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Hemophagocytic syndrome and Kaposi sarcoma after liver transplantation

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Hemophagocytic Syndrome (hemophagocytic lymphohistiocytosis, macrophage activation syndrome) is a rare form of systemic inflammatory response. It usually presents with nonspecific symptoms like fever, lymphoadenopathy, hepatosplenomegaly, cytopenia. Secondary

hemophagocytic syndrome is usually associated with severe infection. We describe a clinical case of a patient after liver transplantation who developed hematophagocytic syndrome secondary to Epstein-Barr virus and Human Herpes virus Type 8. There had been 22 cases of hematophagocytic syndrome after liver transplantation described in literature by the moment of our observation. We found just 1 similar case of a patient suffered from hemophagocytic syndrome in combination with Kaposi sarcoma and Epstein Barr virus infection.

Differential diagnostics of hemophagocytic syndrome is difficult as there are no specific symptoms. Rapid disease progression makes early diagnosis and treatment an actual problem.

Keywords: liver transplantation, Hemophagocytic Syndrome, Kaposi sarcoma, Epstein Barr virus

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ARF, acute renal failure

CMV, cytomegalovirus

CRP, C- reactive protein

DNA, deoxyribonucleic acid

EBV, Epstein-Barr virus

FLF, fulminant liver failure

GCS, glucocorticosteroids

HCC, hepatocellular carcinoma

HHV-8/KSHV, Human herpesvirus-8/Kaposi's sarcoma-associated herpesvirus

HIV, Human Immunodeficiency Virus

HPS, hemophagocytic syndrome

IL, interleukin

INR, International Normalized Ratio

K-ICS, KSHV-induced inflammatory cytokine syndrome

LDH, lactate dehydrogenase

LT, liver transplantation

MCD, multicentric Castleman disease

PTLD, post-transplant lymphoproliferative disease

sCD 25, soluble interleukin-2 receptor subunits

TMA, thrombotic microangiopathy

Hemophagocytic syndrome (HPS) (hemophagocytic lymphohistiocytosis, an activated macrophage syndrome) is a special form of generalized inflammatory reaction of the body caused by an uncontrolled systemic activation of macrophages and T cells, proliferation of histiocytes throughout the reticuloendothelial system, and macrophage absorption by hematopoietic cells. HPS is manifested by fever, lymphadenopathy, the liver and spleen enlargement, cytopenia in at least 2 cell lines. The laboratory markers of HPS include: hypertriglyceridemia, an extremely high blood levels of ferritin and alpha chains of the soluble interleukin-2 receptor (IL-2 sCD-25), as well as a reduction of fibrinogen in blood. There is a possible jaundice development accompanied by increased activities of aminotransferases, the appearance of skin rashes.

There are two forms of HPS: primary (genetic) and secondary (reactive). Genetic (primary, family) HPS can be associated with one of the diseases related to immunodeficiency. This type of HPS is inherited in autosomal recessive manner, occurs with the incidence of 1:50,000--1:100,000 in children population, manifests itself in infancy or early childhood and often had a fatal outcome [1].

Reactive HPS was first described by Risdall et al. (1979) [2]. It usually develops in patients with a compromised immune system. The HPS

development has been described in patients with malignant, autoimmune diseases as a complication of drug therapy. However, the most frequent triggering factor in the development of both primary and reactive HPS is the infectious process.

The exact mechanism of the HPS development is not clear. Its distinctive feature is the disruption of the activity of NK cells [3]. In HPS, there is no efficient elimination of the immune response trigger; there is observed an impairment of the immune system regulation leading to the hypersecretion of pro-inflammatory cytokines (IL-1, IL-6, IL-18, TNF-α, interferon-gamma). The uncontrolled release of proinflammatory cytokines as well as prostaglandins leads to the hyperactivation of antigen-presenting cells and cytotoxic lymphocytes, which, in turn, promotes the proliferation and migration of cells to various organs and tissues, causing the polymorphism of the disease clinical pattern [4].

A timely verification of the diagnosis and early initiation of therapy are necessary as there is a rapid disease progression.

Clinical Case Report

The patient, a 49-year-old man, suffered from hepatitis C virus-related liver cirrhosis for over 2 years. On October 6, 2016, he underwent liver transplantation (LT) from a postmortem donor. The donor was a 37-year-old male who died of cerebral hemorrhage. The early postoperative course was uneventful. The allograft function was satisfactory. Monocomponent immunosuppression included tacrolimus with a target concentration of 7-9 ng/ml (a dose of 0.1 mg/kg × day). Early in February 2017, moderate anemia occurred and was increasing (hemoglobin was 105 g/L), the platelet count gradually decreased (to 130,000 cells/μL). Since February 25, oliguria, and

the skin rash on the legs had been developing. From March 3, oliguria changed into anuria.

On March 6, 2017, the patient was hospitalized to *Burnasyan Federal Medical Biophysical Center (BFMBC) of FMBA* in severe condition with the complaints of weakness, dyspnea at minimal physical exertion. During the latest 2 days before hospitalization, he had vomiting of bile. The patient denied an intake of non-steroidal anti-inflammatory drugs, other nephrotoxic drugs, grapefruit intake. The clinical presentation was consistent with anuria and marked dehydration. On physical examination, there was an evident presence of bright livedo reticularis and petechial hemorrhagic rash on the skin of the shins, splenomegaly (longitudinal size of the spleen was up to 19 cm). Enlarged submandibular lymph nodes were palpated, moderately painful, movable. The laboratory examination revealed an increased blood creatinine level to 594 μmol/L, hyperkalemia 7 μmol/L, hypoalbuminemia 23 g/L, thrombocytopenia to 30,000/μL, and normochromic anemia with a hemoglobin reduction to 56 g/L. WBC count was 3.4 x 10^3/μL. The international normalized ratio (INR) was 1.66. Triglyceride concentration was normal. Despite the resume of HCV replication (2.6 $\times$ 10^6 IU/mL), the results of functional liver tests remained within normal range. The blood level of tacrolimus was 7.9 ng/mL. Acute renal failure (ARF) resolved during the first 2 in-hospital days on a conservative therapy with the replacement of the circulating blood volume without hemodialysis procedures. By March 10, the blood creatinine concentration had decreased to 147 μmol/L, potassium had decreased to 5 μmol/L.

Given the ARF development in association with anemia, thrombocytopenia, and small petechial rash, a differential diagnosis was made considering primarily the diseases caused by thrombotic

microangiopathy (TMA). For hemostatic purpose, the transfusion of packed red blood cells and fresh frozen blood plasma was performed, which made it hardly possible to unambiguously interpret the results of the study for ADAMTS-13 enzyme yielding 28% (the sample was taken on the 3rd day after the last plasma transfusion). No anti-ADAMTS-13 antibodies were found. Antibodies to beta-2-glycoprotein and cardiolipin of M and G classes were within the normal range; no lupous anticoagulant, anti-native DNA antibodies, or cryoglobulins were found in blood. The antinuclear factor was 1/160. The complement C3 and C4 components were seen decreased to 0.42 g/L and to lower than 0.029 g/L, respectively. Urinalysis demonstrated proteinuria 0.2 g/L, leukocyturia 25 cells/μL, at microscopy there were 6-8 white blood cells in the field of vision, 1-2 hyaline cylinders. The daily protein excretion was 0.72 g. The results of the studies prompted a high probability of excluding the antiphospholipid syndrome, systemic lupus erythematosus, hemolytic uremic syndrome, and thrombotic thrombocytopenic purpura.

On March 10 (day 4 of in-hospital stay), the patient reported the occurrence of sore throat at swallowing; the body temperature elevated to 38.5° C in that evening. On March 11, the sore throat increased. The X-ray of the paranasal sinuses showed a total intensive opacity of right maxillary sinus, a mucosa thickening in the projection of the left maxillary sinus. The patient was examined by an otolaryngologist who made the diagnosis of exacerbated chronic pharyngitis, and acute right-side maxillary sinusitis. On March 14, the patient was examined by a dentist who diagnosed severe chronic generalized periodontitis. Given febrile fever with chills, a local process in the oropharynx, and increased C-reactive protein (CRP) to 57 IU/mL, a bacterial infection with a possible septicemia development came

first in the differential diagnosis. Due to a high risk of bleeding in existing thrombocytopenia (13 000/μL), the maxillary sinus puncture was not performed. On March 16, CT scanning demonstrated the persisting thickening of the mucosa maxillary sinuses, the ethmoid bone cells, the basal parts of the frontal sinuses without fluid contents. In connection with the persisting complaints of the pain in the oral cavity, the appearance of soft tissue swelling in the left cheek, the patient was examined by the maxillofacial surgeon. The orthopantomogram revealed the area of bone tissue destruction around the 25th and 27th teeth (under the crowns of the bridge prosthesis). Periodontitis with abscess was suspected. After the packed platelets transfusion on March 24, multiple tooth extractions with suturing holes were made. No pus was found under the bridge prosthesis. On March 29, the maxillary sinus was punctured and sanitized. A scanty amount of mucus was obtained, a bacteriological study revealed the growth of Klebsiella pneumoniae, sensitive to tigecycline.

On March 17, the Epstein-Barr virus (EBV) deoxyribonucleic acid (DNA) of 120 copies/mL was found in blood; DNA of cytomegalovirus (CMV) or herpes simplex virus types 1 and 2 were not found. On March 17 and 19, human immunoglobulin G was administered (0.44 g/kg per each administration) with a clinical effect of improved general condition and a decreased sore throat. A repeated study on April 6, detected no EBV DNA. On March 22, the patient developed increasing jaundice with a predominance of bound bilirubin in blood. Based on the results of radiology studies, an extrahepatic jaundice genesis was rejected. Since March 26, the fever ceased, turning into hypothermia to 35.5° C. By March 30, the bilirubin level reached 172 μmol/L (direct bilirubin was 152 μmol/L). The activities of alanine aminotransferase, aspartate aminotransferase, gamma-

glutamyl transpeptidase, and alkaline phosphatase remained normal; and the CRP content having initially increased to 97 IU/mL by March 24, later gradually decreased to 34 IU/mL by March 31. By March 24, the platelet count had decreased to 6,000 cells/μL and kept at that level thereafter.

Computed tomography revealed the enlargement of axillary, retroperitoneal, pelvic, and inguinal lymph nodes with a tendency to their increase in size to 2-3 cm in repeated studies. Brain tomograms showed no specific symptoms. Focal graft lesions, infiltrative abnormalities in the lungs, and cardiac valve pathologies were excluded. During the entire observation period, hypoalbuminemia persisted, being refractory to replacement therapy with albumin solutions. Meanwhile, the patient did not have clinically significant proteinuria. Since March 13, the positive dynamics of glomerular filtration had slowed down, never coming to normal; and from March 15, the kidney failure again began gradually increasing. The patient had swelling, primarily, in the form of "stockings" that later on developed into anasarca. Despite the continuous infusion of albumin solutions, diuretic therapy, and restricted fluid intake, it was not possible to slow down the edema progression. The patient experienced a severe pain syndrome due to the skin tension; from March 20, the interstitial fluid sweating through the skin was noted. On March 23, an ultrafiltration session was undertaken; 9 liters of fluid were removed within 30 hours. From that day on, the patient was regularly given the sessions of various renal replacement therapies in order to remove the excess fluid, and the nitrogen metabolism products from the body. Due to increasing creatinine level to 260 μmol/L, the patient underwent a hemodialysis session on March 27.

It was difficult to interpret the origin of anemia that was hyperregenerative with reticulocytosis up to 115 ‰ and its correction required repeated transfusions of individually selected erythrocyte mass. On March 22, an increased lactate dehydrogenase (LDH) activity to 278 IU/mL was first noted, having been within normal range in further repeated studies. On March 24, the acutely positive indirect Coombs test was found for the first time. On March 30, a bone marrow test was conducted demonstrating that the bone marrow aspirate was rich in cellular elements; proliferations with normoblasts to 8-10 cells in selected fields of vision were described; the increased number of macrophages with autophagy symptoms were observed. Blood ferritin level was 3425 ng/mL. Taking into account the above-mentioned changes, the HPS was included in the differential diagnosis. On March 31, the therapy with methylprednisolone (200-250 mg/day, intravenously) was initiated with some positive effect in the form of the improved weakness, decreased edema and dyspnea. The patient began ambulating independently within the ward.

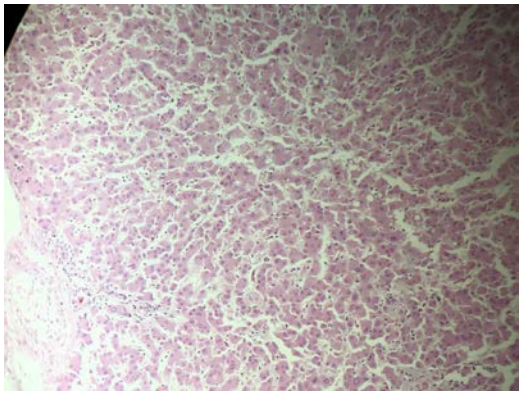
At night from April 5 to 6, the patient's condition considerably worsened: dyspnea increased, a constricting pain arose behind the sternum, anuria resumed, new elements of the petechial rash appeared in the paraumbilical area. The coagulogram demonstrated the signs of hypocoagulation and thrombolysis (the activated partial thromboplastin time 82 s, INR 2, level of D-dimer in blood 4100 μg/L). No evidence of focal myocardial ischemia was seen on electrocardiogram. At noon exactly, on April 6, the patient, after having got out of bed himself and passing through the ward, lost consciousness, the pulse was not palpable. At resuscitation, the heart rate resumed, the patient was transferred to the Intensive Care Unit

where, after 15 minutes, another cardiac arrest was recorded. Resuscitation attempts appeared ineffective.

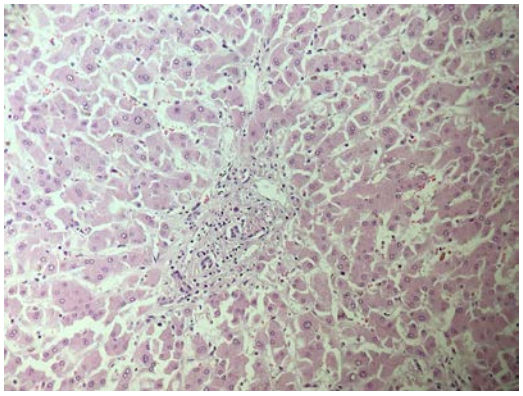
At autopsy, there were para-aortic, retroperitoneal lymph nodes of soft consistency, of brownish-red and cherry-red colour at histological sections, enlarged, joined together forming large conglomerates up to 12 x 7 cm in size. The spleen, weighing 1400 g, was fleshy, having adhesions, its capsule being unevenly thickened, dull, coarse. At section, the spleen tissue was cherry-red, granular, with insignificant bloody scraping. The liver graft was enlarged, having a densely elastic consistency, sandy-yellow in color, with a smooth surface. Brownish-gray masses were found in the lumen of the right coronary artery at 3.5 cm from its ostium, obturating the artery lumen for the extent of 0.5 cm. In the posterior wall of the left ventricle subendocardially, there was a yellow-colored nidus with fuzzy boundaries, irregularly wedge-shaped, approximately 0.8 x 0.6 cm in size, its apex facing the ventricle lumen, of presumably 3 days old. There were pinpoint hemorrhages on the serous surface of all visceral organs and skin. The immediate cause of the patient's death was an acute heart failure caused by multiple focal damage of left ventricular myocardium, apparently, of metabolic origin.

Histological examination of the liver showed the signs of intra- and extracellular cholestasis. Under the capsule and along the portal tracts, there were islets of spindle cells, among which there were small vascular slits resembling capillaries (Fig. 1a, b, c).

a



b



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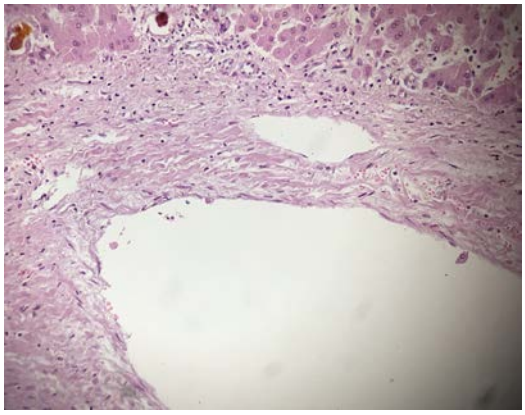


Fig. 1. a, b, c. Liver

Muscle fiber necrobiosis foci with calcium salt deposits in them were identified in different parts of the myocardium (Fig. 2). The microscopic image corresponded to the macroscopically detected infarction area.

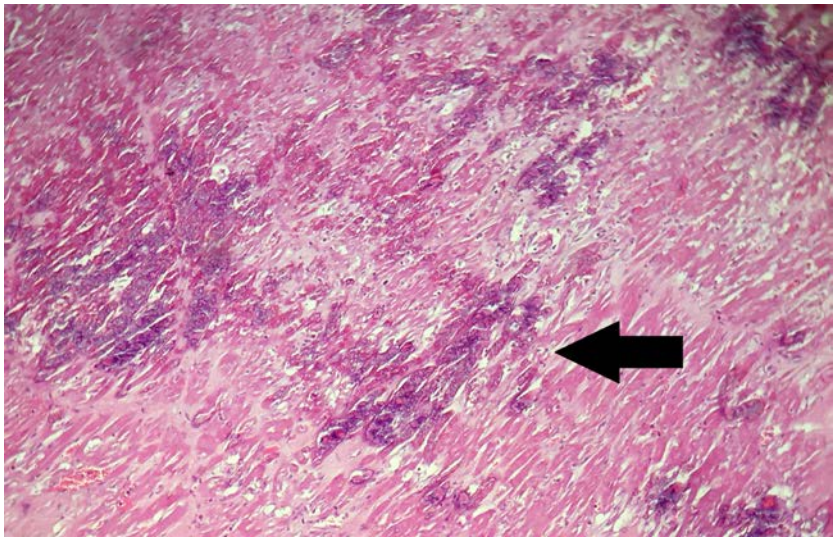
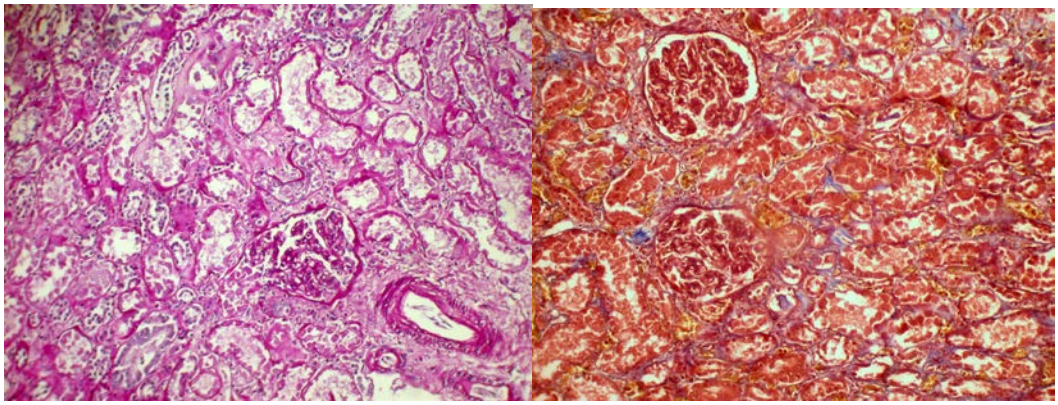


Fig. 2. Dystrophic changes in cardiomyocytes, calcification

Histological examination of the kidney tissue showed no signs of glomerulonephritis. There was a focal interstitium infiltration with mononuclears in the sclerosis areas. Many tubules showed severe damage to the tubular epithelium with its dystrophy and atrophy, the loss of the "brush border", and necrosis of individual tubulocytes and their sloughing into the lumen of the tubules.

Immunofluorescence assay of kidney tissue revealed no luminescence of immunoglobulin chains, complement components, or fibrinogen. There was no evidence of thrombotic microangiopathy (Fig. 3a, b). Bone marrow was rich in cellular elements; all hematopoiesis cell lines were represented. There were numerous erythrocytes among the hematopoiesis elements. There were sites with the presence of macrophages having the signs of erythrophagocytosis.



a. PAS reaction × 100 b. Masson's trichrome stain × 100

Fig. 3 a, b. Histological examination of the kidney. Severe damage to the tubular epithelium with its dystrophy, loss of the "brush border", and necrosis of individual tubulocytes and their slushing into the lumen of the tubules. The glomeruli and arteries look unchanged. There is no interstitial fibrosis

The lymphoid tissue hypoplasia and aplasia is seen in the lymph nodes, with proliferation of the spindle cells folding into bundles. There are red blood cells in the bundle structures in vessels and slit-like spaces. There were hemorrhages of various onset time, hemosiderin deposits, a lot of macrophages with signs of erythro-, lympho- and hemophagocytosis (Fig. 4).

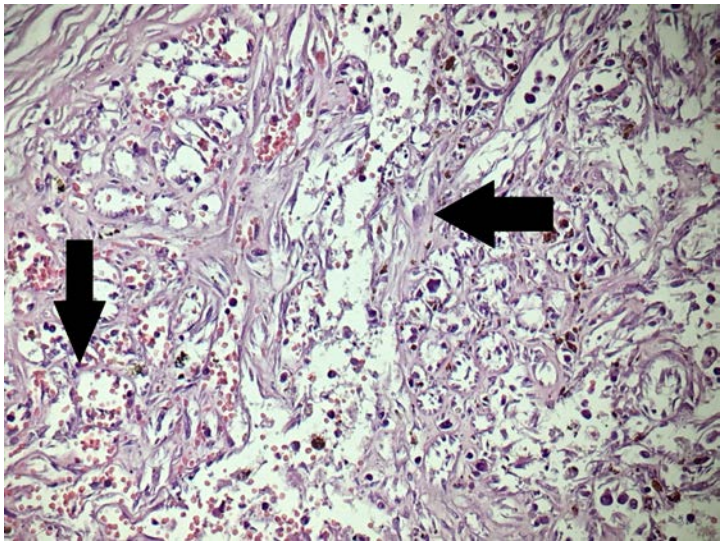


Fig. 4. A lymph node (para-aortic) totally replaced by a tumor tissue: arrows indicate tumour spindle-shaped cells forming irregularly arranged cords; the other arrow indicates tumor capillaries

An immunohistochemical assay performed to specify the nature of cells that form bundle structures revealed the expression of CD31, HHV-8, and FL-1. Morphoimmunohistochemical characteristics of the tumor in lymph nodes corresponded to Kaposi's sarcoma (Fig. 5).

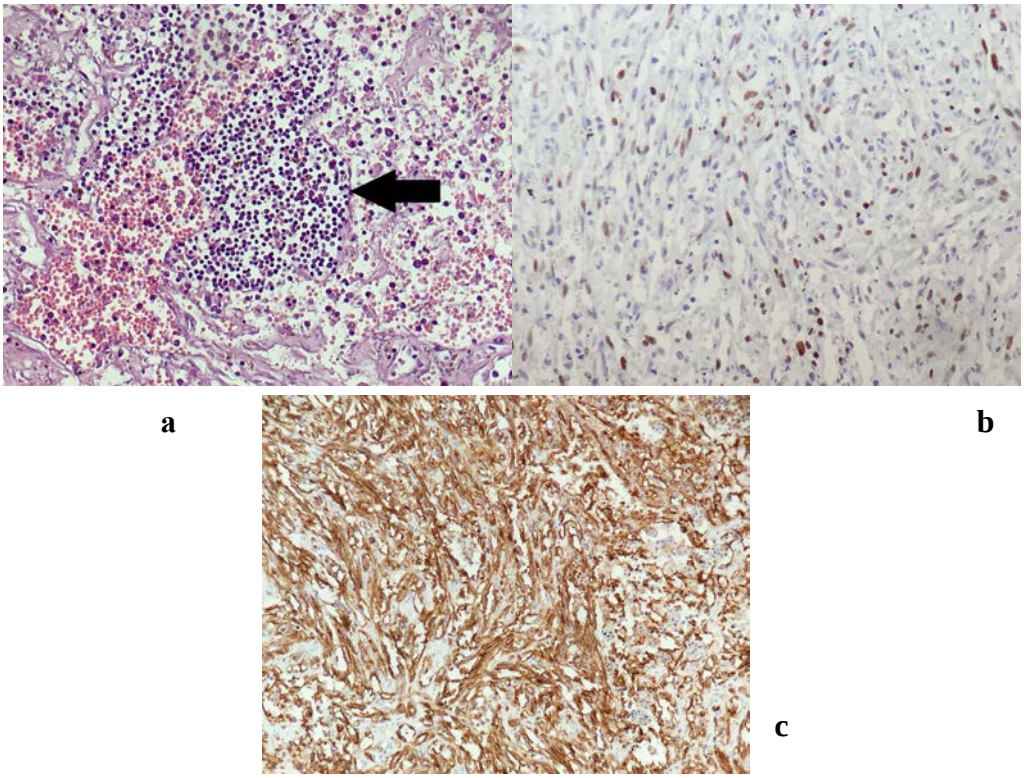


Fig. 5. a) Unaffected fragments of lymph node tissue surrounded by the tumor; b) the assay with antibodies to HHV-8 shows a positive nuclear expression in tumor cells; c) a positive membrane expression of CD31 in tumor cells

Discussion

Prevalence and prognosis of HPS after solid organ transplantation

For the first time in Russia, we have determined and described the HPS development in a patient who underwent LT. Moreover, our description has been the second in the world English-language literature in observing the HPS in combination with Kaposi's sarcoma in the liver transplant recipient. The first description of the HPS after LT dates back to 2001. Chisuwa et al. observed HPS in two infants operated on for atresia of the bile ducts [5]. Ten years later (by 2011), Soyama et al. could find only 14 HPS cases in liver

transplant recipients in the English-language literature, including two their own case reports [6]. At the time of preparing the present article for publication (in May 2017), we found a description of 8 more such cases. Here we give their summarized description (Table. 1). Of these 23 patients (including ours), only 7 survived.

Table 1. Cases of hemophagocytic syndrome development after liver transplantation, reported in the English-language literature, and our observations

Author, reference, year	No.	Age, years	Gender	Donor	Diagnosis at the time of LT	The HPS onset (after LT)	Expected trigger of HPS	Outcome
Chisuwa [5], 2001	1	9 months	F	Live	Biliary atresia	15 days	Not specified	Death
	2	11 months	M	Live	Biliary atresia	134 days	EBV	Death
Karasu [7], 2003	3	38	M	Live	HBV / HDV (cirrhosis)	124 days	Not specified	Alive
Lladó [8], 2004	4	63	M	Deceased	Autoimmune hepatitis	Not specified	Not specified	Death
George [9], 2005	5	10	M	Deceased	Acute liver failure	6 years	EBV	Alive
Taniai [10], 2005	6	37	F	Live	Not specified	11 days	Not specified	Death
Hardikar [11], 2006	7	26 months	M	Deceased	Acute liver failure	15 days	CMV	Alive
Akamatsu [12], 2006	8	59	M	Live	HCV (cirrhosis)	138 days	Aspergillosis	Death
	9	49	F	Live	Primary biliary cirrhosis	315 days	CMV	Death
	10	48	F	Live	HCV (cirrhosis)	50 days	HCV	Death
Yoshizumi [13], 2008	11	63	M	Live	Primary biliary cirrhosis	13 days	Inadequate graft size	Alive
Dharancy	12	49	F	Deceased	Polycystosis	12 days	HHV-6	Death

[14], 2008					(Liver-kidney)			
Zhang [15], 2009	13	6	F	Live	Not specified	6 weeks	EBV	Alive
Satapathy [16], 2010	14	25	M	Deceased	Autoimmune hepatitis, FLF	6 months	Still's disease	Alive
Soyama [6], 2011	15	57	M	Live	HCV (cirrhosis, HCC)	32 days	CMV / HCC	Death
	16	63	M	Live	HBV (cirrhosis, HCC)	81 days	Not specified	Death
Shabbir [17], 2011	17	54	M	Deceased	Not specified	Not specified	Not specified	Death
Imura [18], 2012[1]	18	53	F	Live	Not specified	6 days	Not specified	Alive
Fu [19], 2013	19	45	M	Deceased	HBV (cirrhosis, HCC)	36 days	Not specified	Death
Rodriguez-Medina [20], 2013	20	63	M	Deceased	HCV (cirrhosis)	4 years	AVT tuberculosis, HCV	Death
Okada [21] 2015	21	8	F	Alive	Ornithine transcarbamylase deficiency	12 days	Not specified	Death
Vijgen [22], 2016	22	66	M	Deceased	Alcohol cirrhosis, HCC	11 months	HHV-8	Death
Our observation	23	49	M	Deceased	HCV (cirrhosis)	5 months	HHV-8	Death

[1] Information on the patient is given as per abstract. The article was published in the Journal that ceased to be published. We could not get the full text, because there are no links to full-text articles either on the home page of the previously published Journal, or in PubMed.

Note:

FLF, fulminant liver failure; HCC, hepatocellular carcinoma.

Among those 23 recipients of the liver, men predominated (15 patients, 65%). Besides 6 children, there were 12 people over 45 years of age, 8 of them older 50 years. LT was performed in various indications, including infectious, autoimmune, congenital liver diseases. The HPS development time was known for 21 cases, including 17 (1 our patient) in whom HPS developed in the first 6 months after LT. Unfortunately, only

some authors indicated the total number of studied liver transplant recipients. Thus, Chisuwa et al. (2001) reported only 2 HPS cases (1.5%) of 135 patients transplanted in their clinic during 10 years [5]. Fu et al. (2013) observed only one HPS case (0.13%) in the general cohort that included 741 liver transplant recipients operated on at that center [19].

As we mentioned above, reactive HPS was first identified as an independent syndrome in 1979 by Risdall et al. [2], and among 19 patients with HPS described by the authors, 13 were kidney transplant recipients. In 2010, a group of Russian investigators from MONIKI (Moscow Regional Research and Clinical Institute named after M.F.Vladimirsky) described the HPS development triggered by EBV and Mycoplasma pneumonia in a kidney transplant recipient [23]. Unfortunately, the case presented by the authors, also resulted in death.

Karras et al. (2004) described the series of 17 HPS cases observed on kidney transplant recipients. The authors further searched the medical literature in English and French. They managed to find reports of 34 cases of HPS development after kidney transplantation, including those 13 that were first described by Risdall (1979). Viral infection was the most common cause of HPS development in that group of patients, followed by T-cell lymphomas. The HPS prognosis was unfavorable in most cases. Of 34 reported clinical cases, 15 had favorable outcome; in a series of Karras's own observations, 9 of 17 recipients survived [24]. The authors were unable to identify any specific features of immunosuppression or family and personal history data associated with the development of HPS. A detailed analysis of the HPS incidence after transplantation of kidney and other solid organs goes beyond the scope of our work; however, the reported number of cases

is comparable to that of liver recipients (considering a significantly greater number of kidney transplantations).

HPS etiology

The EBV DNA was found in blood of our patient. Viruses belonging to the herpetic group are the most often triggers for the HPS development, including in the recipients of solid organs [17, 24]. HPS is especially commonly associated with EBV. Up to 75% of all HPS cases in children in Asian countries have been associated with EBV infection. A high incidence of EBV replication in HPS patients may indicate the presence of any genetic characteristics leading to an impaired immune response to the virus. The spectrum of clinical manifestations of EBV-associated HPS varies from inflammation that may resolve spontaneously to a serious disease requiring stem cell transplantation [4]. In patients with infectious mononucleosis, EBV infects B cells, whereas in HPS, the EBV gene is found predominantly in T cells (in Asian populations) or in B and T cells in equal proportions (in European populations) [25, 26].

In liver recipients, EBV is the most common cause of post-transplant lymphoproliferative disease (PTLD) which incidence in liver recipients makes 0.9-2.9 %. One of the patients described by Chisuwa et al. (2001), simultaneously developed HPS (mediated by T-cells) and B-cell lymphoma against the background of the EBV replication after LT [5]. The authors suggest that the patient's death was caused by both these conditions. The EBV replication has also been found in approximately 25% of cases of T-cell PTLD. According to the guidelines of the American Association for the Study of Liver Diseases, PTLD should be included in the range of differential diagnosis in all patients with fever, lymphadenopathy, cytopenia

of an unknown origin. Meanwhile, the presence of EBV DNA in blood is not a diagnostic criterion of PTLD. Moreover, even in case of the PTLD detected in patients with the EBV replication, the beneficial effect of an antiviral therapy on the PTLD outcome has not been proven [27].

Another virus, HHV-8/KSHV, belonging to the herpetic group is associated with a number of malignant and non-malignant diseases that can occur in recipients of solid organs receiving immunosuppressive therapy or in patients infected with the human immunodeficiency virus (HIV). This virus (HHV-8/KSHV) is considered the etiologic factor of Kaposi's sarcoma, the primary effusion (exudative) lymphoma, and also the multicentric Castleman disease (MBC). Non-malignant conditions that can be caused by HHV-8/KSHV include Castleman-like or other atypical HHV8-positive plasmacytic lymphoproliferations, usually not clonal but often fatal; cytopenia, whether or not associated with HPS, and even an acute hepatitis syndrome [28]. All these conditions can be fancifully combined in one patient.

The development of HPS associated with HHV-8/KSHV is much less common than in association with EBV infection. HPS was described as one of the clinical signs of HHV-8/KSHV infection in 5 HIV-infected patients [29], 4 of whom had Kaposi's sarcoma, and 3 had MCD. There are some reports of HPS cases that were caused by HHV-8/KSHV infection after transplantation of solid organs. Luppi et al. (2002) reported of a kidney transplant recipient in whom Kaposi's sarcoma with affected lymph nodes and visceral organs developed at 4 months after transplantation; and a month later, the patient was diagnosed with a clinical presentation of HPS. Perhaps, chronologically, there should follow the report by Vijgen et al (2016). The authors gave the only description in the world literature of the case of

Kaposi's sarcoma combined with HPS in the liver transplant recipient [22]. The patient had the evidence of HHV-8 infection, as well as histological and immunochemical signs of another disease, MCD, the etiological factor of which is HHV-8 in patients with immunodeficiency. Our observations are similar in many respects. As there were no skin manifestations, the diagnosis of Kaposi's sarcoma was made by authors from Switzerland only at autopsy, as well; and the patient's death resulted from HPS complications. Besides, in the above case, as in our observation, the patient had low-concentration EBV DNA in blood, and bacteremia. Comparative characteristics in our observations are summarized in Table 2. Unfortunately, we did not study the HHV-8 viremia in our patient. However, the revealed at autopsy Kaposi's sarcoma involving the lymph nodes suggested the relationship of that virus in the HPS development in our patient. The relation between HPS and EBV in our patient was also possible. After the human immunoglobulin had been administered, EBV DNA ceased to be detected in the patient's blood, so antiviral therapy was not prescribed.

Table 2. Characteristics of the course of the disease in the liver recipients described by Vijgen et al. (2016), and in our observation (2017)

	Vijgen et al .(2016) [22]	Our observation
Gender, age	Man, 66 years old	Man, 49 years old
Cause of LT	Alcoholic liver cirrhosis, HCC	HCV, liver cirrhosis
Immunosuppression	Tacrolimus, mycophenolate mofetil, prednisolone	Tacrolimus
The disease onset time after LT	11 months	4 months
Main clinical manifestations in the approximate sequence of	Fever, weakness, myalgia, dyspnea; mediastinal and mesenteric lymphadenopathy	ARF, rash, dyspnoea, splenomegaly Submandibular

their development	ARF, pleural effusion, ascites, splenomegaly, foci in the liver (0.5 and 0.9 cm)	lymphadenopathy, fever, weakness, mediastinal and mesenteric lymphadenopathy Anasarca, cholestatic jaundice Angina pectoris
Main laboratory manifestations	Anemia, leukopenia, thrombocytopenia, hypoalbuminemia	Anemia, thrombocytopenia, hypoalbuminemia
Functional liver tests	Normal followed by hyperbilirubinemia (58 μmol/L)	Normal followed by hyperbilirubinemia (172 μmol/L)
Ferritin in blood	4447 ng/mL	3425 ng/mL
EBV in blood	Slightly positive (<100 cop./ml)	120 cop./ml
HHV-8 in blood	6,570,000 cop./ ml	Not studied
Bacteremia	Salmonella enteritidis	Klebsiella pneumoniae, Staphylococcus hominis
Antibacterial, antifungal therapy	Ceftriaxone, meropenem, amphotericin B, doxycycline, moxifloxacin, isoniazid, rifabutin	Ceftriaxone, vancomycin, fluconazole
Diagnostic concept while alive	The multicentric Castleman disease (from day 26 of the disease) [1]	TMA, septicemia HPS (from day 25 of hospitalization)
Bone marrow tests	Hemophagocytosis, an increase in the number of macrophages, hypercellularity, trilineage dyspoiesis, lack of clonality, clusters of polymorphic mature plasmocytes, mild diffuse reticulin fibrosis	Hemophagocytosis, an increase in the number of macrophages, hypercellularity
Lymph node biopsy	Not performed because of severe condition	Not performed because of severe condition
Liver biopsy	Activation of Kupffer cells without signs of rejection	Not performed
Antiviral therapy	Ganciclovir	Not performed
Pathogenetic treatment	Reduction of immunosuppression with complete cancellation,	Methylprednisolone, human immunoglobulin, blood ultrafiltration, extracorporeal

	methylprednisolone, rituximab, cyclophosphamide	hemosorption
Cause of death	Shock in the outcome of HPS	Acute cardiovascular failure associated with organic myocardial damage
Autopsy results	Cervical, mediastinal and visceral lymphadenopathy (up to 2 cm), splenomegaly (22 cm, 1150 g), hyperemic foci (up to 1.5 cm) in the lung, liver and pancreas	Cervical, mediastinal and visceral lymphadenopathy (up to 3 cm), splenomegaly (1400 g), multiple foci of left ventricular myocardium necrosis of different onset time
Histological examination of the lymph node	Disrupted structure, hypocellularity, good vascularization; proliferation of plasmablasts organized in small clusters	Hypoplasia and aplasia of lymphoid tissue, diffuse proliferation of elongated cells folding into bundles; signs of lympho-, erythro- and hemophagocytosis
Immunohistochemistry	CD31, HHV-8 LANA-1 in foci in the visceral organs HHV-8 LANA-1, MUM-1, CD79a, PAX-5, IgM with restricted lambda chain in lymph nodes	CD31, HHV-8, FLI-1 expressing the elongated cells in lymph nodes
Diagnosis based on the autopsy results	Kaposi's Sarcoma, multicentric Castleman disease, HPS	Kaposi's sarcoma, HPS

[1] A set of antibacterial drugs administered empirically suggests that bacterial and fungal sepsis and tuberculosis were considered.

The review of a small number of Kaposi's sarcoma cases in combination with HPS in the recipients of solid organs may be completed with the publication of Korean authors (2017). The cutaneous form of Kaposi's sarcoma was detected in a kidney transplant recipient at 5 months after transplantation and did not present any difficulties for the diagnosis. The HPS that developed a month later resulted in severe septic complications and patient's death [30].

Besides viruses of the herpetic group, the HPS development can be associated with protozoa, bacteria, and fungi. The infection persisting in the reticuloendothelial system appears to be an important factor in HPS development: cases of HPS associated with Leishmania, Mycobacterium tuberculosis or Salmonella typhimurium, and a large number of other microorganisms have been described.

Diagnosis and differential diagnosis

Unfortunately, none of the clinical and laboratory symptoms of the disease is highly specific. An exception is, unless, ferritin which blood level can reach several tens of thousands of ng/ml. It has been shown that an increased ferritin content in blood over 10,000 ng/mL has a 90% sensitivity and 96% specificity in the HPS diagnosis in children [31]. The HPS diagnosis is based on a combination of clinical, laboratory, and morphological criteria.

In 1997, the first guidelines for the HPS diagnosis were published, which were revised and refined in 2007 [32, 33] (Table 3). The diagnosis of reactive HPS requires 5 of 8 criteria to be present. Other symptoms and abnormalities in laboratory parameters are less common or their assessment is hardly available for wide clinical practice. The symptom progression increases the specificity of the criteria.

Our patient had 5 main criteria necessary for establishing the HPS diagnosis: fever, splenomegaly, bilineage cytopenia (anemia and thrombocytopenia), high blood levels of ferritin and hemophagocytosis in the bone marrow and in the lymph nodes (according to autopsy data). The triglyceride blood level remained normal, and the fibrinogen concentration in blood plasma gradually decreased from 3 g/L on admission and lowered

to the level of the diagnostic criteria (1.4 g/L) only by March 31 (6 days before the patient's death). Unfortunately, the study of immunological parameters (NK cell activity and sCD-25 level) was not available. In addition, while the patient was taking tacrolimus, their level could have changed. The jaundice that appeared and increased in the patient was also referred to HPS signs.

It should be emphasized that the HPS diagnostic criteria had been developed mainly for the verification of a primary HPS. Their use in patients after LT is associated with a bit of slyness. So, in most of the patients who underwent LT for liver cirrhosis, splenomegaly retains after surgery. After LT, the spleen size reduction can possibly, but not necessarily, occur. Moreover, a dense fibrous capsule that has grown against a long-existing portal hypertension often does not allow a quick response to an active inflammatory process by increasing the spleen size. In our patient, the longitudinal spleen dimension was 17 cm before LT (October 2016), 19 cm in March 2017. Many authors who described HPS after LT considered splenomegaly in their patients as one of the HPS criteria without assessing the changes in the spleen dimensions over time (see Table 1).

Table 3. Criteria for the diagnosis of hemophagocytic syndrome

1. **Hereditary predisposition** / mutation confirmed by genetic assay
2. Clinical and laboratory criteria (the presence of 5 is enough tor make the diagnosis)
Fever
Splenomegaly
Cytopenia (suppression of at least 2 bone marrow cell lines: Hemoglobin <90 g/L (in children under 4 weeks <120 g/L) Platelets $<100 \times 10^9$/L Neutrophils $<1 \times 10^9$/L
Hypertriglyceridemia and(or) reduction of plasma fibrinogen Fasting triglycerides at least 3 mmol/L Fibrinogen in blood <1.5 g/L

Ferritin in blood at least 500 μg/L
sCD 25 in blood at least 2400 U/mL
Reduced activity of NK cells
Hemophagocytosis in the bone marrow, cerebrospinal fluid, or lymph nodes
Additional evidence may be the general cerebral symptoms with moderate pleiocytosis and/or an increased amount of protein, increased aminotransferase activities, bilirubin, LDH

Note: sCD 25 is a soluble IL-2 receptor.

Various mechanisms suppressing the blood cell development up to pancytopenia often complicate the posttransplant course in liver transplant recipients. The clinical and laboratory signs of TMA and HPS are very similar. The key in a differential diagnosis is the study of a bone marrow smear by an experienced cytologist who can recognize hemophagocytosis. At early stages of HPS development, only moderate hyperplasia is commonly revealed in the smear and there are no specific signs (hemophagocytosis). If the diagnosis is not verified and the probability of HPS is high, repeated bone marrow tests are necessary.

The HH-8/KSH virus can cause a specific type of systemic inflammation termed a "KSHV-induced inflammatory cytokine syndrome" (K-ICS). This variant of an excessive inflammatory response was described in patients infected with HIV who had Kaposi's sarcoma [34]. K-ICS can also be observed in patients receiving immunosuppressive therapy for solid organ transplantation, including in the absence of HIV, Kaposi's sarcoma, and other HHV-8/KSHV-associated diseases [35]. Apparently, this variant of "hyper-inflammation" differs from HPS by the absence of hemophagocytosis and a decrease in the cellular composition of the bone marrow. Nevertheless, the presence of the rest HPS criteria allows this diagnosis to be established formally [35], which once again supports the correctness of U.Osler's words who spoke of the need to "weigh rather than

count the symptoms of the disease." A key role in K-ICS development belongs to the virus-encoded homologue IL-6 (vIL-6).

Treatment

The protocols for HPS therapy are adopted as standards, their latest revision took place in 2004 [33]. At the first stage, it is supposed to influence the HPS triggers: infectious, autoimmune ones. The main difference between the protocol of 2004 and the earlier one of 1997 [32] was the cyclosporine administration directly at treatment initiation, rather than from week 9. Both protocols imply the administration of dexamethasone, etoposide, and cyclosporine for 8 weeks to patients with the reactive HPS that has no specific genetic markers of a primary HPS. In cases of primary HPS, chemotherapy should last more than 8 weeks, until transplantation of bone marrow cells becomes possible. When the central nervous system is involved, the intrathecal administration of methotrexate and glucocorticosteroids (GCS) is recommended [33].

Studies by Per Kleynberg and Schiller emphasized the significance of the etoposide timely administration for the treatment of HPS associated with EBV infection, since it is the etoposide alone that is effective against activated histiocytes [36]. The young patients with EBV-associated HPS, whose treatment with etoposide was started in the first 4 weeks after the diagnosis, had significantly better prognosis than the patients who did not receive etoposide at all or began receiving it at later stage [37].

For the treatment of EBV infection, intravenous immunoglobulin, as well as rituximab, has been used. The rituximab efficacy was studied in 42 patients with HPS who had received an average 3 infusions of the drug (1-10 doses) in a median dose of 375 mg/m^2, in combination with GCS, etoposide,

and/or cyclosporine. Rituximab therapy was well tolerated and led to a clinical improvement in 43% of patients. There was a significant reduction in EBV viremia compared to the viremia level before rituximab administration [38]. Since EBV can also infect T and NK cells, a recurrent EBV infection can occur in patients after the treatment with rituximab. In the cases where HPS is refractory to rituximab therapy, alemtuzumab may be useful [39].

In our case, we were not quite confident in HPS diagnosis nearly until the very death of the patient. Nevertheless, we conducted a "mini-pulses" with GCS that produced some effect. The HPS treatment in recipients of solid organ transplants suggests some specific features. The role of the conversion in immunosuppressive therapy from tacrolimus to cyclosporine is not entirely clear. Thus, of 6 liver transplant recipients surviving after HPS whose immunosuppression information was available, tacrolimus was administered in 4 cases [9, 11, 7, 16], and the conversion to cyclosporine was undertaken in 2 [13, 15]. Meanwhile, the outcome was unfavorable in some patients who underwent conversion to cyclosporine [12, 19], or who received it prior to HPS development [20]. Due to a very small number of patients, it is hardly possible to verify the applicability of other provisions from HPS treatment protocol of 2004.

A high level of immunosuppression, or sepsis after solid organ transplantation may be the triggers for the HPS development. In this group of patients, an interruption in immunosuppressive therapy may turn useful, while to treat HPS in patients not receiving immunosuppression its administration is appropriate.

The main aspect of the treatment for Kaposi's sarcoma implies the minimization of immunosuppression, the reverse side of which is the risk of

graft rejection. Favorable therapy outcomes have been reported at replacement of calcineurin inhibitors with sirolimus [40]. Should the HHV-8/KSHV replication be detected, the administration of antiviral drugs is mandatory. There have been reports of an effective use of foscarnet (yet not certified in the Russian Federation) in the treatment of the HHV-8/KSHV-associated HPS in kidney transplant recipients [28]. Finally, the immediate initiation of anti-CD20 treatment may be decisive in the treatment of the inflammatory response triggered by HHV-8 [28, 41]. It can be assumed that the massive elimination of B-lymphocytes against the background of a weekly rituximab infusion can restrain the HHV-8 replication, which leads to the shutdown of the associated inflammatory response.

Conclusion

The hemophagocytic syndrome is a rare complication that can develop after liver transplantation. A key role in its initiation is played by infection, primarily the Epstein-Barr virus and HHV-8/KSHV. Under immunosuppression conditions, these viruses can lead to the development of a number of rare, but fatal diseases, sometimes observed simultaneously. Knowledge of the symptoms of these diseases and timely diagnosis are necessary to save recipient's life. It is necessary to adapt the available diagnostic criteria and treatment protocols for reactive HPS for their use in the recipients of solid organ transplants.

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