reactive hepatitis of high activity. Therapy with glucocorticosteroids (prednisolone 120 mg intravenously with a gradual reduction to 30 mg), S-adenosylmethionine therapy, plasmapheresis was conducted, without significant effect: jaundice remained, pruritus was worsening.

Anamnesis vitae: patient was born in 1957, grew and developed with no delay. The patient has higher education; she was retired at the time of the anamnesis collection, and had no previous occupational hazards. She reported no harmful habits. Gynecological history: 1 pregnancy, 1 delivery. Menopause from the age of 55. The patient did not receive any hormonal replacement therapy. She did not have any allergy. Patient had a family history of oncological disease: patient's sister had breast cancer. Associated diseases: chronic periodontitis, arterial hypertension, stage II, grade 2. The patient had the tendency for hypotension since the disease onset, for that reason she discontinued hypotensive therapy. Previously she took valsartan, indapamide.

Upon objective examination: Condition of moderate severity. The skin was jaundiced and dry. Abdomen and chest skin had red spots left

after scratching not disappearing on pressing. BMI = 20.31 kg/m^2. Body temperature 36.5 °C. Peripheral lymph nodes were not enlarged. Slight swelling of the lower extremities and feet. By auscultation, breathing was vesicular, no rales, respiratory rate was 17 per minute. Clear heart tones, soft systolic murmur at the apex, heart rate 73 beats per minute, blood pressure 100/60 mm Hg. The abdomen was soft and symmetrically involved in the act of breathing by all parts. On superficial and deep palpation, the abdomen was soft and painless. Liver size appeared normal, 10–8–7 cm according to Kurlov. The lower edge of the liver wasn't palpable. Spleen size was 9 cm by percussion, the lower pole wasn't palpable. The symptom of "tapping" on the lumbar region was negative on both sides, no dysuric phenomena, urine was dark. Stool was clear, light, without pathological impurities, regular.

Despite the fact that clinical (light stool staining, dark urine staining) and laboratory data (hyperbilirubinemia predominantly due to direct fraction) indicated obstructive character of jaundice, results of instrumental investigations showed no signs of neoplasms of liver and bile ducts, including malignancy, cholecystolithiasis and choledocholithiasis, cholangitis, abscesses, pancreatitis. The first step of differential diagnosis of liver injury with cholestatic phenotype primarily included causes of nonobstructive cholestasis. Thus, drug-induced liver damage was considered, since two weeks prior jaundice manifestation olokizumab was administered. So CIOMS/RUCAM scale value was calculated: the sum was five, indicating a possible drug-induced liver injury [1]. In an in vitro study on cryopreserved human hepatocytes, olokizumab had an inhibitory effect on bile acid transporter NTCP (Na^+-taurocholate cotransporting polypeptide) activity [2, 3]. Such transporter protein block could serve to cholestasis development. In addition, cholestasis could be caused by sepsis, especially considering existed risk factors: long-term immunosuppression (use of glucocorticosteroids, IL-6 blocker) and long-term stay in different hospitals.

General blood examination revealed leukocytosis (WBC 16.8×10^9/l) with a predominance of neutrophilic leukocytes (neutrophils 13.9×10^9/l (82.8 %)), signs of mild normochromic anemia (Hb 95 g/l) and a significant increase in ESR (Westergren ESR 110 mm/h). At the same time biochemical blood test showed significant increase in the level of total bilirubin, mainly due to conjugated fraction (total bilirubin 601 umol/l, direct bilirubin 384 umol/l), markers of cholestasis (GGTP 1100 u/l, ALT 685 u/l, bile acids 296 umol/l, total cholesterol 30.1 mmol/l) and transaminases (ALT 886 u/l, AST 610 u/l).

R-value is widely mentioned in literature and used to determine the type of liver damage [4, 5]. R = [(ALT level : ALT ULN) : (ALT level : ALT ULN)], where ULN is the upper limit of normal. The R- value was more than 5, which indicates hepatocellular type of damage, but in combination with skin pruritus and elevation of ALP it is considered a mixed type, i.e. combination of hepatocellular and cholestatic patterns.

Increased level of inflammatory response markers (C-reactive protein 13 mg/L, ferritin > 1500 ng/mL, procalcitonin 2 ng/mL, triglycerides 6.19 mmol/L, fibrinogen 8.17 g/L (other coagulogram parameters without deviations from normal values) and hypoalbuminemia (albumin 26 g/L) were also noteworthy.

The laboratory signs of systemic inflammatory response syndrome, anemia, hyperbilirubinemia and hypoalbuminemia provided strong evidence in favor of sepsis, but other signs of its presence had to be carried out.

Ultrasound examination of the abdomen revealed signs of diffuse changes in the liver and pancreas. Size of the liver and spleen were within normal values. According to contrast enhanced CT-scan of the abdomen, the sizes and positions of the organs were unchanged. Signs of moderate steatosis of the liver, small polyps of the gallbladder. No signs of bile ducts distention were revealed. For further assessment of the liver parenchyma and bile ducts condition contrast enhanced (primovist) MRI (fig. 1A) and MRCT (fig. 1B) were performed: no focal changes, biliary tree contrasting defects were revealed. However, there was a delayed excretion of contrast into bile ducts. Esophagogastroduodenoscopy showcased a picture of superficial gastritis. Echo-cardiography was performed for the purpose of signs of infectious endocarditis detection: no signs of hemodynamically significant changes of the valve apparatus, no vegetations of the heart valves were revealed.

Later new complaints occured: pain in the region of the upper jaw, which intensified while eating, discomfort in the chest on the right side. The occurrence of new complaints was accompanied by an episode of fever up to 38.2 °C. This has led to necessary follow-up examination: a CT scan of the chest revealed a picture of bacterial pneumonia on the left side and a CT scan of the cranial bones (Fig. 2) revealed a nidus of chronic infection in the area of the roots of teeth 2.4 and 2.5 (the area of premolars of the right side of the upper jaw). Blood culture came out positive:

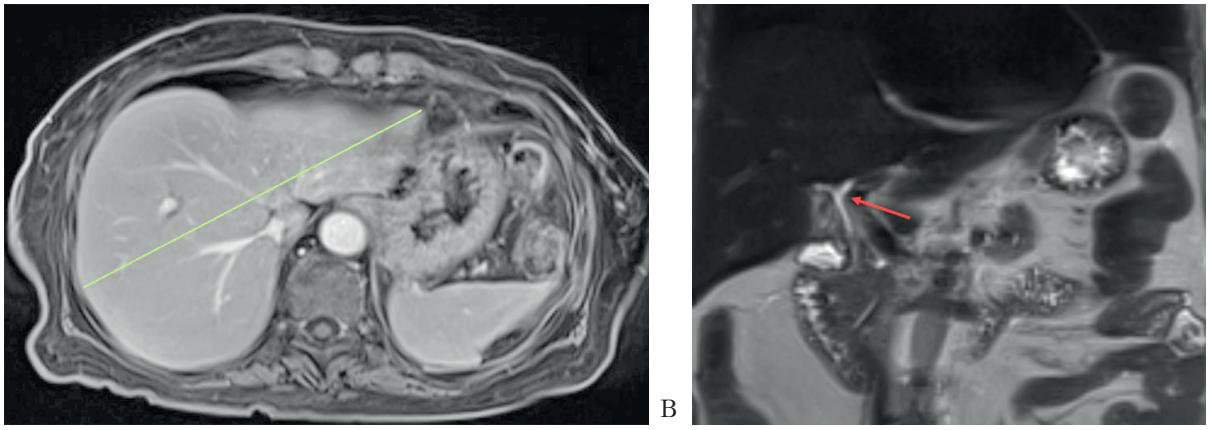


Fig. 1. Contrast enhanced MRI of the abdomen: The liver (oblique size up to 14 cm) and spleen are not enlarged. No excretion of contrast agent into the bile ducts and gallbladder lumen was obtained in the hepatospecific phase 18 min after the contrast agent injection (A). MRCP. Common bile duct is up to 5 mm, contrasts evenly. Intra- and extrahepatic bile ducts are not dilated (red arrow: common bile duct and lobe ducts) (B)

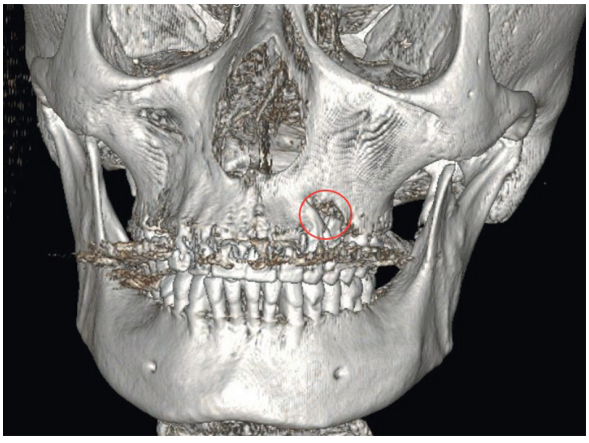


Fig. 2. CT scan of the facial skull bones. Marked area: round-shaped bone thinning revealed in the 2.4, 2.5 teeth root area, — nidus of chronic infection

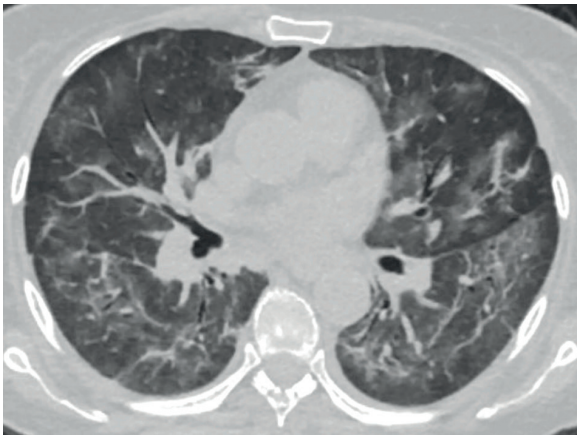


Fig. 3. CT-scan of the chest. Polymorphic areas of «ground glass opacity» and reticular changes with indistinct contours in both lungs, with predominantly central distribution. The cumulative lesion volume is 26–50 % on both sides

Staphylococcus aureus (MSSA, VSSA) was detected.

Identification of infection foci in the upper jaw region, positive blood culture in combination with signs of organ dysfunction (hyperbilirubinemia, hypoalbuminemia were considered as liver failure markers) and systemic inflammatory response syndrome denoted sepsis as one of the causes of cholestatic liver damage. In the study of J.M. Bender et al. [6], the development of jaundice in patients with coronavirus infection was associated primarily with sepsis, as well as "hyperinflammatory" syndrome and ischemic liver damage. The presence of jaundice was associated with more severe course of the infectious disease and higher mortality rate.

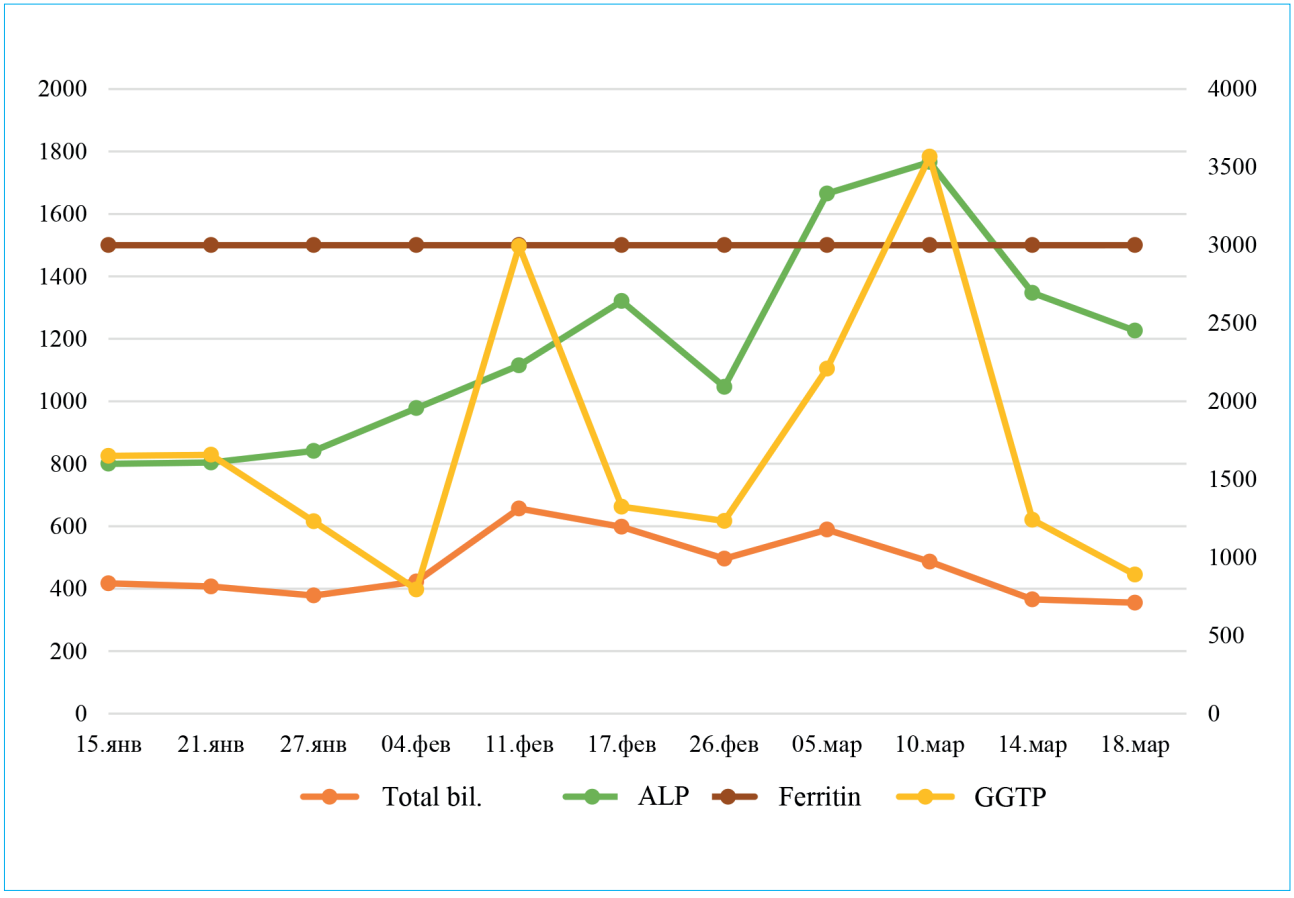
Patient was prescribed broad-spectrum antibacterial drugs in accordance with pathogen and results of antibiotic sensitivity testing: piperacillin/tazobactam and vancomycin. At the same time, surgical sanitation of the focus of infection of the upper jaw was carried out and prednisolone was completely abolished. Ongoing treatment allowed to achieve positive dynamics: pain in upper jaw, discomfort in the chest ceased to disturb, the patient's skin acquired a lighter shade, body temperature normalized, the laboratory tests noted a decrease in markers of cholestasis and inflammation. However, the dynamics were limited: the initial decrease in values of cholestasis markers

stopped at the level of total bilirubin 345 umol/l, ALP 603 u/l, GGTP 406 u/l, and there was no further normalization of values. At the same time, the level of ferritin, triglycerides remained significantly elevated, procalcitonin level remained elevated.

Subsequently, the course of the disease was complicated by the development of an episode of dyspnea of a mixed character, dry cough. On objective examination the respiratory rate was 23 per minute, saturation was reduced to 86 %. According to chest CT (Fig. 3): interstitial changes of the "ground glass opacity" type were revealed, with predominantly central distribution. At the same time, PCR results showed no SARS-CoV-2 coronavirus RNA.

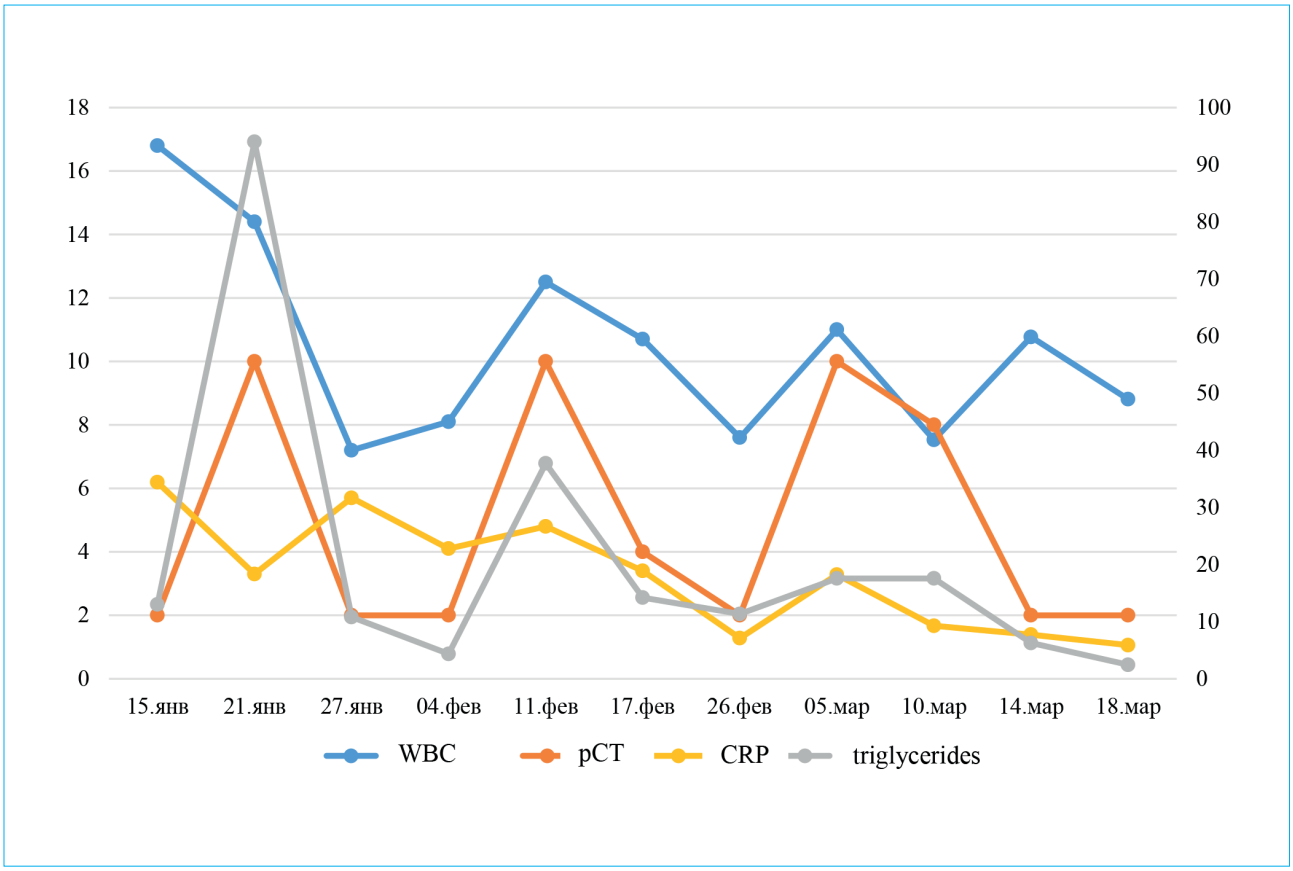
Morphological substrate of radiological "ground glass opacity" syndrome implies the appearance of exudate and/or transudate in pulmonary interstitium and partially alveolar spaces. Acute development of such changes is most often associated with pulmonary edema, acute respiratory distress syndrome, viral pneumonia [7, 8]. Taking into account acute onset, predominantly central location of "ground glass opacity" type changes on CT-scan and negative results of pharyngeal and nasopharyngeal smears, the patient's condition was considered as acute respiratory distress syndrome (ARDS).

This condition was preceded by discontinuation of glucocorticosteroids, and elevation of



	15 jan.	21 jan.	27 jan.	04 feb.	11 feb.	17 feb.	26 feb.	05 march	10 march	14 march	18 march
Total bil., umol/l	417	407	378	423	656,7	598	496	589.1	486.6	365.8	355.1
ALP, u/l	1650	1657	1231	795	2994	1325	1234	2209	3566	1241	890
GGTP, u/l	800	804	841	978	1115	1321	1046	1665	1766	1347	1226
Ferritin, ng/mL	1500	1500	1500	1500	1500	1500	1500	1500	1500	1500	1500

Fig. 4a. Laboratory parameters during follow-up: cholestasis markers and ferritin



	15 jan	21 jan	27 jan	04 feb	11 feb	17 feb	26 feb	05 march	10 march	14 march	18 march
WBC, 109/l	16.80	14.40	7.20	8.10	12.50	10.70	7.60	11.00	7.53	10.77	8.81
pro-CT, ng/ml	2	10	2	2	10	4	2	10	8	2	2
CRP, mg/l	13.00	94.00	10.80	4.35	37.70	14.20	11.34	17.57	17.57	6.26	2.44
triglycerides, mmol/l	1500	1500	1500	1500	1500	1500	1500	1500	1500	1500	1500

Fig. 4b. Laboratory parameters during follow-up: inflammatory markers

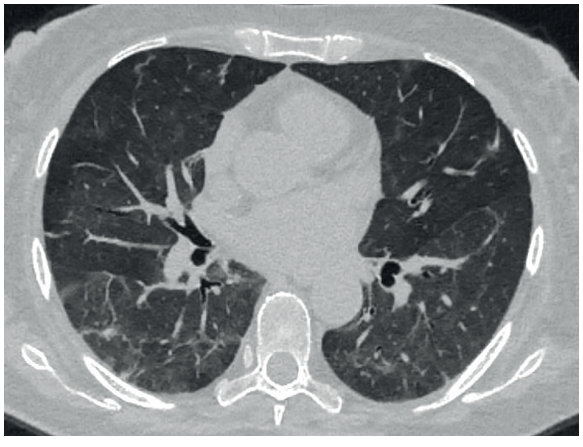


Fig. 5. CT-scan of the chest. Reduction of previously identified lesions

inflammatory markers and cholestasis in blood tests (Fig.4A and 4B).

The patient was administered intravenous dexamethasone in a daily dose of 16 mg, and oxygen therapy was initiated. Given measures had led to a rapid improvement of the patient's condition: dyspnea decreased, saturation was 98 % without oxygen insufflation, CT-scan (Fig. 5) showed resolution of previously identified changes. Upon the next glucocorticosteroid therapy withdrawal, similar episode of ARDS with cholestasis escalation developed. At the same time, patient remained anorexic and continued to lose weight.

The patient was administered intravenous dexamethasone in a daily dose of 16 mg, and oxygen therapy was initiated. Given measures had led to a rapid improvement of the patient's condition:

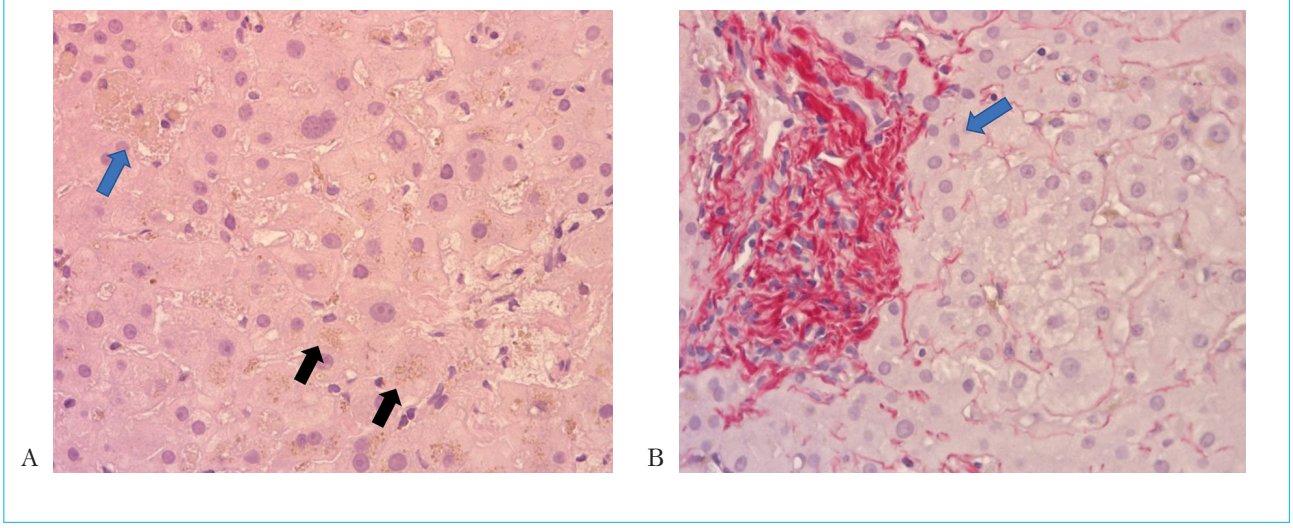


Fig. 6. Morphological examination. Liver biopsy. Staining: hematoxylin-eosin. Magnification ×200. Significant focal bilirubinostasis: majority of hepatocytes cytoplasm contain greenish brown round granules (black arrows), most likely, bilirubin; there are bile plugs in some irregularly dilated Gering tubules. Focal clusters of Kupffer cells filled with ceroid, stained with bilirubin, formed focal clusters similar to small macrophage granulomas — phagocytomas (blue arrow) (A). Morphological examination. Liver biopsy. Staining: picrosirius. Magnification ×200. Vanishing bile ducts syndrome: 8 of 10 portal tracts (blue arrow) missing bile ducts (B)

dyspnea decreased, saturation was 98 % without oxygen insufflation, CT-scan (Fig. 5) showed resolution of previously identified changes. Upon the next glucocorticosteroid therapy withdrawal, similar episode of ARDS with cholestasis escalation developed. At the same time, patient remained anorexic and continued to lose weight.

Sudden development of respiratory failure simultaneously with escalating cholestasis on the background of ongoing antibiotic therapy, that was previously effective, rapid regression of symptoms after the administration of glucocorticosteroids and the remained increase in inflammatory markers put upon inquiry that sepsis is the only factor determining patient's condition. Secondary hemophagocytic lymphohistiocytosis (HLH) could be another contributing factor. It is caused by immune response regulation disorder in genetically predisposed individuals, which occurs when exposed to a trigger (in particular, coronavirus infection), leading to uncontrolled activation of cytotoxic T lymphocytes and macrophages and, consequently, to severe inflammatory organ damage [5, 9]. It should be kept in mind, that sepsis, COVID-19 infection and HLH are united by a common link in the pathogenesis — "cytokine storm". The latter leads to ARDS and acute liver damage. Moreover, according to a number of authors, coronavirus infection can lead to the development of "HLH-sepsis" overlap syndrome. Making a differential diagnosis between sepsis and overlap syndrome is challenging: signs of HLH may occur in patients with sepsis, and conversely, sepsis may develop in the initial stages of HLH [10, 11]. The H-score and HLH 2004 scales are used to verify the diagnosis. In addition to clinical and laboratory criteria, both include an important feature — signs of hemophagocytosis or macrophage activation syndrome on morphological examination of either bone marrow or lymph nodes and spleen. These changes can also occur in the liver [12, 13].

On the following stage bone marrow biopsy and liver puncture biopsy were performed to clarify the diagnosis. According to the results of morphological examination of the bone marrow the picture corresponded to secondary changes, no signs of macrophage activation syndrome were found. Morphological examination of liver biopsy, in turn, showed the following (Fig. 6A and 6B): (1) many Kupffer cells were significantly enlarged in size, had "frothy" appearance of cytoplasm, others were filled with brownish ceroid and with signs of fat dystrophy. Focal clusters of Kupfer's cells filled with ceroid stained with bilirubin formed clusters similar to small macrophage granulomas — phagocytomas; (2) signs of marked focal-spread bilirubinostasis: cytoplasm of many hepatocytes, contained greenish-brown rounded granules of bilirubin; in some irregularly dilated Gering tubules bile plugs of different

color and structure were recognized, indicating recurrent episodes of bilirubinostasis. Bile ducts were absent in 8 of 10 portal tracts, the remaining tracts contained structures resembling small deformed ducts. Upon additional immunohistochemical study (CK7 staining): there were no CK7-positive cells in portal tracts of liver, that confirmed "vanishing bile duct syndrome" suspected by histological study; (3) the picture of moderate hemosiderosis of sinusoid walls cells, that can be observed in intravascular hemolysis and hemophagocytosis episodes.

The syndrome of "vanishing bile ducts" detected by histological and immunohistochemical study is a rare phenomenon, which is characterized by obliteration of small bile ducts and gradual development of biliary cirrhosis [14]. Most commonly this syndrome develops as a result of drug-induced liver injury caused by various antibiotics, anticonvulsants, NSAIDs, biological therapy, to which olokizumab is related [15]. Nevertheless, the drug has a high safety profile, among adverse reactions related to liver and bile ducts only an increase in transaminases was registered, and there was the only administration. In addition, duct vanishing has been observed in paraneoplastic syndrome, autoimmune liver disease, graft-versus-host reaction, HIV-infection, and histiocytosis [14, 16]. In HLH cytokine-mediated (IL-1, IL-6, TNF-α) activation of Kupffer cells and lymphocytes leads to bile duct damage. Signs of hemosiderosis of sinusoid cells are another sign of HLH [16]. Excessive activity of macrophages, not only could be due to macrophage activation syndrome, a hallmark of HLH, but also to bilirubin phagocytosis. After conjugation in hepatocytes a portion of bilirubin had entered the remaining few bile ducts, and the excess had led to hepatocyte destruction.

Taking into account clinical, laboratory and instrumental data, H-score was calculated: the result was 136 points (long-term immunosuppression, hyperferritinemia, hypertriglyceridemia, AST elevation and histological examination data contributed to the final result), which corresponds to 9–16 % probability of HLH.

A legitimate question arose: why was the total H-score only 136 and why were some clinical signs absent? It turned out that hemophagocytic syndrome developed as a result of COVID-19 infection has its own features. Thus, the most common symptoms are hyperferritinemia, AST elevation, fever, hypertriglyceridemia, thrombocytopenia and splenomegaly. In most cases, patients had less than 130 H-score points [17].

Clinical diagnosis was the following:

Underlying disease: co-morbidities: 1. Severe cholestatic hepatitis: "vanishing bile ducts" syndrome 2. Post-COVID-19 hyperinflammatory syndrome: secondary hemophagocytic lymphohistiocytosis (H-score = 136 points). Background: new coronavirus infection COVID-19 in october 2021, treated with glucocorticosteroids and IL-6 inhibitor. Complication of underlying disease: Sepsis (*S. aureus* MSSA, VSSA). Odontogenic infection (surgical sanation of the oral cavity). Left-sided bronchopneumonia in S1–S2. Multiple organ failure: liver failure: hypoalbuminemia. Acute respiratory distress syndrome. Respiratory failure I–II st. Normochromic anemia of moderate severity. Severe protein-energy deficiency of the mixed type.

After resolution of bacterial pneumonia, sanation of foci of infection, antibacterial therapy was discontinued. Therapy with glucocorticosteroids (dexamethasone 8–16 mg/day), ursodeoxycholic acid (15 mg/kg of body weight), transfusion of human immunoglobulin (0.5 g/kg weight No. 2), albumin (20 % 100.0), correction of fluid and electrolyte imbalance, protein and energy deficiency (parenteral nutrition Kabiven), plasmapheresis sessions were continued. Conducted complex of therapeutic measures allowed achieving positive dynamics: the patient noted an improvement in general well-being, increased tolerance to physical exertion, began to gain weight. Laboratory tests showed a decrease in bilirubin, GGTP and ALP levels. Albumin level remained within the normal range. Despite the remained elevated level of ferritin, C-reactive protein and triglycerides gradually decreased to normal levels.

Discussion

Changes in laboratory liver function tests are often found in COVID-19 infection: in the initial stages, elevation of transaminases (ALT, AST) due to ischemic hepatocellular damage occurs most often; in later stages, especially in patients with severe course of infection, cholestatic pattern prevails. The latter is closely associated with increasing inflammatory markers, indicating the presence of common cytokine-dependent molecular mechanisms [18, 19].

It is known, that in some patients coronavirus infection, even after virus elimination, can provoke and maintain excessive activation of the innate and adaptive immune system, leading to excessive cytokine production and development of hyperinflammatory syndromes. Secondary hemophagocytic lymphohistiocytosis is one of them [20, 21]. The pathogenesis of liver damage in HLH remains largely unknown, but frequent

histological findings include infiltration by activated macrophages (Kupffer cells) in the area of portal tracts and sinusoids, dilatation of the latter, signs of hemosiderosis. Further damage of small bile ducts by activated macrophages and lymphocytes causes its obliteration and cholestasis. Hyperferritinemia, the most important laboratory sign, is a reflection of red blood cells phagocytosis by activated Kupffer cells [16]. Prolonged liver damage can lead to the development of DIC syndrome, secondary aggravating liver damage [22]. In addition, hemophagocytic syndrome can be combined with sepsis, independently provoking the development of cholestasis [10, 11]. There are several mechanisms for the development of cholestasis in sepsis. One of them implies the following: the formation of proinflammatory cytokines (IL-1, TNF-α) in response to endotoxinemia leads to decreased expression of basolateral (NTCP, OATP) and canalicular membrane transporter proteins (BSEP, MRP2) of hepatocytes and aquaporins involved in bile formation [23].

Thus, the main etiological factors of jaundice in patients with COVID-19 infection are the "hyperinflammatory syndrome, in particular hemophagocytic lymphohistiocytosis, and sepsis.

The diagnosis of hemophagocytic lymphohistiocytosis is traditionally based on the calculation of the H-score value and the identification of the HLH 2004 scale criteria. Both instruments are widely used in clinical practice and include the main clinical, laboratory and instrumental signs of the syndrome: fever, hepatosplenomegaly, peripheral blood cytopenia, hypertriglyceridemia, hyperferritinemia, signs of hemophagocytosis in bone marrow, lymph nodes or liver, etc. In addition to the presence of the signs themselves, the degree of their severity is taken into account as well. The score of 169 according to H-score (corresponding to a 40–54 % probability of disease) or the presence of 5 of the 8 HLH 2004 criteria is considered to be enough for diagnosis verification [12, 13, 24]. Some of these signs may also occur in patients with severe coronavirus infection, but tend to regress in case of convalescence. Persistence of the signs may suggest the development of HLH [5]. Since the pandemic onset in 2020, the number of cases of HLH has increased markedly. The analysis of 60 of these cases revealed that 5 or more HLH 2004 criteria were met by 13 % of patients, 3–4 criteria by 35 % of patients, and less than 3 criteria by more than 50 % of patients; 12 % of patients had 169 or more H-score points. The most common findings were hyperferritinemia (97 % of cases), AST elevation (93 %), fever (71 %), hypertriglyceridemia (47 %), thrombocytopenia (48 %), and splenomegaly (44 %). Incomplete examination (e.g.: bone marrow biopsy, liver puncture biopsy was available only in 30 % of cases) is identified as the main factor influencing criteria deficiency [17]. Therefore, a number of authors recommend to refrain from using H-score in the diagnosis of HLH in patients after COVID-19 infection due to lack of sensitivity of the method and to rely primarily on the clinical picture [13, 17, 25].

Conclusion

Although hemophagocytic lymphohistiocytosis is a rare syndrome, the number of affected patients has increased since coronavirus infection SARS-CoV-2 outbreak. COVID-19 provokes the development of HLH 10 times more often than other respiratory viral infections. Thus, the possibility of the development of HLH, including as part of an overlap syndrome with sepsis, in all patients with jaundice of unclear genesis, fever and systemic inflammatory manifestations after a coronavirus infection should be considered. Jaundice in the presented case was a reflection of another rare phenomenon — "vanishing bile ducts" syndrome, apparently formed due to damage of bile ducts by activated macrophages and lymphocytes. Routinely used scales and criteria of hemophagocytic syndrome diagnosis in the situation of prior coronavirus infection lack sensitivity, hence a thorough analysis of clinical picture and exclusion of other causes of jaundice is required.

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