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Transplanted liver pathology in the late post-transplant period: analysis of real clinical practice

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Abstract

Background. *Late post-transplant diseases can be latent or present as late graft dysfunction.*

The objective *was to assess the nature of pathological changes in liver transplant recipients in the long-term based on the severity of graft dysfunction.*

Material and methods*. The results of a histological examination of the liver performed no earlier than one year after transplantation in 168 recipients were studied. The median follow-up was 57.8 (26.3;94.9) months. Graft dysfunction was defined as overt if alanine aminotransferase (ALT), aspartate aminotransferase (AST), or alkaline phosphatase (ALP) increased to more than 1.5 times the upper limit of normal (n=73). Borderline dysfunction was defined as an increase in at*

least one of these parameters to more than 1 but less than 1.5 times the upper limit of normal, or an increase in gamma-glutamyl transferase (GGT) to more than 1.5 times the upper limit of normal (n=37). Graft dysfunction was absent in 58 recipients.

***Results**. In the subgroup of recipients without graft dysfunction, a slight increase in body mass index (BMI) (+1.1 kg/m²) was noted compared to BMI at transplantation. Recipients with the borderline graft dysfunction had a lower BMI (25.4 kg/m²), and those with the overt dysfunction had an even lower BMI (23.7 kg/m²), than the subgroup without graft dysfunction (26.8 kg/m²; p=0.015). Clinical signs of the graft dysfunction were absent in 34.5% of recipients at the time of examination; however, only 22.4% of these recipients showed no significant abnormalities on histological examination. Among the remaining recipients with normal liver tests, there was evidence of chronic hepatitis (19%), fatty liver disease (31%), or intralobular fibrosis (25.9%), and in one case, graft cirrhosis. Graft fibrosis was observed in 60.3% of recipients without graft dysfunction. Marked fibrosis (classified by the Liver Allograft Fibrosis (LAF) scoring system* as *LAF > 2) was detected in 31%, and significant portal tract fibrosis (assessed as the meta-analysis of histological data in viral hepatitis (METAVIR) score >2) was found in 20.7% of recipients without signs of graft dysfunction. In the subgroup of recipients with overt graft dysfunction, ductopenia was the only pathological finding in 11.1% of recipients. More than two-thirds of cases of fatty liver disease and intrahepatic fibrosis do not manifest with clinically significant abnormalities in functional liver tests. Histological examination allowed for the clarification of the cause of overt graft dysfunction in 69.4% of cases.*

***Conclusion.** Protocol biopsies in long-term liver transplant recipients enable the detection of pathological changes of varying severity, as well*

as the assessment of hepatitis activity, fibrosis stage, and the cause of graft dysfunction, and the identification of autoimmune disease recurrence.

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

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GC, graft cirrhosis
ACR, acute cellular rejection
GD, graft dysfunction
AIH, autoimmune hepatitis
AILD, autoimmune liver disease
ALD, alcoholic liver disease
ALP, alkaline phosphatase
ALT, alanine aminotransferase
AST, aspartate aminotransferase
BD, bile duct
BMI, body mass index
CH, chronic hepatitis
CN, conditional norm
CNI, calcineurin inhibitor
CYC, cyclosporine
FGD, fatty graft disease
FLD, fatty liver disease
GCS, glucocorticosteroids
GGT, gamma-glutamyl transferase
HCC, hepatocellular carcinoma
ILF, intralobular fibrosis
IPTH, idiopathic post-transplant hepatitis

LC, liver cirrhosis
LFT, liver function test
LPTP, long-term post-transplant period
LRD, living related donor
LT, liver transplantation
NAFLD, non-alcoholic fatty liver disease
NAS, NAFLD Activity Score
PBC, primary biliary cirrhosis
PBCh, primary biliary cholangitis
PD, posthumous donor
PF, portal fibrosis
PSC, primary sclerosing cholangitis
PT, portal tracts
PTLD, post-transplant lymphoproliferative disease
RAI, Rejection Activity Index (acute cellular rejection stage)
SF, significant fibrosis
TAC, tacrolimus
ULN, upper limit of normal

Introduction

Liver transplantation (LT) is the only definitive treatment for patients with end-stage diffuse liver disease and fulminant liver failure. Improvements in surgical techniques, immunosuppressive and antiviral therapy have led to a significant increase in graft and recipient survival [1, 2]. Meanwhile, the risk of dying at the age under 75 years among liver transplant recipients who survive the first year after transplantation is 5.8 times higher than in the general human population [3]. Mortality in the long-term post-transplant period (LPTP) can be associated with both graft pathology and extrahepatic causes.

Transplant diseases in LPTP can be latent or manifest themselves as episodes of a so-called late graft dysfunction, that is, deviations from reference values in liver function tests (LFTs). Graft dysfunction (GD) is caused by typical pathological processes (steatohepatitis, chronic hepatitis, bile duct obliteration due to immune or ischemic damage, fibrosis), leading to irreversible damage and graft loss.

The aim of this study was to assess the nature of pathological changes in the graft in the liver transplant recipients in the long-term post-transplant period with consideration of the presence and severity of graft dysfunction.

Material and methods

A retrospective single-center cross-sectional study was conducted. The results of histological examination of the liver performed no earlier than 12 months after LT were studied in 168 recipients in the LPTP.

The graft biopsy was performed under ultrasound guidance using the automated Bard Magnum System (BD BARD, USA) with a 16G needle. Two liver tissue samples were obtained for each procedure. Liver biopsies containing at least 5 portal tracts (PTs) and at least 10 mm in length were considered acceptable for analysis. In 6 cases, the examined liver tissue sample contained 5–7 PT structures of 7–8 mm in length. These samples were included in the study after an expert pathologist (E.A.D.) opinion relating to the possibility of their complete description. Thus, 168 liver tissue samples were considered suitable for analysis, and the changes found in them were compared with clinical and laboratory data. Moreover, 15 samples contained 5–6 PTs; 43 samples contained 7–9 PTs; the remaining 110 samples contained 10 or more PTs. The median length (Q_1;Q_3) of the assessed liver tissue fragments was 15 (12;17) mm. In 160 cases, the results obtained in liver biopsy samples were analyzed. In 4 cases, the autopsy material was analyzed; in 4 cases the sections of liver grafts (explants) removed during re-L were analyzed.

Since normal LFT results do not guarantee the absence of graft damage [4], the histological examination was included in the list of routine procedures during follow-up examinations in the long-term, regardless of the presence or absence of clinical manifestations of GD.

The median follow-up (Q_1;Q_3) of recipients before histological examination of liver tissue was 57.8 (26.3;94.9) months.

Since reference values of LFT activity differ between men and women, they were standardized using the upper limit of normal (ULN). The graft dysfunction (GD) was defined as overt when the activity of at least one enzyme (alanine aminotransferase (ALT), aspartate aminotransferase (AST), or alkaline phosphatase (ALP) increased greater than 1.5 ULN at the time of histological examination of liver tissue. The GD was defined as borderline with the increased activity of at least one of the three enzymes mentioned above over the ULN but the increase not exceeding 1.5 ULN, or with the increased activity of gamma-glutamyl transferase (GGT) exceeding 1.5 ULN. In the recipients with the overt GD, its type was defined as cytolytic (with an increase in the activity of ALT and(or) AST with normal activity of alkaline phosphatase); cholestatic (with an increase in the activity of alkaline phosphatase with normal activity of ALT and AST), or mixed (increased activity of two or all three enzymes).

Data on a number of laboratory parameters were missing for some of the graft recipients. For example, the data on the lipid profile and/or lipid-lowering therapy were available for 116 recipients. Dyslipidemia was defined as triglyceride levels >1.7 g/L, and/or LDL cholesterol >2.6 g/L, and/or the use of lipid-lowering therapy.

The hepatitis activity grade and the graft fibrosis stage were assessed using the METAVIR scale [5]. The severity of portal tract fibrosis, sinusoid fibrosis, and fibrosis around the central veins were assessed separately (from 0 to 3 points). Based on these assessments, the total Liver Allograft Fibrosis score (LAF from 0–9) was calculated [6]. The acute cellular rejection grade was assessed by the Rejection Activity Index (RAI) according to the Banff group criteria [7]. In the analysis, two

gradations characterizing the number of bile ducts (BDs) were used: a decreased number of BDs (BDs were detected in 50–80 % of PTs) and ductopenia (BDs were detected in less than 50% of PTs). If the histological examination of liver tissue revealed hepatocyte steatosis of more than 5%, the steatohepatitis severity index (NAFLD Activity Score (NAS)) was determined with the separate assessments of the steatosis severity (0–3), intralobular inflammation (0–3), and ballooning degeneration of hepatocytes (0–2). The total score of steatosis activity ranged from 0–8 [8]. Fibrosis stage assessment (0–4) in patients with steatosis was also made separately from the activity assessment. Stage 1 implied perisinusoidal or portal fibrosis (1a: mild (delicate) fibrosis of the acini third zone; 1b: moderate (dense) fibrosis of the third zone; 1c: the portal fibrosis only). Stage 2 implied perisinusoidal and portal/periportal fibrosis. Stage 3 defined septal or bridging fibrosis. Stage 4 corresponded to cirrhosis [8].

The results for quantitative variables are presented as medians and quartiles. The significance of differences between the compared values was determined using the Mann–Whitney U test for quantitative and ordinal variables; and the two-tailed Fisher's exact test was used for comparing proportions. Kruskal–Wallis rank analysis of variance was used to compare independent groups based on quantitative variables. Differences were considered statistically significant if the p-value was less than 0.05. Statistical processing was performed using the Statistica 7.0 software package (StatSoft Inc., USA).

Results

I. General and clinical characteristics of recipients

Diastolic dysfunction was not detected in 58 of 168 recipients. The overt diastolic dysfunction was observed in 73 recipients, the borderline

diastolic dysfunction was seen in 37 recipients. The overt diastolic dysfunction was cytolytic in 4 cases, cholestatic in 27 cases, and mixed in 42 cases.

Demographic data and clinical signs identified in recipients at the time of follow-up examination are presented in Table 1.

Table 1. General and clinical characteristics of recipients as related to the presence and severity of graft dysfunction

Sign	Without GD, n=58	Borderline GD, n=37	Overt GD, n=73	Total, n=168 (n, %)
Recipient gender, n (%)	24 (41.4%)	12 (32.4%)	34 (46.6%)	70 (41.7%)
Age at LT, Me (Q_1;Q_3), years	46.0 (39.6;54.2)	50.0 (41.1;56.8)	47.3 (37.1;55.3)	47.3 (38.5;55.8)
BMI at LT, Me (Q_1;Q_3), kg/m^2	25.6 (23.6;28.4)	23.8 (21.0;27.5)	24.5 (21.0;27.5)	24.7 (21.4;27.9)
Age at the time of investigation, Me (Q_1;Q_3), years	54.0 (44.3;59.4)	56.8 (46.6;62.9)	51.2 (42.0;58.5)	53.3 (43.4;60.0)
Donor organ (LRD), n (%)	33 (56.9%)†	22 (59.5%)	64 (87.7%)†	119 (70.8%)
Male donor gender, n (%)	26 (44.8%)	22 (59.5%)	38 (52.1%)	86 (51.2%)
Donor age, Me (Q_1;Q_3), years	41 (32;48)*	38 (27;46)	34 (27;44)*	36.5 (29;47)
Surgical procedure (primary transplant, n/retransplant, n)	55/3	37/0	70/3	162/6
- Viral LC, n (%)	35 (60.3%)	20 (54.1%)	33 (45.2%)	88 (52.4%)
- AILD, n (%)	7 (12.1%)*	10 (27.0%)	23 (31.5 %)*	40 (23.8%)
- Alcoholic, n/ metabolic LC, n (%)	3/2 (8.6%)	2/1 (8.1%)	3/3 (8.2%)	8/6(8.3%)
- LC of unspecified etiology and other, n (%)	11 (19.0%)	4 (10.8%)	11 (15.1%)	26 (15.5%)
HCC at the time LT, n (%)	9 (15.5%)	3 (8.1%)	16 (21.9%)	28 (16.7%)
Follow-up period after LT, Me (Q_1;Q_3), months	59.3 (30.6;100.6)	61.6 (26.2;97.3)	54.8 (24.0;89.6)	57.8 (26.3;94.9)
Arterial hypertension, n (%)	25 (43.1%)	20 (54.1%)	24 (32.9%)	69 (41.1%)
Diabetes mellitus before LT, n (%)	11 (19.0%)	3 (8.1%)	13 (17.8%)	27 (16.1%)
Diabetes mellitus after LT, n (%)	17 (29.3 %)	5 (13.5%)	17 (23.3%)	39 (23.2%)
BMI at investigation, Me (Q_1;Q_3), kg/m^2	26.8 (23.5;29.4)#	25.4 (21.2;28.3)	23.7 (19.8;28.3)#	25.7 (21.0;28.7)
Change in BMI during the follow-up period, Me (Q_1;Q_3), kg/m^2	1.11 (-0.74;3.16)#	0.76 (-0.40;3.31)*	-0.14 (-2.47;1.75)* #	0.37 (-1.61;2.58)
Obesity (BMI>30 kg/m^2), n (%)	14 (2.4.1%)	8 (21.6%)	11 (15.1%)	33 (19.7%)
Dyslipidemia, n (%)	36 of 44 (81.8%)	25 of 31 (80.6%)	33 of 41 (80.5%)	94 of 116 (81.0%)
GCS at investigation, n (%)	6 (10.3%)	8 (21.6%)	15 (20.5%)	29 (17.3%)
CNIs at investigation: TAC, n/CYC, n/no, n	53/2/3	32/1/4	62/4/7	147/7/14
Everolimus at investigation, n (%)	10 (17.2%)	6 (16.2%)	16 (21.9%)	32 (19.0%)
Vascular complications, n (%)	3 (5.2%)	1 (2.7%)	7 (9.6%)	11 (6.6%)
Biliary strictures, n (%)	10 (17.2%)†	4 (10.8%)†	40 (54.8%)†	54 (32.1%)

Current n (%)	**0 †**	**1 (2.7%)**	**21 (28.8%) †**	22 (13.1%)
Treated, n (%)	10 (17.2%)	3 (8.1%)	19 (26.0%)	32 (19.0%)
HBV replication, n/HCV at investigation, n	1/0	1/1	4/0	6/1

Notes: AILD, autoimmune liver disease; GCS, glucocorticosteroids; HCC, hepatocellular carcinoma; GD, graft dysfunction; LRD, living related donor, CNI, calcineurin inhibitors, BMI, body mass index; TAC, tacrolimus; LT, liver transplantation; CYC, cyclosporine; LC, liver cirrhosis; HBV, viral hepatitis B; HBC, viral hepatitis C

* $p<0.05$; # $p<0.005$; † $p\leq0.0001$. Information on some laboratory parameters was unavailable for some recipients

Most demographic and clinical characteristics of recipients without GD, those with borderline or overt GD were comparable. There were several exceptions: the recipients with overt GD were more likely to have received an organ from a LRD, and their donors were younger compared to the recipients without GD. These differences may be associated with a significantly higher incidence of biliary complications, including anastomotic strictures after related transplants. It is evident that the incidence of biliary strictures in the subgroups of recipients with GD was higher than in the subgroup of recipients without GD, since in a significant number of cases, GD was caused by the development of biliary strictures.

Two identified trends appear to be more interesting: 1) in recipients who developed an overt GD, autoimmune liver diseases had been a more common cause of LT (31.5%) than in recipients with borderline GD (27%) and than in recipients without GD (12.1%). For the trend, $\chi^2=7.76$; df=2; p=0.02; the pairwise comparison statistics is presented in Table 1; 2) BMI in LT was comparable between the subgroups of recipients with and without further GD. At the time of the follow-up examination performed a year after LT, the recipients without GD had a normal BMI of 26.8 kg/m^2, and on average, it had increased compared to BMI at LT (+1.1 kg/m^2). In recipients with borderline GD, the BMI value at the

examination was lower (25.4 kg/m^2), and its increase in relation to the BMI at LT (+0.76 kg/m2) was less pronounced than in the subgroup of recipients without GD. Finally, in the subgroup of recipients with overt GD, the BMI value at the examination was even lower (23.7 kg/m^2) than in the other two subgroups; a decrease in BMI in relation to the BMI at LT (-0.14 kg/m^2) was also noted. For BMI, the Kruskal–Wallis test yielded a p-value of 0.015, and for the increase in BMI, it yielded a p-value of 0.008; pairwise comparison statistics are presented in Table 1.

II. Comparison of graft pathology in patients with and without graft dysfunction

Comparative incidence of pathological changes in liver recipients depending on the GD presence and severity at the time of examination are presented in Table 2.

Table 2. Incidence of pathological changes in liver recipients depending on the presence and severity of graft dysfunction at the time of investigation

Sign	Without GD, n=58	Borderline GD, n=37	Overt GD, n=73	Total, n=168
Impaired liver lobular structure, n (%)	1 (1.7)*	1 (2.7)	9 (12.3)*	11 (6.5)
Fatty hepatosis >5%, n (%)	21 (36.2)*	12 (32.4)	16 (21.9)*	49 (29.2%)
Balloon dystrophy of hepatocytes, n (%)	14 (24.1)*	6 (16.2)	23 (31.5)*	43 (25.6)
Single hepatocytes, n (%)	12 (20.7)	5 (13.5)	19 (26)	36 (21.4)
Multiple focuses, n (%)	2 (3.4)	1 (2.7)	2 (2.7)	5 (3.0)
Common, n (%)			2 (2.7)	2 (1.2)
BD disappearance of (50%<PT<80%), n (%)	**18 (31.0)‡**	**15 (40.5)**	**37 (50.7)‡**	70 (41.7)
Ductopenia (<50%), n (%)	**0†#**	**6 (16.2)#**	**21 (28.8)†**	27 (16.1)
Cirrus degeneration of hepatocytes, n (%)	27 (46.6)*	23 (62.2)*	43 (58.9)*	93 (55.4)
BD proliferation, n (%)	40 (70.0)*	26 (70.3)*	52 (71.2)*	118 (70.3)
Canalicular cholestasis, n (%)	**0#**	**1 (2.7)‡**	**14 (19.2)‡ #**	15 (8.9)
Intracellular cholestasis, n (%)	45 (77.6)*	26 (70.3)*	53 (72.6)*	124 (73.8)
Activity grade (METAVIR),	**18 (31.0)#**	**14 (37.8)‡**	**45 (61.6)# ‡**	77 (45.8)

n (%)				
A1, n (%)	17 (29.3)*	12 (32.4)*	31 (42.5)*	60 (35.7)
A2, n (%)	1 (1.7) ‡	2 (5.4)	10 (13.7) ‡	13 (7.7)
A3, n (%)	0*	0*	4 (5.5)*	4 (2.4)
A2+A3, n (%)	**1 (1.7)‡**	2 (5.4)	**14 (19.2)‡**	17 (10.1)
Focal necrosis of hepatocytes, n (%)	6 (10.3)*	**2 (5.4) ‡**	**16 (21.9)* ‡**	24 (14.3)
Interstitial hepatitis, n (%)	1 (1.7) ‡	0	10 (13.7) ‡	11 (6.5)
Bridging necrosis, n (%)	0*	0	2 (2.7)*	2 (1.2)
Mallory bodies, n (%)	0*	0	2 (2.7)*	2 (1.2)
Apoptotic bodies, n (%)	0*	1 (2.7)	3 (4.1)*	4 (2.4)
ACR (RAI>3), n (%)	3 (5.2)* ‡	7 (18.9) ‡	12 (16.4)*	22 (13.1)
Graft fibrosis (LAF >1), n (%)	35 (60.3)*	18 (48.6)*	54 (74.0)*	107 (63.7)
PT fibrosis (METAVIR>1), n (%)	**12 (20.7)†**	**7 (18.9)#**	**39 (53.4)# †**	58 (34.5)
Sinusoidal fibrosis (LAFs >0), n (%)	14 (24.2)*	9 (24.3)*	25 (34.2)*	48 (28.6)
Pericentral fibrosis (LAFl >0), n (%)	33 (56.9)*	17 (45.9)*	33 (45.2)*	83 (49.4)
Conditional norm, n (%)	13 (22.4)* ‡	7 (18.9%)*	6 (8.3%) ‡	26 (15.6)

Notes: ACR, acute cellular rejection; BD, bile ducts; PT, portal tracts; GD, graft dysfunction
Pairwise comparisons (two-tailed Fisher's test): * p>0.05 (NS); ‡ p<0.05; # p≤0.005; † p≤0.0001

A significant proportion of overt GDs were associated with biliary complications, which were observed at the time of examination in 21 (28.8%) of 73 patients with GD. Moreover, in none of the 58 cases (recipients) without GD signs eof were there any biliary complications at the time of examination. This may explain the differences between the groups of recipients with overt GD and no signs of GD in terms of the frequency of detecting the signs of intraductal cholestasis, active hepatitis (assessment of Grade by METAVIR), portal fibrosis (Stage assessment by METAVIR), and partially in terms of the frequency of identifying ductopenia.

More interesting is the absence of significant differences between the groups of recipients with and without GD in the frequency of detecting 1) the signs characterizing intrahepatic, sinusoidal fibrosis; 2) the signs characterizing the impaired bile secretion by hepatocytes (intracellular deposits of bile pigments, feathery degeneration of hepatocytes, BD proliferation); 3) dystrophic changes (steatosis,

ballooning) in hepatocytes. In other words, the frequencies of detecting the corresponding signs in the presence or absence of GD are comparable. Also, no significant differences were found in the frequency of detecting the conditionally normal histological pattern in borderline GD and in GD absence, which indirectly confirms the validity of the cutoff threshold used in identifying the overt (clinically significant) GD.

III. Histological patterns of graft pathology and “findings” in transplant biopsy in LPTP

Individual pathohistological changes form "patterns." For example, a combination of fatty and ballooning degeneration of hepatocytes, along with lobular inflammation, is characteristic of steatohepatitis. Severe fibrosis of the grafts, with inflammatory cell infiltration and the appearance of stepwise or even bridging necrosis, is characteristic of chronic hepatitis (CH). Acute cellular rejection (ACR) is characterized by venous endotheliitis, inflammatory damage to the bile ducts (BDs), and the graft infiltrate. Clearly, several different pathological processes in the liver can occur simultaneously. Nevertheless, to simplify the analysis, while understanding and accepting a certain degree of conventionality, we have identified the predominant histological patterns of graft pathology.

In defining patterns of graft pathology, we focused on the presence and distribution of fibrosis, the severity of inflammation, and the presence of fatty degeneration of hepatocytes. This allowed us to relatively consistently distinguish between 5 main patterns of histological changes in the graft: 1) conventional norm (CN); 2) chronic hepatitis/portal fibrosis (CH/PF); 3) fatty graft disease (FGD); 4) lobular and sinusoidal (intralobular) fibrosis (LF); 5) significant graft fibrosis and cirrhosis (SG/CT). We would like to emphasize once again that the identification of these patterns is largely conditional, and we analyze them further with

the appropriate reservations. Thus, in the presence of fatty hepatosis (5% or more), we preferred to classify the biopsy as fatty liver disease unless this conflicted with the expert pathologist's conclusion made in real-life clinical practice. Disruption of lobular structure combined with severe fibrosis (development of graft cirrhosis) is the final stage of progression of most pathological processes occurring in the liver. It is often impossible to determine the primary process; a combination of several may occur. This justifies the classification of advanced SF/GC as a distinct pattern. The criteria for distinguishing patterns of conditional normality and graft pathology are presented in Table 3.

Table 3. Histological patterns of graft pathology in liver recipients in the late post-transplant period

Pattern	Number (%) of cases	Characteristic
Conditional norm	26 (15.5%)	No inflammation or fibrosis. Lobular structure is preserved, steatosis not exceeding 5%, hepatocyte ballooning is absent or present in individual cells. Minimal inflammation within the lobule or in the portal tract without disruption of the border plate is acceptable. Minor PT fibrosis (1 point) or intralobular fibrosis (1 point) is acceptable. Total LAF ≤1. Index for Grading and staging of disease Activity (IGA) not exceeding 1. No other histological findings. RAI≤2.
Chronic hepatitis/ portal fibrosis	69 (41%)	Inflammatory infiltrate, predominantly in the portal tracts (A>0) in combination with fibrosis, predominantly of the PT. Or PT fibrosis (F1; LAF-1 or F2-3; any LAF score). Lobular structure is preserved
Fatty graft disease	37 (22%)	Steatosis of 5% or more in combination with ballooning of hepatocytes; or steatosis of 10% or more in the absence of other significant pathology or in combination with fibrosis with preserved lobular structure, unless otherwise reported by expert pathologists
Intralobular fibrosis	26 (15.5%)	Significantly marked perisinusoidal and pericentral fibrosis, with insignificant PT fibrosis manifestation; (F 0-1, LAF >1), absent or minimal inflammation (A0); steatosis of 5% or less
Significant fibrosis/cirrhosis	9 (5.4%)	Impaired lobular structure of the liver, F3–4
Other findings	1 (0.6%)	Malformation of the ductal plate as donor pathology

Predominant histological patterns of graft changes reflect the pathological processes occurring in the liver graft and may serve as a background against which background other pathological features may be detected. Many pathological features were present in a single biopsy in various combinations. For example, since we were studying the pathology of the LPTP, such a significant pathological process as rejection usually accompanied (developed on top of) another pathological process. Acute cellular rejection was detected in 22 cases, being mild (RAI score 4–5) in 18 cases, moderate (RAI score 6–7) in 4 cases. The background morphological pattern of liver damage in patients with ACR was chronic fibrosis in 14 cases, ILF in 4 cases, and FLD in 4 cases. In two cases, the severity of fibrosis at the time of ACR detection was minimal, and degenerative changes in hepatocytes were absent. It can be assumed that in the absence of ACR, these biopsies would have been classified as "conditionally normal." However, since the presence of ACR by definition cannot be considered a histological norm, we were forced to consider it within the framework of one of the pathological patterns. Loss of the BDs usually accompanied fibrosis of varying severity degrees and was not always a manifestation of chronic rejection.

Obliterating arteriopathy was detected in two cases. Importantly, in both cases, the patients underwent hepatic artery stenting. In one case, the graft loss occurred due to significant cholestasis, and we analyzed the autopsy results. In the other case, a biopsy was performed due to mixed-type GD. Apart from obliterating arteriopathy, pathological changes were minor. There was also mild portal fibrosis (LAF 1) and minimal PT inflammation (A1). No BD losses were observed.

Concentric periductal fibrosis, in the "onion skin" pattern, was detected in 11 biopsies. In 3 recipients whose LT was caused by primary sclerosing cholangitis (PSC), the changes were considered to be a

recurrence of this disease in the graft. Liver graft biopsies in these patients were performed against the background of mixed cirrhosis with a predominance of cholestasis. In the other 3 recipients (women aged 24, 47, and 57 years), the cause of cirrhosis was not clarified. In all three cases, concentric periductal fibrosis was detected during protocol biopsy without signs of overt ductosis. It was combined with BD losses not reaching the degree of ductopenia (25–36 %) and PT fibrosis (F1 in two recipients; F3 in one). These findings led us to hypothesize that we had detected an early recurrence of latent PSC during routine graft biopsy and, therefore, that PSC was the cause of LT in these recipients. A repeated review of the histological specimens of the native liver (explant) removed during transplantation confirmed our hypothesis in one of these three cases. In the other two cases, no etiologic features were detected in the cirrhotic explant. In two additional cases (women aged 33 and 52 years), the etiology of the liver disease leading to LT was primary biliary cholangitis (PBCh). At the time of examination, these recipients had overt biliary cholangitis with predominant cholestasis. We hypothesized the presence of PSC/PBCh overlap syndrome in these patients at the time of LT and the recurrence of this disease at the time of examination. Upon review of the removed liver specimens from these patients, one indeed showed signs of PSC and PBCh; in another case, the picture was consistent with PBCh. In another case, concentric periductal fibrosis was discovered at examination of the liver explant during retransplantation. Graft loss was caused by multiple non-anastomotic strictures resulting from prolonged cold ischemia of the donor organ. The last two recipients of these 11 underwent LT due to viral cirrhosis and alveolar echinococcosis.

Non-caseating granulomas in the PTs were detected in 3 recipients operated on for PBCh with a cholestatic pattern of GD, which allowed us

to confirm the PBCh recurrence in the graft, and in a patient with an initial diagnosis of viral cirrhosis without signs of GD at the time of biopsy.

Thus, in a number of cases, a “protocol” liver biopsy in the LPTP made it possible to clarify the etiology of the liver disease that led to transplantation or to identify an early relapse of an autoimmune graft disease that had been proceeding latently.

IV. Histological patterns and graft dysfunction

The distribution of histological patterns depending on the GD severity is presented in Table 4.

Table 4. Frequency of histological patterns in relationship to the presence and severity of graft dysfunction

Histological pattern	Without GD, n=58	Borderline GD, n=37	Overt GD, n=72
Conditional norm, n (%)	13 (22.4) ‡	7 (18.9)	6 (8.3) ‡
Chronic hepatitis/ portal fibrosis, n (%)	11 (9.0) ‡ †	16 (43.2) ‡	42 (58.3) †
Fatty transplant disease, n (%)	18 (31.0) ‡	8 (21.6)	11 (15.3) ‡
Intralobular fibrosis, n (%)	15 (25.9)#	5 (13.5)	6 (8.3)#
Significant fibrosis/cirrhosis, n (%)	1 (1.7)	1 (2.7)	7 (9.7)

Note: A patient with ductal plate malformation was excluded from the data analysis;

‡ $p<0.05$; # $p<0.01$; † $p<0.00001$

As expected, normal histological patterns were more common in the subgroup of recipients without GD than in those with overt GD. More interestingly, abnormal patterns such as FGD and ILF were statistically significantly more common in the subgroup of recipients without GD than in those with overt GD. The subgroup of recipients with borderline GD, however, was intermediate in the frequency of normal and these

abnormal patterns, showing no statistically significant differences compared to the other subgroups.

In contrast, CH/PF was observed significantly more frequently in the subgroup of recipients with overt GD and even in the subgroup of recipients with borderline GD than in recipients without GD signs. Interestingly, in one case of a patient without GD signs, the histological examination revealed pronounced fibrosis (F3) with disruption of the liver lobular structure. Conversely, in 6 recipients (8.3%), despite the clinical picture of overt GD, no pathological changes were found. The histological pattern corresponded to conventional norm.

If we rotate the matrix 90° and analyze the same data (Table 5), we can see that a conditionally normal histological picture in a quarter of recipients manifests itself clinically with the signs of overt GD. However, more than two-thirds of cases of FGD (70.2%) and ILF (76.9%) do not manifest with significant abnormalities in the LFT.

The only consistent pattern is the correlation of the CH/PF pattern with the GD incidence and severity.

Table 5. Graft dysfunction occurrence rate in different histological patterns

Graft function	CN n=26	CH/PF n=69	FLD n=37	ILF n=26	SF/GC n=9
Without DT, n (%)	13 (50.0)	11 (15.9)	18 (48.6)	15 (57.7)	1 (11.1)
Borderline DT, n (%)	7 (26.9)	16 (23.2)	8 (21.6)	5 (19.2)	1 (11.1)
Overt DT, n (%)	6 (23.1)	42 (60.9)	11 (29.7)	6 (23.1)	7 (77.8)

Note: A patient with ductal plate malformation was excluded from the analysis. CN, conditional norm; CH/PF, chronic hepatitis/portal fibrosis; FLD, fatty liver disease; ILF, intralobular fibrosis; SF/GC, significant fibrosis/ graft cirrhosis.

V. Function of the transplanted liver and histological changes depending on the time after transplantation

At the time of the examination, the periods after 167 LTs varied from 12 to 154 months. To study possible relationships between graft function, histological changes, and time after LT, the cases were stratified into three equal groups: “T1”: from 12 to 36 months (n=57), “T2”: from 37 to 79 months (n=54), and “T3”: from 80 to 154 months (n=56). There were no statistically significant differences between the groups in key demographic and clinical characteristics. The frequencies of detecting the borderline or overt delayed graft dysfunction were 14 (25%) and 24 (42%) in “T1” group, 9 (17%) and 26 (48%) in “T2” group, and 14 (25%) and 22 (39%) in “T3”, χ^2=1.66; p=0.799. Normal LFT values were recorded in 19 (33%), 19 (35%), and 20 (36%) cases, respectively.

Banff scores 4 cases or more are shown in Fig. 1.

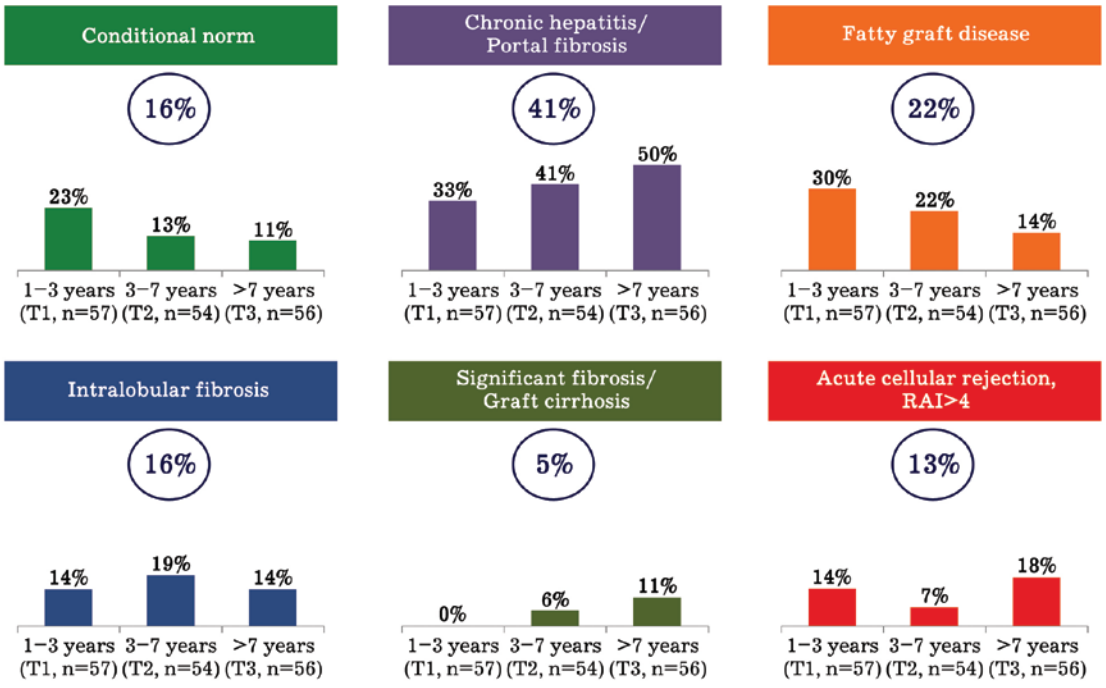

Fig. 1. Frequency of detecting the typical histological patterns and acute cellular rejection depending on the timing of liver graft biopsy

Despite the absence of formal statistically significant differences with increasing time after LT, there were trends toward an increased frequency of detecting of CH/PF and SF/GC in biopsies, while the incidence of CN and FGD decreased. This dynamics reflects natural, consistent, and interrelated changes in the histoarchitecture of the transplanted liver under the impact of a changing set of immune and non-immune factors.

VI. Clinical and histological changes in patients without graft dysfunction in the long-term post-transplant period

Fifty-eight recipients had no clinical or laboratory signs of GD at the time of examination. Biliary and vascular complications were absent at the time of examination in all 58 recipients; in 10 cases, biliary complications had been successfully treated previously. One patient had HBV replication as part of a hepatitis B infection de novo. In the remaining recipients, no HBV or HCV replication was detected at the time of examination.

Despite normal ALT, AST, and ALP activities, most of the recipients we examined showed some signs of graft pathology during the postoperative period (Table 2). Among the most common morphological findings were the signs of impaired excretion of bile components from hepatocytes. Thus, the detection of bile pigments (intracellular cholestasis) was noted in 77.6% of the examined patients, BD proliferation in 70%, and feathery degeneration of hepatocytes in 46.6%. However, in no case, any signs of impaired bile outflow at the level of the bile ducts were detected.

The next most frequently detected (but more clinically significant!) pathological sign in our group of patients was graft fibrosis. It was found in 60.3% of liver recipients without signs of GD. Fibrosis was completely

absent in only 3 recipients (5.2%). In another 20 cases (34.5%), the LAF score was 1 (minimal fibrosis), which, in the absence of other pathological signs, allowed these patients to be classified as belonging to the CN pattern. Significant graft fibrosis (assessed by METAVIR>1) was detected in one in five recipients without GD.

We identified pronounced liver graft fibrosis (LAF>2) in 18 recipients without GD (31%). The LAF score was 3 in 10 cases (7.2%), 4 in 7 cases (12.1%), and 5in one case (1.7%). In one recipient, severe fibrosis was accompanied by disruption of the liver lobular structure. In half (n=9) of the cases, LT was performed for cirrhosis resulting from chronic hepatitis C. HCV infection was cured only in the post-transplant period, and the virus remained in the graft for some time, which may explain the presence of fibrosis in these patients. One of these 9 recipients had HBV infection de novo at the time of examination. In other 5 recipients, fatty liver disease may have led to graft fibrosis. In the remaining 4 cases, no obvious potential causes for the development of severe graft fibrosis could be identified. These cases may be classified as the cases of so-called idiopathic fibrosis.

The following group of histological signs may characterize manifestations of immunosuppression deficiency. The RAI assessment (according to *the Banff group classification*) does not fully reflect the degree of delayed ACR developed in LPTP [4, 7]. Nevertheless, until other validated criteria have been proposed, the professional community continues to use this assessment [7]. Histological signs of mild ACR (RAI=4) were found in 3 recipients (5.2%) against the background of lobular fibrosis (n=1), steatohepatitis (n=1) or chronic hepatitis (n=1) of moderate activity. Loss of small BDs may be a consequence of a wide variety of processes: recurrence of autoimmune cholestatic diseases of the liver graft, ischemic cholangiopathy due to arterial complications, chronic

graft rejection. Ductopenia (no BDs in more than 50% of PTs) was absent in the group of recipients without GD. However, significant disappearance of BDs was observed in one-third of patients (BDs were detected in less than 80% of PTs).

Fatty hepatosis (fatty degeneration detected in >5% of hepatocytes) was observed in one third of our recipients (36.2%), with steatosis being the predominant pathological pattern in 18 cases (31%). In 12 recipients (20.7%), steatosis was combined with hepatocyte ballooning, and in 7 of them (12.1%), lobular inflammation of varying severity was also present, which allowed us to establish the presence of steatohepatitis in these patients. Mallory bodies were not found in any case. The NAS score was 5 of 8 possible one recipient, 4 in 3 recipients, 3 in 4, and 2 in 4 recipients. Fibrosis assessment in FLD is performed separately from the activity assessment (NAS). One of our recipients with steatohepatitis was found to have septal fibrosis (score 3); 3 had a combination of PT fibrosis and perisinusoidal fibrosis; in the remaining 8 recipients, fibrosis was predominantly periportal (1c in 7 cases) or dense perisinusoidal (1b in 1 case).

Only in 13 cases (22.4%) (less than a quarter of the examined recipients without GD) the histological pattern corresponded to CN.

VII. Possibilities of clinical examination methods and the role of histological examination of liver tissue in identifying the causes of graft dysfunction

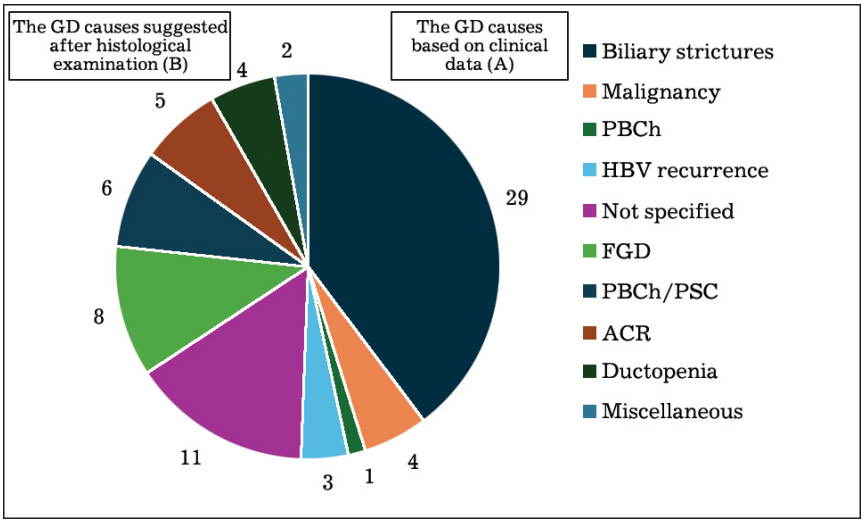

Fig. 2. Causes of overt graft dysfunction in 73 examined recipients

Of the 73 recipients with overt GD, the causes of its development could be assumed in 37 cases before histological examination (Fig. 2A). In 29 cases, biliary strictures (anastomotic and non-anastomotic) were present; in 4 cases, graft involvement in the tumor process as part of HCC progression (n=3) or post-transplant lymphoproliferative disease (PTLD) (n=1). In one case, the PBCh recurrence was previously diagnosed, and in two other recipients, hepatitis B de novo was identified. Finally, in one recipient, the HBV replication was observed against the background of biliary complications, so there were at least two possible causes for the development of GD. In the remaining 36 cases, the cause of GD was not determined before histological examination of the liver tissue.

After histological examination, the cause of GD was clarified in 25 (69.4%) of 36 recipients (Fig. 2B). The most common cause was FLD, detected in 8 recipients (22.2%) (in the form of steatohepatitis in 6 of

them). Recurrence of graft cholestatic diseases (PBCh or PSC) was confirmed in 6 cases. In 5 cases (13.9%), ACR was named as the leading cause of GD development. Ductopenia was detected in 4 recipients (11.1%). This pathological sign required further clinical interpretation. In 1 recipient, who died from PTLD, the graft was involved in an oncohematological process, while in another, the histological examination revealed a ductal plate malformation (pathology of the donor organ).

Based on the results of histological examination, the cause of GD in a recipient with biliary stricture and hepatitis B was clarified. The presence of active hepatitis, septal fibrosis, and nodular regenerative hyperplasia left no doubt about the viral cause of GD.

In 11 cases, the cause of the overt GD development was not clarified during histological examination of liver tissue.

Discussion

We were the first in Russia to conduct a large-scale study assessing graft pathology in the long-term period in adult liver transplant recipients.

The etiology of the disease leading to LT is important for the choice of maintenance immunosuppression regimen. Early detection of autoimmune disease recurrence in the graft is also important. The proportion of patients with cryptogenic cirrhosis among patients awaiting LT is still quite high [1, 2]. It is believed that cryptogenic cirrhosis mainly represents cases of undiagnosed alcoholic liver disease (ALD), is the outcome of autoimmune diseases and "burned-out" steatohepatitis associated with metabolism [9]. In our study, performing "protocol" biopsies in the LPTP gave reason to assume that the cause of cryptogenic cirrhosis in 3 patients was PSC. In 3 other recipients, in whom the cause of LT was known as PSC, the histological examination in the LPTP revealed the signs of PSC recurrence in the absence of GD. Finally, in 6

patients with GD, the clinically suspected diagnosis of recurrent PSC or PBCh was confirmed histologically.

The concept of "graft dysfunction" has no universally accepted criteria. It is typically defined as the deviation of the graft function (LFT results) from the reference values. Given the differences in graft function reference values between individual centers, as well as between men and women, it is common in the literature to express the severity of graft function deviation from the reference values as multiples of the upper limit of normal (ULN). Thus, Yu. O. Malinovskaya and co-authors (2024) proposed to define late GD as an excess in the activity of at least one of the enzymes (ALT, AST, GGT, and ALP) by more than 1.5 ULN [10]. This approach creates an obvious “gray zone” between patients with significant deviations in LFT parameters from the reference values and the norm. To overcome this limitation, we studied separately the subgroups of recipients with minor deviations in LFT results and those with considerably high LFT values, defining them as patients with borderline or overt GD. Recipients with normal LFT values were considered separately from the above mentioned subgroups.

It has been shown that standard biochemical tests do not reliably identify graft pathology in the early or long-term post-transplant periods [11-14]. J.C. Duclos-Valee et al. (2003) reported recurrence of autoimmune hepatitis (AIH) in 7 of 17 recipients at 10 years after LT, and in 4 of them (57%), the histological signs of disease recurrence, identified based on the results of a “protocol” biopsy, preceded the deviations in the LFT results by 1–5 years [15]. M. Sebagh et al. (2003), based on the analysis of “protocol” biopsies performed on recipients 10 years after LT, calculated that the sensitivity and specificity of LFT for detecting histological abnormalities were only 75% and 54%, respectively [13]. Finally, M. Berenguer et al. (2001) found pathological changes one year

after LT in 9 (11%) of 82 patients who underwent LT for non-HCV related diseases, despite a normal ALT activity [16].

For ease of analysis, we defined 5 patterns of liver graft pathology. In the studies similar to ours, the investigator teams have addressed this issue in different ways. Thus, the researchers from the USA (Universities of Pittsburgh, Houston, and Mayo Clinic, 2008), when analyzing 165 biopsies obtained from 100 recipients with normal LFT values, identified 1) a normal pattern; 2) minimal changes (non-aggressive portal or lobular infiltration by mononuclear cells or steatosis <10%); 3) any pathology, which was further analyzed according to etiologic criteria [17]. Since the aforementioned study was conducted with the aim of investigating the nature and severity of liver damage in liver recipients with normal LFT s based on the results of “protocol” biopsies, it is of interest to compare the results with ours. In most of our recipients with normal LFTs, pathological patterns were found. CN was seen in only 22% of cases. In contrast, the majority (73%) of recipients from US university hospitals had a normal pattern (41%) or minimal changes (32%). Pathological signs that the authors regarded as significant were found in 27% of cases. These included non-alcoholic gastrointestinal tract (10.9%), central venulitis (6.1%), recurrent graft disease PBCh (5.5%), hepatitis C (3.6%), ALD (0.6%), and sarcoidosis (0.6%); transplant-specific diseases (central venulitis or "portal" ACR and ILF of acinus zone 3). The authors identified more than one "anomaly" in 7 (4.2%) of 165 biopsy samples. We conducted the study amid the successful cure of hepatitis C in all our patients. Apparently, the more frequent detection of graft pathology in our group of recipients may be associated both with stricter criteria of "normal", and the differences in the studied populations. Of 165 biopsies obtained at three US centers, 36 were obtained less than a year before LT, the rest were from 1 to 5 years after LT. The study included both adults

and children: the age of recipients ranged from 1 year to 67 years at the time of LT. Our single-center study included a subgroup of 58 adult recipients with normal LFTs, whose histological examination was performed from 1 year to 13 years after LT. Despite significant differences in the detection rates of fibrosis, FLD, and CH, the ACR detection rates were comparable in our (5.2%) and American (7.3%) recipient populations. In one case, in a subgroup of patients without fibrosis, we detected the developing graft cirrhosis. Previously, J. Neuberger et al. (1998) also reported cryptogenic graft cirrhosis detected during a “protocol” biopsy in a recipient with normal LFTs [12].

It seems particularly surprising to us that in the study by authors from the USA, in no case was CH detected that was not associated with the recurrence of the previous liver disease, the so-called idiopathic post-transplant hepatitis (IPTH). According to reports by a number of authors, IPTH is observed in 30–70 % of cases when analyzing biopsies performed in the LPTP [11, 18, 19]. Researchers from Birmingham (UK, 2009) retrospectively analyzed the results of protocol biopsies performed in adult recipients with normal LFT values [20]. The results of histological studies were distributed into 6 categories (patterns): normal or nearly normal biopsies; unexplained CH; FGD (steatosis and steatohepatitis); recurrent graft disease (AIH or PBCh); AIH de novo; other findings (siderosis, nodular hyperplasia). Biopsies with abnormalities consistent with more than one pathological diagnosis were classified according to the predominant abnormalities. The classification proposed by the authors involves a mixture of etiological and morphological principles.

The authors compared the incidence of chronic hepatitis in recipients who underwent LT for ALD (60 patients), on one part, and AIH (28 patients) or PBCh (147 patients), on the other part. The median

follow-up after LT was 2–3 years. IPTH was observed in 28%, 18%, and 34% of cases of ALD, AIH, and PBCh, respectively. Fibrosis was present in 65% of cases of ALD with IPTH (18% of all ALD cases), in 60% of cases of AIH with IPTH (11% of all AIH cases), and in 63% of cases of PBCh with IPTH (24% of all PBCh cases). Interestingly, chronic hepatitis C developed equally frequently in recipients who underwent LT for immune-mediated diseases (AIH and PBCh) and in recipients who underwent LT for non-immune-mediated diseases (ALD). We did not analyze the etiologic structure of chronic hepatitis C in this study; therefore, we do not report the proportion of IPTH in the chronic hepatitis C structure. Graft fibrosis was also observed in 60.3% of liver recipients without signs of graft dysfunction. Severe fibrosis (LAF>2) was detected in every third (31%) liver recipient, and significant portal tract fibrosis (METAVIR>1) in every fifth (20.7%) liver recipient without signs of GD. Fibrosis was completely absent in only 5.2% of recipients. In a UK cohort of patients with normal LFTs, normal or near-normal liver histology was reported in 30%, 29%, and 24% of ALD, AIH and PBCh cases, respectively [20], which is comparable to our results (22.4%).

Despite the histological examination, the cause of significant deviations in LFTs from the norm was not clarified in 11 cases. It is possible that it was due to a pathological process with minimal morphological manifestations, for example, an alloimmune process mediated by antibodies or minor bile flow disturbances associated with developing strictures, which were previously considered clinically insignificant. It is certain that the increased LFT activity cannot be entirely "innocent." The search for the causes of overt GD must be continued.

Conclusion

Our study has confirmed the diversity of pathological changes of varying severity that can be detected in the transplanted liver at the long-term post-transplant examination. Some findings are easily explained, while others require further diagnostic investigation. One of the important results of this study, in our opinion, is the rationale for returning to the practice of performing "protocol" biopsies in adult liver recipients. To clarify known and identify new pathophysiological mechanisms leading to functional and structural impairments late after transplantation, and to search for biological targets and new therapeutic strategies, primarily immunosuppressive and tolerogenic ones, studies of large series of protocol biopsies will be crucial. The required frequency of such studies should be clarified in longitudinal studies.

Based on the above we may make the following conclusions:

1. In the subgroup of recipients with normal liver function test values at the time of examination, a slight increase in the body mass index (+1.1 kg/m^2) was observed compared to the body mass index at transplantation. In recipients with a borderline graft dysfunction, the body mass index was lower (25.4 kg/m^2), and in those with an overt dysfunction, it was even lower (23.7 kg/m^2) than in the subgroup of recipients without graft dysfunction (26.8 kg/m^2; p=0.015). In the subgroup of recipients with an overt graft dysfunction, a decrease in body mass index was observed relatively to the body mass index at transplantation (-0.14 kg/m^2).

2. Histological examination of liver tissue in the long-term post-transplant period can sometimes clarify the reason for transplantation or identify early recurrences of latent autoimmune graft

disease. Histological examination allowed us to clarify the cause of an overt graft dysfunction in 69.4% of cases.

3. Clinical signs of the graft dysfunction were absent in a third (34.5%) of recipients at the time of examination, with only 22.4% of them showing no significant abnormalities on histological examination. The remaining recipients with normal liver function tests had chronic hepatitis (19%), fatty liver disease (31%), or intralobular fibrosis (25.9%), and in one case, graft cirrhosis.

4. Graft fibrosis was also observed in 60.3% of liver recipients without signs of graft dysfunction. Severe fibrosis (LAF >2) was detected in one in three (31%) liver recipients, and significant portal tract fibrosis (METAVIR>1) was detected in one of five (20.7%) liver recipients without signs of graft dysfunction. Fibrosis was completely absent in only 5.2% of recipients.

5. Ductopenia was not detected in recipients without the graft dysfunction. In the subgroup of recipients with an overt graft dysfunction, ductopenia was the only pathological finding in 11.1% of recipients.

6. More than two-thirds of cases of fatty liver disease (70.2%) and intrahepatic fibrosis (76.9%) do not manifest clinically significant abnormalities in liver function tests.

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