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Original Research Article

Post Transplant Liver Biopsies: A Clinicopathological Study from South India

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Abstract

Introduction: The spectrum of diseases encountered in post-transplant liver biopsies is broad. The pathologist plays an important role in defining these process.

Aim: The aim of this study was to evaluate liver allograft biopsies performed for graft dysfunction by analysing the pattern of injury and intensity, and the timeline of occurrence of graft dysfunction. The pathological features of explant liver of these patients were also looked into.

Materials and Methods: Retrospective study was carried out on 110 liver allograft biopsies from 65 patients and their histological findings with clinical presentation were correlated. The period of study was from January 2013 to December 2016.

Results: The most common histological lesion was preservation-reperfusion injury (PRI) in 40 (36.36%) biopsies followed by acute cellular rejection (ACR) in 32(29.09%) biopsies. Biliary obstruction, sepsis and chronic rejection was present in 5 (4.55%) biopsies each. Five biopsies (4.55%) showed idiopathic posttransplant hepatitis. Steatohepatitis and ischemic necrosis were seen in 4 (3.64%) cases each. Three biopsies (2.73%) showed acute cholangitis. Recurrence of HCV was reported in 1 (0.91%) case and HBV reactivation in one (0.91%) case. Nonspecific changes like focal mild lobular and focal portal inflammation and mild steatosis were present in 4 (3.64%) cases.

Conclusion: Reperfusion injury (PRI) in time zero biopsies was the most common finding in our study followed by ACR. 70.9% of biopsies with ACR were observed within 6 months post transplant. Analysis of explant liver specimens showed cirrhosis associated with alcoholic steatohepatitis to be the most common etiology of end stage liver disease leading to transplant.

Keywords: Reperfusion Injury; Acute Cellular Rejection; Chronic Rejection; Explant; Transplant.

Introduction

The spectrum of diseases encountered in post-transplant liver biopsies is broad [1-5]. These have been divided as belonging to one of three categories: (1) new-onset/de novo post-transplant abnormalities (early and late), (2) rejection, and (3) recurrence of original disease [1]. Early new onset conditions are mostly related to surgical complications, donor factors and ischemia to the graft. These include reperfusion/preservation injury, lipopeliosis, small for-size-syndrome, biliary sludge syndrome and hepatic artery thrombosis [1,2,5]. The various forms of rejection include cellular, chronic, antibody-mediated, and late atypical rejection [1-5,7]. Most

chronic liver diseases can recur in the graft [1,2,5]. They may display features that overlap with de novo conditions [1,2,5,6]. A careful correlation of histological features with clinical, imaging and laboratory findings, and comparison with previous sequential and follow-up biopsies is needed for accurate diagnosis [1-5,9,10]. Late onset new diseases include biliary strictures, idiopathic chronic hepatitis and de novo autoimmune hepatitis [1-5].

Pathological evaluation of liver allograft biopsies plays an integral role in the management of patients following liver transplantation [1,3,4,9-11].

The pathologist plays an important role in defining these processes, especially since the patterns of liver enzyme abnormalities and other clinical parameters leading to a liver biopsy are not always clear-cut in differentiating between diverse conditions [1,2,4,5].

In certain conditions, such as liver allograft rejection, histology is regarded as the 'gold standard' because no other reliable diagnostic marker exists [1,5,8,12,13].

In other conditions such as cytomegalovirus (CMV) infection, the cause of graft dysfunction can be identified using other methods, but liver biopsy provides additional information [1,2,5]. In recurrent and de novo diseases, the liver biopsy may provide prognostic information such as grade and stage and can reveal superimposed pathology or signs of biliary or vascular abnormalities [1,2,5,6,26,27].

Liver enzymes are quite sensitive to hepatocellular (transaminases) or biliary (alkaline phosphatase) injuries. In some cases, abnormalities of liver function (bilirubin, albumin and coagulation parameters) are either from failure to normalise post-transplant or as a result of severe or advanced-stage post-transplant injuries [1,2,3,11].

In most cases, liver allograft biopsies are performed in response to changes in liver enzyme levels, abnormality in one or more liver function parameters, imaging abnormalities or functional abnormalities, to follow-up an earlier biopsy, or as part of a protocol that requires time-specific biopsies [1-5,9,10].

Specific indications for liver allograft biopsy in an individual patient typically depend on the age of the graft (ie, time from transplant grafting) and they can be divided into early and late periods [1,2,5,7].

Early graft dysfunction refers to changes occurring within the first 3 months of transplantation, while late changes refer to those occurring after 6 months.The period of 3–6 months represents an intermediate time, when early and late changes overlap.

Commonest indication (around 70%) for liver transplantation is end stage chronic liver disease [2,5,3,411].

Approximately 10% of liver transplant operations are carried out for acute or subacute hepatic failure [2,5]. Liver transplantation has also been used in the treatment of hepatic neoplasms, metabolic diseases associated with liver damage and also to correct metabolic defects in which the liver itself shows little or no signs of damage [2,5].

Aims and Objectives

The aim of this study was to evaluate liver allograft biopsies performed for graft dysfunction. Evaluation was done by analysing the pattern of injury and intensity, and the timeline of occurrence of graft dysfunction. The pathological features of explant liver of these patients were also looked into. The main aim of the study was to find the pattern of pathology in post transplant liver biopsies, in this part of the country.

Materials and Methods

A retrospective study was carried out for a period of four years from January 2013 to December 2016 in our centre. A total of 110 needle biopsies were obtained from 65 patients. Time zero reperfusion biopsies are done using 18 gauge liver biopsy needle while all other allograft biopsies were performed under ultrasound guidance using 20 gauge liver biopsy needle. Specimen was fixed in 10% buffered formalin and embedded in paraffin-wax. Paraffin sections were cut at 4 µm thicknesses and stained with Haematoxylin and Eosin (H&E), Periodic Acid Schiff (PAS), Periodic Acid Schiff- Diastase(PASD), Masson's trichrome , Prussian blue and Reticulin stains. Immunohistochemical studies such as CMV (Cytomegalovirus) and EBV (Ebstein Bar virus) were carried out whenever needed. The biopsy was considered adequate if six portal tracts were identified in one section. Preservation-reperfusion injury (PRI) was graded based on neutrophilic infiltration, apoptosis and hepatocyte cell drop out. Acute cellular rejection (ACR) is characterized by mixed inflammatory cell infiltrate in portal tracts, venous endothelitis and bile duct injury/ inflammation [2,5,12,13,15].

The three histological parameters underlying ACR were scored on a scale of 0–3 to give a total RAI (Rejection Activity Index)on a scale of 0–9, using the Banff 1997 criteria [12]. Chronic rejection (CR) was characterized by ductopenia and obliterative arteriopathy [8]. The features of HCV recurrence were portal lymphocyte predominant infiltrate, focal duct damage and mild fatty change [2,5,26,27].

Explant liver from all transplant patients were subjected to histopathological study. Representative sections were taken from both lobes, hilum and suspicious areas. H&E sections with relevant special stains were studied for a possible etiology. Necroinflammatory activity was also asessed.

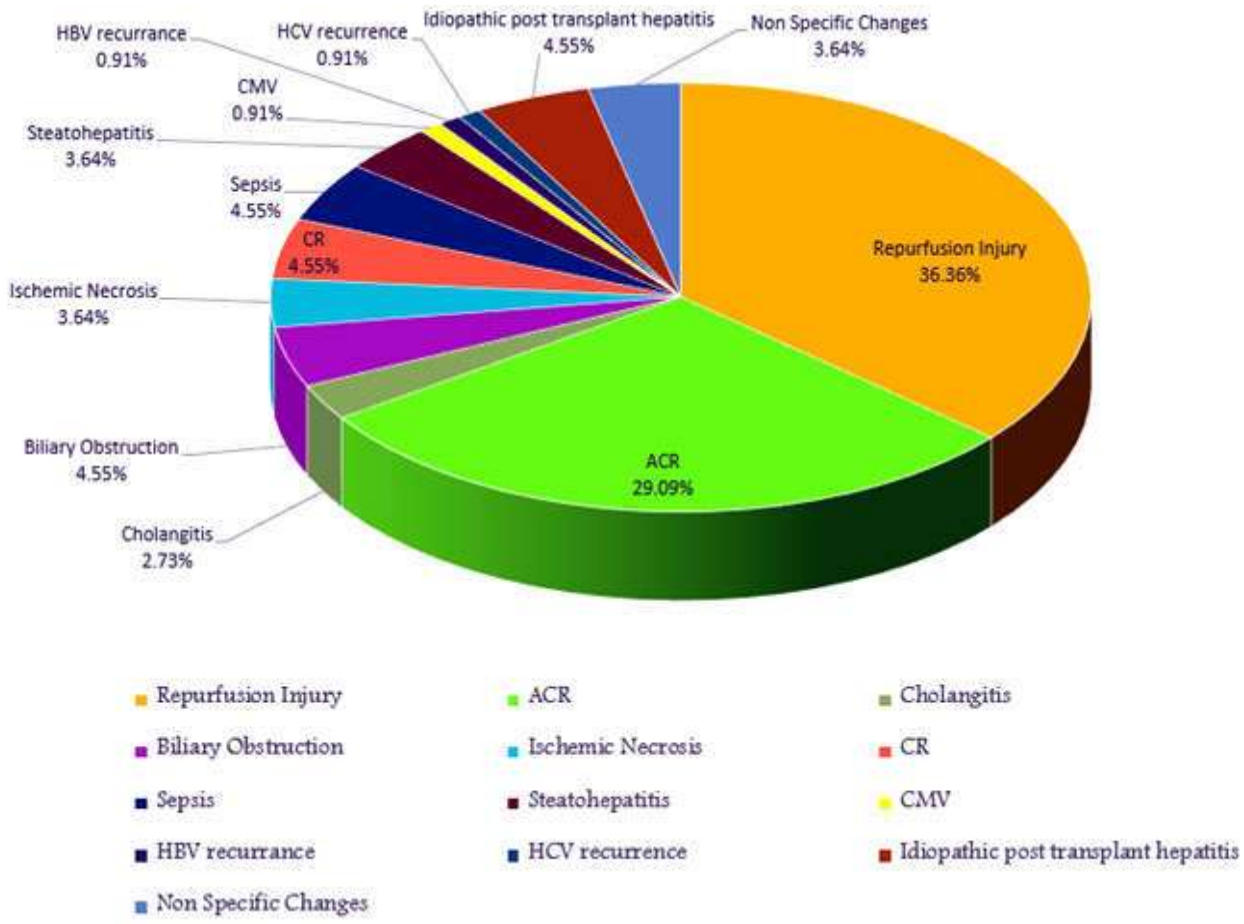
Results

A total of 65 liver transplants were done in our centre from 2013-2016. Out of 65 liver transplants, 44 cases were deceased donor liver transplants (DDLT) and 24 were live donor liver transplants (LDLT). Out of 44 deceased donor liver transplants, two cases were combined liver kidney transplants for primary hyperoxaluria. Among 65 transplant recipients, 6 were of paediatric age group. All the rest were adult males in the age group ranging from 20 to 69 yrs. The mean age was 50.01 years.Out of 65 liver allograft recipients, 58 recipients were subjected to 110 needle biopsies. Postoperative time interval for biopsy ranged from first postoperative day to 844 days post-transplant.

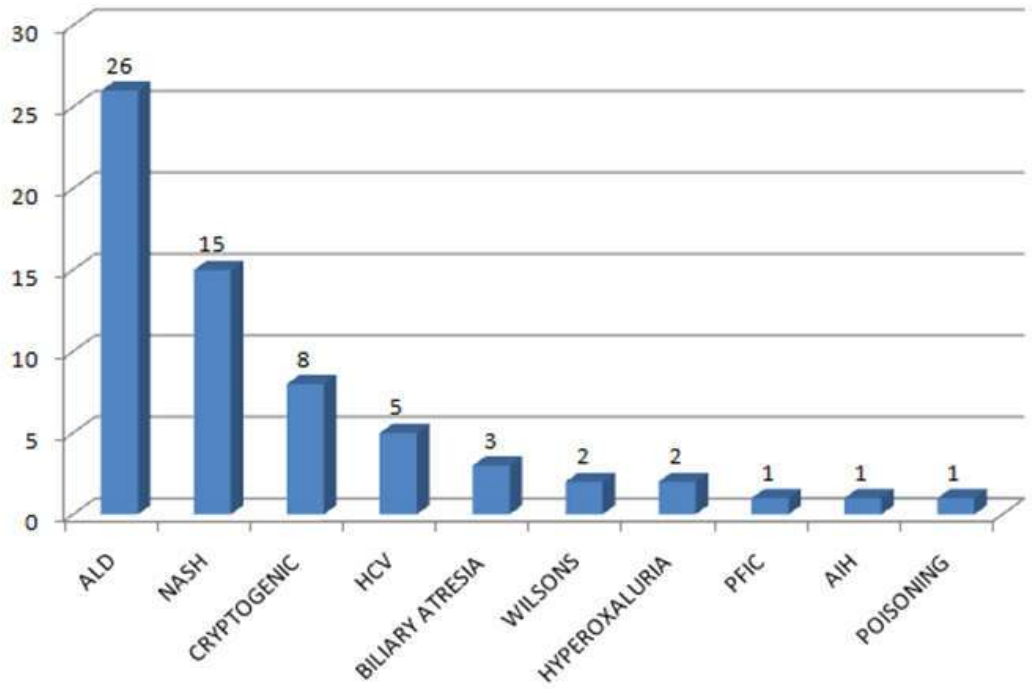
PRI was the most common lesion in our study reported in 40 (36.36%) biopsies. Reperfusion biopsy (Time zero biopsy) was graded into mild, moderate and severe. Reperfusion injury was mild in 2 2 (55%) cases, moderate in 15 (37.5%)cases and severe in 3(7.5%) cases (Figure 1).

The second common lesion was ACR (Figure 2) reported in 32 (29.09%) biopsies and intensity ranged from mild ACR in 15 (46.87%) and moderate ACR in 17 (53.125%) biopsies. Twenty two (70.9%) biopsies with diagnosed ACR were obtained within 6 months of post transplant and 9 (29.03%) were obtained after 6 months post transplant. 3 patients had 3 recurrent episodes of ACR. 2 episodes of ACR was seen in five patients. In mild ACR, a RAI score of 3/9 was seen in 11 cases and 4/9 was seen in 4 cases. In moderate ACR, RAI score of 5/9 was seen in 8 cases and 6/9 was seen in 12 cases. ACR was reported earliest at the 7th day and latest at 844 day post transplant. One case of late ACR presented with central perivenulitis (Figure 3) along with lobular inflammation and was difficult to distinguish from hepatitic pattern of injury. Two cases of ACR showed steroid resistance. Both these patients did not respond to the initial steroid pulse dose. After steroid pulsing, biopsy was repeated in both these cases and biopsies did not show any reduction in the inflammatory

Histopathological diagnosis in liver tarnsplant biopsies



Graph 1:



Graph 2: Indications of Liver Transpalnt

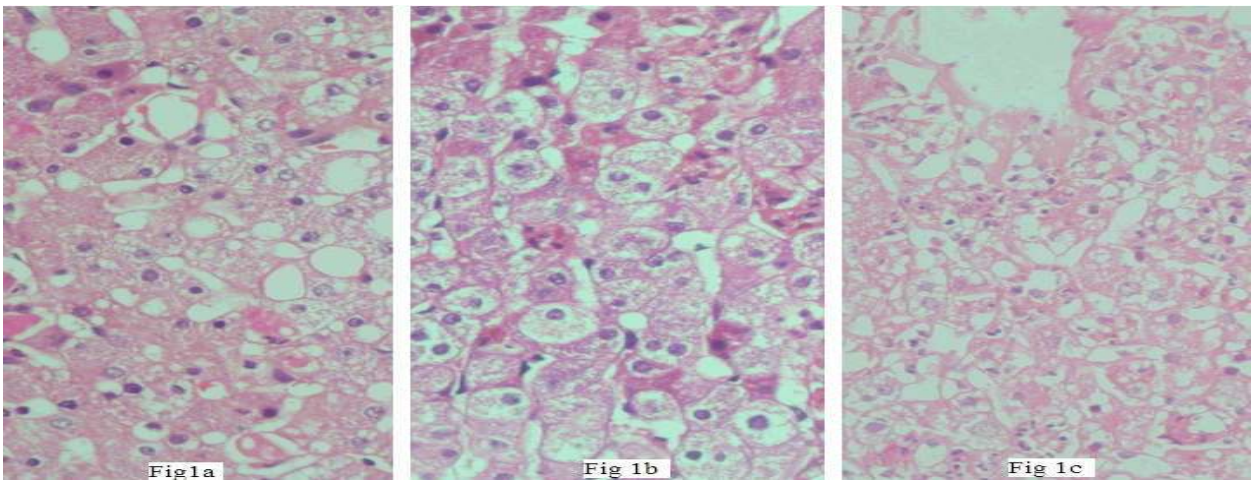


Fig. 1a,b,c: Showing mild, moderate, severe reperfusion injury respectively (H&E X200)

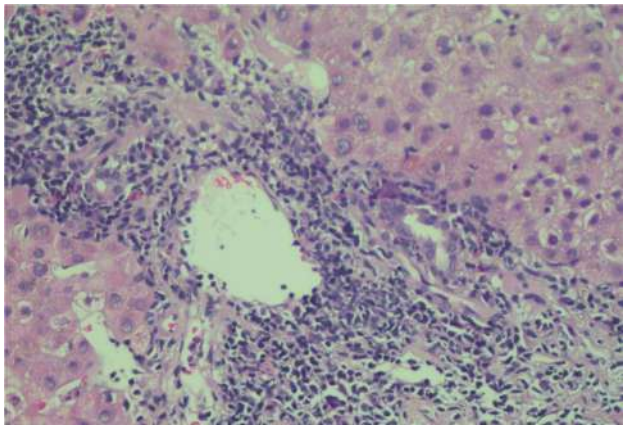


Fig. 2: Acute cellular rejection showing mixed inflammatory cell infiltrate in the portal tract with bileduct damage and endothelitis (H & E X100)

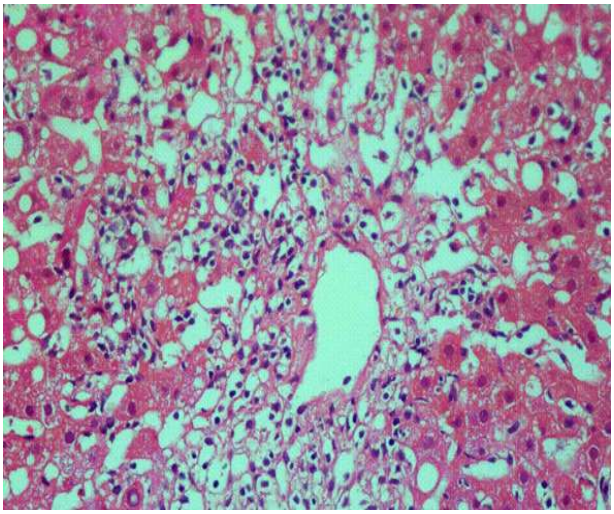


Fig. 3: Atypical acute cellular rejection presenting as isolated central perivenulitis (H&E X200)

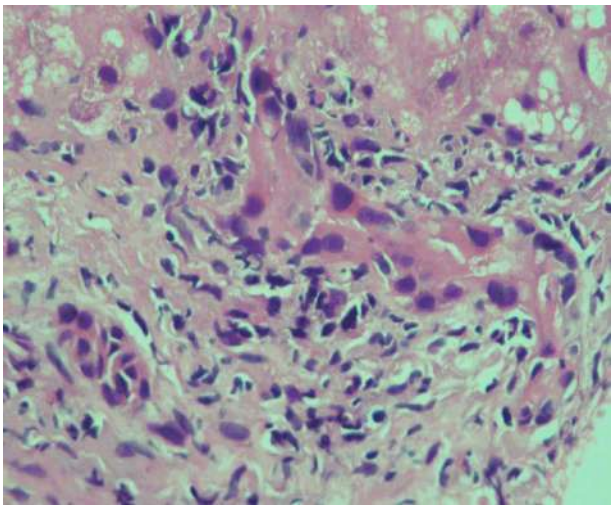


Fig. 4: Early chronic rejection showing mild lymphocytic inflitrate in the portal tract, portal fibrosis and senescent changes in the bile ducts (H&E X200)

infiltrate. Following this, these patients were given Antithymocyte globulin and both cases responded well. After treating with Antithymocyte globulin, biopsy was repeated in both the cases and both these biopsies showed much reduction in the inflammation and bileduct damage.

Early chronic rejection was observed in 5 (4.55%) biopsies obtained from 3 patients. Two patients had two biopsies. All these biopsies showed mild lymhocytic cholangitis with biliary senescence changes in the form of eosinophilic transformation of cytoplasm, nuclear hyperchromasia and loss of polarity (Figure 4). Bile duct loss was <50% in all these cases. No arteriolar loss was seen. Two of the cases showed subendothelial and perivenular inflammation of terminal hepatic venules and perivenular hepatocyte drop out. All the 3 cases we could pick it up at an early stage without much ductopenia and could save the graft. Chronic rejection occurs mostly within the first few months after transplantation. In our study time period of chronic rejection ranged from 361 days to 831 days . Among three, two patients had two episode of ACR and one patient had three episodes of ACR prior to CR. None of our cases showed humoral rejection.

Features of biliary obstruction were present in 5 (4.55%)cases. In four cases it was seen within 2 weeks of biopsy and in one case 3 years after transplant. Biopsies showed predominantly neutrophilic portal inflammation, periductal edema, and intraepithelial and intraluminal neutrophils within true portal bile ducts. Ductular proliferation and centrilobular hepatocanalicular cholestasis were also seen. Acute cholangitis was also noted in 3 (2.73%) cases.

Five (4.55%)cases showed sepsis. These biopsies showed neutrophils in the parenchyma, hepatocanalicular and cholangiolar cholestasis. These cases improved on treatment with antibiotics.

Posttransplant CMV infection was observed in one (0.91%) case. It was in a 7year old boy who developed fever and deranged liver enzymes after 3 weeks of transplant. Initial biopsy showed mild lobular inflammation with a few neutrophils and spotty necrosis. There were no intranuclear or intracytoplasmic inclusions in this biopsy. A repeat biopsy done 2 weeks later showed confluent hepatocyte necrosis and large intranuclear inclusions consistent with CMV. Immunohistochemistry with CMV antibody confirmed the same. This patient succumbed to the infection.

Features of HCV recurrence was seen in One (0.91%) case. Time period from transplant to HCV recurrence was 4 months. Biopsy showed mild to moderate portal inflammation rich in lymphocytes with mild interface hepatitis, duct damage, spotty necrosis and cholestasis. Unlike ACR there were no activated lymphocytes or eosinophils. HBV reactivation happened in one (0.91%)case. Time period from transplant to HBV recurrence was 621 days. Four biopsies (3.64%) showed steatohepatitis. This could be recurrence of non alcoholic steatohepatitis . Ischemic necrosis was observed in 4 (3.64%) cases. Five (4.55%) biopsies showed hepatitic pattern of injury. In all these five biopsies, serology for Hepatitis B,C , EBV and CMV were negative. Nonspecific changes like focal mild lobular and focal portal inflammation and mild steatosis were present in 4 (3.64%) cases.

The most common indication of liver transplant was alcoholic liver disease (ALD) in 26 (40%), nonalcoholic steatohepatitis (NASH) in 15 (23.08%), cryptogenic cirrhosis in 8 (12.31%), Hepatitis C (HCV) in 5 (7.69%), biliary atresia

in 3 (4.62%), Wilson disease in 2 (3.08%) and Primary hyperoxaluria in 2 (3.08%) patients. Progressive familial intrahepatic cholestasis (PFIC), Hepatitis B (HBV) and autoimmune hepatitis (AIH) was noted in 1 (1.54%) each. There was 1 (1.54%) case of zinc phosphide poisoning . 58 explants showed mixed micro and macronodular cirrhosis with mild and moderate activity. Four cases showed micronodular cirrhosis. Two patients (one at the age of 7 years and another at 20 years) underwent combined liver kidney transplantation for primary hyperoxaluria in which no cirrhotic changes were found. Explant livers in these two cases showed macroscopically normal liver and on microscopy oxalate crystals were present. There was one case of zinc phosphide poisoning , the explant liver of which showed severe mixed micro and macronodular cirrhosis with confluent necrosis. Hepatocellular carcinoma was found in five cases in which one was multifocal. Iron deposits were present in 12 explants in which four cases showed grade 4 deposits with features suggestive of hemochromatosis. Grade 3 deposits were seen in four cases and grade 2 in four cases. Large cell dysplasia was seen in 6 explants. Six explants showed macroregenerative nodules. Granulomatous inflammation consistent with tuberculosis was present in two cases. Six out of 65 transplants were done in paediatric patients . Three of these were done for biliary atresia, 2 had primary hyperoxaluria and one had PFIC.

Discussion

Pathological evaluation of liver allograft biopsies plays an integral role in the management of patients following liver transplantation [1,2,5,11]. In conditions such as liver allograft rejection, histology is regarded as the 'gold standard' because no other reliable diagnostic marker exists [1,2,3,5]. In our study among 65 transplant recipients, 6 were children in the age group of 10 months to 12 years. All the rest were adult males in the age group ranging from 17 to 69 yrs. The mean age was 50.01 years. Male to female ratio was 59:1 in adults. Reperfusion biopsy was done in 40 cases of DDLT. Indication of all other post transplant liver biopsies in our study was elevated liver enzymes and/or serum bilirubin. Alcoholic liver disease was the most common cause for liver transplant in the present study. However, other studies have reported HCV as the major cause of transplantation [2,5,6].

Preservation or harvesting injury(PRI) refers to tissue damage that causes dysfunction immediately after transplantation [2,5,11]. Insults that contribute to preservation injury include donor and recipient hypotension and other causes of warm ischemia, metabolic abnormalities, cold ischemia during organ preservation, and reperfusion injury [1,2,521]. Usually seen in the first 4 weeks after transplant [2,5,21]. In our study PRI was the most common injury and was observed in 36.36% of biopsies done in a post transplant period of 1 week to 4 weeks. Other studies have shown ACR as the commonest cause of graft dysfunction [3,9,10]. Reperfusion biopsy (Time zero biopsy)was performed in 40 cases of DDLT and was graded into mild, moderate and severe. Reperfusion injury was mild in 22(55%)cases, moderate in 15 (37.5%)cases and severe in 3(7.5%) cases. In mild PRI, predominant features are microvesicular steatosis, mid zone 3 hepatocellular swelling, canalicular cholestasis and in severe injury centrilobular hepatocellular swelling, severe neutrophilic exudation, necrosis and cholestasis [2,5,21].

The histological pattern of acute rejection was first described by Snover et al. [7]. ACR was graded according to Banff criteria for grading liver allograft rejection-1997 [12]. Criteria for evaluating chronic rejection was based on Banff criteria published in 2000 [8] ACR remains the commonest cause of early graft dysfunction with incidence ranging from 24-80% with a mean of 49.8% [3,9,10,11]. ACR (29.09%) was the second most common lesion in our study. ACR was graded into mild, moderate and severe according to Rejection activity index (RAI) [12]. Mild ACR was the most common finding followed by moderate and severe ACR. Factors determining the incidence of ACR include type of immunosuppression, perioperative factors (ischaemia, infections) and donor characteristics (including age, cadaveric versus living, etc) [1,12,13,15-19]. Twenty two (70.9%) biopsies with diagnosed ACR were obtained within 6 months of post transplant and 9 (29.03%) biopsies were obtained after 6 months post transplant. Steroid resistant ACR was noted in 2 cases . Among this, one was a young male of 17 years who presented with steroid resistant rejection within a month of transplant. The other patient developed steroid resistant rejection after 2 years of transplant. The second case was not on regular follow up and developed rejection after inadequate immunosuppression. Incidence of steroid resistant rejection early after transplant is rare [5]. Both the cases responded well with Antithymocyte globulin. Biopsy findings in late ACR differed from early ACR [2,12,16]. Late acute rejection showed fewer blasts, slightly greater interface activity, and more lobular activity. In some cases it was difficult to differentiate from chronic hepatitis and an expert opinion was sought whenever needed. One case of late acute rejection showed atypical features in the form of isolated central perivenulitis. In this biopsy parenchymal changes predominated portal changes with perivenular hepatocyte dropout. It was a difficult to rule out a hepatitic pattern of injury in this case and we had to take a second opinion from an expert to confirm the same.

Early chronic rejection is characterized by presence of ductopenia involving <50% of portal tracts. Portal tract changes in early chronic rejection include mild

lymphocytic cholangitis which leads to biliary epithelial cell senescence changes . This is eventually followed by loss of small bile ducts in the late stages [12]. Compared with acute rejection, portal inflammation in chronic rejection is usually less severe and contains primarily lymphocytes, plasma cells, and mast cell. In our study, the incidence of CR was 4.55%. Other authors have reported the incidence of CR as 3-5% in liver allograft recipients [5,20]. Chronic rejection is an important cause of late liver allograft dysfunction and failure. The occurrence of CR is due to repeated ACR, high donor age, long cold ischaemic period and inadequate/suboptimal immunosuppression or poor compliance [1,20,24]. Chronic rejection occurs mostly within the first few months after transplantation.

Biliary tract complications occur in 15% of whole cadaveric allografts and in up to 30% of reduced-size and living donor allografts [5]. The conditions included are anastomotic dehiscence, transmural necrosis, bile leakage, cholangitic abscesses, ascending cholangitis, bile casts, strictures, obstruction, ampullary dysfunction, and biliary-vascular fistulas [1,2]. Features of biliary obstruction were present in 5 (4.55%)cases. In four cases these features were noted within 2 weeks of transplant and in one case 3 years after transplant. Acute cholangitis was also seen in 3 (2.73%) cases. Pathologic distinction between preservation injury and obstruction/cholangitis can be difficult in the initial few weeks after transplant [2,21,25]. We had faced this problem and could sort it out only by looking at the true bile duct carefully. In obstruction or cholangitis, the usual findings are periductal lamellar edema surrounding true bile ducts, accompanied by neutrophils within the lumen or infiltrating between biliary epithelial cells. Acute pericholangiolitis is seen in preservation injury. Both disorders can show marked centrilobular hepatocanalicular and/or cholangiolar cholestasis and intralobular neutrophil clusters. Five (4.55%) cases showed sepsis. Biopsy was taken in these cases to rule out rejection. These cases improved on tapering the steroid dose and on treatment with antibiotics.

CMV is the most common opportunistic viral infection in liver allograft recipients, but effective prophylactic and presumptive therapy has greatly decreased the incidence, and impact, of symptomatic disease [2,5]. Symptomatic cases usually begin between 3 and 8 weeks after transplantation, either at the end of or shortly after a cycle of increased immunosuppressive therapy used for treatment of acute rejection. Pediatric recipients and a minority of adults may not have been previously exposed to the viruses. Previously unexposed allograft recipients usually develop more severe disease compared with previously exposed patient [5]. Our patient was a paediatric case who developed wide spread CMV infection which was fatal. Liver biopsy showed submassive necrosis and CMV inclusions. Despite widespread CMV infection, submassive or massive necrosis from CMV alone has never been documented. But our case had this finding. CMV infection is believed to be a risk factor for hepatic artery thrombosis, especially in pediatric patients [5]. Submassive necrosis in our case might have been due to hepatic artery thrombosis.

Hepatitis C recurrence is nearly universal after transplantation. The posttransplant course of hepatitis C is associated with a more rapid progression of fibrosis than in the native liver, with the development of cirrhosis after 5 years in 28% of cases [11,26]. Samuel D et al., mentioned that early recognition and intervention of recipients with rapidly evolving recurrent hepatitis C following orthotopic liver transplantation (OLT) is the only practical approach to improve outcome of these patients [11,27]. Out of 2 patients of HCV, one developed HCV recurrence in our study. We had one case of HBV reactivation in our study. Five post transplant biopsies showed hepatitic pattern of injury. In all these five biopsies, viral serology was negative. This could be taken as idiopathic post transplant hepatitis.

Patients with NAFLD before transplantation, usually maintain the original risk factors that precipitated liver disease and thus, may recur in the transplant liver as well. The addition of immunosuppressive agents after transplant may also contribute to the development of NAFLD by increasing insulin resistance [2]. Four biopsies (3.64%) showed steatohepatitis. This could be recurrence of non alcoholic steatohepatitis .

Conclusion

During the four year period of our study, we analysed and studied patterns of liver injury according to etiology. Reperfusion injury (PRI) in time zero biopsies was the most common finding in our study followed by ACR. Pathological distinction between preservation injury and obstruction / cholangitis can be difficult in the early post transplant period. 70.9% of biopsies with ACR were observed within 6 months post transplant. Features of late onset ACR and recurrent/ reactivation of hepatitis overlap and hence is always a diagnostic challenge. Analysis of explant liver specimens showed cirrhosis associated with alcoholic steatohepatitis to be the most common etiology of end stage liver disease leading to transplant.

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