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Liver allograft pathology in the late post-transplant period

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Abstract

Annually increasing quantity of liver transplants and the growing population of long-survived recipients determine the relevance of late allograft dysfunction study. Variety of morphological and functional disorders of the transplanted liver complicates their timely diagnostics. Moreover, in some patients, serious graft damage may proceed for a long time without clinical manifestations and laboratory abnormalities.

The review summarizes the structure, prevalence, risk factors and prognostic value of different liver allograft pathology determined by histological examination in the long term after transplantation.

Keywords: liver transplantation, biopsy, non-alcoholic fatty liver disease, chronic hepatitis, idiopathic post-transplantation hepatitis, graft rejection, fibrosis, primary sclerosing cholangitis, primary biliary cholangitis, autoimmune hepatitis, recurrence

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AIH, autoimmune hepatitis

ALD, alcoholic liver disease

AMR, antibody-mediated rejection

AMA, antimitochondrial antibodies

BMI, body mass index

CR, chronic rejection

DAA, direct acting antiviral

DSA+, donor-specific antibodies

HCC, hepatocellular carcinoma

IPTH, idiopathic post-transplant hepatitis

LC, liver cirrhosis

LFT, liver function test

LT, liver transplantation

MAGFD, Metabolically Associated Graft Fatty Disease

NAFLD, non-alcoholic fatty liver disease

NASH, non-alcoholic steatohepatitis

PBC, primary biliary cholangitis

PLTR, pediatric liver transplant recipient

PSC, primary sclerosing cholangitis

PTMS, post-transplant metabolic syndrome

re-LT, liver retransplantation

TE, transient elastography

Introduction

Liver transplantation (LT) is the only radical treatment for patients with end-stage diffuse liver disease and fulminant liver failure. Currently, the 10-year survival rate for adult recipients in most countries reaches 70% [1, 2]. Despite the undoubted successes of transplantation in recent decades, the risk of dying among transplant recipients under the age of 75 years who survived the first year after transplantation is 5.8 times higher than that compared with the general population [3]. The structure of morbidity and mortality in liver transplant recipients has changed significantly over the recent three decades. These changes are due to advances in the treatment of viral hepatitis B and C and an increase in the proportion of patients requiring LT for the end-stage fatty liver disease in the context of obesity epidemic [4].

Mortality in the late post-transplant period can be associated with graft pathology and also with extrahepatic causes (infections, cardiovascular diseases, renal failure, malignant neoplasms). Usually graft pathology is clinically manifested by episodes of the so-called "late graft dysfunction".

From a clinical point of view, the graft dysfunction is a consequence of recurrent or newly appeared (*de novo*) graft diseases, rejection, or "idiopathic chronic inflammation". From a histological point of view, several variants of graft pathology can be distinguished, such as fatty disease (steatosis, steatohepatitis), chronic hepatitis, loss of bile ducts due to immune or ischemic damage, and, as a result, fibrosis and cirrhosis of the graft. All these processes can proceed both with increases in the activity of liver enzymes and the bilirubin level, and with normal or subnormal values in the liver function test (LFT) results.

At the end of the last century, the so-called protocol-based graft biopsies became widespread in clinical transplantation. On the basis of

regular histological studies performed at regular intervals, the natural course of the post-transplant period and the response to the therapy for rejection were studied; and early diagnosis of the graft disease recurrence was made. The experience gained from those studies led to several conclusions.

Serious histological changes in grafts received by recipients many years before the study may not have been accompanied by clinical manifestations of graft dysfunction and/or abnormal liver function tests. Protocol-based liver biopsies performed in recipients with normal liver tests several years after LT may reveal latent diseases such as autoimmune disease recurrence, progressive fibrosis, chronic rejection, or non-alcoholic fatty liver disease (NAFLD). Early detection of graft damage allows better control of the adequacy of immunosuppressive therapy, avoiding its redundancy or insufficiency, which leads to increases in the graft and recipients survival rates. Latent processes such as idiopathic post-transplant hepatitis (IPTH), nodular regenerative hyperplasia, perisinusoidal fibrosis, sinusoidal dilatation, granulomatosis, and graft peliosis have been described.

The aim was to summarize the available literature data on the liver graft pathology in the late post-transplant period in recipients with normal and altered liver function test results.

Allograft fatty disease

Non-alcoholic fatty liver disease (NAFLD) is the indication for LT worldwide that is fastest growing and promises to become a major indication in the near future. At the time of writing this review, the problem of NAFLD as a cause of liver cirrhosis (LC) in Russia was less relevant than in Europe and North America. The most frequent causes leading to LT continue to be end-stage viral hepatitis and hepatocellular

cancer (HCC). However, non-alcoholic steatohepatitis (NASH) is the leading cause of HCC without cirrhosis, and thus leads to an increase in the pool of potential recipients.

Liver transplant recipients (regardless of the cause leading to LT) are predisposed to the development of post-transplant metabolic syndrome (PTMS) and metabolic-associated graft fatty disease (MAGFD). It is assumed that the main mechanism for the development of MAGFD is associated with insulin resistance. Risk factors for PTMS and MAGFD include obesity, diabetes mellitus, hyperlipidemia, arterial hypertension, alcohol abuse, and donor organ steatosis [5, 6]. Due to the side effects of immunosuppressive drugs (calcineurin inhibitors, glucocorticosteroids) and also concomitant components of PTMS, transplant recipients are at risk of *de novo* NAFLD/MAGFD [6]. Those recipients who have been operated on for NAFLD are particularly at risk of disease recurrence [7].

There are a number of reports, according to which the incidence of graft NAFLD (both recurrent and de novo) is high. Unfortunately, the true extent of this problem remains unclear. Most of the existing evidence comes from single-centre retrospective studies with diverse inclusion and exclusion criteria and different time frames for evaluating outcomes [6, 8–10]. Liver biopsy remains the "gold standard" for diagnosis. Thus, a group of researchers from the Mayo Clinic (Rochester, USA; 2019) analyzed the outcomes of 588 LT performed in 1999–2006. [11]. After 10 years of follow-up, graft steatosis developed in 78% of transplant recipients for NAFLD and in 45% for causes unrelated to NAFLD. In another study, among recipients with recurrent NAFLD diagnosed by non-invasive methods, a histological examination performed 3–5 years after living donor LT revealed NASH accompanied by grade 1–2 fibrosis in 35% [12].

A meta-analysis has recently been published covering 17 retrospective studies including 2378 patients. Seven studies assessed the recurrence rate of NAFLD/NASH, three assessed the incidence of *de novo* NAFLD/NASH, and 7 studies assessed both variants of NAFLD. The recurrence rate of NAFLD at 1 and 3 years, and after 5 years or more was 59%, 57%, and 82%, respectively; the incidence of NAFLD *de novo* made 67%, 40%, and 78%. NASH recurrence rates at 1, 3 years, and after 5 years or more were 53%, 57%, and 38%; the incidence of NASH *de novo* was 13%, 16% and 17%, respectively. The most significant risk factors for the development of steatosis and graft steatohepatitis were body mass index (BMI) and hyperlipidemia [13]. Both of these factors are referred to modifiable. Clinicians should focus on correcting the body weight and dyslipidemia, which are common in liver transplant recipients. Despite marked differences in inclusion and exclusion criteria, and the duration of follow-up across studies, the recurrence of both NAFLD and NASH was observed in more than half of all recipients from the first year after LT. Of particular concern is the fact that the incidence of NAFLD *de novo* after LT was also extremely high, with a 5-year incidence of 78%.

Another meta-analysis examined only NAFLD that developed *de novo* [14]. The analysis covered 12 studies including 2166 subjects. In all cases, the diagnosis was based on histological examination of the liver tissue. The incidence of NAFLD *de novo* was 26% (95% CI [20;31]%), and that of NASH was only 2% (95% CI [0;3]%). The highest incidence of NAFLD *de novo* was found in the recipients who underwent LT for alcoholic cirrhosis (37%) and cryptogenic cirrhosis (35%), as well as in the recipients who took tacrolimus (26%). Meanwhile, the risks of developing NAFLD were comparable between the recipients taking tacrolimus or cyclosporine.

The proportion of patients with cryptogenic cirrhosis among patients waiting for LT is still quite high [1, 2]. Cryptogenic cirrhosis appears to be mostly undiagnosed alcoholic cirrhosis, the outcome of autoimmune hepatitis and "burnt-out" NASH [15]. The etiological structure of cryptogenic cirrhosis remains unspecified. If a graft pathology that is not associated with acquired infections, ischemia, or immunosuppression deficiency is detected, one can indirectly judge, which particular disease relapse is in question.

Despite the significant number of recipients included in the meta-analyses, the authors have emphasized their low evidentiary value due to high heterogeneity of studies. There are no common criteria for diagnosing NAFLD, NASH, the severity of fatty hepatosis and its characteristics (large droplet, small droplet).

The researchers from France studied the impact of histological signs of liver graft damage on the quality of life of recipients at 10 years after LT. Seventy two recipients were examined. Graft fibrosis was found in 38 (53%) of them, with 9 (13%) having severe fibrosis (F3) or cirrhosis of the graft. Steatosis was found in one third of the recipients, predominantly the large-droplet one, with a mean lesion of 19±17% of the graft parenchyma, and was associated with a worse quality of life according to several questionnaire assessments. Recipients with evidence of graft steatosis had a higher incidence of fibrosis than recipients without evidence of graft fatty disease [16].

Steatosis and steatohepatitis are more common in recipients who return to alcohol abuse compared to recipients who have abstained from alcohol after LT [17–20]. However, steatosis and steatohepatitis are not specific signs of alcohol use; their presence in recipients who do not drink alcohol may be associated with PTMS, rather than with unrecognized alcohol intoxication. In any case, evidence of liver graft steatosis or

steatohepatitis on histological examination should alert the clinician to a more thorough search for a return to alcohol abuse.

Chronic hepatitis

Chronic hepatitis in a transplanted liver is the same typical pathological process as the fatty disease. It can be caused by viral and immune-mediated (auto- and alloimmune) diseases. The lack of adequate prevention of HBV infection after LT can lead to the virus reactivation in the donor liver during immunosuppressive therapy [21]. Until recently, an important cause of the development of various pathological processes in a liver graft was hepatitis C, which made a significant contribution to the structure of the graft pathology and the mortality of recipients. With the introduction of direct-acting antivirals (DAAs) into routine clinical practice, the proportion of patients with recurrent hepatitis C after LT is steadily decreasing due to the infection eradication at the preoperative stage. And the few cases of recurrent hepatitis C that still occur in liver transplant recipients are usually cured in the early post-transplant period. However, the impact of long-term HCV infection on graft status (especially the severity of fibrosis) in recipients who were operated on in the era before the widespread introduction of DAAs into routine practice has not been studied well enough. In some cases, against the background of immunosuppressive therapy in HCV infection, the formation of antibodies is slowed down. Differential diagnosis of graft dysfunction at various times after LT should include mandatory determination of HCV RNA [22]. Chronic hepatitis E is the most difficult diagnostic problem among chronic viral hepatites of transplanted liver [23]. The lack of commercially available test systems for determining the HEV genome in blood and tissues does not allow routine detection of the virus in liver

transplant recipients with clinical and histological presentation of chronic hepatitis. There are no specific histological features of this infection.

IPTH is a generalized term for otherwise unexplained portal and/or lobular inflammation in a liver graft. The main features of IPTH include predominantly mononuclear (lymphocytes, histiocytes, and plasma cells) portal inflammatory infiltrates, without bile duct injury or portal venulitis. These changes may be accompanied by interstitial or intralobular inflammation with focal or multilobular hepatic necrosis of varying severity [24].

Although the term "idiopathic" implies that the cause is unspecified, there is growing evidence to suggest that many cases of IPTH represent an immune response. Most recipients with IPTH have auto- and/or allo-antibodies that interact with the donor's hepatocytes and/or cholangiocytes. More than a quarter of recipients with severe portal inflammation have anti-nuclear antibodies and/or anti-smooth-muscle antibodies in their blood [25]. These recipients have a history of cellular rejection episodes; signs of acute or chronic rejection may be detected by a careful histological examination. In addition, in those recipients who receive maintenance doses of glucocorticosteroids, the inflammation and fibrosis are less pronounced, suggesting that IPTH may be a chronic slowly developing rejection that occurs under the mask of hepatitis [26–28].

An intermediate conclusion in the discussion about the causes of the IPTH development was drawn by a working group of Banff experts who published in 2016 a consensus opinion on the results of the work of XI, XII and XIII conferences dedicated to the discussion of antibody-mediated rejection (AMR) [28]. “Most cases of IPTH are currently classified as late T-cell rejection and/or chronic AMR in patients who have donor-specific antibodies (DSA+)”. It is important to note that the expert community has

introduced some uniformity in the terminology used to describe the processes associated with liver graft rejection (Table).

Table. Updated terminology [29]

Outdated terminology	New (preferred) terminology
Humoral rejection	Antibody mediated rejection
(Acute) cellular rejection	T cell-mediated rejection
Autoimmune hepatitis de novo	Plasma cell hepatitis
Plasmocytic (plasma cell) rejection	

Many authors have noted an association between donor anti-HLA DSA and progressive fibrosis leading to a graft dysfunction and loss [30-33]. Researchers from Germany have recently published the results of an analysis that included all patients who referred for care after LT performed from 1989 to 2016. Recipient and donor HLA antibody (DSA) studies were performed in 291 and 271 recipients, respectively. The authors found that the presence of antibodies against HLA and DSA correlated with histological signs of inflammation (OR: 4.43; 95% CI [1.67;12.6]; p=0.0035), aminotransferase activity, but not with the severity of graft fibrosis. [34]. In contrast, Italian investigators could not confirm a correlation between DSA and liver graft inflammation or fibrosis in a retrospective analysis of 134 liver biopsies obtained from 94 recipients. The frequency of DSA detection depended on the time elapsed since the moment of LT. DSAs were detected within 1 to 3 years in 1 recipient (7%), within 4 to 9 years in 5 recipients (36%); and after 10 years and more in 8 recipients (57%) [35].

Researchers from Kyoto (Japan) analyzed the results of protocol-based liver graft biopsies at 5–20 years after LT in pediatric liver transplant recipients (PLTRs) [36]. The authors found a significant correlation between DSA and fibrosis of stage 3 and 4. Meanwhile, the

severity of inflammation in the previous biopsy samples in recipients with DSA was significantly higher than in those without DSA. Meantime, studies conducted at the Mayo Clinic (USA) showed that inflammation in patients with DSA does not differ in severity from that in patients without DSA [37], and T-cell alloreactivity in liver transplant recipients is reduced, regardless of the DSA presence in them [37]. Finally, M. Vij et al. (2022) published a detailed review on IPTH and graft fibrosis as a consequence of sluggish AMR [24].

There have been reports to the contrary. Thus, a group of investigators from Barcelona have recently published the results of the analysis of biopsies and transcriptomic profile of liver tissue obtained from adult recipients followed-up for more than 10 years. Recipients with recurrent liver disease, biliary or vascular complications, chronic rejection, and LFT abnormalities were excluded from the study. The most commonly observed pathological pattern was portal inflammation with varying degrees of fibrosis, present in 67% of biopsies. Meantime, the liver tissue gene expression profile in a large proportion of these patients resembled the T-cell mediated rejection profile. Samples with the highest levels of expression of rejection-associated genes were associated with progressive liver damage upon follow-up. The fact that the gene modules that correlated with portal inflammation and interstitial hepatitis activity were characteristic of the liver T cell-mediated rejection transcriptome may argue against a significant role of AMR in the development of IPTH. Most of the patients included in this study received very low doses of immunosuppressive therapy [25]. This publication raises the question of the place of non-specific and clinically often ignored histological findings as signs of subclinical rejection, suggesting essentially a new disease of the late post-transplant period. The recognition of subclinical rejection as

a widespread and clinically significant condition forces us to reconsider the attitude towards the adequacy of modern immunosuppressive therapy.

G. Mells et al. (2009) retrospectively analyzed the results of protocol-based biopsies performed in adult recipients with normal LFT [38]. The authors compared the incidence of chronic hepatitis in recipients who underwent LT for alcoholic liver disease (ALD), on the one hand (60 patients), and autoimmune hepatitis (AIH; 28 patients) or primary biliary cholangitis (PBC; 147 patients), on the other. The median follow-up after LT was 2–3 years. Idiopathic post-transplant hepatitis was observed in 28%, 18% and 34% of cases of ALD, AIH, and PBC, respectively. Fibrosis was present in 65% of ALD with IPTH cases (18% of all ALD cases), in 60% of AIH with IPTH cases (11% of all AIH cases), and in 63% of PBC cases with IPTH (24% of all PBC cases). Interestingly, chronic hepatitis was equally common in recipients who underwent LT for immune-mediated diseases (AIH and PBC) and in recipients who underwent LT for a non-immune-mediated disease (ALD). In this cohort of patients with normal LFT, normal or nearly normal liver histology was reported in 30%, 29%, and 24% of cases of ALD, AIH, and PBC, respectively.

The recurrence of AIH after LT is observed in 17–42% of patients [39, 40]. Autoantibodies in the recipient blood usually persist for a long time after LT. The histological presentation of AIH resembles acute cellular rejection; the treatment of both diseases involves increased immunosuppression. Prior to the advent of modern DAAs, recurrent AIH was the third most common (after recurrence of hepatitis C and primary sclerosing cholangitis (PSC)) cause of graft loss among all recurrent liver diseases [41]. Meanwhile, the duration of the disease course before the graft loss was significantly shorter than in other recurrent diseases

(median 525 days). The AIH recurrence in recipients who underwent liver retransplantation (re-LT) was observed in 50–67% of cases [42].

A return to alcohol abuse in liver transplant recipients for alcoholic liver disease results in decreased graft and recipient survival. A return to alcohol use occurs in 10–42% of recipients [43]. A recent study in transplant recipients with a graft dysfunction following a return to heavy drinking found that alcoholic hepatitis was responsible for the clinical presentation in only 50% of them. In other cases, there was an acute or chronic rejection associated with low compliance to immunosuppressive drug therapy [44].

There is an obvious need to clarify the etiology of the identified histological abnormalities, especially in recipients with a clinically asymptomatic course and good graft function. It can be assumed that most cases of post-transplant chronic hepatitis, excluding viral causes, originate from immune pathology (recurrent or *de novo* AIH, late rejection with atypical signs); and increased immunosuppression may be justified. Further studies are needed to determine the role of immunosuppression in the treatment of chronic graft hepatitis.

Graft fibrosis

Graft fibrosis is an excess accumulation of extracellular matrix proteins (including collagen) in the transplanted liver due to the activation of stellate cells and portal fibroblasts in response to chronic injury (infectious agents, alcohol, xenobiotics, auto- or alloimmune inflammation, or impaired bile outflow). Progressive graft fibrosis can lead to graft cirrhosis and graft loss.

In recent years, non-invasive methods for assessing liver fibrosis have been widely used in routine clinical practice, which include a number of parameters based on the determination of biomarkers in the

blood, as well as instrumental (ultrasound or magnetic resonance) assessment of liver density, that is elastography [45]. The main problem with the use of these methods is the need to validate each of them in a large population of patients who have undergone an adequate histological examination of liver tissue (ideally with morphometry, or at least a semi-quantitative assessment of fibrosis according to one of the accepted assessment tools). High liver density measurement results can be originated from not only fibrosis, but also from steatosis, inflammatory infiltration, cholestasis, and blood stasis in the sinusoids [46].

The most comprehensively studied and relatively well-validated method of elastography is the shear wave elastography (transient elastography (TE) [47]. This method makes it possible to distinguish between the patients with minimal and severe fibrosis (cirrhosis) of the liver, but is less suitable for accurately determining the stage of fibrosis according to one of the generally accepted semi-quantitative assessment tools. But even within the framework of the most well-studied nosology, i.e. hepatitis C, the results of TE differ significantly between immunocompetent patients and liver transplant recipients [48].

Biopsy remains the "gold standard" in the diagnosis of liver graft fibrosis. There are a lot of publications on studying the severity of graft fibrosis based on the results of protocol-based biopsies. Currently, many centers have refused to perform protocol-based biopsies in the absence of clinical and laboratory evidence of graft dysfunction. In addition, a significant number of studies have been performed in pediatric liver transplant recipients (PLTRs). This is related to several reasons. First, the life expectancy of PLTRs is higher than that of adult recipients. There are studies that evaluate a 25-year follow-up of PLTRs [49]. Second, in this group of patients, the minimization of immunosuppression up to its complete cancellation is more often undertaken. In addition, indications

for LT in childhood are mainly the diseases that do not recur after LT. It seems to us especially important to study the long-term outcomes of LT performed in adult patients from a clinical and histological point of view.

A detailed review of studies on the relationship between IPTH and graft fibrosis in PLTRs was made by D. Kelly et al. (2016). Twelve studies published from 2005 to 2014 analyzed from 24 to 164 protocol biopsies performed within 1 to 10 years after LT [50]. So, H.M. Evans et al. (2006) studied 164 biopsies performed in 158 PLTRs at 1, 5, and 10 years after LT. The incidence of IPTH was 22%, 43%, and 64% at 1, 5, and 10 years, respectively. The incidence and severity of fibrosis also increased over time, with 52%, 81%, and 91% of recipients developing fibrosis at 1, 5, and 10 years, respectively. At 10 years after LT, bridging fibrosis or liver cirrhosis was detected in 50% of recipients. Researchers have identified a significant relationship between chronic hepatitis and graft fibrosis [51].

Studies by authors from the United States and Finland also revealed a correlation between the inflammation grade and the graft fibrosis severity in PLTRs [52, 53]. The correlation between IPTH and progressive fibrosis has been demonstrated in many studies. Interesting design and the results were in a study by scientists from Belgium, who traced the temporal relationship between inflammation and fibrosis, based on consecutive graft biopsies (a total of 5 biopsies within 10 years). The authors showed that the main predictor of graft fibrosis was portal inflammation observed in a previous biopsy. Moreover, the severity of inflammation correlated with the risk of developing fibrosis in a subsequent biopsy [54]. Moreover, the authors revealed a genetic predisposition to the development of graft fibrosis. They have shown that the HLA allele DRB 1*03/04 and DSA class II are associated with portal fibrosis. Portal tracts are immunologically active zones with a high

concentration of stellate cells that have profibrogenic properties under conditions of inflammation, and fibrinolytic properties at rest. The authors have hypothesized that DSA-mediated inflammation-induced fibrosis is limited to the portal tracts.

On the contrary, according to the results obtained by R. Scheenstra et al. (2009), graft fibrosis in PLTRs was not associated with either the inflammatory changes characteristic of chronic hepatitis or with signs of rejection. The incidence of portal fibrosis at 1, 3, 5, and 10 years after LT was 31%, 48%, 65%, and 69%, respectively. At the same time, in most cases, recipients with liver fibrosis retained normal or close to normal LFT values. The incidence of severe fibrosis increased from 10% at 5 years to 29% at 10 years. In contrast, graft portal fibrosis was associated with factors such as prolonged cold ischemia time, an early age at the time of LT, high donor-to-recipient age ratio, and the use of liver lobe/segment grafts [55]. There are other studies in which no correlations have been confirmed between chronic hepatitis and portal fibrosis.

In the years following the publication of the review by D. Kelly et al. (from 2016 to 2022), a number of similar studies were conducted. Investigators from Poland analyzed the results of 61 protocol-based liver biopsies in 61 PLTRs at 9–17 years (median 12 years) after LT. Various pathomorphological abnormalities were found in a more than half of the recipients, having normal laboratory parameters in most cases. Graft fibrosis (scored 3 or more by the Ishak Score) was identified in 17 recipients, and 7 of them (11.5%) had severe fibrosis (Ishak Score 5-6) [56]. The authors did not find any abnormalities in 26 biopsies (42.6%). None of the recipients showed signs of acute or chronic rejection. In 23 samples (37.7%), nonspecific lymphoid infiltrates had occurred.

Recently, researchers from the UK published the results of a histological study of 460 extracted liver grafts in 276 adults and 118

children who underwent re-LT from 1987 to 2014. Of particular interest was the analysis of a subgroup of recipients who underwent re-LT in the long term (more than 10 years after LT). In adult recipients, the most common cause leading to re-LT was the recurrence of the original liver disease (54%); the next followed were IPTH (19%); and hepatic artery thrombosis (15%). In PLTRs, the main causes of re-LT in the long term were IPTH (40%), biliary tract complications (20%), and chronic rejection (15%). In terms of the course duration from the moment of LT to re-LT, IPTH ranked first in PLTRs (10.8 years) and second in adults (8.7 years) after a relapse of autoimmune liver disease. Hepatitis C was the main cause among recurrent liver diseases. Due to advances in the treatment of hepatitis C, IPTH will become the main indication for late re-LT both in PLTRs, but also in adults [57].

In liver transplant recipients, three main types of graft fibrosis can be distinguished: portal, sinusoidal, and perivenular (centrilobular). The pathogenesis and clinical significance of these forms of fibrosis are not well understood. It is possible that greater severity of perivenular and sinusoidal fibrosis in liver recipients in the late post-transplant period, as compared with immunocompetent patients with chronic liver diseases, causes higher TE values, with the same METAVIR scores.

The generally accepted systems for assessing the native liver fibrosis stage make it possible to correctly assess only portal fibrosis, rather than other variants of graft fibrosis [58-60]. This required the development and validation of a separate scale for assessing the fibrosis severity in a transplanted liver. In 2012, Belgian scientists proposed a new liver allograft fibrosis (LAF) scoring system, which scored separately (from 0 to 3 each) the severities of portal tract fibrosis, sinusoidal fibrosis, and fibrosis around the central veins. Based on these scores, the total graft fibrosis score (0–9 points) was calculated [61]. The

LAF score showed good reproducibility across repeated examinations by the same and different experts, as well as a higher correlation with fibrosis quantification by morphometry than METAVIR or Ishak fibrosis scores. The results of subsequent studies by the same group of scientists confirmed that LAF can be a useful tool in assessing the dynamics of fibrosis progression in serial liver graft biopsies [62]. Unfortunately, the applicability of LAF has only been studied in the PLTR population (albeit in the long-term [up to 20 years] after LT). We believe it is necessary to study the applicability of LAF in the adult population of liver transplant recipients.

While chronic hepatitis (IPTH or liver disease relapse in the graft) or transplant-associated factors may play a role in the development of portal fibrosis [55], the causes of perivenular and sinusoidal fibrosis are less studied.

V. Fouquet et al. (2005) found perivenular fibrosis in 22% of recipients with normal graft function who received immunosuppressive therapy for 10 years after LT [63]. Many years later, almost identical results were published by M. Markiewicz-Kijewska et al. (2021), who found perivenular fibrosis in 21.3% of PLTRs [56]. H. Egawa et al. (2012) suggest that these changes may be associated with too low immunosuppression or its complete withdrawal in the long term after LT in PLTRs [64]. S. Varma et al. (2016) specifically studied the distribution of fibrosis in a liver graft in PLTRs. The authors found that LT from a post-mortem donor is the only factor predisposing for central fibrosis. Inflammation in the lobules, in contrast to the portal tracts, was neither a predictor of fibrosis nor associated with DSA class II, but rather associated with the antibodies not directed against the HLA complex [54]. The relationship between the sinusoidal fibrosis presence and autoantibodies 10 years after LT has been confirmed by researchers from Korea [65].

M. Pinon et al. (2022) retrospectively analyzed 134 biopsy specimens from 94 PLTRs [35]. Graft fibrosis was assessed using the LAF score [61]. Fibrosis was found in 87% of cases (mild in 30%, moderate in 45%, and severe in 12%), in most cases (80%) in the portal tracts. An increase in fibrosis severity was found among the groups of recipients who underwent biopsy 1–3 years and 4–6 years after LT. Inflammation was observed in 44% of recipients, in 90% of cases being in the portal tracts. Portal fibrosis was associated with portal inflammation in the 1-3-year group. At the same time, sinusoidal fibrosis correlated with a low level of immunosuppression and the presence of DSA.

C. Venturi et al. (2014) suggested that the early development of fibrosis may be associated with ongoing graft damage. The authors noted a correlation between portal fibrosis and prolonged ischemic time, post-mortem donor graft, and prior lymphoproliferative disease. In their study, they also identified biliary tract complications as a risk factor for sinusoidal fibrosis, while vascular complications, the presence of autoantibodies, and high levels of gamma globulin were associated with centrilobular fibrosis [62].

The authors hypothesized that there were three periods in the evolution of graft fibrosis in PLTRs: the early phase in the first 2 years was associated with the fibrosis accumulation, the second period (3–7 years) when both immunosuppression and liver fibrosis remained stable, and the third period, starting from 7 years after transplantation, when there was usually a decrease in immunosuppression, when graft fibrosis again began slowly increasing or remained the same with normal liver function [62].

Researchers from the UK studied graft pathology in 60 clinically asymptomatic PLTRs receiving low doses of immunosuppressive drugs. In 14 (23%) cases, signs of acute or early chronic rejection were found,

and immunosuppression was increased. Fibrosis was found in 36% of PLTRs at 5 or more years after LT [66].

When discussing the results described above, the question arises, whether trying to minimize immunosuppression is always justified. And can excessive minimization or complete withdrawal of immunosuppression serve as a trigger for the development of graft fibrosis? Usually, in the long term after LT, the LFT parameters are normal and are not satisfactory markers of sluggish rejection and a progression of graft fibrosis. The pathogenesis and long-term consequences of latent fibrosis in liver transplant recipients still need to be clarified. Moreover, it remains unclear whether IPTH and post-transplant fibrosis are two different forms of the disease, or IPTH can progress over time with the development of liver graft fibrosis.

Graft cirrhosis

The most severe form of chronic graft dysfunction is graft cirrhosis. Interesting are the results of the study by M. Seyam et al. (2007) based on a retrospective analysis of 1287 adult liver transplant recipients who survived the first year after LT. Graft cirrhosis developed in 48 cases (3.7%). Meantime, it was associated with the recurrence of the graft disease in 29 cases, and with the development of the specified graft disease *de novo* in 9 cases. In the remaining 10 cases (21%), the cause of graft cirrhosis could not be identified. Previous biopsy specimens showed signs of chronic hepatitis. Not surprisingly, the incidence of such "cryptogenic" graft cirrhosis was significantly higher in the recipients who underwent LT for fulminant seronegative hepatitis (6%) than in the recipients who underwent LT for other diseases (0.3%). Chronic hepatitis is the most common underlying pathological process in cases where the cause of cirrhosis remains unspecified [67].

Researchers from France observed severe forms of return to alcohol abuse in 73 (20%) of 369 liver transplant recipients operated on for ALD and survived 1 year after LT. The results of the histological examination of the graft were available in 56 recipients. Alcoholic graft cirrhosis developed in 18 of them (32%) at a mean of 6 years after LT. The cumulative risk of severe fibrosis (F4) was 15% at 3 years, 32% at 5 years, and 54% at 10 years after resuming alcohol abuse [68]. Similar results were reported by another group of French researchers. Of 712 recipients transplanted for ALD, 128 (18%) experienced a return to heavy alcohol abuse. In 41 of them (32%), alcoholic graft cirrhosis developed at 5 years after LT and 4 years after the resumption of alcohol intoxication, [69].

Vanishing bile duct syndrome

Occasionally, bile ducts are not found in every portal tract on histological examination of a liver graft. This histological pattern is called "vanishing bile duct syndrome". If the ducts are absent in more than half of the portal tracts, it is customary to speak of ductopenia. The most common causes of vanishing bile ducts are the chronic rejection (CR) and ischemic cholangiopathy.

The main mechanism of damage and loss of the bile ducts during rejection is a direct immunological destruction of the biliary epithelium. The histological pattern of cellular rejection is characterized by lymphocytic invasion and degenerative changes in the biliary epithelium. The phenomena of cholangiolitis are less pronounced in CR. Lymphocyte cultures derived from rejected liver graft tissue showed cytotoxic activity directed at donor HLA antigens. In CR, ischemic mechanisms also play a role. Indirect ischemic injury develops as a result of the chronic arteriopathy obliterans process, which is suggested by the simultaneous vanishing of the bile ducts and arteries in liver graft samples [70]. It is

generally accepted that CR is a pathology of the first year after LT. In recent years, studies have appeared demonstrating the possibility of developing CR in a very long-term (up to 25 years) after LT [49]. In early studies analyzing protocol-based liver biopsies, ductopenia was frequently detected. So, M. Sebagh et al. (2003) reported the detection of ductopenia 5 years after LT in 34%, and 10 years later in 49% of recipients. At the same time, 80% of the examined patients had normal LFT results [71]. The clinical significance of these findings needs to be clarified.

Ischemic cholangiopathy is characterized by multiple diffuse strictures of large and small ducts, as well as by a vanishing bile ducts syndrome up to the development of ductopenia. Ischemic cholangiopathy develops in 3%–17% of cases in the late post-transplant period as a result of pathological processes in the outcome of hepatic artery thrombosis or stenosis suffered in the early post-transplant period. Usually it is manifested by cholestasis and cholangitis. In the pathogenesis of ischemic cholangiopathy, such cofactors as long cold and warm ischemia time, transplantation from a non-heart-beating donor play a role [72].

Another group of diseases in which the vanishing bile duct syndrome can be observed is represented by recurrent PBC and PSC in the graft. We recently published the results of our own study on the recurrence of autoimmune diseases after LT [73]. We observed a recurrence of PBC in 10%, and PSC in 17% of cases. According to literature reports, PSC recurrence happens in 50% of liver transplant recipients within 5 years after LT and may lead to a graft loss in 25% within 5 years. The PSC recurrence is associated with an almost 5-fold increase in the risk of death, with 1-, 5-, and 10-year graft survival rates of 98%, 84%, and 56%, respectively, compared to 95%, 88%, and 72% in patients who develop no PSC in the graft [74]. The diagnosis of PSC

recurrence is based primarily on radiological findings. Histological examination of the liver tissue is of secondary importance.

The incidence of PBC recurrence after LT ranges from 21 to 37% after 10 years and approximately 40% after 15 years [75]. The histological examination of the liver tissue plays a more important role for diagnosing the recurrent PBC of the graft. Histological signs of PBC recurrence include: lymphoplasmacytic infiltrate in the portal tracts; lymphoid accumulations; epithelioid granulomas; bile duct injury [76].

Antimitochondrial antibodies (AMA) are low-informative markers of PBC recurrence. The content of AMA remains elevated after LT in most recipients. On the contrary, it has been shown that with the PBC recurrence, the total IgM is increased compared to the patients without recurrence. This laboratory parameter can be used to select recipients for diagnostic liver biopsy [75]. Recently, authors from Finland published the results of protocol-based biopsies performed on clinically healthy liver transplant recipients with a history of PBC or PSC. Normal graft histology without any abnormalities was reported in 12% of biopsies from PBC recipients (14/117) and in 26% of PSC recipients (34/133). The disease relapse was diagnosed in 15% (18/117) of PBC patients and 3% (4/133) of PSC patients. Chronic hepatitis was present in 14% (16/117) of PBC patients and in 7% (10/133) of PSC patients. Steatohepatitis was found only in 2/133 patients with PSC. Vanishing bile duct syndrome was present in 1% (1/117) of biopsies in recipients after PBC and 2% (2/133) of biopsies after PSC [77].

A number of authors have reported cases of graft loss and recipient deaths from the development of end-stage graft cirrhosis. P. Manousou et al. (2010) reported the mean time of 6.7 years from PBC recurrence to decompensation [78]. I.A. Rowe et al. (2008) noted that the median time to graft loss caused by PBC recurrence was 7.8 years. However, the

authors found no significant difference in survival between patients with and without PBC recurrence [41]. We observed the PBC recurrence in 5 recipients; in all 5 cases, there occurred a graft loss [73].

Conclusion

The detection of graft pathology in liver recipients in the late post-transplant period is of great clinical importance both in the presence of graft dysfunction, and in the uneventful course of the post-transplant period. A key role here belongs to the histological examination of the liver tissue. An auxiliary place belongs to non-invasive methods for assessing fibrosis, the detection of auto- and alloantibodies. According to the literature data, 5 years after transplantation, a normal histological pattern is seen in no more than a third of recipients. The most common cause of late graft dysfunction in adults is the recurrence of the original liver disease. In recipients who received a graft in childhood, the main causes of graft pathology leading to its loss are idiopathic post-transplant hepatitis and liver fibrosis. Idiopathic post-transplant hepatitis and "idiopathic" graft fibrosis have also been described in recipients who underwent liver transplantation in adulthood. Moreover, the location and spread of fibrosis in liver transplant recipients differs from those in immunocompetent patients with chronic hepatitis. Other common findings in recipients with normal liver function tests include asymptomatic or oligosymptomatic reduction in the number of bile ducts, the signs of graft fatty disease. The etiological and pathogenetic relationship between all the described changes and their prognostic value require studying.

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