Liver Transplantation: An Experience in Post-Operative Follow Up Of 80 Patients

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Abstract: Background: Orthotopic liver transplantation (OLT) is regarded as the only choice for treatment of patients with end stage liver disease (ESLD) and liver failure. Outcome for those patients is much better after liver transplantation resulting in reasonably good quality of life, provided complications are detected and treated promptly. Evaluation of needle liver graft biopsies and extensive clinicopathological correlation play an important role in the determination of liver allograft dysfunction after transplantation. **Objective:** To evaluate possible post-transplant outcome of patients underwent OLT. **Methods:** We analyzed 80 patients with liver cirrhosis who underwent deceased donor liver transplantation (DDLT) over a 10–year period in a cohort and observational study. The study was performed from June 2000 to June 2010 and included 75 men and 5 women. **Results:** Among all patients; origin of cirrhosis was post-viral in 76 patients, brimary biliary cirrhosis (PBC) in 2 cases, autoimmune hepatitis (AIH) in one case and cryptogenic cirrhosis in another case. The cases of post-viral cirrhosis were all of viral C etiology with 20 cases associated with hepatocellular carcinoma and 2 associated with hepatitis B viral infection. The patients are followed up for at least 18 months after enrolling in the study. They all had routine tests at the start of the study used as baseline for each patient. These tests are repeated according to the requirements of the individual patient. All patients had Tacrolimus (FK 506) as an immunosuppressive agent. Patients with hepatitis B viral infection had hepatitis B immunoglobulin, along with Lamivudine for relapse prophylaxis. Out of 80 patients, postoperative liver biopsy was performed, at least once, for 73 patients. The results of the biopsies revealed that recurrent HCV was detected in 46 (63.01%) cases, acute rejection in 14 (19.18%) cases, chronic rejection in 4 (5.48%) cases, cirrhosis in 2 (2.74%) cases, fibrosing cholestatic hepatitis in 2 (2.74%) cases, chronic active hepatitis with cholangitis and bile duct obstruction in 2 (2.74%) cases, recurrent primary biliary cirrhosis in 2 (2.74%) cases and one case (1.37%) with acquired schistosoma japonicum. A total of 24 (30%) patients died during follow up. **Conclusion:** The results of liver graft biopsies revealed that recurrent HCV is the prominent cause of organ dysfunction. Meanwhile; organ rejection was less frequently encountered. The complications of liver transplantation can be controlled and managed if diagnosed promptly and treated early.

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Keywords: Orthotopic liver transplantation, Post operative follow up, Experience.

Abbreviations: AIH: Autoimmune hepatitis, CMV: Cytomegalovirus, DDLT: Deceased donor liver transplantation, ESLD: End stage liver disease, HCV: Hepatitis C virus, OLT: Orthotopic liver transplantation, PBC: Primary biliary cirrhosis

1. Introduction

Once regarded as a last resort therapy for patients with end stage liver disease, liver transplantation has become a viable therapeutic option because of improvement in surgical techniques and the development of more powerful immunosuppressive agents. Orthotopic liver transplantation (OLT) is now the therapy of choice for liver failure that results from all types of acute and chronic liver disease as well as hepatic neoplasms. The pathological evaluation of liver allograft biopsies plays an integral role in the management of patients following liver transplantation. In certain cases it is regarded as the "Gold Standard" because no other reliable diagnostic marker exist. The clinicians relies on the pathological interpretation of liver biopsy report to diagnose or rule out graft rejection, drug toxicitiy, recurrence of transplant disease (e.g. viral hepatitis) or development of a new disease (e.g. Cytomegalovirus infection or de novo autoimmune hepatitis) (1). Since the early 1980`s, there has been a consistent improvement in the results of liver transplantation and current one year survival is almost 80%. (2).

Liver transplantation is potentially applicable to any acute or chronic conditions, in both children and adults, resulting in irreversible liver dysfunction provided that the recipient does not have other conditions that will preclude a successful transplant.

The major indications in children are biliary atresia and inherited or genetic disorders of metabolism associated with liver failure (3).

Since the start of hepatic transplantation as a treatment for end-stage hepatic diseases, various factors, such as the surgical techniques, postoperative treatments, and immunosuppressant drugs have improved exponentially. These improvements have ultimately decreased morbidity and mortality, as well as increased global survival of both the graft and the patient. Currently, this procedure offers a 5-year survival rate of 70%. However, it is not free from complications (4).

After liver transplantation, there are three types of graft rejection that may occur. Hyperacute rejection (which is humoral B cell mediated) is a rare event that happens within minutes to hours after transplantation. The presence of dual blood supply protect the organ from ischemia. Kupffer cell binding of performed antibodies and removal of immune complexes reduces the susceptibility of the liver to hyperacute humoral rejection. Acute rejection is T cells mediated reaction that involves direct cytotoxicity and cytokine mediated pathways. It occurs within days, weeks, or months after transplantation and it is the most common form of rejection. Chronic rejection is the presence of any symptom or sign of rejection after 1 year. The cause of chronic rejection is still unknown but an acute rejection is a strong predictor of chronic rejection (5).

The aim of this study is to evaluate possible post-transplant outcome of patients underwent OLT in other centers and presented to Police Hospital, Giza, 3 months after liver transplantation for following up .

2. Patients and Methods

This Study conducted on 80 patients with cirrhosis underwent liver transplantation and presented to Police Hospital, Giza (three months after transplantation) during the period from June 2000 to June 2010; (As liver transplantation is performed only in highly specialized tertiary care centers, a significant proportion of cases are followed elsewhere according to the residence, health insurance or other factors). It was a cohort non randomized and observational study. Liver transplantation was performed in England (n=69), China (n=10) or Germany (n=1), and it was cadaveric liver in all cases. All patients had certain routine laboratory, radiologic and clinical studies at the start of the follow up used as baseline for follow up. These were repeated according to the requirement of the individual patient. The investigations included complete blood count, coagulation profile, liver function tests, kidney function tests, antimitichondrial and antinuclear antibodies, electrolytes, blood sugar and serum immunosuppressive level. All patients also had baseline ultrasound and CT or MRI images. Cytomegalovirus PCR, IgM and IgG are also performed. If liver transplantation was due to hepatitis B viral (HBV) infection, then HBs Ag and anti -HBV were investigated. If transplantation was due to HCV, then PCR for HCV RNA was tested. All patients receive immunosuppressive treatment according to indicated regimen. Patients having transplantation secondary to hepatitis B receive immunoglobulins every month (according to anti HBs Ag level) in addition to Lamividine.

Percutaneous Liver biopsy was performed under ultrasound guidance at least once for 73 patients. Adequate core including at least 6 small portal tracts was obtained. The samples were fixed with 10 % formaldehyde, embedded in paraffin. Three to four micrometers sections were cut and routinely stained with haematoxylin-eosin, PAS and Masson's trichrome stains. Immunostain for CK 7 was performed whenever needed. The liver biopsies were evaluated for hepatitis activity and fibrosis according to the modified Knodell`s as well as METAVIR scoring systems · For allograft rejection; we used Banff schema and template for allograft liver biopsies (6).

Patients who enrolled early in the study were followed up for 10 years whereas the last patient enrolled was followed up for 18 months, thus the majority of the patients were followed up for more than 5 years .

3. Results:

Results are shown in Tables 1-5 and Figures 1-12.

Among 80 patients; 75 were males and 5 were females. Their ages ranged from 38 to 60 years apart from one girl aged 6 years with a mean age of 51.1 ±6.4 years**.** The causes of liver failure and indication for liver transplantation of all studied patients are shown in table (1). The main indication for liver transplantation was predominantly HCV infection 76 (95%); with 20 (26.31%) patients associated with hepatocellular carcinoma (HCC) and 2 (2.63%) accompanied with HBV infection. Other indications included primary biliary cirrhosis (PBC) in 2 (2.5%) autoimmune hepatitis (AIH) in 1(1.25%), and cryptogenic cirrhosis in 1(1.25%).

Out of 76 patients with HCV infection; 61(80.3%) showed preoperative associated diseases as featured in table (2). Also preoperative interferon therapy performed for 32 cases, and sclero-therapy in 2 cases for oesophageal varices.

During the post-operative follow up period, operative complications or newly acquired diseases are demonstrated in table (3).

Out of 80 patients, postoperative liver biopsy was performed, at least once for 73 patients. It was indicated by elevated liver enzymes or sonographic findings. For the remaining 7 cases, no biopsy was obtained, at least during our follow up. The results of

the histopathological examination of liver graft biopsies revealed that recurrent HCV is the prominent cause of organ dysfunction. Meanwhile; organ rejection was less frequently encountered. These results are detailed in table (4) and figures (1-12).

During our follow up; 24 (30%) patients died for various causes and at various post operative periods of survive as mentioned in table (5). To summarize the causes of 24 deaths; HCV represented the major cause (14 cases, 58.3%) , Graft rejection (4 cases,16.6%), RI (1 case,4.2%), HBV (1 case, 4.2%), Recurrent PBC (1 case, 4.2%), operative complications (1 case, 4.2%) and acquired infection such as tuberculosis and fungal infection (2 cases, 8.3%).

Table (1): Indications for liver transplantation, age and sex distribution of 80 cases

Indications for liver transplantation	No of patients	Age (range) at time of transplantation	Sex	
			M (no)	F (no)
-HCV:	76 (95%)	38-60 Y	73	3
HCV+HCC	20/76(26.31%)	45-59 Y	20	0
HCV+HBV	2/76 (2.63%)	45-60 Y	2	0
-PBC	2 (2.5%)	6-38Y	1	1
-AIH	1(1.25%)	48 Y	0	1
-Cryptogenic cirrhosis	1(1.25%)	40 Y	1	0

AIH: Autoimmune hepatitis, F: Female, M: Male, PBC: Primary biliary cirrhosis

Table (2): Preoperative associated diseases in 61 HCV patients:

Associated diseases	No. of patients
• Hepatitis B virus (HBV)	2
• Hepatocellular carcinoma (HCC)	20
• Bilharziasis	3
• Hypertension (HTN)	16
• Renal impairment (RI)	5
• Diabetes mellitus	11
• Portal vein thrombosis (PVT)	3
• Tuberculosis (TB)	1
Total	61

Table (3): Post-operative complications or acquired diseases in all studied patients (no=80):

Disease	No. of patients
• Recurrent HCV	76 (all HCV cases)
• Diabetes Mellitus (DM)	19
• Renal impairment (RI)	1
• Acquired HBV (donor)	2
• Cytomegalovirus (CMV)	6
• Pulmonary fungal infection	1
• Tuberculosis (TB)	1
• Biliary stricture	6
• Acquired (donor) schistosomiasis	1

Table (4): Results of postoperative liver graft biopsy examination in 73 patients:

Diagnosis of liver biopsy	No. of patients
• Chronic active hepatitis (CAH)	46 (63.01%)
• CAH associated with cholangitis and biliary obstruction	2 (2.74%)
• Cirrhosis	2 (2.74%)
• Fibrosing cholestatic hepatitis	2 (2.74%)
• Acute rejection	14 (19.18%)
• Chronic rejection	4 (5.48%)
• Recurrent primary biliary cirrhosis	2 (2.74%)
• Acquired schistosoma japonicum in transplanted liver	1 (1.37%)
Total	73

Table (5): Duration of post-operative survival and cause of death in 24 transplanted patient.

Surviving period (Y)	No. of cases	Cause of death	Original disease
‹ 1 year	2	T.B.& Pulmonary fungal infection (1) Operative complication (1)	AIH (1) HCV (1)
2 years	2	HCV relapse	HCV
3 years	8	HCV relapse (7) RI (1)	HCV (4) HCV+HCC (3) HCV+HCC+PVT (1)
4 years	3	HCV relapse	HCV (2) HCV+HCC (1)
5 years	1	HCV relapse+ RI	HCV+HCC+ Grade II nephropathy
6 years	1	Acquired HBV+ Gilbert syndrome	HCV
7 years	1	Recurrent PBC	PBC
8 years	5	CR (3) CR +PVT (1) TB peritonitis (1)	HCV
9 years	1	HCV relapse+ Cirrhosis	HCV
Total	24		

AIH: autoimmune hepatitis, CR: chronic rejection, HBV: hepatitis B virus, HCC: hepatocellular carcinoma, HCV: hepatitis C virus, RI: renal impairment, PVT: portal vein thrombosis, T.B: tuberculosis.

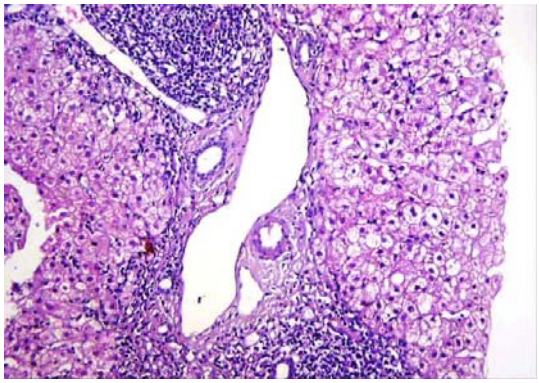

Figure (1): Recurrent viral C hepatitis with portal expansion by lymphocytic aggregates, fibrosis, interface hepatitis, dilated portal vein and fibrosis. Bile ducts are near normal, (Hx&E x200).

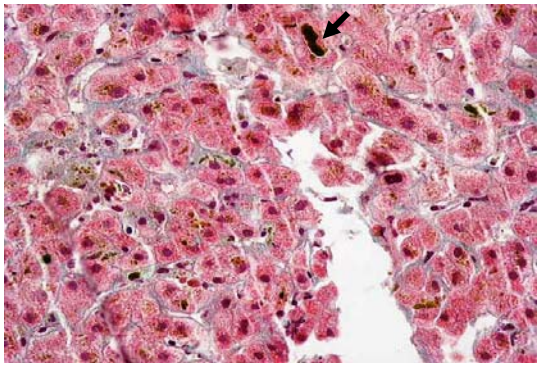

Figure (2): Fibrosing cholestatic variant of recurrent viral hepatitis C showing diffuse swelling of hepatocytes with intracellular cholestasis and bile thrombi (arrow). No significant lobular inflammation noticed (Masson Trichrome stain x400).

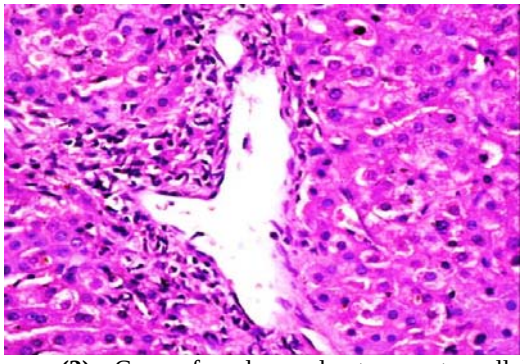

Figure (3): Case of early moderate acute cellular rejection showing portal venulitis .Few lymphocytes adhere to the luminal surface of endothelium , subendothelial lymphocytic infiltrate, lifting of the endothelial lining and perivenular parenchymal inflammation, (Hx&E x400)

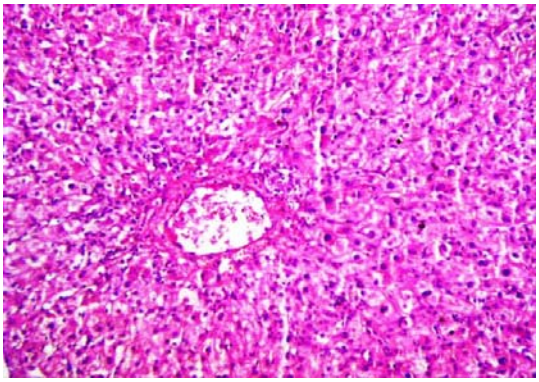

Figure (4): Acute cellular rejection showing perivenular central zonal necrosis, hemorrhage and inflammation with drop out of hepatocytes. No evidences of steatosis. (Hx&E x200).

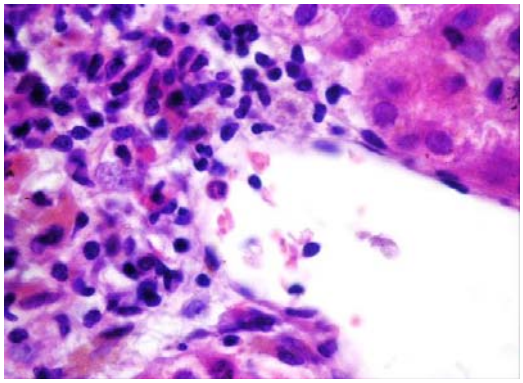

Figure (5): Case of acute cellular rejection with portal mixed inflammatory cell infiltrate including neutrophils, eosinophils, blast cells and lymphocytes with focal venulitis . The interface is mostly respected in this examined field, (Hx&E xOil).

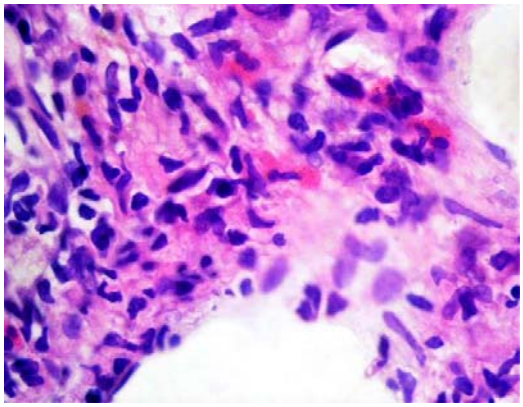

Figure (6): Aportal tract showing many eosinophils, lymphocytes and blast cells, (Hx&E xOil).

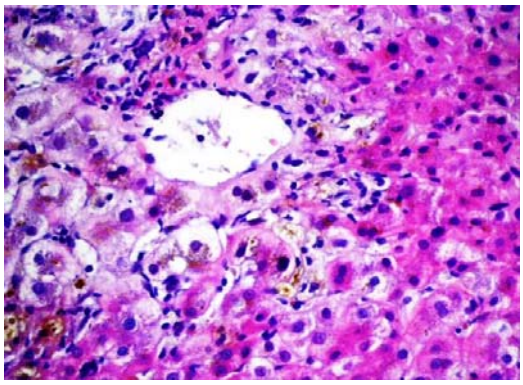

Figure (7): Evolving chronic rejection. Pericentral ballooning degeneration of hepatocytes, hepatocyte drop out and sinusoidal inflammation with cholestasis, (Hx&E x400).

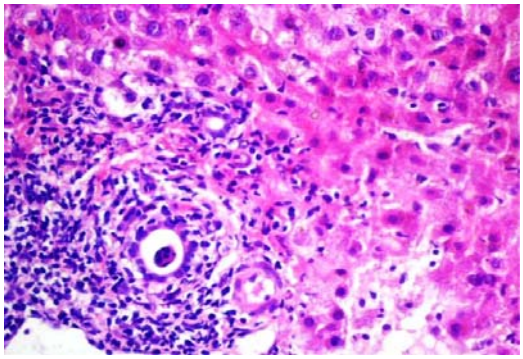

Figure (8): Case of acute cellular rejection showing portal mixed inflammatory infiltrate and periductal cuffing by inflammatory cells with luminal exfoliation of epithelial lining .No evidences of hepatocellular steatosis detected. Adjacent portal artery is present (Hx&E x200)

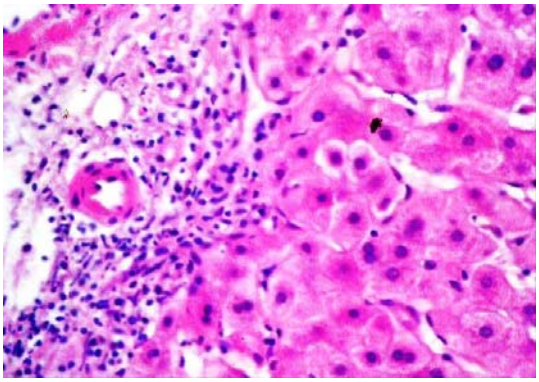

Figure (9): Case of chronic rejection showing portal tract devoid of bile ducts and widow artery with reduction in the overall degree of cellular infiltrate of portal tract and minimal interface inflammation (Hx&E x400).

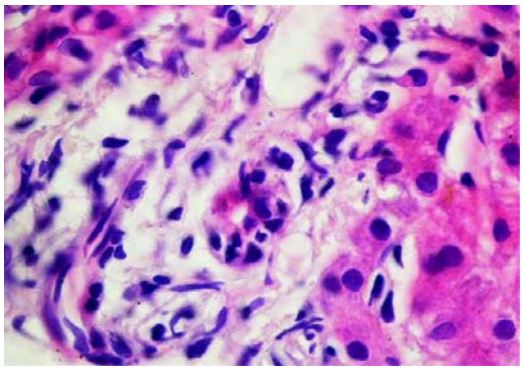

Figure (10): Evolving chronic rejection .An interlobular bile duct shows lymphocytic infiltration ,nuclear pleomorphism, hyperchromasia and disordered polarity . Scanty portal inflammatory cells with no prominent interface reaction noticed (Hx&E x Oil).

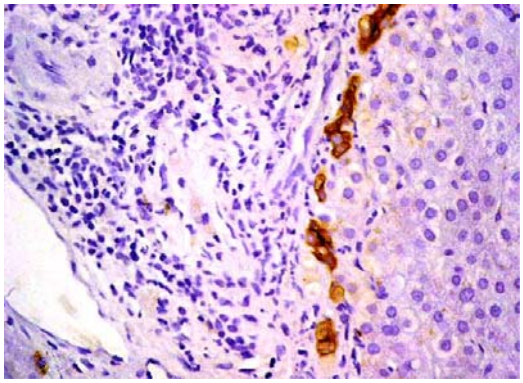

Figure (11) : Case of chronic rejection showing paucity of bile ducts in the portal tract, with preservation of the normal marginal bile ductules, (immunostain for CK7 x400).

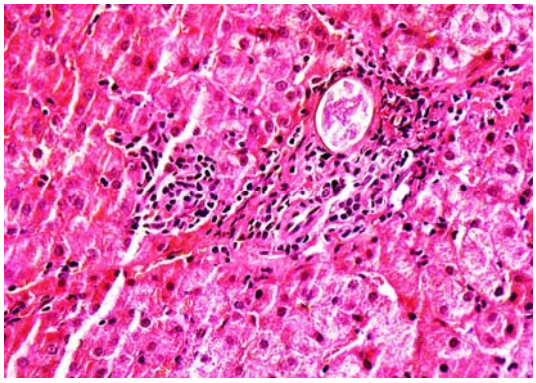

Figure (12): Case of postoperative bilharziasis of the liver showing ova of acquired schistosoma japonicum, (Hx&E x200).

4. Discussion:

It could be seen by reviewing data of our study that outcome for end stage liver disease patients is much better after liver transplantation resulting in reasonably good quality of life, provided complications are detected and treated promptly. Our results reveal survival rate about 70 %. Post transplant 3 and 5 year survival figures in excess of 70% are also achieved in many other places (7). Evaluation of needle biopsies and extensive clinicopathological correlation play an important role in the determination of liver allograft dysfunction after transplantation. Interpretation of these biopsies can be quite difficult because of the high incidence of recurrent diseases that show histopathological, clinical and serological features that overlap with each other and with rejection (3). The main challenge for biopsy examination was to differentiate recurrent viral infection from graft rejection. Accurate diagnosis is important for reduction of immunosuppression as immunodeficiency is likely to be the most important predisposing factor leading to unchecked viral replication. Some of the features may be helpful in distinguishing recurrent viral hepatitis from acute cellular rejection (8).

This study involved 80 patients with liver cirrhosis who underwent orthotopic liver transplantation (OLT) over a 10–year period in a cohort and observational study. The study is performed from June 2000 to June 2010. The patients are followed up for at least 18 months after enrolling in the study. They all had routine tests at the start of the study used as baseline for each patient. Our study included 75 men and 5 women.

Out of 80 patients, postoperative liver biopsy was performed, at least once, for 73 patients. The results of the liver graft biopsies revealed that recurrent HCV is the prominent cause of organ dysfunction 46 (63.01%) cases. Meanwhile organ rejection was less frequently encountered (acute rejection in 14 (19.18%) cases, chronic rejection in 4 (5.48%) cases, cirrhosis in 2 (2.74%) cases, fibrosing cholestatic hepatitis in 2 (2.74%) cases, chronic active hepatitis with cholangitis and bile duct obstruction in 2 (2.74%) cases, recurrent primary biliary cirrhosis in 2 (2.74%) cases and one case (1.37%) with acquired schistosoma japonicum. Moreover; there was no recurrence for HCC encountered in this study (20 cases).

Hepatitis C recurrence is nearly universal after transplantation. It leads to chronic hepatitis and liver cirrhosis in a significant proportion of patients and lowers graft and patient survival. The most useful feature pointing to the diagnosis of acute rejection and differentiating it from recurrent viral hepatitis is the presence of mixed population of inflammatory cells in portal tract infiltrate. These lesions show considerable variation in intensity and it is therefore recommended that a minimum of 5 portal tracts are available for examination (9).

Occasional patients with recurrent HCV after liver transplantation will have an aggressive course characterized histologically by pericellular /sinusoidal fibrosis and cholestasis, known as fibrosing cholestatic hepatitis (FCH). The presence of cholestasis and fibrosis with mild to moderate recurrent HCV should raise the suspicion of FCH. When studying the evolution of these cases, the first abnormality to appear is recurrent HCV and cholestasis, fibrosis develops soon after, and both continue to worsen until the point of allograft failure (10). Schluger et al, 1996 suggests that a minority of patients with recurrent hepatitis C after undergoing liver transplantation develop a severe progressive to cholestatic hepatitis and liver failure (7).

In this study ; there were 2 cases (2.74%) diagnosed as fibrosing cholestatic hepatitis . It is an aggressive and unusual fatal form of viral hepatitis in immunosuppressed patients. It is characterized by progressive cholestasis leading to hepatic failure, and characteristic histopathological features including: periportal fibrosis,

ballooning degeneration of hepatocytes, cholestasis, with minimal inflammation. FCH has only been described in immunosuppressed patients with chronic hepatitis B or C . In contrast to the pathogenesis of chronic hepatitis in immunocompetent patients, attributed to the cellular immune-mediated hepatocytolysis, FCH has been postulated to result from unimpeded viral replication within hepatocytes, culminating in a direct cytopathic effect, in the setting of immunosuppression (11, 12).

Hepatitis recurrence may be difficult to distinguish from cellular rejection. At an early stage following recurrence, acidophilic bodies, minimal portal inflammation and inconstant fatty infiltration favor hepatitis C, whereas portal inflammation with activated lymphocyts including eosinophils suggests associated rejection. Later, the changes of hepatitis recapitulate those seen in the non – transplanted setting. They may show an intimate association with both small bile ducts, which are infiltrated, but not destroyed, and portal venules, which may mimic endotheliitis (12). The associated mild lobular hepatitis and the presence of fatty infiltration do favors HCV infection, but acidophil bodies are similarly found in the rejection and not as useful as in the early stage to discriminate hepatitis C from rejection. In most cases where doubt subsists, the changes are generally mild and HCV RNA results and level of immuno-suppression may be of assistance. It is important to remember that untreated mild rejection is often innocuous, whereas high dose steroids may have a deleterious effect on hepatitis C (13, 14).

The histological diagnostic triad of acute rejection included portal inflammation, bile duct damage and venular endotheliitis. At least two of these features are required for diagnosis of acute rejection. It is suggested that perivenular necrosis may be important as an early diagnostic feature of evolving chronic rejection (12).

All of these inflammatory cell types are implicated in mediating damage of the bile ducts and endothelial cells in rejection. The presence of large number of eosinophils appears to correlate with the more severe degree of rejection and may have a prognostic significance in predicting poor response to additional immunosuppressive therapy (15). A system devised at the Royal Free Hospital, London incorporate portal tract eosinophilia as a fourth feature resulting in overall score ranging from 0 to 12 (16). Eosinophils, for some author a defining feature of acute rejection, are not constant; when present in large number, they may correlate with a more severe degree of rejection and predict a poor response to steroids. Perivenular injury with cholestasis, apoptotic bodies, cell ballooning and confluent cell drop out may reflect a more severe rejection (generally asscociated with hepatic venulitis), a harvesting / reperfusion injury or an ischaemic element (17).

Acute cellular rejection reveals various histologic combinations of the classic triad of mixed portal tract inflammation, bile duct injury and venular endotheliitis (3). The universal incidence of graft failure from chronic rejection was 2.4%. The diagnostic features of chronic rejection are loss of bile ducts and obliterative arteriopathy affecting large or medium sized arteries. The fact that these arteries are not usually biopsied, and that bile duct loss is not always apparent, makes it somewhat difficult in diagnosis (2).

Histological changes of liver allograft rejection have been well characterized, but features which somewhat depart from classical description and newly recognized post transplant complications, especially at a later stage after surgery, may raise diagnostic problems. Important is to evaluate the histological changes in conjunction with clinical information, in particular the primary liver disease and the timing after surgery which are essential (15).

In patients presenting with progressive jaundice, the following histological findings should make early chronic rejection a serious consideration: [1] dysplastic or atrophic bile ducts, [2] pericentral ballooning degeneration of hepatocytes, hepatocyte drop out and intimal or sinusoidal inflammation, [3] cholestasis in the absence of ductular proliferation. An early diagnosis of chronic rejection is imperative so that salvage therapy can be initiated. It is easier to diagnose advanced chronic rejection but the clinical value of this is limited (9).

In USA, pathologists predict features of poor response to immunosuppressive drugs and progression to chronic irreversible rejection. These included bile duct paucity, arteritis, perivenular ballooning and dropout, interstitial hemorrhage and moderate to severe lobular inflammation. These features are then used to define severe acute rejection (13).

Chronic rejection can be defined as immune mediated damage to the liver allograft which is characterized histologically by two main features; loss of bile ducts in more than 50% of portal tracts (chronic ductopenic rejection) and obliterative vasculopathy (chronic vascular rejection) affecting large and medium sized arteries. The vascular lesions do not generally affect small arterial branches and thus seldom detected in needle biopsy. So, the diagnosis of chronic vascular rejection is only made when the whole liver is available. Absence of ductular proliferation or periportal fibrosis distinguishes chronic rejection from other bile duct losing diseases (14).

Chronic rejection remains a diagnostic problem due to inconsistency, insidious development and uneven distribution of the histologic changes and overlapping features with ischaemic cholangitis. Morphologically, chronic rejection is characterized by a progressive loss of the intrahepatic bile ducts (Ductopenic Rejection), an obliterative foam –cell

arteriopathy (Vascular Rejection) and perivenular cell dropout and fibrosis. Most cases will present between 2 and 12 months after transplantation following episodes of acute, or more insidiously over period of months, without previously recognized acute rejection; protracted cases up to 10 years after transplantation are now well recognized and generally follow inadequate immunosuppresion (16).

Persistent perivenular parenchymal cell drop out, supposedly an ischaemic lesion, when associated with early ductopenia, is highly suspicious of evolving chronic rejection, despite of the absence of foam-cell arteriopathy, which is rarely sampled by biopsy needles. Perivenular fibrous tissue deposition is observed later and may reach the stage of extensive centro-central bridging septa with an apparent severe lobulation. Peripheral ductular reaction remains minimal or absent, but it may be conspicuous and bile-duct loss may be delayed when a major bile duct stricture is associated (15).

Early histological changes may show a transitional period when acute cellular rejection persists but the cellular infiltration of morphologically abnormal bile ducts gradually lessens as cholangio-destruction progresses. Light portal inflammation and oedema with degenerative changes affecting the small interlobular bile ducts, perivenular hepatocyte ballooning and drop-out with canalicular cholestasis and a distinctive absence of periportal ductular reaction characterized the early stage. Subsequent biopsy specimens will show a progressive disappearance of the interlobular bile ducts, 50% or more of portal tracts devoid of ducts having been arbitrarily considered minimal diagnostic criteria (17).

Six cases with cytomegalovirus infection were reported in this cohort study. Cytomegalovirus is the most commonly encountered opportunistic viral infection of the liver allograft. The incidence of the disease increases with the overall potency of non-specific immunosuppression. The infection may be the result of recrudescence in a carrier, transmission through blood products or the donor organ, or as acquired disease. It is usually characterized by mild lobular disarray and microabscesses or microgranulomas which are scattered randomly throughout the lobules. The infected cells show nuclear or cytoplasmic inclusions (1).

During this cohort study 24 patients died for several reasons mainly HCV represented the major cause in 14 (58.3%) cases , graft rejection in 4 (16.6%) cases , RI in 1(4.2%) case , HBV in 1(4.2%) case, Recurrent PBC in 1 (4.2%) case , operative complications in 1(4.2%) case and acquired infection such as tuberculosis and fungal infection in 2 (8.3%) cases. Current 1-year survival rates for liver transplantation recipients in the United States are 85% to 90%, and 5-year survival rates are 70% to 75%. Hepatic replacement has gradually shifted from a risky, mostly unsuccessful operation to a routine procedure. One of the most important risk factors for an increased risk of severe post-transplant hepatitis C is treated acute cellular rejection. Another well recognized complication of solid-organ transplant is hyperglycemia and transplant diabetes mellitus. As a result; much attention has been focused on the diabetogenic effect of immunosuppression (17).

By analogy with other solid organ transplantation, rejection may in theory be hyperacute, acute, cellular (the most common form) and chronic (uncommon and seemingly on the decline). Unique to the liver graft is that small bile ducts and vascular endothelia, unlike hepatocytes, normally bear MHC antigens, which make them main targets of the immune attack; a dual blood supply with the portal vein endothelium being first met by allo-reactive T cells (endotheliitis) and a most efficient scavenger system - the kupffer cells –ready to moped up immune complex being formed (15).

In conclusion, the results of graft liver biopsies in the present study revealed that recurrent HCV is the prominent cause of organ dysfunction. Meanwhile organ rejection was less frequently encountered. The complications of liver transplantation can be controlled and managed if diagnosed promptly and treated early and that can be achieved through direct communication between hepatologist and pathologist to avoid insufficient clinical informations and to obtain a correct diagnosis. Moreover; familiarity with the uncommon histological findings, a careful search for subtle morphologic changes and the use of standard terminology could improve the quality of liver transplant biopsy interpretation.

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References:

1- Busuttil R.W. and Lake J.R.: Role of tacrolimus in the evolution of liver transplantation. Transplantation 2004; 77(9 suppl) : S44-S51.
2- Multimer D.: Liver Transplantation. Medicine international, liver Disorders 2006; 07(1):105-8.
3- Demetris A J, Adeyi O, Bellamy CO et al.: Liver biopsy interpretation for causes of late liver allograft dysfunction. Hepatology, 2006; 44(2):489-501.

4- Pérez-Saborido B, Pacheco-Sánchez D, Barrera-Rebollo A, et al.:Eight years experience with liver transplantation in rio hortega hospital. Transplant Proc. 2011 Apr;43(3):729-31
5- Hubscher S.G. And Portmann B.C.: Transplantation pathology. In: Pathology of the liver, edited by: Mac Sween RNM, Burt AD ,Portmann BC, et al., 5th edition; 2007,Chapter (16) :815-879.
6- Ishak K, Baptista A, Bianchi L, et al. Histological grading and staging of chronic hepatitis. *J Hepatol.* 1995; 22(6): 696-699.
7- Schluger L K, Sheiner P A, Thung S N et al.: Severe Recurrent Cholestatic Hepatitis C Following Orthotopic Liver Transplantation. Hepatology 1996; 23(5): 971-976.
8- Darwish MA, Faris R, Darwish N, et el.: Hepatitis C and cirrhotic liver disease in the Nile Delta Of Egypt: a community based study. Am J Trop Med Hyg 2001; 64(3-4):147-53
9- Dienstag JL.: Liver Transplantation. In: Harrison`s principales of internal medicine 16th edition Vol 11; 2005:1873-80.
10- Coffin CS, Burak KW, Hart J and Gao ZH.: The impact of pathologist experience on liver transplant biopsy interpretation. Modern Pathology 2006; 19(6):832-838.
11- Wasley A and Alter MJ.: Epidemiology of hepatitis C: geographic differences and temporal trends. Semin Liver Diseases 2000; 20(1):1-16
12- Saleh F., Ko HH., Davis J.E., Apiratpracha W., et al.: Fatal hepatitis C associated fibrosing cholestatic hepatitis as a complication of cyclophosphamide and corticosteroid treatment of active glomerulonephritis.Ann Hepatol 2007; 6(3):186-189.
13- Dixon L.R. and Crawford J.M.: Early histologic changes in fibrosing cholestatic hepatitis C. Liver Transpl 2007; 13(2), 2:219-226).
14- Yeh MM, Larson AM, Tung BY, et al.: Endotheliitis in chronic viral hepatitis: a comparison with acute cellular rejection and non alcoholic steatohepatitis. Am J Surg Pathol. 2006; 30(6): 727-33.
15- Portman B C.: Posttransplantation Liver Biopsy: Pathological Aspect .The 24th biennual meeting of The International Association for the Study of the Liver (IASL)In collaboration with the African Association for the study of Liver Diseases (AfASLD), Cairo, Egypt September 2006.
16- Hubscher S.G and Portman B.: Transplantation pathology In AD Burt, BC Portman, LD Ferrel(eds) MacSween Pathology of the Liver, 5th ed.. Edinburgh: Churchill Livingstone-Elsevier, 2006: 815-80
17- Khettry U, Backer A, Ayata G, et al.: Centrilobular histopathologic changes in liver transplant biopsies. Hum Pathol 2002; 33(3): 270-6.

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