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Seronegative fibrosing cholestatic hepatitis C after liver retransplantation for unresectable neuroendocrine tumor liver metastases

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Abstract

We present an uncommon case of liver graft dysfunction caused by seronegative hepatitis C-related fibrosing cholestatic hepatitis after cadaver liver transplantation for unresectable liver metastases of neuroendocrine small intestine cancer followed by living relation donor liver fragment retransplantation for primary graft nonfunction. Early postoperative period was complicated by hepatic artery thrombosis, cerebral hemorrhage, acute cellular rejection, bilateral polysegmental pneumonia, bleeding into neck soft tissues, severe surgical site infection, and sepsis. Anticoagulant therapy, as well as the absence of Hepatitis C Virus antibodies made difficult early diagnostics of fibrosing cholestatic

hepatitis. A present-day antiviral therapy produced a complete clinical and virological response. At control examination performed at 240 days after surgery, there were neither signs of cancer progression no graft dysfunction. Liver transplantation in that case was an example of radical and effective treatment method for unresectable liver metastases of neuroendocrine small intestine cancer. Timely diagnosis and proper treatment of fibrosing cholestatic hepatitis made it possible to save the liver graft and patient's life.

Keywords: neuroendocrine small intestine cancer, metastases, seronegative hepatitis C-related fibrosing cholestatichepatitis, seronegative hepatitis C, recurrent hepatitis C, liver allograft, dysfunction, liver transplantation, complications

Conflict of interests Authors declare no conflict of interest

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ACR, acute cellular rejection

ALT, alanine aminotransferase

AST, aspartate aminotransferase

AVT, antiviral therapy

CT, computed tomography

DAA, direct-acting antiviral (drug)

FCH, fibrosing cholestatic hepatitis

HA, hepatic artery

HAT, hepatic artery thrombosis

HIV, human immunodeficiency virus

LT, liver transplantation

PGNF, primary graft nonfunction

reLT, liver retransplantation

Introduction

Treatment of patients with unresectable metastases of neuroendocrine cancer is a serious challenge for oncologists and surgeons around the world . A low malignancy potential of some neuroendocrine tumors makes it possible to consider liver transplantation (LT) as the only radical method of treatment for this category of patients. In leading clinics in the US and the EU, LT criteria have been developed and successfully applied to patients with unresectable metastases of neuroendocrine cancer.

Thanks to the development of surgical technologies and standardization of organ donation approaches, protocols of immunosuppressive and antiviral therapy, the incidence of dangerous complications such as a primary graft non-function (PGNF), hepatic artery thrombosis (HAT), postoperative wound infection, sepsis, fibrosing cholestatic hepatitis (FCH), rejection in the early post-transplant period have been decreasing. Each of the listed complications can be fatal, and their combination in one patient requires a very high professional level from doctors and a coordinated teamwork to save the patient's life.

We present a case report of a successful LT in a female patient with unresectable metastases of neuroendocrine small bowel cancer. In the postoperative period, the patient had all of the above listed (and also some other) complications, and the cause of a severe graft dysfunction appeared unexpected and brought about significant diagnostic difficulties.

Clinical Case Report

A female patient S., 40 years old, was referred for the first time to the State Research Center – Burnasyan Federal Medical Biophysical Center of Medico-Biological Agency (FMBA) of Russia in December 2017 for the multiple masses of the liver identified at a prophylactic medical examination at an outpatient department at the place of residence. According to the results of computed tomography (CT) of the abdomen, a tumor infiltrate of 30 mm x 20 mm in the mesentery of the small intestine was identified, multiple bilobular tumor lesions of all liver segments were confirmed (at least 11 foci sized from 10 to 117 mm, Figure 1). According to the results of histological and immunohistochemical studies of the biopsy specimen obtained from the lesion in the right lobe, a neuroendocrine tumor G1 (NET1 G1, Ki 67 less than 2%) was diagnosed. Neuroendocrine cancer of the small intestine (T4N1M1) with metastatic invasion in the liver was suspected; the diagnosis was completely confirmed by the results of subsequent surgical treatment. In January 2018, the resection of the small intestine segment containing the tumor followed by making enteral-enteral anastomosis, and atypical resection of liver S2–3, 5–6, 7 were performed. Biotherapy with an extended release octreotide was administered at a dose of 30 mg every 28 days. In 2018–2019, five courses of superselective transarterial chemoembolization of liver metastases with hepaspheres (HepaSphere™ microspheres of 300–500 μm in size, Biosphere Medical, France) loaded with doxorubicin At examination (positron emission tomography scan (PET) 18 months after surgery, signs of liver metastatic lesions persisted with an increased accumulation of the radiopharmaceutical; no signs of extrahepatic tumor invasion were seen.

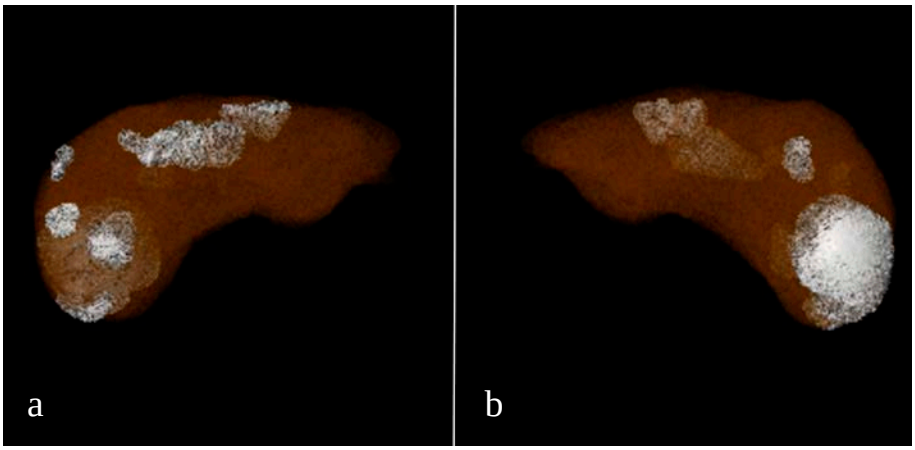

Fig. 1. Preoperative computed tomogram. Multiple bilobar lesions of all liver segments. A. Reconstruction of the frontal section of the liver, anterior view. B. Reconstruction of the frontal section of the liver, posterior view

As far as a radical resection of liver metastases was impossible, so on October 25, 2019, LT from a posthumous donor was performed to the patient in accordance with the criteria of the Mayo Clinic, UWO (University of Western Ontario), ENETS (European Neuroendocrine Society). Induction immunosuppression was performed according to the standard protocol, which included 1000 mg of methylprednisolone in the anhepatic period and basiliximab. At the time of LT, no anti-HCV or HBsAg were detected in the patient's blood. In the perioperative period (LT and liver retransplantation [reLT]), the patient received a total of 5800 mL of quarantined blood components (fresh frozen plasma and erythrocyte suspension) transfused. The postoperative period was complicated by PGNF. On October 29, 2019, retransplantation of the liver right lobe from a related donor was performed, making two hepatico-caval anastomoses, the reconstruction of liver S5 venous outflow with an autovein, making the hepatico-enteral anastomosis on the excluded-by-Roux loop under conditions of temporary drainage of the bile ducts through a suspended enterostomy.

The second day of the postoperative period was complicated by HAT with increased alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activities up to 2500 IU/L. Endovascular mechanical thrombextraction from the hepatic artery (HA), angioplasty, and stenting of the native HA were urgently performed (Figure 2-4).

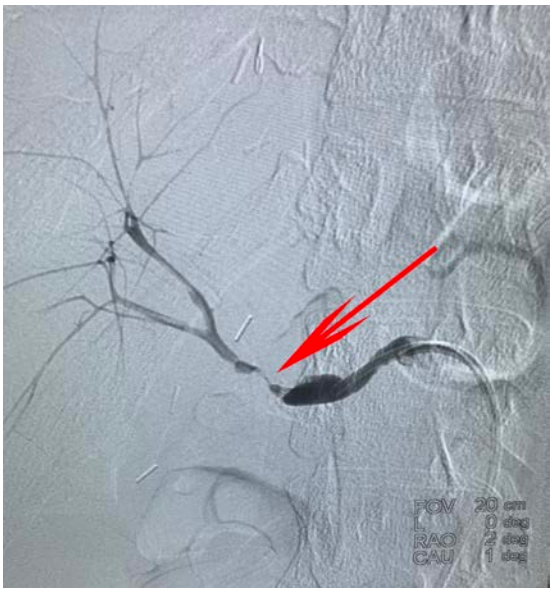

Fig. 2. Direct angiography. The arrow indicates the hepatic artery occlusion due to thrombosis

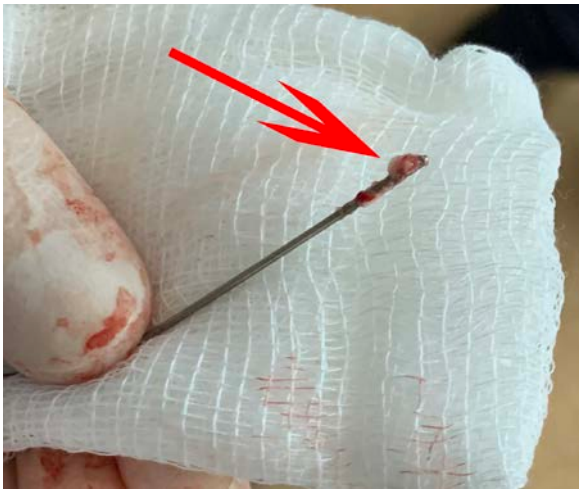

Fig. 3. Photo of thrombus after mechanical thrombextraction from the hepatic artery

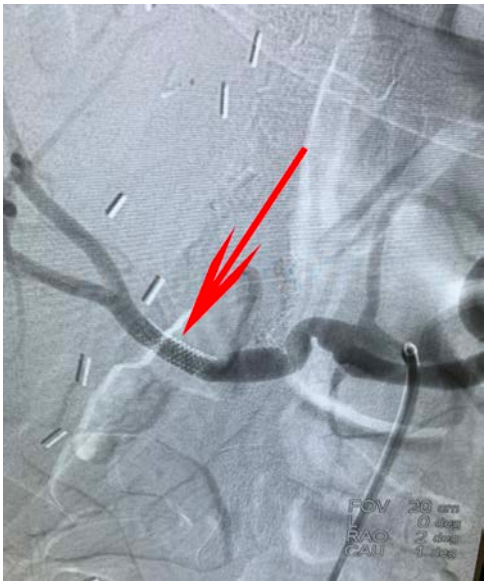

Fig. 4. Direct angiography after hepatic artery stenting. The arrow indicates the stent in the artery

Against the received anticoagulant and antiplatelet therapy, on the next day, the patient showed depression of consciousness to the level of deep stunning, stupor. At CT of the brain, an intracerebral hematoma of 54x37x24 mm in size with moderately pronounced perifocal edema was revealed in the left frontal lobe. Parenchymal-subarachnoid ventricular hemorrhage was diagnosed in the left frontal lobe. Given a high risk of thrombosis of the HA stent, the therapy with anticoagulants and antiplatelet drugs was continued in the volume of continuous intravenous infusion of heparin controlled by the target level of activated partial thromboplastin time (45-50 seconds) and clopidogrel 75 mg per day for 2 weeks, followed by switching to enoxaparin 0.4 mg once a day, and clopidogrel 75 mg daily for a long time.

A conservative treatment in the Intensive Care Unit was provided within 3 weeks. Due to the respiratory failure developed in association with bilateral polysegmental pneumonia, the mechanical lung ventilation via a tracheostomy tube was performed for a week. From that time on, the

patient experienced the gradually increasing jaundice with simultaneously decreasing aminotransferase activities.

Considering a significant number of complications developed, a maintenance immunosuppressive therapy with tacrolimus in minimal doses was started on day 5 after reLT. On day 7, the blood bilirubin was 125 μmol/L, ALT was 370 IU/mL, the blood level of tacrolimus was 0.7 ng/mL. Considering the time elapsed after retransplantation, the increasing jaundice, leukocytosis with rejuvenation of neutrophil and absolute eosinophilia without obvious signs of infection, and minimal maintenance immunosuppression, it was reasonable to suspect the development of acute cell rejection (ACR) associated with the ischemic injury of the graft. Histological verification of the diagnosis was not performed due to a high risk of bleeding in the course of anticoagulant therapy. A bolus injection of methylprednisolone of 500 mg daily for 3 days was undertaken with the following effect: by November 10, 2019, bilirubin had decreased to 56 μmol/L, ALT to 110 IU/mL.

From that time on, the patient developed suppuration of the postoperative wound with a partial eventration, which required the removal of sutures and an open wound management with daily debridement dressings. The sepsis caused by *Klebsiella pneumoniae* was diagnosed. The blood level of procalcitonin reached 20 ng/mL, *C*-reactive protein was 89 mg/L. Due to the development of infectious complications, the immunosuppressive therapy was discontinued for a week. With the broad-spectrum antibiotic therapy (meropenem, tigecycline), the patient's condition gradually improved, the wound cleared, the blood level of procalcitonin dropped to 1.7 ng/mL. Tacrolimus was resumed at a dose of 1 mg per day, and its blood level was maintained at 2-4 ng/mL. Later on, as the postoperative wound was

healing, the tacrolimus dose was increased to 4.5 mg per day, and its blood level was maintained at 5–8 ng/mL.

After immunosuppression withdrawal and against the treatment of infectious complications, the patient's jaundice resumed increasing. By December 3, 2019 (day 35 after reLT), total bilirubin was 200 μmol/L, ALT was 350 IU/mL, AST was 580 IU/mL. Neither cytomegalovirus DNA, nor HBsAg or anti-HCV antibodies were detected in blood. The diagnostic "zugzwang" occurred. Making the liver biopsy was still restricted due to a high risk of bleeding during anticoagulant therapy, and the withdrawal of that therapy was limited by the risk of the HA stent thrombosis. Moreover, the intensification of the immunosuppressive therapy might have created the risk of recurrent purulent complications. The Doctors' Council discussion recognized ACR as the most probable cause of the graft dysfunction, and, taking into account all the above risks, as well as the success of the first course of pulse therapy, methylprednisolone at a daily dose of 1000 mg for 3 days was empirically administered again. Unfortunately, this treatment was unsuccessful. The ALT and AST activities decreased, having reached the minimum (62 IU/L and 74 IU/L, respectively) by December 10, 2019, but the bilirubin level (almost entirely owing to the conjugated fraction) increased to 300 μmol/L, and to 360 μmol/L a week later.

Due to a growing graft dysfunction of an unknown origin and jaundice, plasmapheresis was decided to be given to the patient. An attempt to insert a perfusion catheter for plasmapheresis on 09.12.2019 was complicated by the bleeding from the superior thyroid artery, pulsating hematoma with compression of the trachea and esophagus, which required an emergency surgical treatment. The patient underwent several sessions of plasmapheresis with a transient effect.

By day 50 after reLT, the patient's case had been discussed by the Doctors' Council again. Taking into account the predominantly cholestatic nature of jaundice in the absence of biliary hypertension signs, as well as the medical history data, it was proposed to make a differential diagnosis between rejection (likely, steroid-resistant?) and ischemic post-thrombotic cholangiopathy. Considering the fundamentally different treatment tactics, histological examination of liver tissue became extremely necessary. Despite the absence of HBsAg and anti-HCV antibodies in blood, it was decided to test for HBV DNA, HCV RNA.

Against a short-term withdrawal of anticoagulants, and the transfusion of fresh frozen blood plasma, a needle biopsy of the liver was performed on December 23, 2019. The histological examination of the liver tissue showed the lobular structure kept preserved. Vascular and ductal structures were present in all seven portal tracts. In three tracts, there was an unpronounced inflammatory infiltration with a predominance of neutrophil granulocytes penetrating into the epithelium of the small bile ducts; it did not extend beyond the parenchyma. There was pronounced intracanalicular centrilobular cholestasis, the accumulation of bile in hepatocytes, with pronounced degenerative abnormalities of the latter, up to microscopic necrosis (one to two dozen cells). The bile accumulation in cytoplasm and the dystrophic changes increased from zone I to zone III of acinus; in zone III hepatocyte necrosis was detected. The central veins were without abnormalities. According to histologists' conclusion, cholestasis and dystrophic changes in the parenchyma dominated. There were no signs of ductopenia or rejection in the studied material (Figure 5). The following day, the results of the study for the genomes of hepatitis viruses were obtained. In the patient's blood, HCV genotype 2 RNA was found, of over 10^8 IU/mL, while anti-HCV antibodies (IgM and IgG) were still not detected.

Based on the clinical manifestations of the disease, the results of histological examination of the liver tissue, and HCV viremia tests, FCH C was diagnosed. On December 27, 2019, the antiviral therapy (AVT) with daclatasvir and sofosbuvir in standard doses was started giving a rapid positive effect. After 4 weeks of AVT, jaundice was arrested, the bilirubin level was actually normalized (26 μmol/L), ALT was 47 IU/mL, AST was 37 IU/mL. HCV viremia decreased to 10^4 IU/mL. The patient was discharged home in a satisfactory condition with recommendations to continue the AVT on an outpatient basis. Following the discharge in February 2020, everolimus was added to the maintenance immunosuppressive therapy with tacrolimus (target baseline concentrations of 3-5 ng/L). To prevent the progression of neuroendocrine cancer, biotherapy with extended release octreotide at a dose of 30 mg every 28 days was recommended.

The patient received the combination of sofosbuvir and daclatasvir for 16 weeks. From week 4 of AVT, HCV viremia (10^4–10^5 IU/mL) persisted; and from week 8, there was an increase in the ALT and AST activities of up to 150–100 IU/mL. The study of drug resistance mutations to HCV genotype 2 was not available to us, and the AVT was empirically changed to a fixed drug combination of glecaprevir and pibrentasvir; based on the results of an 8-week course, a complete biochemical and stable virological response was obtained. Throughout the entire observation period, the patient was repeatedly tested for anti-HCV antibodies. All tests gave negative results (Figure 6).

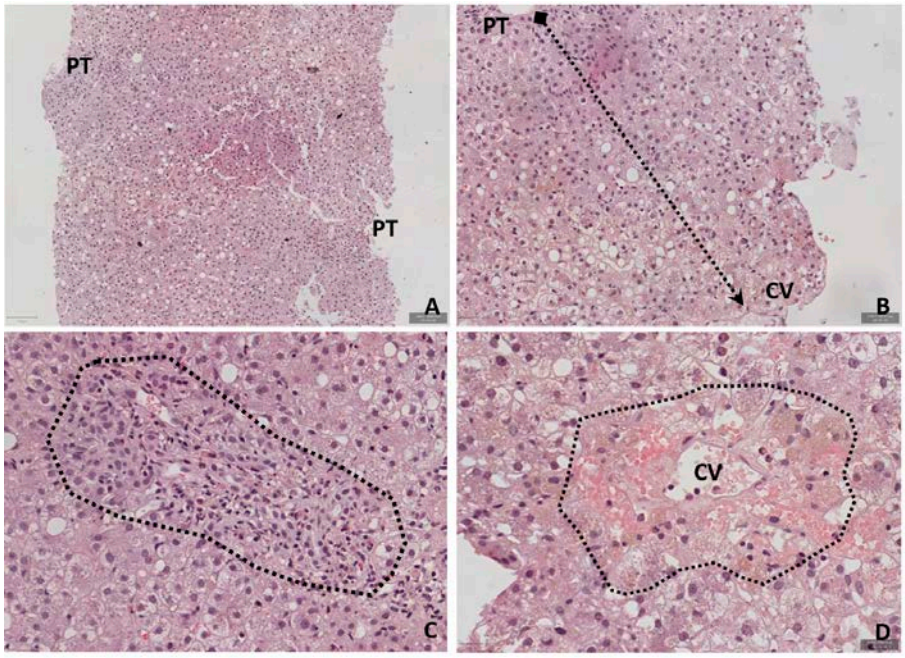

Fig. 5. Photo of the liver graft core-needle biopsy micropreparation. Stained with hematoxylin and eosin. A. Objective lens magnification 10x. Indistinct large droplet fatty degeneration; portal tracts (PT) are without significant inflammatory infiltration. B. Objective lens magnification 20x. The gradient of dystrophic alterations is shown by an arrow from the portal tract (PT) to the central vein (CV) with the increase in severity, up to necrosis. C. Objective lens magnification 40x. Portal tract with ductal response and reactive abnormalities in the epithelium of the bile ducts (the area is circled), which commonly accompanies fibrosing cholestatic hepatitis. The inflammatory infiltrate is not pronounced, it is represented by lymphocytes with an admixture of neutrophil granulocytes. Adjacent hepatocytes have minimal degenerative alterations. D. Objective lens magnification 40x. There is hepatocyte necrosis around the central vein (CV) (the area is circled). Bile pigment is present in the hepatocytes with ballooning degeneration outside the specified area

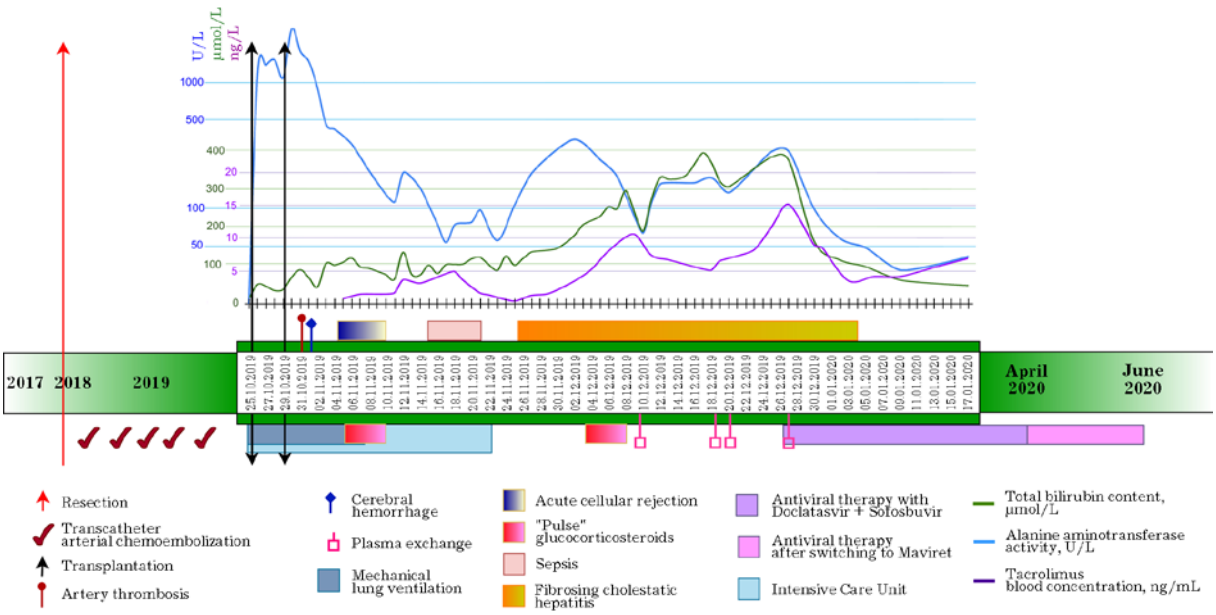

Fig. 6. The Chart of key events and laboratory parameters in the course of the patient's treatment

At the follow-up examination 8 months after the liver fragment retransplantation, there were no signs of neuroendocrine cancer progression (Figure 7).

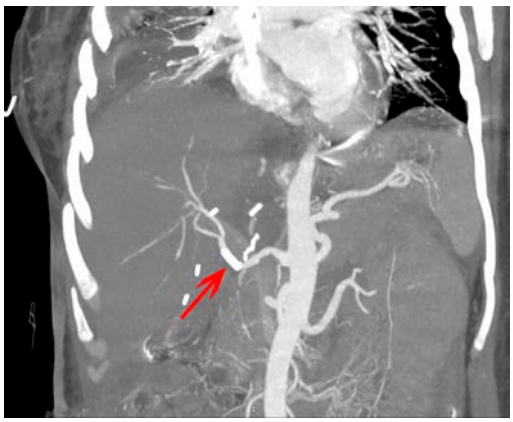

Fig. 7. Computed tomography at 8 months after retransplantation. No findings of tumor recurrence. Hepatic artery stent (arrow) is patent

Discussion

Liver transplantation to patients with unresectable metastases of neuroendocrine cancer has been an actively developing area of modern oncology in the recent two decades. According to the review of publications since 1990, including the studies on at least 10 patients, more than 830 LTs have been performed worldwide for unresectable metastases of neuroendocrine cancer with a 5-year survival rate of 50% to 80%.

The resectability of these neoplasms has been enhanced thanks to the elaboration of up-to-date transplant technologies, the development of new immunosuppressive therapy drugs, as well as the experience gained.

In some cases, the relapse-free survival after LT for unresectable metastases of neuroendocrine cancer has reached more than 10 years. However, the authors point out the need for a careful selection of patients, taking into account certain criteria. All the proposed criteria (of the Mayo Clinic, the University of Western Ontario [UWO], the European Neuroendocrine Society [ENETS]) imply a mandatory removal of the primary cancer lesion, Ki-67 index under 2%, the absence of extrahepatic metastases, the process stabilization with the ongoing therapy for at least 6–12 months [4]. Thus, LT can be considered as the only radical treatment for this category of patients.

Our patient met the proposed criteria completely. The time from the removal of the primary tumor to LT was 20 months, which made it possible to make sure that there was no tumour extrahepatic spread. During that period, the patient underwent five sessions of transarterial chemoembolization for liver metastases. This technique makes it possible to control the oncological process in patients with neuroendocrine cancer metastases to the liver during the observation and selection for LT, as

well as to increase the waiting time for LT in patients who have been on the waiting list for a posthumous donor organ.

The case is also interesting in that the post-transplant period was complicated by a number of "major" life-threatening complications, each of which could lead to patient's death. Subsequently she developed the most dangerous complications of the early post-transplant period, such as PGNF (requiring retransplantation), HAT (requiring endovascular thrombextraction and HA stenting), cerebral hemorrhage, suspicion of ACR (requiring pulse therapy), bilateral polysegmental pneumonia, total wound suppuration (requiring its open management and prolonged debridement dressings), sepsis (requiring a broad-spectrum antibacterial therapy), and bleeding into the soft tissues of the neck with the trachea compression (requiring urgent surgical treatment). According to literature reports, the PGNF incidence makes from 4% to 6%. The incidence of HAT after LT is 3–4%. More than 60% of recipients develop infectious complications in the first year after LT, which remain the main cause of death. Finally, early ACR after LT occurs in about 16%.

The development of all these complications in one patient is an extremely rare and serious challenge to the teamwork and professional skills of the transplant center team. The development of these complications was of particular difficulty in conditions of limited diagnostic capabilities due to the anticoagulant therapy and graft dysfunction of an unclear origin.

Fibrosing cholestatic hepatitis is a specific form of liver disease caused by HCV or HBV in an immunosuppression setting, characterized by a rapidly progressing course and a frequent graft loss. There are literature reports of FCH in patients with human immunodeficiency virus (HIV) co-infection, and in patients with oncological diseases, recipients of bone marrow and solid organs. The largest number of FCH C case

reports have been published in liver transplant recipients. FHG differs fundamentally from chronic hepatitis, the most common form of HCV-caused liver disease, by its scarce inflammatory response in the presence of pronounced degenerative changes in hepatocytes. As the name implies, parenchymal cholestasis predominates in the clinical pattern of FCH. The virological characteristics of FCH include ultra-high viremia, low heterogeneity of the HCV population (quasispecies), and the immunological characteristics include the predominance of T-helper type 2 response. All of the above allows us to assume that under conditions of immunosuppression, HCV implements a direct cytopathic effect, which is associated with clinical and morphological manifestations of the disease. This variant of liver injury is observed in 2–9% of patients with recurrent hepatitis C after LT.

An important feature of our case, which led to the delayed diagnosis, was the absence of HCV serological markers. Cases of HCV infection in the absence of antibodies in patient's blood have been known since the first years of the virus discovery. This course of infection is possible in conditions of a compromised immune response , but it can also occur in healthy donors . In their review, Kazmierczak et al. (2014) reported rather high rates of seronegative hepatitis C in patients with HIV co-infection (3.2–13.2%), as well as in patients receiving a hemodialysis treatment (1–15%). Among organ donors seronegative for anti-HCV, the HCV RNA is generally detected in less than 1% (0.2–0.9%) of cases. A particularly low incidence of seronegative hepatitis C has been reported among immunocompetent blood donors (0.0004–0.08%) . The pathogenesis of seronegative HCV infection is still incompletely understood. Most likely, this type of infection develops due to the immune system dysfunction, leading to the inability to correctly recognize HCV antigens and produce specific antibodies. Another

mechanism could be the infection with an atypical viral strain. A detailed review of the seronegative hepatitis C causes is beyond the scope of our case report.

The source of our patient being infected with the virus is of particular interest. The patient's first donor underwent a multi-organ explantation. We reported of the possible risk of infection to other transplantation centers, and all kidney and heart transplant recipients were tested negative for HCV RNA. The patient's live related donor (the son) was re-examined. Probably, the virus was acquired by the patient via transfusion, and the absence of anti-HCV antibodies in the components of donor blood did not allow it to be discarded in a timely manner. In this case, the incubation period was about a month, and the first episode of the graft dysfunction effectively treated with methylprednisolone pulse therapy, had actually been associated with ACR. Finally, our patient herself could have been a carrier of HCV infection before transplantation and develop a FCH manifestations as recurrent hepatitis C against the immunosuppressive therapy.

In the absence of effective antiviral therapy, FCH usually resulted in a graft loss. This was the case in the era of using pegylated interferon, which efficacy in the treatment of recurrent hepatitis C did not exceed 30%.

With the implementation of direct-acting antiviral drugs into routine clinical practice, the situation considerably changed. A cure can be achieved in the overwhelming majority of cases, including those with the FCH development. Unfortunately, reports on effective DAA therapy courses for FCH have been limited to individual case reports or descriptions of case series. The efficacy of drug combinations of sofosbuvir with daclatasvir or sofosbuvir with ledipasvir has been the most studied in FCH. The duration of an effective course of AVT for

FCH has not been determined. Leroy et al. (2015) published the results of a prospective study in which 15 recipients with FCH were treated with sofosbuvir, daclatasvir, and ribavirin for 24–48 weeks. A sustained virological response was obtained in all patients. Forns et al. (2015) retrospectively analyzed 11 liver transplant recipients who received sofosbuvir and ledipasvir in combination with ribavirin as part of SOLAR1,2 trials. Seven patients received AVT for 12 weeks, and 4 patients did for 24 weeks. HCV eradication was achieved in all patients . Unfortunately, patients with FCH were not included in clinical trials of the efficacy of other current regimens (sofosbuvir/velpatasvir and glecaprevir/pibrentasvir) in recurrent hepatitis C after LT [22, 23].

Despite the standard 12-week course of current direct-acting antiviral drugs (DAAs) without adding ribavirin has been found sufficient to achieve a virological response in the vast majority of patients with recurrent hepatitis C, patients with FCH may require a longer therapy. A group of investigators from Italy reported 2 cases of repeated treatment for FCH in patients after an unsuccessful therapy course with sofosbuvir in combination with velpatasvir for 12 weeks. A 16-week course of AVT with glecaprevir and pibrentasvir was a success.

Our patient's HCV viremia persisted after 16 weeks of treatment, which was another specific feature of our reported case. We cannot reliably say whether our patient developed a drug resistance to one of the AVT components (sofosbuvir or daclatasvir). The long-term persisting viremia was possibly associated with the same features of the virus, which prevented from the anti-HCV antibodies to be formed that we could have been detected in a standard blood test. Using the combination of glecaprevir and pibrentasvir made it possible to achieve a complete cure of the HCV infection and the FCH disease it had caused. One should note that FCH remains a serious problem even in the DAA era. There are

reports of unsuccessful treatment of FCH in a patient infected with genotype 2 HCV, who, despite the timely initiation of therapy with glecaprevir and pibrentasvir, died of the liver failure.

Conclusion

Thus, liver transplantation in our patient was a radical method for the treatment of unresectable metastases of small intestine neuroendocrine cancer into the liver. Unexpectedly for the team of our Liver Transplantation Center, the patient developed a succession of severe complications, each of which carried a high risk of the graft loss and a threat to the recipient's life. The treatment of surgical complications was performed against the background of severe graft dysfunction, which cause was not obvious, and the possibilities of using invasive diagnostic techniques were limited by the need for continuous anticoagulant therapy. The use of present day technologies made it possible to successfully cope with all life-threatening complications. We observed for the first time and possibly described for the first time a case of seronegative fibrosing cholestatic hepatitis non-associated with a serological window in the development of acute hepatitis C virus infection. Efficient antiviral therapy with modern direct-acting antiviral drugs led to patient's recovery, but the lack of standards for antiviral therapy, especially in relation to its duration for patients with fibrosing cholestatic hepatitis C, requires further studying.

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