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Seventh-Day Syndrome after liver transplantation in a patient with hepatocellular carcinoma

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Abstract

Background. *Seventh-Day Syndrome following liver transplantation is a rare but serious complication characterized by a sudden deterioration of the graft function after initial normalization, often leading to death. The peak occurrence of this syndrome is in the late first or early second week post-transplant. Currently, there are no established treatment standards for Seventh-Day Syndrome, and its natural course usually results in a graft loss.*

Objective. *To present a clinical case of Seventh-Day Syndrome after liver transplantation and analyze strategies for early diagnosis and treatment.*

Results. *A patient who underwent liver transplantation for viral cirrhosis and hepatocellular carcinoma was diagnosed with Seventh-Day Syndrome on the eighth day post-surgery, which was accompanied by acute deterioration in the graft function and the development of fulminant liver failure. Despite a timely diagnosis and immediate treatment, including high doses of methylprednisolone, immunoglobulin administration, and plasmapheresis, the patient's condition persistently worsened, resulting in death on postoperative day 11.*

Conclusion. *Despite a timely diagnosis and treatment, the prognosis for Seventh-Day Syndrome remains poor, underscoring the need for further research.*

Keywords: liver transplantation, Seventh-Day Syndrome, fulminant liver failure, graft dysfunction, non-thrombotic hemorrhagic infarction of the liver, rejection

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Abbreviations

7DS, Seventh Day Syndrome
ACR, acute cellular rejection
ALT, alanine aminotransferase
AMR, antibody-mediated rejection
APTT, activated partial thromboplastin time
AST, aspartate aminotransferase
BAR, Balance of Risk scoring system
CMV, cytomegalovirus
CRP, C-reactive protein
CT, computed tomography
HCC, hepatocellular carcinoma
HCV, hepatitis C virus
INR, International Normalized Ratio

LT, liver transplantation
SOFT, Survival Outcomes Following Liver Transplantation score

Introduction

According to current data from large registries, a 30-day survival rate of the adult patients undergoing liver transplantation, including for hepatocellular carcinoma (HCC), is about 90% [1]. One of the leading causes of early mortality is a severe graft dysfunction or primary non-function of the graft.

In our own analysis of a series of 500 consecutive liver transplants (LTs), we obtained results comparable with registry estimates: a 30-day survival rate after primary transplants in the entire cohort of recipients was 93%, with 96% (n=357) after transplantation of a liver fragment from a living related donor; 85% after LT from a decease donor (n=122) [2]. Earlier, when studying the immediate outcomes of 131 LTs from deceased donors, we found that of the 21 cases of graft loss that occurred within the first month, more than half were associated with primary non-function (n=5) or severe early dysfunction of the graft (n=7) [3].

As a rule, early unfavorable outcomes are caused by a combination of donor and recipient risk factors, each individual of which is not fatal [4, 5]. Meanwhile, the absence of known risk factors, uncomplicated course of surgery and first postoperative days, as well as satisfactory initial function of the graft do not exclude the development of critical, life-threatening conditions.

One of the rare but extremely severe complications after LT is the so-called a Seventh-Day Syndrome (7DS), which is characterized by a sudden and rapid increase in the alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activities after the initial normalization in the early stages after LT. The syndrome received its name based on the time of its development after LT. There are descriptions of the 7DS

development in the period from the 4th to the 20th day, most often from the 5th to the 10th day after LT. The 7DS development is accompanied by high mortality, reaching 90% in the absence of retransplantation and 73% when repeat LT is performed [6]. The pathogenesis of 7DS is unclear, which complicates diagnosis and treatment. In the prodrome of 7DS, fever may be observed, followed by a rapid and significant increase (> 1,000 U/L) in ALT and AST activities in the setting of clinical well-being with retained patency of the vessels feeding the graft, and the absence of infections.

Below we have presented a case report of 7DS, which developed in a patient who underwent surgery for HCC resulted from underlying liver cirrhosis of viral etiology.

Case Report

Patient H., 63 years old with chronic hepatitis C (HCV RNA detected in patient's blood), which was first diagnosed in autumn of 2022 at the stage of decompensated liver cirrhosis (edematous-ascitic syndrome). Antiviral therapy was not performed. In March 2023, HCC was first detected (foci in S3 and S7 of 4 cm and 2 cm, respectively); alpha-fetoprotein was 7 ng/mL. The patient having MELD-Na score of 16 points, Child-Pugh score of 10 points (class C) was placed on the waiting list for liver transplantation from a deceased donor.

Transplantation was performed from a posthumous donor with identical blood type at A.I. Burnazyan Federal Medical Biophysical Center on May 14, 2023. At the time of surgery the estimated MELD-Na was 17 (the risk of death within the next 3 months was assessed as 6%).

The donor was a 49-year-old man who died as a result of acute cerebrovascular accident leading to the brain death. His peripheral blood tests showed the following results: AST 62 U/L, ALT 36 U/L, total

bilirubin 2.6 μmol/L, creatinine 108 μmol/L, sodium 149 mmol/L in the. Hemodynamics was stable against the background of continuous norepinephrine infusion at a dose of 180 ng/kg/min. Liver explantation was technically uneventful. The predicted duration of static cold preservation was 8.5 hours.

The assessment of the individual preoperative risk of early unfavorable outcome of transplantation using the prognostic model[1] developed in our Center was 2%. Assessments by SOFT and BAR scoring 11 points and 10 points, respectively, did not indicate the high risks, either. A lymphocytotoxic crossmatch test was not performed.

The surgery duration was 5 hours 45 minutes, cold ischemia time for the graft was 9 hours, warm ischemia time was 40 minutes. The surgery was uneventful. Blood loss did not exceed 1000 ml; 1250 ml of fresh frozen plasma was transfused, blood autoreinfusion made 520 ml. For the intraoperative immunosuppression induction, 500 mg methylprednisolone and 20 mg basiliximab were administered intravenously before the reperfusion of the liver graft.

A retrospective histological examination of the donor liver revealed no significant manifestations of steatosis or inflammatory changes. After transplantation and restoring the arterial blood flow under conditions of

[1] Probability of a graft loss within the first 3 months after transplantation when assessed based on preoperative donor and recipient data:

$$p = \frac{e^{logit(p)}}{1 + e^{logit(p)}} \times 100\%,$$

where logit(p) = 5.0561 · Tx.Type + 2.2324 · Tx.No – 2.7390 · LT.Ind + 0.0310 · MDRD.Rec.0 + 0.0006 · D.MELD + 0.0362 · Max.AST.ALT.Don + 0.6099 · CIT.Est – 14.0849.

Tx.Type is the transplant urgency (1, urgent; 0, standard); Tx.No is the transplant number (1, repeated; 0, primary); LT.Ind is the indication for transplantation (1, viral LC; 0, other); MDRD.Rec.0 is the recipient glomerular filtration rate before transplantation as calculated using the MDRD4 formula, ml/min/1.73m^2; D.MELD is the product of donor age (number of full years) multiplied by the current value of the recipient's MELD index (points); Max.AST.ALT.Don is the highest of the donor's AST or ALT values before the organ removal; CIT.Est is predicted static cold ischemia time for the donor liver (hours).

posthypoxic ischemia, the initial morphological signs of ischemic reperfusion injury were observed (Fig. 1).

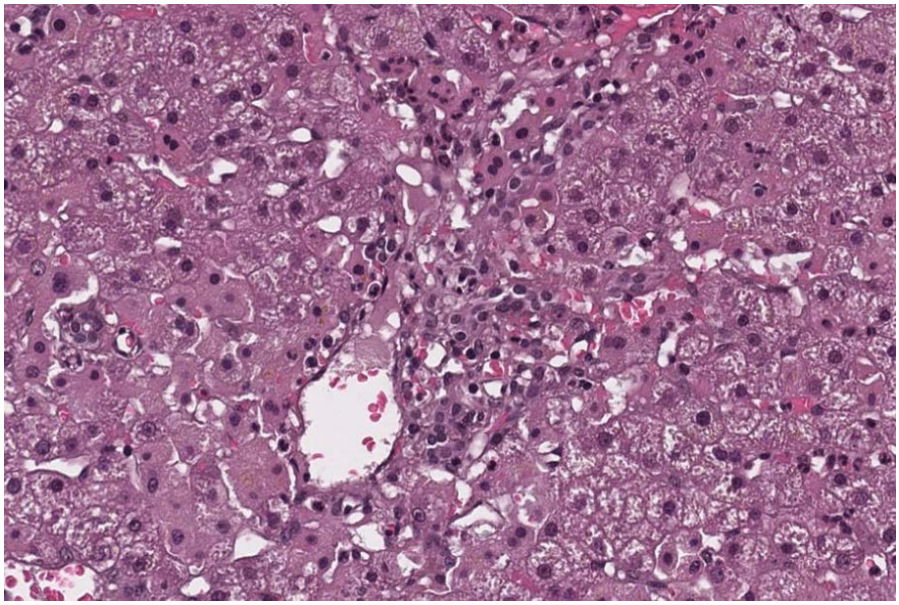
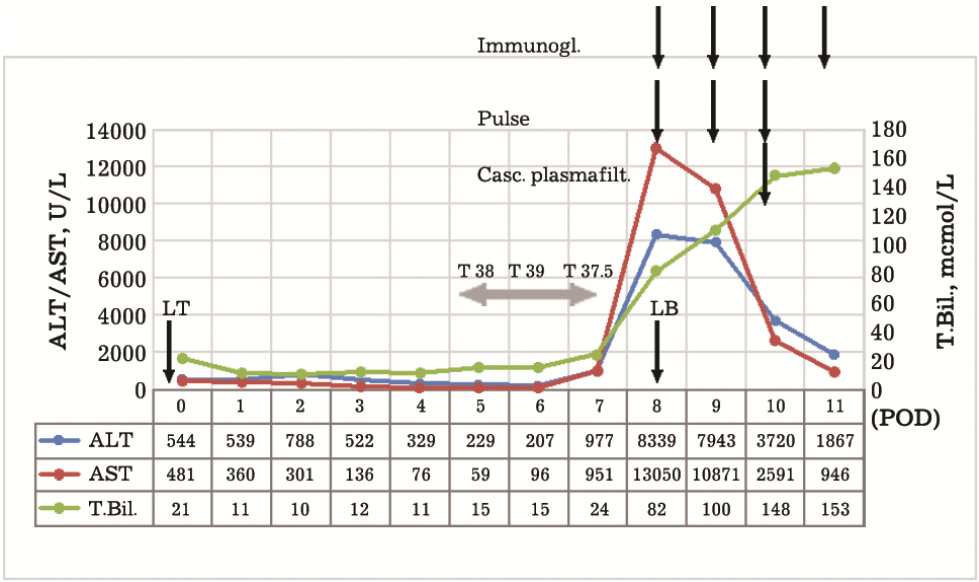


Fig. 1. Micrograph taken after the start of reperfusion. Fragment of the donor liver parenchyma with the preserved lobular structure, uneven plethora of sinusoids, the presence of diffusely scattered neutrophilic leukocytes in their lumens. Pericentrally located hepatocytes are characterized by intracytoplasmic deposition of fine-grained brown pigment. (Hematoxylin/eosin, at magnification x200)

Six hours after the surgery completion, the patient was extubated, the vasopressor support was discontinued. The laboratory tests at the end of the first day yielded the following results: arterial blood lactate 1.2 mmol/L, AST 360 U/L, ALT 540 U/L, international normalized ratio (INR) 1.32, total bilirubin 11 μmol/L, creatinine 56 μmol/L. The graft function was assessed as satisfactory, there was no acute kidney injury.

On the 2nd day after the operation, the patient was transferred to the surgical unit, where the immunosuppressive therapy was continued according to the standard protocol (oral methylprednisolone 16 mg/day,

tacrolimus at a dose of 1 mg/day with further dose increase guided by blood levels of the drug; on day 4, the second infusion of basiliximab 20 mg) and antibacterial prophylaxis was given with meropenem at a dose of 3 g/day. In the following days, the patient's condition remained stable, the function of the transplanted organ was satisfactory (Fig. 2).



	0	1	2	3	4	5	6	7	8	9	10	11
ALT	544	539	788	522	329	229	207	977	8339	7943	3720	1867
AST	481	360	301	136	76	59	96	951	13050	10871	2591	946
T.Bil.	21	11	10	12	11	15	15	24	82	100	148	153

Fig. 2. Graph of changes in alanine aminotransferase and aspartate aminotransferase activities and bilirubin content in patient Kh. after liver transplantation. ALT (alanine aminotransferase); AST (aspartate aminotransferase); Total bilirubin (T.Bil.). LT, liver transplantation; Immunogl., immunoglobulin; Pulse, pulse therapy; LB, liver biopsy; Casc. plasmafilt., cascade plasmafiltration; POD, postoperative day.

On postoperative day 5, fever up to 38°C, watery diarrhea free from blood, green or mucus were observed. The blood leukocyte count was 6.4×10^9 /L, without signs of lineage rejuvenation, C-reactive protein was 31 mg/L. Contrast-enhanced computed tomography (CT) of the chest and abdomen, virology and bacteriology studies of blood, urine and feces did not reveal data for clostridial or herpes (cytomegalovirus (CMV), Epstein-Barr virus, herpes types 1 and 2) infection. Therapy with

meropenem was continued at the previous dose, CMV prophylaxis was started (ganciclovir at a dose of 500 mg per day).

On postoperative day 7, the body temperature and stool returned to normal, but a significant increase in the activity of liver enzymes was noted: AST raised up to 951 U/L, ALT to 977 U/L.

In the morning of postoperative day 8 AST was 13,050 U/L, ALT was 8,235 U/L, there was an increase in bilirubin content from 24 to 82 μmol /L, a three-fold increase in creatinine concentration from 63 to 198 μmol/L was seen (see Fig. 2, Table 1). CT was performed again showing the patent hepatic artery and portal vein; the blood outflow from the graft was unimpaired (Fig. 3). The condition was assessed as a possible acute cellular rejection (ACR) of the graft; a biopsy was performed. Without waiting for the results of the histological examination, a high-dose therapy with methylprednisolone (500 mg/day for 3 days) and intravenous immunoglobulin (0.5 g/kg/day) was started. At the same time, preemptive antiviral treatment for hepatitis C was initiated with a fixed-dose combination of sofosbuvir and velpatasvir. At that time, the patient was first suspected of having 7DS.

Table 1. Dynamics of laboratory parameters in the postoperative period

Day	Glucose (mmol/L)	Lactate (mmol/L)	CRP (mg/L)	Leukocytes (10^9/L)	Platelets (10^9/L)	Tacrolimus (ng/mL)	Creatinine (μmol/L)	MNO	APTT (sec)
0	12.7	3.2	-	5.5	123	-	75	1.6	103
1	7.9	1.2	-	7.2	77	-	56	1.3	61
2	6.8	-	46.8	11.2	-	-	48	1.2	33
3	5.1	-	21.2	8.2	87	0.5	54		
4	5.3	-	26.8	4.1	51	-	40	1	34
5	4.7	-	31	6.4	-	4.2	57		
6	5.5	-	79.7	8.3	107	-	63	1.2	45
7	7.2	-	86.3	8.5	112	-	63	1.4	43
8	8.5	2.7	62.4	-	-	4.9	198	3.2	72
9	5	-	47.8	7.4	53	8.9	300	3.8	75
10	5.2	-	33.5	11.3	51	9.2	409	5.9	82
11	2,2	13.2	16.6	16.8	103	-	431	4	102

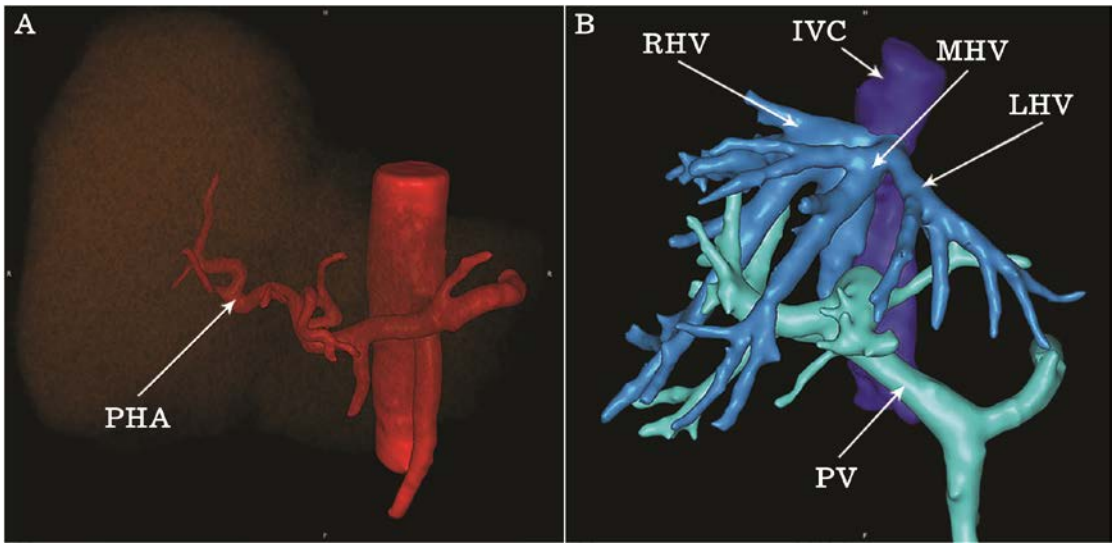


Fig. 3. Computed tomography of the liver on day 8 after liver transplantation, 3D reconstruction. PHA, proper hepatic artery; LHV, left hepatic vein; MHV, middle hepatic vein; RHV, right hepatic vein; PV, portal vein; IVC, inferior vena cava. PHA, PV, LHV, MHV, RHV are patent

The results of the liver tissue histology examination were obtained the following day with 11–12 portal tracts available for examination. Multiple hepatocyte necroses were noted in the centrilobular and intermediate zones, occasionally confluent; relatively intact hepatocytes in the centrilobular zones with signs of intracellular cholestasis were visualized. Extravasation of erythrocytes was observed centrilobularly into the Disse spaces, among which there were single lymphocytes and neutrophilic leukocytes; without signs of lobular inflammation. In the portal tracts, there was a weakly expressed cellular infiltration, not extending beyond the border plate, represented by lymphocytes, plasma cells, eosinophils. Native interlobular bile ducts were visualized in all portal tracts, without signs of inflammation. There were epithelial cells of the bile ducts with weakly expressed reactive changes in the form of hyperchromia of nuclei without atypia and in the form of a shift in the nuclear-cytoplasmic index. No signs of perivenulitis within the examined material were seen. Portal veins were without signs of thrombosis (Fig. 4).

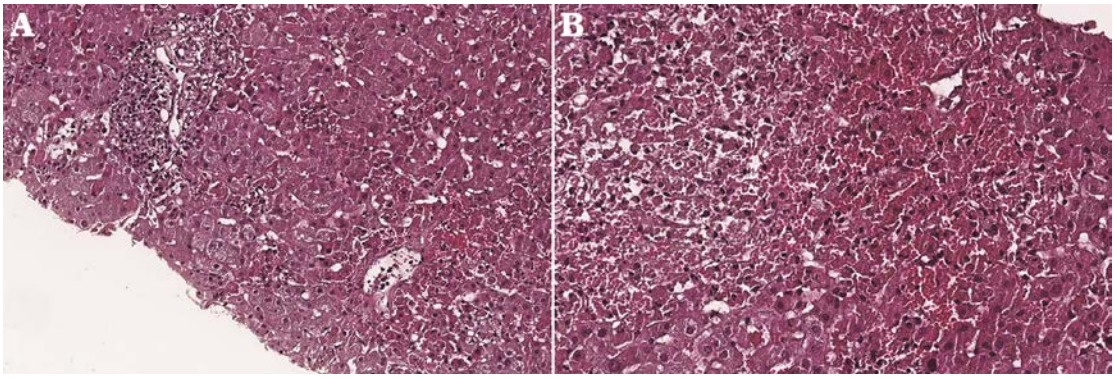


Fig. 4. Micrograph of the liver on day 8 after surgery. A. Changes in the portal tracts (magnification x100). B. Changes in the centrilobular and intermediary zones (magnification x200). Staining: hematoxylin/eosin

Thus, histological examination revealed no signs of ACR or active hepatitis. The morphological pattern, primarily hemorrhagic necrosis of the center of the lobules, neither contradicted the diagnosis of 7DS, nor excluded the antibody-mediated rejection (AMR). During the 9th postoperative day, the patient's condition remained satisfactory. Laboratory monitoring showed a slight decrease in AST and ALT activities, the increase in bilirubin levels slowed down as compared to the previous day.

On day 10, taking into account the possible antibody-mediated mechanism of graft damage, a cascade plasma filtration session was performed (Plasmaflow + Cascadeflow EC-20W, Asahi Kasei Medical, Japan; treated plasma volume was 4100 mL). Due to high risks of infectious complications and HCV replication, it was decided to refrain from administering rituximab.

During the day, the patient's condition began to deteriorate: there were complaints of decreased visual acuity and weakness in the left limbs. Magnetic resonance imaging of the brain did not reveal focal lesions or circulatory disorders. Treatment was continued in the Intensive

Care Unit. The patient was placed on the Waiting List for Liver Retransplantation with the assignment of urgent status.

By the end of the day, the results of multiplex assay (Luminex) of the blood serum sample taken before the plasma filtration and immunohistochemical study of the transplanted liver biopsy were obtained: neither anti-HLA antibodies, nor fixation of the C4d complement component on the vascular endothelium or in the stroma of the portal tracts were found.

Due to the developed respiratory failure and hypotension, the patient was placed to mechanical lung ventilation, a vasopressor support was started. The severity of multiple organ failure increased rapidly, which led to to a fatal outcome on the 11th day after LT.

Pathological examination

The liver allograft in orthotopic position, weighing 1530 g and measuring 24.5×17.0×13.0×6.0 cm, was extracted and examined both macroscopically and microscopically. Liver surface was red-brown with whitish-yellow areas and rough yellowish overlays. In the area of the porta hepatis there was a surgical area with traces of thermal exposure, the structures of the porta hepatis were visually hermetic, the formed vascular anastomoses are competent, patent along the entire length. On the section, the liver tissue was variegated, light brown with red-brown mottling. The lobar and segmental bile ducts and vessels were visually patent along the entire length (Fig. 5A).

The microscopical examination showed liver fragments with subtotal parenchymal necrosis with the development of stromal collapse, hepatic trabeculae discomplexation and severe edema of Disse spaces, relatively intact hepatocytes with protein dystrophy and intracellular cholestasis. Visible portal tracts were minimally fibrotic, not edematous,

contained minimal lymphocytic infiltration, with visualized bile ducts without signs of inflammation. No signs of endothelitis or perivenulitis were seen (Fig. 5B).

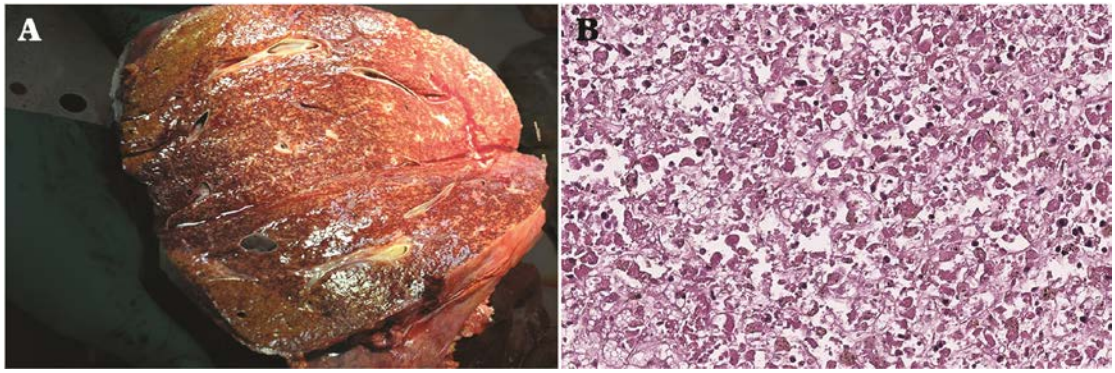


Fig. 5. A. Liver photograph at autopsy section. B. Micrograph. Submassive hepatocellular necroses (magnification x200). Staining: hematoxylin/eosin

The immediate cause of death was the cerebral edema with dislocation and herniation of the brainstem structures and cerebellar tonsils into the foramen magnum, which developed with underlying fulminant liver failure.

Discussion

In the presented clinical case, a severe dysfunction of the transplanted liver manifested itself after a week of a generally smooth postoperative period. The peak of enzyme elevation occurred on the 8th day, after which which there was a decrease in the activity of aminotransferases with a simultaneous increase in jaundice and coagulopathy, followed by the development of hypoglycemia, vasoplegia and multiple organ failure.

The histological examination of donor liver biopsy specimens obtained during removal and before the transplantation completion, the course of

anesthesia, and the first postoperative days excluded severe ischemic reperfusion injury, which is often the cause of early graft dysfunction.

An acute increase in aminotransferase activity in the days immediately following transplantation usually occurred as associated with hepatic artery thrombosis. Daily ultrasound examinations and two CT scans (on the 5^{th} and 8^{th} days) indicated the absence of any disorders of blood supply to the graft.

One of the possible complications that could lead to the graft dysfunction is a steal syndrome. This syndrome is characterized by a decreased blood flow in the hepatic artery due to the redistribution of blood in favor of other vascular beds, such as the splenic or gastroduodenal arteries, which leads to ischemia of the transplanted liver [7]. The steal syndrome usually develops early after transplantation and is manifested by increased activity of transaminases, alkaline phosphatase, and bilirubin or persistent ascites in the absence of acute cellular rejection, infection or toxicity [7]. The diagnosis of the steal syndrome is based on the data of Doppler ultrasound and angiography. In this syndrome, patients usually exhibit a high (IR>0.8) or low (IR<0.5) hepatic artery resistance index with low diastolic blood flow velocity or even diastolic flow reversal. The systolic blood flow velocity in the hepatic artery is usually reduced (<35 cm/s), indicating poor blood flow [7]. In our case, the steal syndrome was excluded, since the daily Doppler studies showed that the blood flow velocity in the hepatic artery up to the 7^{th} postoperative day exceeded 35 cm/s and amounted to 85 cm/s on the 7^{th} day, and the resistance index on the 7^{th} day was 0.68.

Herpes simplex virus infection, types 1 and 2, may also result in a significant increase in aminotransferase activity in the first 2 weeks after LT. ACR may be observed at approximately the same time, but the severity of graft damage is usually much less pronounced (ALT and AST

activities lower than 1,000 U/L), and the prognosis for the graft and recipient is favorable.

It is evident that reinfection of the graft with the hepatitis C virus – which undoubtedly occurred in our patient – could not have led to the development of acute hepatitis within such a short timeframe and therefore did not account for the clinical presentation. Moreover, preemptive antiviral therapy with highly effective drugs against hepatitis C was initiated in the early postoperative period.

It is also obvious that fever primarily requires the exclusion of infectious complications and the empirical administration of a broad-spectrum antibacterial therapy if the patient has not received it yet. The microbiological test results, the absence of leukocyte rejuvenation signs, and neutropenia, the undertaken adequate antimicrobial prophylaxis excluded an infectious origin of graft dysfunction. Antifungal prophylaxis was not performed due to the absence of high-risk factors for invasive fungal infections before transplantation, such as retransplantation, long-term surgery, etc. [8]. However, with the development of a severe transplant dysfunction and retransplantation planning, a decision was made on the need for prophylactic antifungal therapy.

Liver transplantation from a donor with an identical blood type, as well as the absence of sensitizing events (multiple blood transfusions, organ transplantation) in the patient's medical history, which could lead to the production of pre-existing antibodies to the molecules of the major histocompatibility complex, made it possible to consider the risk of AMR to be minimal.

The strength of our observation was the availability of a series of donor organ biopsies and graft biopsy. A thorough examination of the donor organ made it possible to exclude the prerequisites for the development of extensive necrosis due to the quality of the donor organ.

Thus, the observed clinical presentation, chronology of events, and dynamics of laboratory parameters most closely corresponded to the so-called seventh-day syndrome, which was confirmed by intravital and postmortem histological studies of liver tissue. The term 7DS was first proposed by UK researchers in 2001 to describe a swift increase in aminotransferase activities in recipients by the end of the first week after LT against the background of a decrease in signs of graft damage as a result of ischemia and reperfusion [9]. The pathological substrate was centrilobular hemorrhagic impregnation without significant inflammation in the setting of the patent large vessels. There were also earlier descriptions of the development of non-thrombotic hemorrhagic infarctions of the transplanted liver parenchyma; the clinical pattern in this case was consistent with the syndrome that was subsequently called 7DS [10]. Fever is an important clinical manifestation that appears to reflect the development of massive hepatic necrosis but usually precedes the recording of excessively high aminotransferase activity.

In 2022, a group of researchers from Birmingham University Hospital (UK) published a review of a series of 7DS cases, which included a total of 44 cases. The rarity of this pathology can be judged by the fact that the researchers who retrospectively, in a biased manner analyzed 1,907 LTs performed between 2010 and 2020, identified and had in their own archive only 6 cases of 7DS, that is, its incidence was 0.3% [11]. On the other hand, it is possible to assume the existence of less severe forms of 7DS, in which high doses of methylprednisolone delay the progression of the syndrome, as described by researchers from Korea [12]. Perhaps in these cases, there was a combination of 7DS with ACR. There were descriptions of 7DS after LT from both posthumous and living donors. In the last 2 years since after publication of the review by the British authors, we were able to find a single publication of a case of

7DS that occurred in a child who received a liver fragment (K. Hartjes et al., 2024) [13]. Despite the measures taken (thymoglobulin, rituximab, immunoglobulin and plasmapheresis), the graft could not be saved. Retransplantation was performed on the 11th day after LT. Interestingly, a child who received another fragment of the same liver (split transplantation from a postmortem donor) had an uncomplicated postoperative course.

This complication occurred so rarely that neither clinical guidelines nor even any pathogenetically substantiated advice have been developed. One of the important observations is the ineffectiveness of glucocorticosteroids in patients with 7DS. There is reason to believe that the development of 7DS is (at least partially) based on the same mechanisms that are involved in liver damage within the framework of AMR. A good example is the case of post-transplant sinusoidal obstruction syndrome associated with AMR, described by Spanish authors [14]. The researchers found a predominance of intralobular damage over portal tract abnormalities, the fixation of the C4d-complement component in the sinusoids, and identified donor-specific anti-HLA antibodies in recipient's blood. The use of steroid "pulses" and defibrotide practically did not lead to an improvement in histological manifestations, but plasmapheresis sessions in combination with the administration of immunoglobulin turned out to be effective. T. Matsuura et al. (2021) reported on the efficacy of rituximab, plasma exchange, and intravenous administration of high-dose immunoglobulin in the treatment of a patient with 7DS [6].

According to a meta-analysis of 48 observations, the mortality rate of patients with 7DS was 75% [11]. Only 6 recipients of 50 (including the authors' own case series) survived without retransplantation on a conservative therapy.

In our case, a cascade plasma filtration was performed; however, taking into account the analysis of the literature sources, plasma exchange would probably be more appropriate, since it allows for the removal of not only antibodies, but also decay products released during massive necrosis of the liver parenchyma.

One should critically interpret individual cases where the use of lymphocyte-depleting antibodies, including rituximab, in combination with high-dose immunoglobulin and plasma exchange sessions commonly used to treat AMR or preoperative desensitization could lead to 7DS regression. It is possible that in these cases, despite the absence of classic signs (donor-specific anti-HLA antibodies, a positive immunohistochemical reaction to C4d), the cause of the dysfunction was actually the rejection caused by antibodies against MICA or ATII-1R rather than 7DS. Variants of C4d-negative AMR are also known. Nevertheless, if 7DS is suspected, we believe that an immediate initiation of plasmapheresis sessions and high-dose immunoglobulin administration is a justified approach, which, if not leading to graft salvage, will at least expand the therapeutic window for retransplantation.

In our case, a repeat transplant was not possible due to the rapidly progressing deterioration of the patient's condition and the lack of a potential donor at that time.

Conclusion

Although seventh-day syndrome is a rare complication in liver transplant recipients, its high fatality rate makes it particularly critical. The physician has only hours – not days – to establish the correct diagnosis and initiate appropriate treatment. A prompt decision regarding the need for retransplantation is essential, even when there is an apparent

discrepancy between the patient’s seemingly stable clinical condition and the catastrophic deterioration in liver function tests.

Our case report emphasizes the need for further research into the seventh-day syndrome and the development of new approaches to its diagnosis and treatment. We suggest that future studies aimed at investigating the immunological and ischemic mechanisms of graft injury will help improve treatment outcomes and increase recipient survival rates.

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