IL06 COMPLICATIONS FOLLOWING LIVER TRANSPLANTATION – SINGLE CENTRE EXPERIENCE

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INTRODUCTION: Liver transplantation (LT) is the treatment of choice for appropriately selected patients with end-stage liver disease. The major indications for OLT in adults mirror the most common forms of liver disease, chronic hepatitis C and chronic hepatitis B, alcoholic liver disease, primary biliary cirrhosis, primary sclerosing cholangitis, and autoimmune hepatitis. The cardinal indications for LT are based on disease severity that reflects hepatocellular failure, such as coagulopathy and jaundice; complications of portal hypertension, such as refractory ascites and recurrent variceal bleeding; or the combination of portosystemic shunting and diminished hepatocellular function, as in hepatic encephalopathy. During the past decade, survival rates after liver transplantation have steadily improved, with one-year survival exceeding 85 percent. The improved survival has been attributed to a number of factors including new and more conservative use of immunosuppressive agents, improved diagnostic methods for identifying and preventing infections, and better surgical techniques. Despite advances in liver transplantation and improved long-term survival, these patients are requiring very careful monitoring due to complications seen in this patient population. Many of the disorders related to long-term survival after OLT are common diseases, including systemic hypertension, hyperlipidemia, and diabetes. Regular determination of a complete blood count, electrolytes, liver biochemical tests, and immunosuppressive drug levels should be arranged in order to detect any abnormality reflecting a graft injury or systemic complication in transplanted patient. Several medical problems are routinely encountered by clinicians caring for patients after liver transplantation. These include: Acute or chronic rejection, Complications of immunosuppression including hypertension, renal insufficiency, infection, malignancy, a variety of dermatologic conditions, and metabolic diseases such as diabetes mellitus, obesity, hyperlipidemia, and bone disease, biliary complications, recurrence of the primary liver disease.

THE AIM OF THIS STUDY: is to define the most prevalent forms of complications during short and long term follow-up of adult patients with liver transplantation and to demonstrate its outcome so far.

MATERIAL AND METHODS OF THE STUDY: The study group consisted of 19 pts transplanted in various transplant centers abroad and regularly followed at the Clinic of Gastroenterohepatology after the discharge of the transplant center. The review of relevant material in medical files and records of transplanted patients was done. This study

focuses on the types and severity of complications occurred in this population as well as on their management and final outcome.

RESULTS: Nineteen adult patients were treated with liver transplantation due to advanced chronic liver disease in last three decades. The main demographic and clinical data of transplanted patients are summarized in table 1. The period of follow-up ranged from 21 years (as longest) to 1 year (as shortest). Seventeen persons are alive and have good quality of life. One patient died 21 years after transplantation under clinical presentation of multiorgan failure. The second patient died early after the transplantation due to early graft malfunction, despite retransplantation

Year of LT	Etiology	Gender	Age (Years)	Type of LT	Outcome	Treatment
1991	PSC	M	24	Cadaver.	Died	Cyclosporine
1997	HBV	M	42	Cadaver.	Alive	Cyclosporine,MMF, HBIG, Tenofovir, Everolimus, Entecavir
1999	HBV	M	38	Cadaver.	Alive	Cyclosporine, Lamivudine
2000	Crypt.	F	36	Cadaver.	Alive	Cyclosporine, Tacrolimus Prednisone
2001	Crypt.	M	17	Cadaver.	Alive	Cyclosporine
2007	Wilson	F	16	LDLT	Alive	Cyclosporine
2009	HBV	M	53	LDLT	Alive	Rapamune, HBIG, Lamivudine
2011	HBV	M	43	LDLT	Alive	Tacrolimus, MMF, Lamivudine
2012	Autoimmune.	F	31	LDLT	Alive	Tacrolimus, MMF, Prednisone
2012	HCV	M	35	LDLT	Alive	Tacrolimus, MMF
2012	Alcohol	M	57	LDLT	Alive	Tacrolimus, MMF
2012	Autoimmune	F	29	LDLT	Alive	Tacrolimus, Prednisone
2013	HBV	M	44	LDLT	Alive	Tacrolimus, Prednisone, Lamivudine, HBIG
2013	HBV	M	52	LDLT	Alive	Tacrolimus, Prednisone, Tenofovir, HBIG
2013	PSC	M	20	LDLT	Alive	Tacrolimus,
2013	HBV	M	44	LDLT	Alive	Tacrolimus, Lamivudine, HBIG
2014	PSC	M	49	LDLT	Alive	Tacrolimus
2015	ALD	M	44	LDLT	Dead	Re-transplantation
2015	HCV+HCC	M	54	LDLT	Alive	Everolimus

Table 1. Main clinical features of transplanted patients.

Living donor liver transplantation was used in the majority of transplanted patients (14pts). As usually, liver donors are close family members (in 10 cases) or spouses (in 4 cases). In 4 pts with LDLT the donors were healthy adults with ABO blood type compatibility older than the transplant candidate, but less than 55 years of age.

Type of complication	N°	Treatment	Outcome
Biliary stricture	3	Interventional endoscopy Surgery	Resolved
Septic cholangitis	3	Combined antibiotic therapy	Resolved
Cholangiolitic abscesses	2	Antibiotic	Resolved
Protein loosing enteropathy	1	Albendazol Rifaximine Prednisolone Albumin substitution	Resolved
Metabolic disorders	8	According to the type of the disorder	Under control
Malignancy	1	CHOP protocol + Rituximab	Remission
Acute cellular rejection	1	Pulls therapy with methylprednizolone	Resolved
Nephrotoxicity	4	Switch to/dose modification	Resolved
Early graft malfunction	1	Retransplantation	Death

Table 2. Complications in post-transplant period

Four patients of our serie have demonstrated favorable results so far (two with live donor transplantation and two with cadaveric liver transplantation). No notable complication was registered in this group. The majority of successfully transplanted patients have developed various types of complications with severe impact on liver graft condition. Table 2 contains the main features of complications occurred in post transplant period, their management and outcome.

ACUTE REJECTION: Acute hepatocellular rejection was found in one patient. Clinical signs and symptoms observed in this patient have included fever, malaise, abdominal pain, hepatosplenomegaly, and ascites. The clinical presentation was associated with acute onset of hepatocellular necrosis and very high level of aminotransferase activity. This episode was successfully treated with high dose of metilprednisolone. Later, the same patient had cholangitis and biliary obstruction. MRCP and ERCP have shown irregular appearance of biliary tree, suggesting ischemic cholangitis, although the CT angiography did not reveal features for hepatic artery thrombosis. The biliary endoprothesis was placed with very good outcome and normalizartion of all biochemical and morphological abnormalities.

INFECTIVE COMPLICATIONS were registered in five patients. All of them have had severe forms of infections as following: cholangiolitic abscesses (two cases), septic bacterial cholangitis four cases, and one case a parasitic infestation of intestine with severe form of protein loosing enteropathy. He was treated with albendazol, rifaximine, albumin substitution and prednisolone. De novo HBV infection with high level of HBV DNA viremia was found in one case, initially HBsAg negative. Additionally, acute CMV infection was found in one case. CMV infection increases the risk of other infections, which may in part be due to the immunomodulatory effects of this virus.

BILIARY COMPLICATIONS were common (3 of 19 or 15 percent). The biliary stenosis ranged from moderate to severe anastomotic biliary stricture and biliary stenosis of biliary tree, indicating ischemic cholangitis. These biliary disorders were developed in late postransplant course. One patient was referred to surgery after several percutaneous dilatations of stenotic biliary anastomosis associated with jaundice, fever and itching that was neither relieved nor improved. Upon reoperation when a hepatico-jejunoanastomosis (Roux-en-Y reconstruction) was performed, the graft liver appeared normal with no intraabdominal pathology. The biliary anatomy on transhepatic cholangiogram also appeared normal. In the following period he was monitored with regular outpatient visits in our Clinic. A mild rise of the cholestatic enzymes was noticed a year after the reoperation, for which a control MRCP was performed. The radiologic report stated absence of stenosis of the biliodigestive anastomosis, while clinically the patient did not report any cholestatic complaints. Laboratory findings were negative for inflammation. Consequently, the patient was monitored with close regular ultrasonographic examinations. Six months later a mild intrahepatic biliary dilatation was detected upon ultrasonogrpahic examination with concomitant rise of the cholestatic parameters (ALP 192 – ref. 38-116; GGT 119 – ref. 9-64; total bilirubin 41 – ref. 6.8-20.5). After that, the patient has developed several episodes of secondary cholangitis that were amenable for a conservative antibiotic therapy with no significant deterioration of the clinical condition. Control MRCP was done and was confirmative for a stenosis of the hepatico-jejunoanastomosis in the middle part (length 1.5 cm) and one more proximal but shorter stenosis closer to the hilus was detected (length up to 1 cm). There was associated mild intrahepatic biliary dilatation. The patient also complained of intermittent pruritus and laboratory findings were consistent of cholestasis (ALP 415 - ref. 38-116; GGT 430 - ref. 9-64, total bilirubin 30 - ref. 6.8-20.5) with positive inflammation markers (CRP 19.2 – ref. 0-6). In the meantime he received antibiotic treatments on several occasion due to rise of the CRP associated with fever and pruritus. Due to occurrence of stenosis at the site of reanastomosis associated with progressive intrahepatic dilatation, with right segment bile duct diameter of up to 4-5 mm and mild dilatation of the subsegmental right bile ducts, the percutaneous dilatation was indicated. The procedure was partly efficient and stabilization of cholestatic features has been achieved. Additionally, nonhomogenous structure of the liver graft was found, portal vein dilatation up to 17 mm, without presence presence of intraperitoneal fluid. Although current condition of liver graft is stable, further progression of re-stenosis could be an indication for liver retransplantation. The biliary stricture at the site of end to end biliodigestive anastomosis was detected in second case with such complication after an onset of severe acute cholangitis when hospital admission was necessary. ERCP and MRCP

showed marked biliary stenosis and an attempt to manage this finding through retrograde endoscopy approach, unfortunately was not successful. Therefore, surgical intervention was necessary when the anastomosis was converted to a Roux-en-Y anastomosis. The third case with biliary stenosis was diagnosed with appropriate investigations (ERCP, MRCP) as diffuse intrahepatic strictures. The CT angiography was not confirmative with thrombosis of hepatic artery. The biliary stenosis was managed with endoscopically approach and placement of biliary stent. The procedure was followed by normalization of liver biochemistry and loss of morphological findings of biliary obstruction. The follow-up of this patient in last two years shows completely stable condition.

METABOLIC ALTERATIONS: De novo diabetes was found in three patients, high blood pressure had four pts, and hyperuricemia with clinical presentation of gout- one patient. **Nephrotoxicity** related to immunosuppressive therapy was found in four cases. In two cases Cyclosporine toxicity was responsible for kidney injury and elevated serum creatinine level. The therapy changing was necessary in 3 pts, whereas in one case the dose modification of tacrolimus was sufficient.

MALIGNANCY: One case developed a **non-Hodgkin lymphoma** after 8 years of immunosuppressive therapy. The treatment with chemotherapy (CHOP' protocol) and rituximab was successful in terms of remission of malignant disease.

RECURRENCE OF LIVER DISEASE: Two pts with HCV infection have recurrence of graft infection. Liver biopsy and liver biochemistry remain normal in one patient, although the preventive therapy with IFN free regimens should be advisable. The second case started with this treatment which is not available in our country.

OTHER: One case had signs of liver damage associated with coagulopathy in course of acute onset of thyreotoxicosis. The management was complex – after the normalization of thyroid gland function tests, the prolonged therapy with tinzaparine (LMWH) has been administrated.

DISCUSSION: Despite improvements in immunosuppressive therapy, hepatic allograft rejection remains an important cause of morbidity and late graft loss in patients undergoing liver transplantation. Morbidity and mortality due to infectious complications also remain major problems. In many centers, infection is the most frequent cause of death following liver transplantation which cannot be explained only in the setting of immunosuppressant. Infections occurring immediately following transplantation are similar to those seen in immunocompetent hosts following surgery. Bacterial infections usually have a nosocomial source such as central vascular access sites, external drainage catheters, or prolonged endobronchial intubation. One of our patients had surgical drain due to post transplant formation of biloma. The bile catheter was removed and the same bacteria was identified at the drain and in blood culture. Microbiological tests of all access sites of the body and appropriate antibiotics combination are essential in fighting this kind of infections. The two major sites of infection during this time period are the abdomen and the lungs, both of which may be associated with bacteremia. Various other risk factors for infection after liver transplantation have been reported. Many are related to surgical complications of the transplant operation (for example, prolonged operative time (>12 hours) and reoperation. Biliary tract complications are an important cause of morbidity and mortality in liver transplantation (LT) recipients. The most frequent are biliary tract

strictures, bile leaks, and bile duct stones. Biliary complications following LT can be categorized as early (within four weeks) or late. Biliary strictures can be further divided into anastomotic, nonanastomotic, and diffuse intrahepatic strictures. Biliary complications are more common in recipients who underwent adult-to-adult living donor liver transplantation (LDLT) compared with liver transplantation with deceased donors. The overall incidence of biliary complications in LDLT recipients ranges from 6 to 40 percent. All pts in our study had a late form of stenosis. Two cases had anastomotic strictures and one nonanastomotic, probably ischemic stenosis. The incidence of biliary strictures in our group was 15%. According to various reports, the estimated incidence of these complications ranges between 10 and 25 percent. Most of the cases with a duct-to-duct anastomosis can be managed successfully with endoscopic approach. An anastomotic stricture in a choledochocholedochostomy is usually managed initially by balloon dilation, followed by placement of a temporary internal stent. Surgical intervention is reserved for patients who do not respond to this approach, in which case the anastomosis is converted to a Roux-en-Y anastomosis. In our experience, endoscopical approach was successful in one case, and surgical intervention was necessary in two pts. Anastomotic stricturing which occurred at the site of a hepaticojejunostomy, requires a percutaneous approach, to dilate the stenotic area. This procedure was temporary efficient in patient with stenosis of Roux-en-Y anastomosis. Risk factors for the development of biliary complications after LT (particularly strictures) are acute hepatic artery thrombosis (HAT), hepatic artery stenosis, technical factors during surgery (excessive dissection of periductal tissue during procurement, excessive use of electrocautery for biliary duct bleeding control in both donor and recipient, and tension of the duct anastomosis), small caliber of the bile duct and mismatched size between donor and recipient bile ducts, ischemia/reperfusion injury, pre-LT diagnosis of cytomegalovirus (CMV) infection, donation after cardiac death (DCD), ABO blood group mismatch, older age of donor, prolonged cold and warm ischemia times, and primary sclerosing cholangitis. Higher incidence of biliary complications including bile leaks and cholangitis is found in patients with T-tubes placement after LT. In patients with Roux-en-Y choledochojejunostomy, in whom ERC is often unsuccessful, management with PTC and dilation followed by placement of a percutaneous transhepatic catheter is indicated. Surgical revision (usually a repair or conversion to a Roux-en-Y choledochojejunostomy) may be an alternative in stable patients with a duct-to-duct stricture that is difficult to treat.

CONCLUSION: Patients who underwent liver transplantation requires regular and careful long term follow-up. A follow-up includes biochemistry, dosing of immunosuppressive drugs and abdominal ultrasound. A patient with asymptomatic elevations in liver enzymes or bilirubin and clinical suspicion of biliary pathology, should proceed directly to endoscopic retrograde cholangiography (ERC), or magnetic resonance cholangiopancreatography (MRCP). A liver biopsy may be necessary if rejection or recurrent disease is suspected. Percutaneous transhepatic cholangiography is reserved for patients with Roux-en-Y anatomy or ERC failures.

REFERENCES:

- Berg CL, Gillespie BW, Merion RM, et al. Improvement in survival associated with adult-to-adult living donor liver transplantation. Gastroenterology 2007; 133:1806
- Fishman JA. Infection in solid-organ transplant recipients. N Engl J Med 2007; 357:2601
- San Juan R, Aguado JM, Lumbreras C, et al. Incidence, clinical characteristics and risk factors of late infection in solid organ transplant recipients: data from the RESITRA study group. Am J Transplant 2007; 7:964.
- García Prado ME, Matia EC, Ciuro FP, et al. Surgical site infection in liver transplant recipients: impact of the type of perioperative prophylaxis. Transplantation 2008; 85:1849.
- Husain S, Tollemar J, Dominguez EA, et al. Changes in the spectrum and risk factors for invasive candidiasis in liver transplant recipients: prospective, multicenter, case-controlled study. Transplantation 2003; 75:2023.
- Adams DH, Neuberger JM. Patterns of graft rejection following liver transplantation. J Hepatol 1990; 10:113
- Wiesner RH, Demetris AJ, Belle SH, et al. Acute hepatic allograft rejection: incidence, risk factors, and impact on outcome. Hepatology 1998; 28:638.
- Kim C, Aono S, Marubashi S, et al. Significance of Alanine Aminopeptidase N (APN) in Bile in the Diagnosis of Acute Cellular Rejection After Liver Transplantation. J Surg Res 2011
- Rerknimitr R, Sherman S, Fogel EL, et al. Biliary tract complications after orthotopic liver transplantation with choledochocholedochostomy anastomosis: endoscopic findings and results of therapy. Gastrointest Endosc 2002; 55:224.
- Pfau PR, Kochman ML, Lewis JD, et al. Endoscopic management of postoperative biliary complications in orthotopic liver transplantation. Gastrointest Endosc 2000; 52:55.
- Thethy S, Thomson BNJ, Pleass H, et al. Management of biliary tract complications after orthotopic liver transplantation. Clin Transplant 2004; 18:647
- Sharma S, Gurakar A, Jabbour N. Biliary strictures following liver transplantation: past, present and preventive strategies. Liver Transpl 2008; 14:759