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DEVELOPMENT OF GRAFT-VERSUS-HOST DISEASE IN A LIVER RECIPIENT. CLINICAL OBSERVATIONS AND LITERATURE REVIEW

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Graft-versus-host disease (GvHD) after liver transplantation (LT) occurs in 0.2–0.3% of liver transplant recipients. Each case is characterized by individual peculiarities of the clinical picture. There are no standards or clinical guidelines for the treatment of GvHD in solid organ recipients; mortality remains very high among these patients. We present two clinical cases of verified GvHD that developed early after LT, and we offer a brief review of the current state of the art in the study of this problem.

Keywords: liver transplantation, graft-versus-host disease.

INTRODUCTION

GvHD develops in recipients of allogeneic hematopoietic cells and solid organs whose body is unable to reject donor lymphocytes. Clinical manifestations of this response are associated with the fact that donor lymphocytes trigger an immune-mediated reaction against the recipient's antigenically distinct tissues. A distinction is made between cellular and humoral GvHD. Humoral GvHD most often occurs in case of ABO or Rh incompatibility of the donor and recipient and leads only to usually insignificant hemolytic anemia (passenger lymphocyte syndrome) [1]. Cellular GvHD, which we discuss in this paper, is associated with activation and clonal expansion of immunocompetent donor liver lymphocytes with subsequent tissue damage in the recipient. Post-LT cellular GvHD was first described in 1988 [2]. Fortunately, in real clinical practice, there are quite rare GvHD cases occurring following solid organ transplantation. Indirectly, the incident of GvHD in recipients of solid organ transplantation and LT in particular, can be judged from a systematic review published in 2018 by researchers from the Meyo Clinic [3]. In a thorough literature search, up to 2016, the authors found 115 cases of post-transplant GvHD accompanied by dermatologic manifestations. At the same time, the development of solid organ transplant-associated GvHD (SOT GvHD) with dermatologic manifestations was observed in 81 (64.3%) cases. Whereas dermatologic manifestations of GvHD are observed in at least half of the total number of patients with GvHD (the incidence is reported to be up to 92–94% [4, 5]), the number of SOT GvHD cases described so far does not exceed 200. Researchers from the same Clinic recently reported a 0.3% incidence of GvHD (12 cases) in an analysis of all LTs performed between January 1, 2010 and December 31, 2021 (4,585 operations) [6]. In an analysis of the OPTN database, which included 77,416 adult patients who underwent LT between 2003 and 2018, the incidence of fatal GvHD after LT was 0.2% (121) [7].

Our description of cutaneous GvHD in a liver recipient with a review of the state of the art of the study of this problem in 2010 was the first in the national literature [8]. In this paper, we present two clinical cases of verified GvHD that developed early after LT and provide a brief review of the current state of the study of this problem.

Solid organ allografts contain varying numbers of donor leukocytes, which are a mixed population including monocytes, natural killer cells (NK cells), T-cells, and other hematopoietic cells. Transplantation of these immunocompetent cells along with the organ, along with immunosuppressive therapy the recipient receives to prevent rejection, can create conditions for the development

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of tolerance or GvHD. Usually, due to high levels of HLA mismatch, the recipient's immune system destroys the donor lymphocytes. During this time, the donor lymphocyte population in the transplanted organ is replaced by the recipient's lymphoid cells. Less commonly, donor lymphocytes may attack the recipient, causing GvHD.

The theory of GvHD pathogenesis was proposed in 2004 by Taylor et al. [9]. According to this theory, before transplantation, an immunocompromised state that is characterized by increased expression of major tissue compatibility complexes on antigen-presenting cells (APCs) should develop in the recipient's body. In the second step, donor passenger lymphocytes enter the recipient's body and are activated from encountering host APCs. Subsequently, their clones proliferate, mediated by the recipient's interleukin-2 (IL-2). In the final third phase, donor T-cells attack the recipient's tissues, leading to clinical manifestations of the disease [10]. Much evidence confirming the elements of this theory have been accumulated. Thus, an increase in IL-2 level in the vicinity of activated cytotoxic T-cells and accumulation of lymphocytes with donor karyotype in target tissues have been shown [11].

Risk factors for post-LT GvHD include a large age difference between the donor and recipients (the recipient is much older), heterozygosity of the recipient and homozygosity of the donor for the same HLA antigens [12, 13], pre-existing immunosuppression in the recipient, autoimmune diseases, recipient age >65 years, lymphocytopenia before transplantation, cytomegalovirus infection, and multi-organ transplantation [10, 11, 14].

The clinical picture of GvHD in liver recipients is characterized by multi-organ involvement, with the graft being the only organ not involved in the disease. Most commonly, GvHD manifests with fever (identified in 66% of patients [4]), or skin rash or a combination of both. Within a few weeks, the following symptoms of damage to one or more organs and systems are added:

– A rash appears on the skin (in 94% of patients), which becomes confluent and covers all body surfaces, including the palms and soles [4]. Bullae formation and desquamation on large body surfaces is possible [10].
– Gastrointestinal (GI) involvement is most often manifested by diarrhea (in 54% of recipients) [4]. There may be ulceration of the oral mucosa [10] and esophageal ulcerative lesions [15]. In our first observation, there was pronounced gastritis, duodenitis; ileitis and colitis, which may lead to intestinal obstruction [11] or GI bleeding [14] have also been described [14].
– Most recipients develop pancytopenia. Partial variants of hematopoiesis disorders have also been described, such as thrombopenia and leukopenia [16], isolated neutropenia [17].
– A case of isolated lung damage against post-LT GvHD is described. The diagnosis was histologically verified, the authors managed to identify donor cells in the peribronchial space [18].
– There are two descriptions of central nervous system involvement [17, 19]. In one case, development of lymphoproliferative disease (LPD) could not be completely excluded either. Unfortunately, the authors of this case do not provide postmortem data that could confirm or refute the neuro-GvHD version.

Diagnosis of GvHD is based on histological examination of the affected tissue. The diagnosis is most often made on the basis of material from the GI tract [20] or skin biopsy [13, 15]. Immunohistochemical methods can be used for differential diagnosis between different dermatologic diseases [21].

When a donor blood sample is available (usually in liver lobe transplantation from a living donor), a blood test for lymphocyte chimerism (estimation of the percentages of donor lymphocytes to the total number of lymphocytes in the peripheral bloodstream) may be useful in GvHD diagnosis. It should be noted that donor lymphocytes in recipient blood are detected quite frequently. A group of authors from the Meyo Clinic (Rochester, USA) detected these cells in 38 out of 49 recipients 8 weeks after LT [22]. The high incidence of chimerism suggests that it is not the cause of GvHD by itself. There is an assumption that chimerism provides immune tolerance of the recipient and graft. Currently, most researchers distinguish micro- and macrochimerism. The boundary between normal (microchimerism) and pathological (macrochimerism) percentage of donor lymphocytes in the recipient's bloodstream is defined differently by different authors; the proposed variants range from 1 to 10% [10]. Macrochimerism is considered a predictor of GvHD. In some cases, donor lymphocytes may not be detected in the peripheral bloodstream but may be present in target tissues in a GvHD patient [23]. If the donor and recipient are of different genders, it is possible to differentiate lymphocytes in the recipient's tissues by Y-chromosome fish response [14].

To date, there are no standards and clinical guidelines from professional societies for the treatment of GvHD in solid organ recipients. The key issue in the treatment of this patient cohort is the impact on the immune system. Diametrically opposite approaches are discussed: intensification of immunosuppressive therapy or, on the contrary, temporary withdrawal of immunosuppression.

The most common practice in the treatment of GvHD is the use of high-dose glucocorticoids (GCs) (2–10 mg/kg) as first-line therapy. This approach is effective in GvHD patients after bone marrow transplantation [22], but is usually unsuccessful in liver recipients [13]. Attempts to use drugs for induction of immunosuppression directed against T cells have been described. Antithymocyte globulin (ATG) [10, 13, 17, 22], basiliximab or daclizumab [22], and alefacept [17] have been used. Unfortunately, all the described observations ended fatally.

There is a description of the successful use of basiliximab shortly after high-dose methylprednisolone (MP) administration in two patients who developed GvHD symptoms with skin and intestinal lesions 3–5 weeks after LT. The rash disappeared within 3 and 2 weeks, respectively, after basiliximab administration. However, both patients continued to have severe GI symptoms, they developed acute intestinal obstruction, underwent intestinal resection, and only then recovered [11].

Immunosuppression reduction is less frequently used in the treatment of GvHD.

In the literature, there is a report of two patients with relatively mild GvHD, whose symptoms resolved with immunosuppression reduction [24]. In addition, there is a description of successful treatment of GvHD after conversion from tacrolimus to cyclosporine, which was performed due to suspected drug intolerance [14]. In our case (observation 1), such therapeutic tactics were not successful. In a number of GvHD cases, routine maintenance immunosuppression, which should have been prescribed according to the protocol, was canceled, but drugs with multidirectional, including immunosuppressive action (ATG, infliximab, granulocyte colony-stimulating factor, alefacept, MP, interleukin-11, immunoglobulin) were prescribed [10, 16, 17, 22]. Unfortunately, the authors usually did not justify their choice of therapy.

There are suspicions associated with the use of ruxolitinib (a selective JAK inhibitor). Its use in the treatment of GvHD in solid organ recipients is borrowed from the practice of hematologists, for whom the search for effective therapy for glucocorticoid-resistant GvHD after stem cell transplantation is a pressing issue [25]. There is a case in which a patient with advanced GvHD responded to treatment in 10 days, and chimerism regressed after one month of treatment [12].

Two cases of host immune cell infusion have been reported. In an earlier observation, autologous bone marrow transplantation was performed after GvHD was diagnosed using host cells collected before LT, leading to resolution of GvHD [26]. In another case, lymphocytes were harvested from a patient after the development of GvHD and were enriched ex vivo to "transform" into recipient lymphocytes. These cells were then reinfused into the patient, presumably resulting in subsequent recovery of the recipient [27]. In addition, the literature discusses the possibility of liver retransplantation with the aim of eliminating immune aggression from the donor tissues and counting on greater immune tolerance of the new graft.

CLINICAL CASE 1

Patient A., female, 54 years old, was on October 3, 2016, transplanted with the right lobe of the liver of her daughter (28 years old) for cirrhosis as a result of chronic hepatitis C on the background of persistent HCV viremia. Blood group of donor and recipient was I(0), Rh(+). HLA typing: donor A(24), B(48), DRB1(12); recipient A(24), B(38), B(48), DRB1(04), DRB1(12).

Immunosuppression was induced according to standard protocol: 20 mg basiliximab, 1000 mg methylprednisolone (MP) in the liverless period. From day 2, the patient received tacrolimus with target blood concentration of 10–13 ng/mL. The postoperative period was uneventful. She was discharged from the hospital on day 24.

On day 45 after LT, the patient went to a hospital around her place of residence complaining of rash and facial swelling. As a result of glucocorticoid therapy (MP 500 mg IV for 3 days, with continuation of oral prednisolone (PSL) with gradual withdrawal), there was a significant decrease in the rash. On day 59, the patient was hospitalized at the surgical ward of Burnazyan State Medical Research Center with complaints of weakness, maculopapular rash with a tendency to generalization, diarrhea. Examination revealed Coombs-positive hemolytic anemia (erythrocytes 1,350,000/μL), leukopenia (1,400/μL) and thrombocytopenia (61,000/μL). Differential diagnosis was made between acute GvHD, allergic (drug) dermatitis. Immunosuppression was converted to cyclosporine, and drug therapy was minimized. Within 3 days, 1000 mg MP was administered intravenously with subsequent oral administration of PSL at a dose of 125 mg/day. During treatment, an increase in red blood cell count up to 2.5 million/μL and an increase in white blood cell count up to 3,600/μL were noted, diarrhea stopped and skin rash slightly decreased. Allergic dermatitis was diagnosed according to the results of histological examination of skin biopsy. Due to development of diabetes mellitus, a gradual reduction of PSL dose was initiated.

On day 90 after LT, at a PSL dose of 80 mg/day, the rash increased again: papular elements on the background of bright erythema of the skin of the face, chest, abdomen, with involvement of palms and soles (Fig. 1). The situation was considered as resistance to GC. To overcome this, a repeated course of therapy with 1000 mg MP was carried out for 5 days, PSL oral dose was increased to 100 mg/day, biopsy of the changed skin was repeatedly performed: GvHD was verified. Linear chimerism study revealed 9.8% of donor leukocytes in the recipient's peripheral blood. Bone marrow study did not reveal myelopoiesis suppression. Despite the slight positive dynamics in the patient's condition, GCs therapy did not lead to GvHD resolution. PSL reduction was initiated, mycophenolic acid (MFA, 2160 mg/day) was added, and basiliximab (20 mg) was administered twice. The MFA dose was selected taking into account hypoalbuminemia (21 g/L), concomitant therapy with high-dose cyclosporine (400 mg/day), and guided by doses used by hematologists in the treatment of acute GvHD after bone marrow transplantation. Shortly after starting MFA, the rash turned pale, and by day 134 after

GvHD, the skin rashes had completely cleared (Fig. 2). Despite successful treatment of skin manifestations, the patient remained anemic and developed nephrotic syndrome (histologically, membranous nephropathy).

The patient was discharged from the hospital on day 158 after LT, 113 days after the appearance of the first cutaneous manifestations of GvHD. At discharge, the patient's condition was satisfactory, rash regressed completely, and signs of secondary Cushing's syndrome were observed. Steroid-induced diabetes and high blood pressure were compensated.

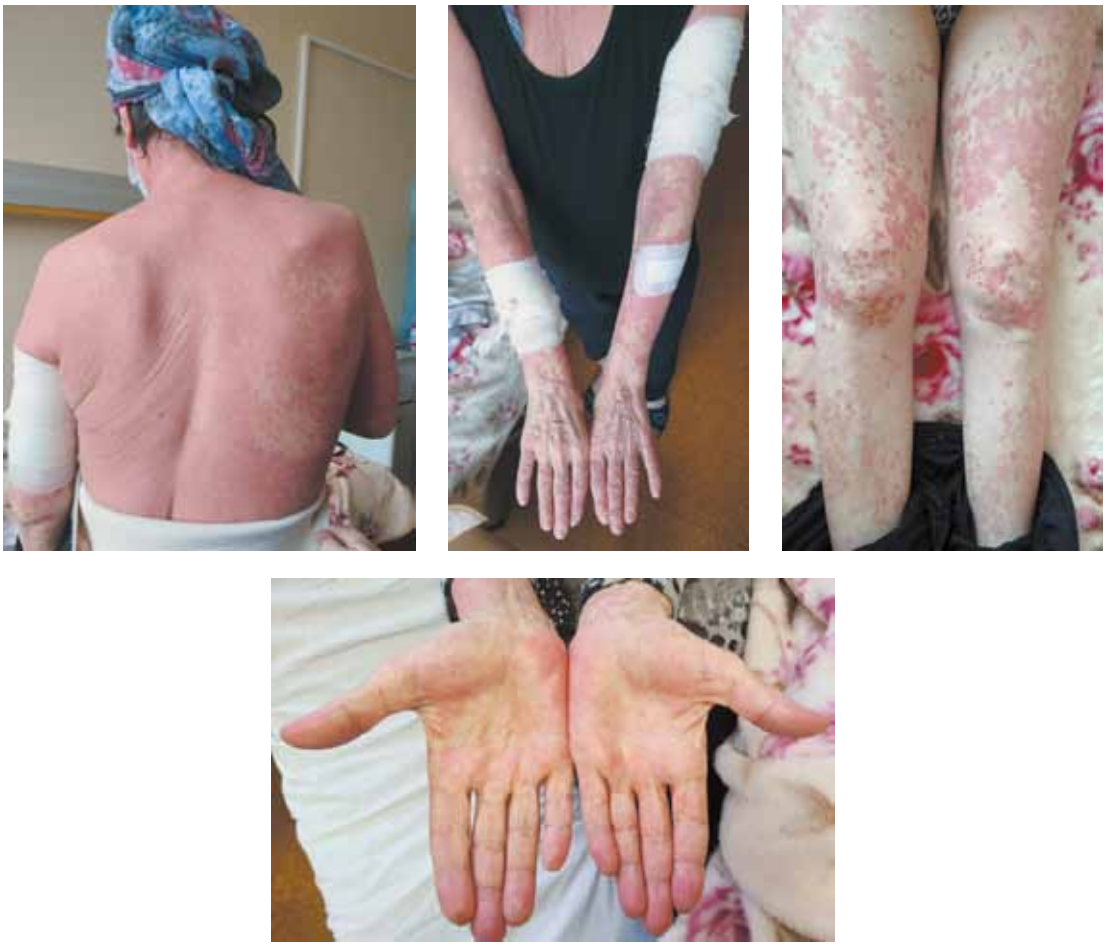

Fig. 1. Clinical case 1. Cutaneous manifestations

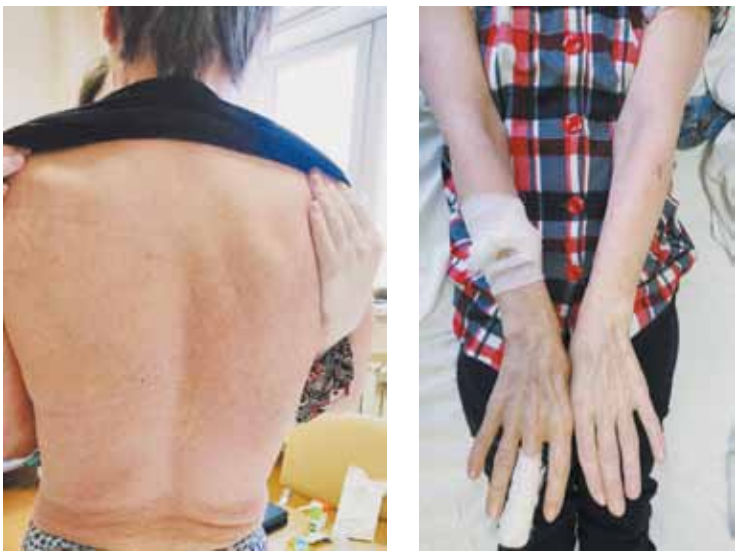

Fig. 2. Clinical case 1. Dynamics of cutaneous manifestations

Four weeks later, on April 10, 2017, the patient was hospitalized again at Burnazyan State Medical Research Center in Moscow with complaints of severe weakness, diarrhea, resistant to treatment, lack of appetite, and resumption of skin rash. Hypoalbuminemia (31 g/L), anemia (hemoglobin 100 g/L), leukopenia 3.1 × 10^9/L with normal platelet levels were observed.

During the first days of hospitalization, dysphagia appeared and increased. Gastroscopy showed that the gastric walls were sharply edematous, there was contact bleeding, and microabscess formation was noted. Peristalsis could not be traced. Biopsy was not taken because of the high risk of bleeding. Progression of GvHD with GI involvement was suspected.

There was an attempt at ATG therapy at a dose of 10 mg/kg. After two administrations, diarrhea decreased, dysphagia was relieved, and skin rash regressed. At the same time, due to adverse events – leukopenia, thrombocytopenia, general weakness – the drug dose was reduced to 5 mg/kg at the third administration, and then ATG infusion was stopped due to increasing weakness. On day 205 after LT, aspiration of gastric contents occurred, which resulted in the development of severe multisegmental pneumonia. Death came the next day.

Autopsy revealed moderate ascites, hydrothorax, multiple hemorrhages, and graft hypertrophy. Particularly severe was digestive tract lesion, whose symptoms were determining the severity of the patient's condition for a relatively short time. On examination of the stomach, most of the mucosa was found to be intact, the folds were flattened. There were pinpoint hemorrhages all over the surface, defects up to 5 mm in diameter along the posterior wall of the body (Fig. 3). The small intestine mucosa was with numerous rounded superficial erosions (0.3 to 0.7 cm in diameter) (Fig. 4). The large intestine had numerous ulcers and circular banded hemorrhages in the mucosa, there were no macroscopic intact mucosal areas.

CLINICAL CASE 2

Patient V., born in 1961, was admitted at the surgical ward of the Center for Surgery and Donor Coordination (CSDC), Rostov Regional Clinical Hospital on November 27, 2022, with complaints of general weakness, jaundice, increased abdominal volume, no effect

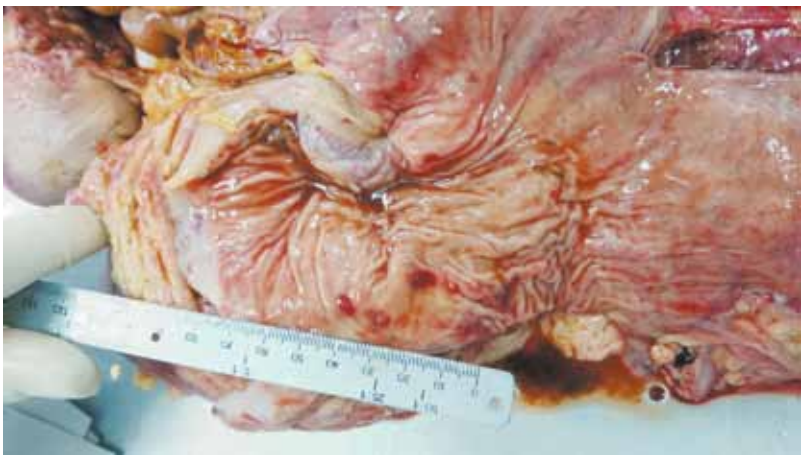

Fig. 3. Clinical case 1. Stomach. Autopsy

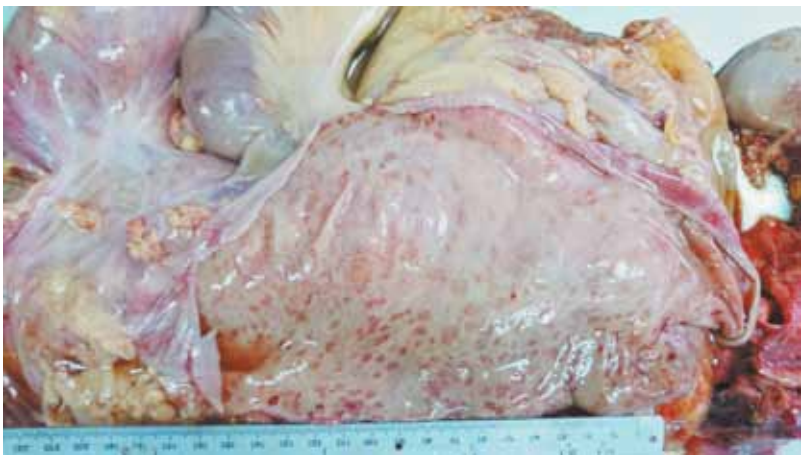

Fig. 4. Clinical case 1. Small intestinal mucosa. Autopsy

of diuretics, dyspnea on exertion, leg swelling, impaired attention and sleep, periodic loss of orientation in time and space. She considers herself a patient since 2013, when cirrhosis of mixed etiology (hepatitis C virus and alcohol) was first diagnosed. Antiviral therapy was not performed; she continued to take alcohol. Signs of decompensation – ascitic-edematous syndrome, jaundice, and hepatic encephalopathy – started appearing from 2020. In October 2022, she was placed on the LT waitlist.

On November 27, 2022, orthotopic LT from a single-group deceased donor was performed. Introductory immunosuppression with basiliximab and methylprednisolone was administered according to the standard protocol. The early postoperative period was uneventful. Given the presence of HCV RNA in the blood, MP was canceled after 7 days, maintenance immunosuppression was limited to extended-release tacrolimus (3.5 mg/day, tacrolimus concentration from 4.5 to 13.0 ng/mL).

She was transferred to the surgical ward on day 7. Anaemia (haemoglobin 92 g/L, erythrocytes 3.4 × 10^{12}/L, hematocrit 25%), leukopenia (3.0 × 10^{9}/L), thrombocytopenia (93.0 × 10^{9}/L) were observed. Functional liver test indicators and creatinine levels remained within normal values.

On day 11 after LT, creatinine increased to 343 μmol/L and urea to 45 mmol/L. The estimated glomerular filtration rate, eGFR, (CKD-EPI) was 12 mL/min/1.73 m^2, diuresis was 1600 mL/day.

Nausea, weakness, tremor, and ascites gradually increased. Conversion of immunosuppressive therapy was performed: tacrolimus was canceled, everolimus was prescribed (blood concentration 7.3–8.9 ng/mL). On day 17 after LT, ultrasound revealed increased linear blood flow rate up to 360 cm/s in the projection of hepatic artery anastomosis. Selective hepatic angiography revealed an arterial anastomosis stenosis up to 80%. Therefore, 3 BioMime intravascular stents were implanted with subsequent balloon catheter dilation. Control angiography showed that the hepatic artery was patent, no residual restenosis was detected. Abdominal cavity drainage was also performed – ascitic fluid without impurities and no microflora growth was obtained.

On day 18 after LT, remittent fever, low blood pressure, intractable nausea and vomiting, diarrhea up to 12 times a day, thrombocytopenia increased. Extracorporeal hemocorrection procedures (veno-venous hemodiafiltration sessions, plasma collection) were performed, renal function was normalized. On day 24 after LT, rashes appeared on the patient's neck, upper and lower limbs in the form of petechial elements, confluent erythematous patches up to 7–8 cm in diameter (Fig. 5). Thrombocytopenia increased (26 × 10^{9}/L), agranulocytosis developed (0.1 × 10^{9}/L). Kidney dysfunction persisted (creatinine, 174 μmol/L; eGFR, 27 ml/min/1.73 m^2). Alanine aminotransferase and aspartate aminotransferase activity was slightly increased (less than 2 times the upper limits of the norm).

Given the presence of fever, rash, diarrhea, and severe cytopenia, we assumed that the patient had GvHD. Differential diagnosis was made with sepsis, including fungal sepsis (repeated blood cultures for mycoses). Antibacterial (tigecycline, ceftazidime with avibactam, cefepime with sulbactam) and antifungal therapy (anidulafungin) was performed. Despite the therapy, the patient's condition did not improve, dermatologic manifestations progressed, which is not typical for fungal and bacterial sepsis, therefore, we decided to take a skin flap for histological examination.

The results obtained show phenomena of dyskeratosis, parakeratosis and hyperkeratosis (Fig. 6). In the

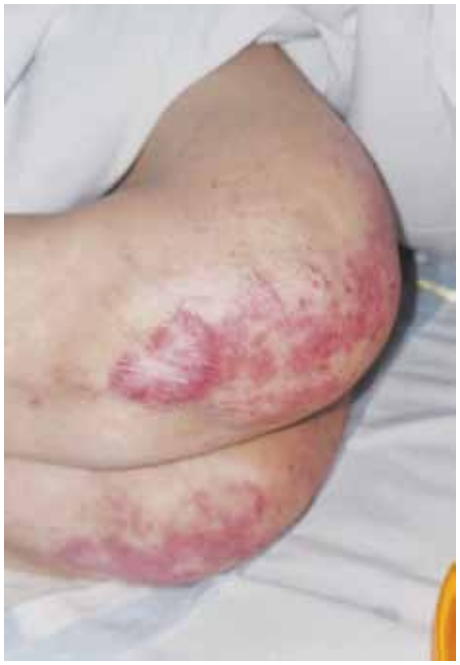

Fig. 5. Clinical case 2. Cutaneous manifestations

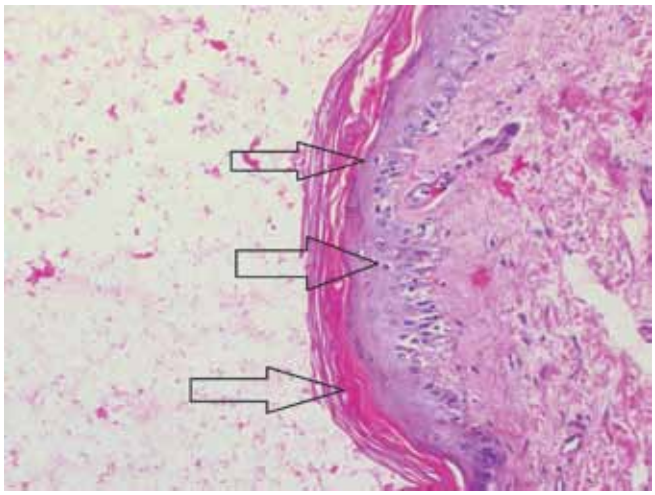

Fig. 6. Clinical case 2. Histologic examination of skin flap. Dyskeratosis, parakeratosis and hyperkeratosis phenomena

basal layer of epidermis, there was pronounced vacuolization of epitheliocytes with focal formation of slits at the border with the dermis (Fig. 7); in the adjacent dermis there was lymphoma-infiltrating macrophages with tropism to the basal layer of epidermis. According to Coons' immunohistochemistry: CD3 fixation was detected in the lymphoid infiltrate of the upper layers of the dermis and basal layer of the epidermis. Fixation of IgG, IgM, CD20 was not detected (Fig. 8). The histological picture is characteristic of grade 2–3 GvHD. Esophagogastroduodenoscopy (EGD test) shows that the mucosa of the duodenal bulb was markedly edematous, covered with whitish plaque (Fig. 9).

Histological examination showed fragments of the duodenal mucosa with pronounced lymphoid infiltration of the intrinsic fibrous lamina on the border with the epithelium, erosions on the epithelium surface and extensive spore clusters of microscopic fungus, morphologically similar to Candida fungi (Fig. 10). The histologic picture is characteristic of GvHD; there was widespread fungal lesion of the duodenal mucosa. GvHD with skin lesions, invasive candidiasis was diagnosed. On December 12, 2022, bacteriological blood test results were obtained: growth of Candida glabrata was detected, caspofungin was added to the therapy.

The patient received parenteral nutrition. Immunosuppression with everolimus (1 mg/day) was continued. The patient's condition worsened, febrile fever and dyspeptic syndrome, pancytopenia persisted. Filgrastim was prescribed, transfusions of thromboconcentrate and fresh frozen plasma were performed.

On day 25 after LT, guided by the escalating skin manifestations, the results of histological examination of the skin flap and literature data on the use of high-dose GCs as first-line therapy in the treatment of GvHD, the team decided to perform pulse therapy (intravenous pulses of 1000 mg methylprednisolone) for three days under the cover of antibacterial and antifungal reserve drugs (polymyxin B, caspofungin). The patient's condition remained extremely severe with increasing multi-organ failure, anemia, hemorrhagic syndrome, and psychomotor agitation. The patient died on December 28, 2022, day 32 after LT.

At autopsy, the mucosa of the esophagus, stomach and small intestine was flattened, thin, red-brown in color, with dotted and spotty hemorrhages 0.3–0.8 cm in diameter. On the section, the colon wall layers were indistinguishable. According to histological examination, there were areas of esophageal mucosa ulceration,

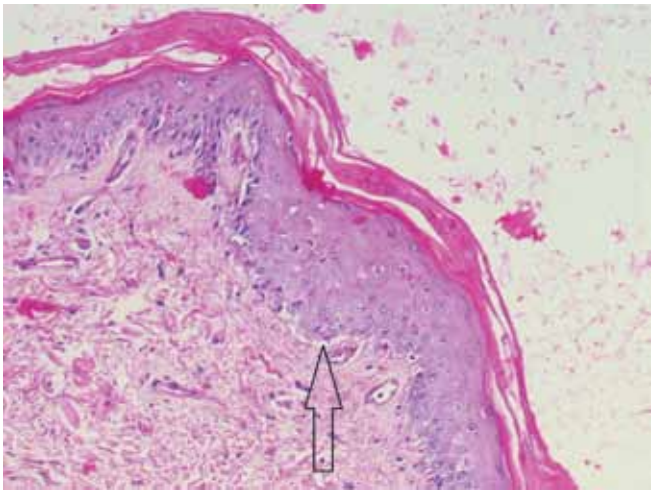

Fig. 7. Clinical case 2. Histological examination of skin flap. Vacuolization of epithelial cells with focal formation of gaps at the border with the dermis

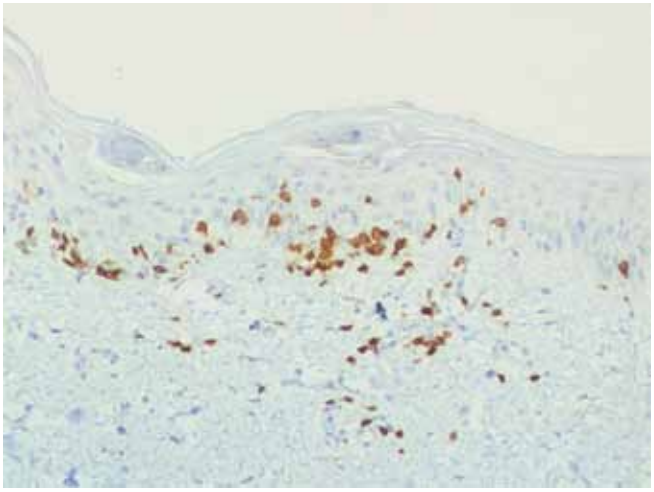

Fig. 8. Clinical case 2. Immunohistochemistry (IHC) analysis by Albert Coons method: CD3 fixation was detected in the lymphoid infiltrate of the upper layers of the dermis and basal layer of the epidermis

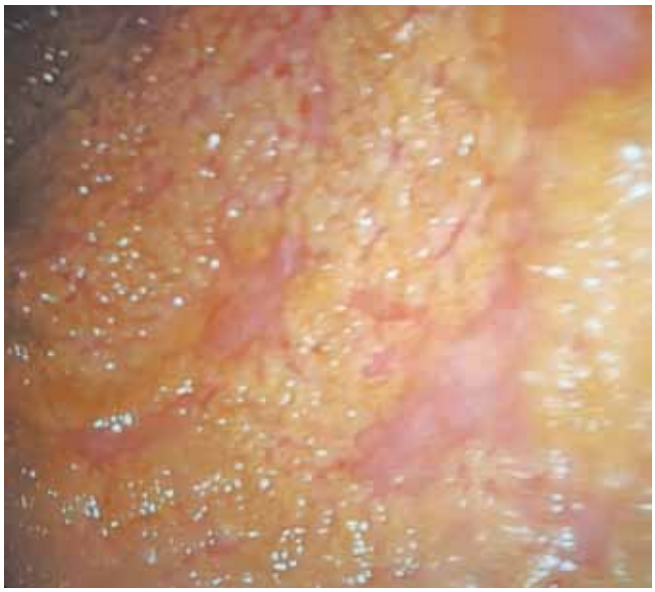

Fig. 9. Clinical case 2. Mucosa of the duodenal bulb. Esophagogastroduodenoscopy (EGD test) data

subtotal desquamation of the mucosa of the small and large intestine with extensive hemorrhages, leukocytic infiltration and multiple accumulations of blastospores of microscopic fungus. The liver graft was edematous, plethoric, the anastomoses were consistent (Fig. 11). Microscopically, there were multiple microabscesses with leukocytic infiltration and accumulation of mycotic flora (Fig. 12).

The bone marrow was sharply hypocellular, represented by maturing forms of granulocytic sprout, with sharp hypoplasia of erythroid and megakaryocytic sprouts.

Pathologists confirmed the clinical diagnosis of GvHD, an acute form with skin and GI mucosa lesions. The course of the underlying disease was complicated by septicopyemia caused by mycotic microflora (Candida glabrata). Subtotal necrosis of the epithelium of convoluted tubules was detected in the kidneys, which, together with pulmonary and cerebral edema, was the immediate cause of the patient's death.

DISCUSSION

We have cited two clinical cases of a cellular modulation of acute GvHD that developed early after LT. It should be noted that these observations are very rare (one in each LT center over decades of clinical practice). The last review that is known to us, which addresses this issue dates back to 2012, featuring 87 patients [4]. To date (according to our estimates), there are no more than 200 descriptions of this pathology in world literature.

Both of our patients had the main clinical manifestations of GvHD (fever, typical rash, diarrhea, pancytopenia). Diagnosis in both cases was confirmed histo-

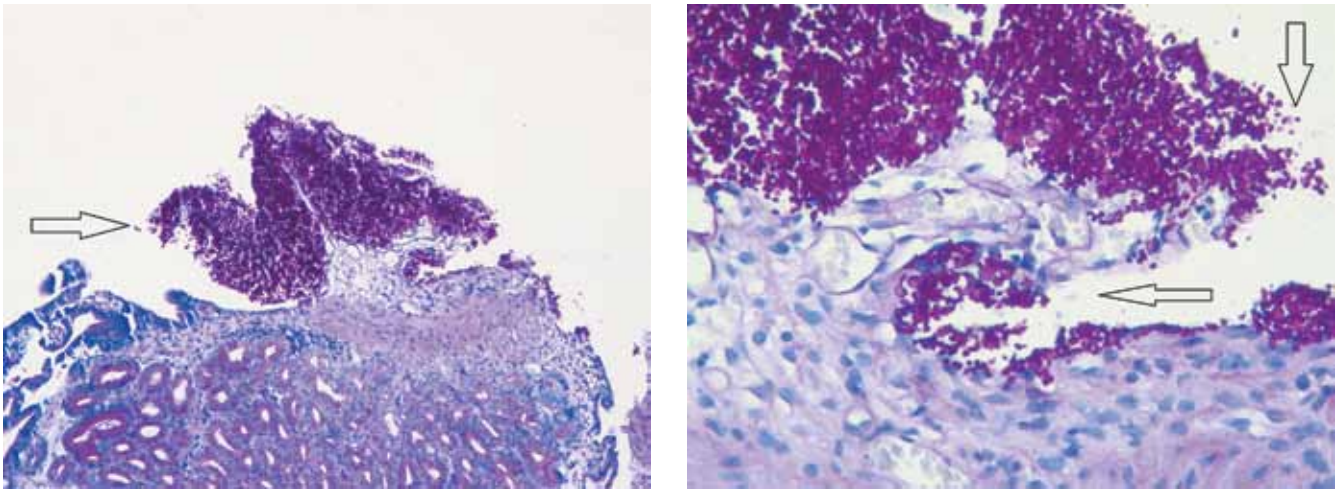

Fig. 10. Clinical case 2. Duodenal mucosal fragments with marked lymphoid infiltration of the intrinsic fibrous lamina at the border with the epithelium, erosions on the epithelial surface and extensive accumulations of spores of microscopic fungus

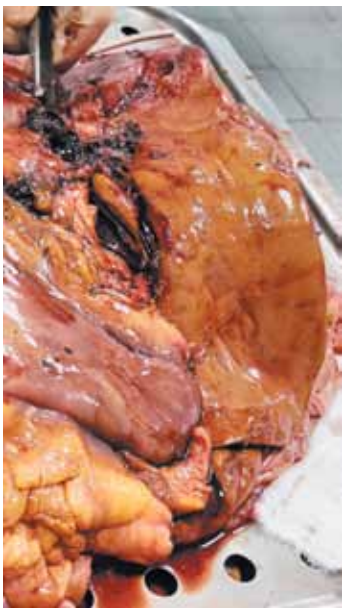

Fig. 11. Clinical case 2. Liver. Autopsy

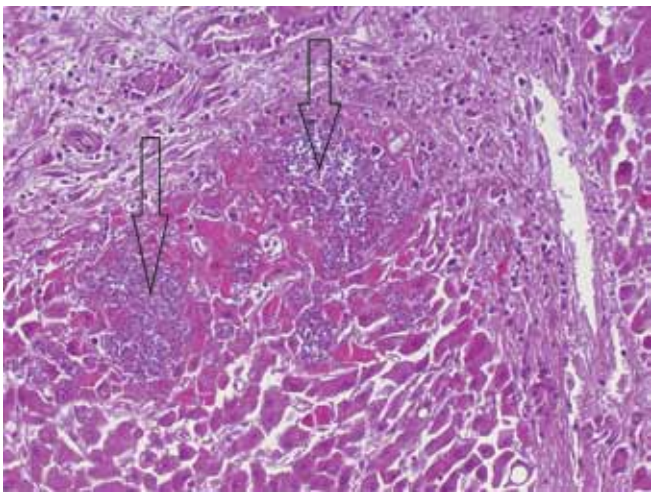

Fig. 12. Clinical case 2. Accumulations of blastospores of microscopic fungus in the liver tissue. 400× magnification, H&E stain

logically. Characteristic histological features of GvHD, detected during skin examination, include basal vacuolar changes, dyskeratosis, apoptosis, lymphocytic infiltration, and in severe cases, subepidermal cleft formation. On the oral mucosa, there were ulcerations, dyskeratotic epithelium with atypia, acute and chronic inflammatory infiltrates in the intrinsic lamina. In the GI mucosa, apoptosis of epithelium or crypts, destruction of glands, and lymphocytic infiltration were detected [28].

In the first case, we had access to donor and recipient HLA studies. Our patient's donor was homozygous for the three alleles for which the recipient was heterozygous,. This is considered to be one of the most significant risk factors of GvHD [29]. Since in the second case, LT was performed from a deceased donor, such a study was not available.

MFA drugs have been successfully used by hematologists to prevent and treat GvHD that complicates bone marrow transplantation. We have not been able to find any experience with MFA for the treatment of GvHD after solid organ transplantation. Administration of MFA in our first patient resulted in a temporary success with regression of dermatologic manifestations. MFA dose was calculated considering drug interactions with cyclosporine and peculiarities of pharmacokinetics in patients with hypoalbuminemia [30]. At the same time, the use of MFA in GvHD patients should be treated with caution because of the risk of drug-induced colitis, which may occur under the guise of GvHD-associated colitis [31, 32].

Unfortunately, despite the therapy, both patients died.

The prognosis of solid organ recipients with GvHD remains unsatisfactory. Mortality exceeds 75–85% [5, 9, 22]. The main causes of death in these patients include infectious complications, which, on the background of deep neutropenia, become septic in nature. For instance, 10 (83.3%) out of 12 liver recipients with acute GvHD observed at the Meyo Clinic (Rochester, USA) developed severe infections that resulted in death [6]. Nosocomial bacteremia caused by intestinal bacteria such as vancomycin-resistant enterococci and gram-negative bacilli was the most common. Invasive fungal infections, cytomegalovirus reactivation, and colitis caused by clostridial flora, have also been reported. The authors suggest that treatment strategies should be determined based on the degree of neutropenia – inhaled levofloxacin and pentamidine for prophylaxis of pneumocystis pneumonia, posaconazole for prophylaxis of invasive mycoses, and valganciclovir. Other causes of death in patients with GvHD include hemorrhage and multi-organ failure.

CONCLUSION

Despite the rarity of post-organ transplant GvHD, its mortality rates are high, and therapy has not been developed. Diametrically opposite approaches have been proposed, such as increasing immunosuppression or decreasing it up to complete cancellation. The experience of treatment of GvHD after bone marrow transplantation cannot be mechanically transferred to solid organ recipients, which is confirmed by our cases. The descriptions of patients with post-LT GvHD, which are available in the world literature, need to be generalized and analyzed, both in terms of risk factor identification, early diagnosis, and optimization of treatment protocols. Infectious complications are the main causes of death in liver transplant recipients who develop GvHD. Therefore, increased prophylaxis for suspected GvHD, followed by an intensified immunosuppression protocol, is necessary. We believe it is important to perform early upper and lower GI endoscopy in solid organ recipients with suspected GvHD. These examinations will allow to detect GI lesions before the development of clinical manifestations, and possibly reevaluate the severity and prognosis of the disease.

The aim of this publication is to sensitize physicians on the problem of GvHD after solid organ transplantation in the hope of reducing mortality. To this end, it is important to be alert to the diagnosis of GvHD and to initiate treatment early enough. The authors recognize the lack of scientific validity of conclusions that are based on descriptions of individual cases or case series. However, in a rare disease such as GvHD after solid organ transplantation, individual cases are the best data we have. Physicians should report any experience with GvHD treatment.

The authors declare no conflict of interest.

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