REVIEW ARTICLES

LIVER TRANSPLANTATION: FROM A HISTOPATHOLOGIST'S PERSPECTIVE

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ABSTRACT

Liver transplantation is a standard clinical treatment for both adult and pediatric patients with acute liver failure, end-stage liver diseases and/or hepatocellular carcinoma. The histopathologist can facilitate many of the clinical decisions concerning the indications for liver transplantation, assessment of donor suitability and management of liver allograft dysfunction syndromes. However, the histopathologist also faces many challenges, especially with regards to the histologic interpretation of the myriad causes of liver allograft dysfunction. A close working relationship with the rest of the liver transplant team including clinicians, surgeons and radiologists is essential to arrive at the most appropriate diagnosis and achieve the best patient outcomes.

Keywords: Biopsy, Liver transplantation, Pathology.

INTRODUCTION

Liver transplantation (LT) is well-established as a therapeutic option for acute liver failure, end-stage liver diseases and hepatocellular carcinoma (HCC) and is a major undertaking requiring input and coordination between many different parties, including the donor, recipient, surgeon, hepatologist, internist and ancillary staff. The histopathologist is an integral part of the liver transplant team, and contributes to the decision-making process in both the pre- and post-transplant settings[1]. The variables associated with patient and graft outcome after LT include (i) donor factors, (ii) procurement logistics, (iii) recipient factors, and (iv) operative factors. This article explores the role of pathologists in LT from evaluation of the donor and recipient to follow-up of the liver allograft, and highlights the importance of interpreting all histologic findings in the appropriate clinical context to achieve the best patient outcomes.

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(I) Pre-transplant diagnosis of recipients' liver disease

In the pre-transplant setting, the histopathologist is involved in the diagnosis and assessment of severity of the recipient's liver disease. The identification of a specific etiology for the liver injury allows the initiation of appropriate therapy that can down-stage the liver disease, as well as prevent recurrence of the disease in the allograft. Admittedly, most common causes of end-stage liver disease can be identified solely through clinical and laboratory markers such as viral serology and antibody titers, as well as radiologic investigations. However, histologic examination of liver biopsies is still useful for assessment of disease severity/progression, identifying concurrent unsuspected pathologies such as the increasingly common non-alcoholic fatty liver disease (NAFLD), and obtaining diagnostic clues in cases of so-called "cryptogenic" cirrhosis, which can have implications on the recurrence risk and thus prognosis in the liver allograft.

The use of pre-operative biopsies to determine the histologic grade of HCC as a selection criterion for LT is controversial. Most centers currently utilize the Milan or UCSF criteria, which are based on tumor size and number, to select and prioritize recipients with HCC. However, there is increasing evidence on

the prognostic value of poor tumor differentiation, and the selection of patients based on pre-operative tumor grade has been practiced and advocated by some centers[2,3]. Unfortunately, issues of sampling in multiple and heterogeneous tumors, as well as intra- and

Table-1: Common allograft syndromes in liver transplants.

Syndromes	Clinical associations	Clinical observations	Exclusion criteria
Preservation/ reperfusion injury	Long cold (>12 hr) or warm (>120 min) ischemia time Donor >60 years old Hemodynamically unstable donor DCD Repeat anastomosis	Poor bile production Prolonged cholestatic phase predisposes to biliary sludge syndrome	AMR ACR Biliary obstruction Pancreatitis, sepsis Cholestatic hepatitis
Antibody-mediated rejection	ABO-incompatible donor High-titer (>1:32) lymphocytotoxic crossmatch DSAs Persistently low platelet counts and complement levels during first several weeks after LT	Accounts for allograft failure in 10 - 20% of "idiopathic early allograft failures" (<90 days after LT) in sensitized patients	Preservation injury Biliary ischemia or obstruction
Acute cellular rejection	30% incidence Younger, healthier female Inadequate IS Long cold ischemia times Disorders of dysregulated immunity (e.g. AIH, PBC, PSC)	Non-selective elevation of liver enzymes Leukocytosis & eosinophilia	Biliary obstruction HBV, HCV AIH
Chronic rejection	3 - 5% incidence Inadequate IS (e.g. infections, tumors, PTLD or non-compliance) History of moderate/severe or persistent ACR episodes	Cholestatic or biliary pattern of injury (preferential elevation of GGT & ALP) Jaundice, sludge, strictures	Biliary ischemia or obstruction HBV, HCV AIH
Hepatic artery thrombosis	Suboptimal/difficult anastomosis Pediatric or small caliber vessels Large difference in vessel caliber across anastomosis Suboptimal arterial flow (vasospasm in small-for-size syndrome) Donor and/or recipient atherosclerosis Hypercoagulopathy	Liver tests reflect: Biliary complications: Frank necrosis, leakage, cholangitic abscesses, non-anastomotic stricture, biliary sludge syndrome, ischemic cholangiopathy Parenchymal ischemia	Resolving ACR with ischemic cholangiopathy Chronic rejection
Biliary tract obstruction or stricture	Arterial insufficiency or thrombosis Long cold ischemia time DCD Difficult biliary anastomosis AMR Recurrence of original PSC	Anastomotic stricture Non-anastomotic stricture	Ischemic cholangiopathy Mechanical obstruction
Hepatic venous outflow obstruction	Difficult piggyback hepatic vein reconstruction Cardiac failure	Elevation of transaminases Ascites (Budd-Chiari syndrome)	Portal vein thrombosis CPV
Small-for-Size Syndrome (SFSS) or Portal hyperperfusion	Reduced size* and living donor transplants *<30% of standard or expected liver volume of recipient or <0.8% of recipient body weight	Postoperative coagulopathy Liver dysfunction Progressive cholestasis Portal hypertension Ascites	
Opportunistic viral (e.g. CMV, EBV, adenovirus) and fungal infections	Seropositive donors to seronegative recipients (often pediatric) Excessive IS	Elevation of transaminases Serological confirmation	
Recurrent or new-onset viral hepatitis (e.g. HBV, HCV, HEV)	Original disease HBV, HCV, or acquired HEV-induced hepatitis in patients in contact with animals or culinary exposures	Hepatitic pattern Serological confirmation	ACR LAR ("hepatitic pattern") AIH DILI
Recurrent AIH, PBC, PSC De novo AIH	Original disease AIH, PBC or PSC	*AIH*: Hepatitic pattern; appropriate serological correlates *PBC*: Cholestatic pattern; serum AMA may persist after LT *PSC*: Cholestatic pattern; appropriate cholangiographic corroboration	*AIH*: Viral hepatitis, LAR, other causes of plasma cell hepatitis *PBC*: Chronic ductopenic rejection *PSC*: Biliary obstruction or strictures, chronic ductopenic rejection
Alcohol abuse	Recipient psychiatric comorbidity or social instability Noncompliance with treatment protocols	Hepatitic pattern GGT/ALP ratio >1.4	NASH
Nonalcoholic steatohepatitis	Original disease of NASH or cryptogenic cirrhosis Persistent/worsening risk factors for NASH	Hepatitic pattern	Alcohol abuse

inter-observer variability currently pose significant challenges to the adoption of this criteria based on pre-operative tumor biopsies[4].

The use of novel radiologic assessments such as positron emission tomography-computed tomography (PET-CT) to facilitate targeting of the most biologically aggressive lesion for sampling may alleviate these problems, and the additional prognostic information obtained from molecular analyses performed on biopsy tissue may enhance the value of pre-transplant biopsies[5,6]. Non-invasive dynamic imaging techniques to assess tumor biology are also being investigated, and may eventually circumvent the need for pre-transplant biopsies altogether[7].

Common indications for LT in the adult population in the Americas and Europe include hepatitis C virus (HCV) infection followed by alcohol-induced liver disease and NAFLD-induced cirrhosis. In Asia, hepatitis B virus (HBV)-induced cirrhosis tops the list. Other indications include autoimmune hepatitis (AIH), primary sclerosing cholangitis (PSC), primary biliary cirrhosis (PBC), and Wilson disease, and causes of acute fulminant hepatic failure such as drug/toxin-induced liver injury. In the pediatric population, cholestatic diseases such as extrahepatic biliary atresia/post-failed Kasai procedure and paucity of intrahepatic small bile ducts account for the majority of LTs, followed by metabolic diseases[8].

Donor liver assessment

The evaluation of the suitability of a donor liver for transplantation is a complex process incorporating clinical data, laboratory data and histologic data in the context of the recipient's medical need. The donor risk index (DRI) developed by Feng et al. for deceased donors identifies clinical criteria and transplant factors correlating with poor allograft function[8], however, many studies have also demonstrated macrovesicular steatosis to be an independent risk factor for graft survival[10], and this may necessitate histologic assessment. In addition, due to the growing need for liver allografts, deceased donors with further risk factors are also being considered for transplantation. These extended criteria donors (ECD) can be separated into two broad categories: those associated with risk for poor function based on physiologic stress or liver injury in the donor, and those with the risk of disease transmission (viral or malignancy) from donor to recipient[11].

The decision to utilize or discard these "marginal" donor livers depends on the balance of the overall donor risk and recipient characteristics. For example, most centers prefer to utilize livers with no more than mild macrovesicular steatosis (≤30%), however, ECDs with macrovesicular steatosis of moderate severity (30% to 60%) are still acceptable in recipients without additional risks[12]. Hepatitis C positive donor livers with no significant septal fibrosis and minimal inflammation are also suitable for HCV positive recipients[11,13].

Visual inspection during surgery for steatosis and fibrosis is thus an important step in deciding the suitability of the deceased liver allograft, especially in ECDs. However, this process is dependent on the experience of the surgeon, and studies have shown discrepancies between visual inspection by surgeons and the histologic results, which may result in inappropriate use or discarding of potential donor organs[13,14]. In ambiguous situations, some surgeons may make the decision for an intra-operative frozen section of the potential graft to support their clinical impression, especially in centers which offer a 24/7 frozen section service. The major concerns of the histopathologist during frozen section evaluation are thus the extent of macrovesicular steatosis, as well as other factors that are considered relative or absolute contraindications to transplantation such as marked steatohepatitis, severe fibrosis, severe necrosis or malignancy. The difficulties of accurately assessing the degree of macrovesicular steatosis during frozen section analysis are however well-known (fig-1), especially in situations of mild macrovesicular steatosis[15], and in the presence of additional artifacts from suboptimal specimen transport and processing, such as air drying, placing the biopsy on a gauze/towel, or saline[13]. Although the estimation of fibrosis is often also imprecise

due to the lack of special stains and subcapsular nature of the intra-operative biopsy, septal fibrosis, which is the major concern, can usually be safely identified during frozen section. Therefore, although the increasing use of ECD potentiates the need for allograft liver biopsy, all histologic findings should still be corroborated with the clinical / surgical impression[14].

The issue of percutaneous pre-transplant biopsies as a pre-requisite in living donor liver transplantation (LDLT) continues to be debated[16], and is especially relevant in countries

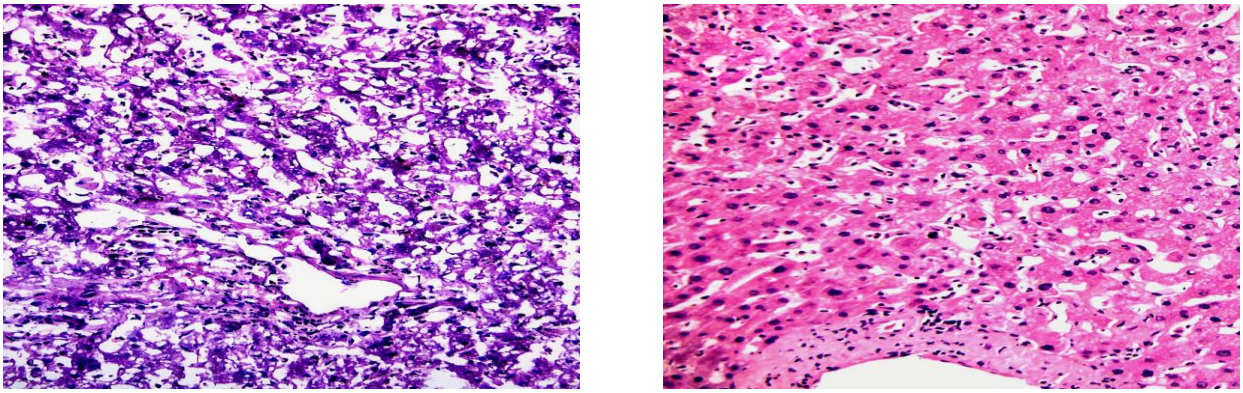

Figure-1: Showing left panel (1) x200 (RGB) & Right panel.
Left panel: Intraoperative frozen section of a wedge liver biopsy shows apparent intracytoplasmic vacuoles, reported as mild micro- and macrovesicular steatosis. (H&E stain, original magnification x 200). Right panel: Formalin-fixed, paraffin section of the same specimen shows hardly any macrovesicular steatosis. (H&E stain, original magnification x 200)

such as in Southeast Asia where the pool of deceased donors is limited due to various factors. Donor safety is the foremost consideration in LDLT, and many clinical parameters and non-invasive radiologic techniques such as computed tomography densitometry for the assessment of hepatosteatosis have been developed to circumvent the small but present risk of percutaneous liver biopsies[17,18]. However, a substantial number of biopsies performed in apparently healthy potential liver donors with normal laboratory and radiologic results still reveal histologic abnormalities, including nonsteatotic findings[9-21]. While the precise significance of the presence and extent of these histologic abnormalities for both the donor as well as the recipient remains to be clarified, most surgeons and hepatologists will probably be reluctant to proceed in these cases out of concern for donor risk[22]. Achieving a balance between donor safety and recipient necessity continues to be fraught with difficulties, and depends on the clinician's overall judgement for each individual potential donor.

(II) Examination of explanted liver

The pathologic examination of the explanted liver confirms the pre-transplant diagnosis, and can identify additional comorbidities as well as causes of cryptogenic cirrhosis, especially for etiologies such as biliary diseases that may be heterogeneous and not sampled on liver biopsies (fig-2). Accurate determination of the pathologic grade and stage of malignancies and their response to local therapy such as transarterial chemoembolization (TACE) or radiofrequency ablation (RFA) also provides important prognostic information with respect to the biological aggressiveness of the tumor[23]. Many end-stage liver diseases also have an increased risk for malignancy, and the discovery of clinically undetected early HCC or cholangiocarcinoma with their attendant prognostic implications is not unexpected in such patients.

(III) Post-transplant assessment of the graft

Post-transplant assessment of the allograft is without doubt the most challenging aspect of liver transplant pathology. The causes of graft dysfunction are wide-ranging, including rejection, surgical/technical complications, recurrence of disease, new onset/de novo disease, opportunistic viral infections, drug induced injury, malignancy and post-transplant lymphoproliferative diseases (PTLD), and these varied etiologies often have overlapping morphologic features. Furthermore, the pathologist has to consider the alteration of classic histologic findings by the immunosuppressed post-transplant state of the patient as well as changes induced by medical therapy instituted prior to biopsy. Laboratory findings that would have helped strengthen certain histologic diagnoses before transplantation may also no longer carry the same significance, such as the persistence of autoantibodies in patients transplanted for PBC and AIH. This increases the reliance on histologic findings despite their somewhat non-specific nature. To add to the confusion, the cause of graft dysfunction is often multifactorial, and it can be difficult to tease out the contribution of each cause to the overall picture.

Formulating a useful interpretation of an allograft biopsy thus requires a review of all prior biopsies if possible and close clinicopathologic correlation and input from clinicians and surgeons. For example, the histologic features of chronic rejection may resemble other causes of bile duct damage such as ischemic cholangiopathy. A clinical and pathologic history of inadequate immunosuppression or persistent/ unresponsive acute rejection would be invaluable in establishing the diagnosis of chronic rejection, which has serious implications on the prognosis of the allograft. Even in situations whereby the pathologist is unable to come to a definitive conclusion, giving definite negative diagnoses such as the absence of histologic features for acute cellular rejection can be useful to the treating physician.

Several reviews have covered the liver biopsy interpretation for various causes of early and late liver allograft dysfunction and their occurrence at specific time periods[1,24-26], and the interested reader is referred to these articles for a more in-depth coverage of the topic. Table-1 gives an overview of the major post-transplant allograft problems highlighting key clinical associations/observations and differential diagnoses that are of great relevance to all members of the transplant team. Fig-3 gives the timeline of the occurrence of the clinical syndromes after transplantation..

Adapted from: Demetris et al. Pathology of Liver and Hematopoietic Stem Cell Transplantation. In: Odze, Goldblum, eds. Surgical Pathology of the GI Tract, Liver, Biliary Tract, and Pancreas (3rd ed). Philadelphia: Elsevier Saunders; 2015: 1413 (table-52.2). This table was originally adapted from: Demetris et al. Histologic patterns of rejection and other causes of liver dysfunction. In: Busuttil, Klintmalm, eds. Transplantation of the Liver. Philadelphia: Saunders; 2005:1057-1128.

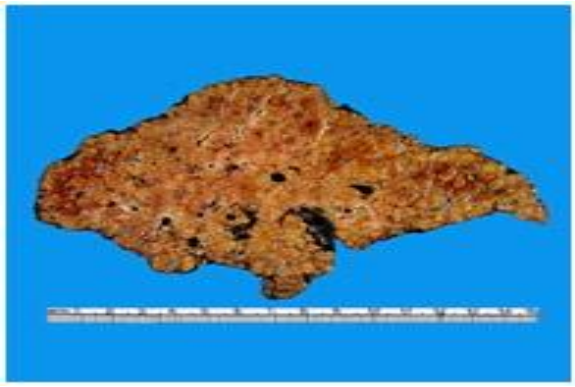

Figure-2: Explant (Liver explant from an adult patient with hepatitis C-induced cirrhosis).

ACR, Acute cellular rejection; AIH, Autoimmune hepatitis; ALP, Alkaline phosphatase; AMA, Anti-mitochondrial antibody; AMR, Antibody-mediated rejection; CMV, Cytomegalovirus; CPV, Central perivenulitis; DCD, Donor after cardiac death; DILI, Drug-induced liver injury; DSA, Donor-specific antibodies; EBV, Epstein-Barr virus; GGT, γ-glutamyl transferase; HBV, Hepatitis B virus; HCV, Hepatitis C virus; HEV, Hepatitis E virus; IS, Immunosuppression; LAR, Late-onset acute rejection; LT, Liver transplantation;

NASH, Nonalcoholic steatohepatitis; PBC, Primary biliary cirrhosis; PSC, Primary sclerosing cholangitis; PTLD, Post-transplantation lymphoproliferative disorder

In this article, we highlight one of the major diagnostic issues faced by histopathologists in liver transplant pathology, as well as the role of protocol allograft biopsies.

Hepatitis C versus cellular rejection

The differentiation of recurrent Hepatitis C from cellular rejection has major implications on the therapeutic decision. Unnecessary augmentation of immunosuppression can accelerate fibrogenesis in chronic HCV or trigger cholestatic hepatitis[27], however, untreated acute cellular rejection can progress to chronic rejection. Late-onset acute rejection (LAR) has slightly different features from the typical acute cellular rejection seen early after transplantation: fewer blastic lymphocytes, slightly greater interface activity, less endotheliitis and slightly more lobular activity[28]. Cases of LAR can also present with isolated central perivenulitis. The histologic features may therefore greatly resemble chronic hepatitis. Some useful clues that favor acute cellular rejection include a mixed portal inflammatory infiltrate with eosinophils, bile duct damage that is more diffuse and severe than expected in chronic hepatitis, possible ductopenia, central perivenulitis that involves majority of central veins and less lobular necroinflammatory activity and interface activity[24]. (Fig-4). However, none of these features are specific on their own and the favored diagnosis oftentimes is a subjective assessment based on the severity / extent of each feature[29]. Furthermore, it must be remembered that both processes can co-exist, and in such situations the predominant process should be identified as far as possible so that treatment can be directed towards the primary process[24]. The advent of new non-invasive technologies such as measurement of graft-derived cell-free DNA to detect rejection at early stages and adjust immunosuppression levels[30], as well as the introduction of direct acting antivirals against hepatitis C[31], may help resolve such ambiguous situations in future and render this dilemma moot.

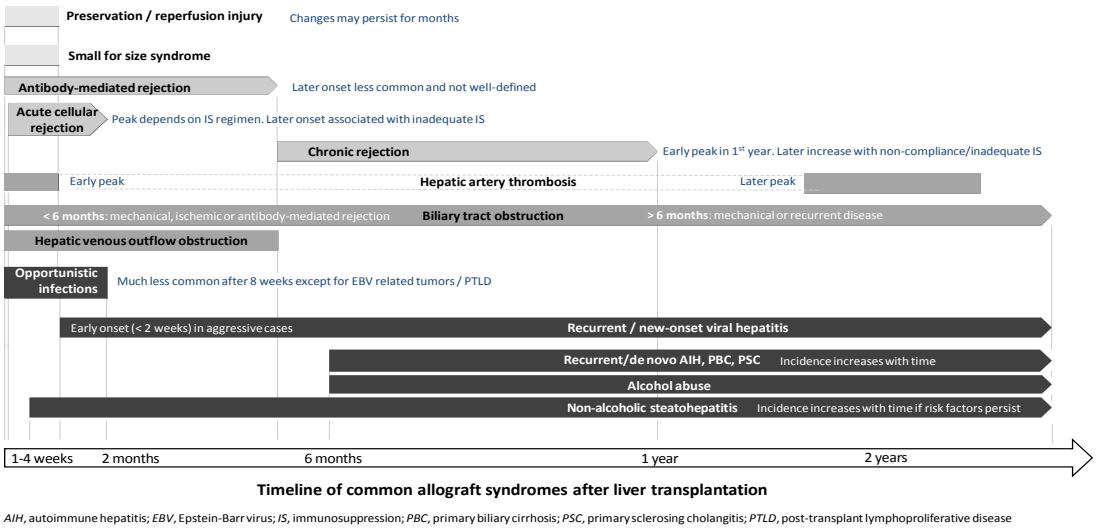

Figure-3: Timeline of occurrence of allograft syndromes after liver transplantation.

Role of protocol biopsies

Protocol liver allograft biopsies are liver biopsies undertaken at specific time points as part of the routine management of the transplant recipient, rather than to investigate

changes in the clinical state or liver tests. While initially part of standard practice in the early years when knowledge of post-transplant liver histology and the causes of allograft dysfunction was rudimentary, the practice is now largely abandoned except for patients with HCV. In HCV infection, where graft infection is almost universal[32], planned interval protocol biopsies help assess the progression of fibrosis, which is often more rapid than in the native liver[33]. Histologic changes at 1 year predict the subsequent course of recurrent hepatitis C and provide an early indication of which patients should receive antiviral treatment[34].

The decrease in use of protocol liver biopsies is partly accounted for by a better understanding of the major causes of allograft dysfunction and their clinicopathologic correlates, the cost and risk of liver biopsies, sampling issues and interobserver variability in the histology interpretation[35]. For example, expression of hepatitis B virus (HBV)-DNA in the liver correlates with serum HBV-DNA positivity, making allograft histology less useful than serological estimations of viral load for monitoring recurrent hepatitis B in patients who undergo liver transplantation for HBV-related liver disease[36].

However, some centers believe that protocol liver biopsies do still provide useful information for clinical management. A retrospective analysis by Ali et al[37]. showed that patients graded with severe ischemia-reperfusion injury (IRI) on routine time-zero biopsies had an almost 50% chance of graft loss or death within the first year of transplantation. This is especially pertinent with the increasing use of ECD which are particularly susceptible to IRI[38]. The identification of such patients could allow for a decision on either early re-transplantation or the commencement of adjunct therapies that specifically target reperfusion injury. There are a few randomized clinical trials on pharmacological strategies to minimize hepatic IRI in deceased donor liver transplantation such as the protective effects of inhaled NO[39], although these remain to be incorporated into routine clinical practice.

Abnormal allograft histology on late protocol biopsies has also been reported in 27% to 72% of liver allograft recipients despite normal liver function tests (LFT)[40-42]. While clinicians may be hesitant to treat patients who are asymptomatic and have normal laboratory findings, some of these histologic findings may be clinically significant and allow early treatment of clinically inapparent disease. For example, up to approximately one-third of recipients with normal LFTs have idiopathic / unexplained CH detected on protocol biopsies[43] and, therefore, are at risk of progressive fibrosis, cirrhosis, and graft loss. There is suggestion that this may be thwarted by changes in the immunosuppressive regimens[44]. Normal histologic findings on protocol biopsies may also be useful to support the decision to reduce the level of immunosuppression, especially in patients with impaired creatinine clearance.

Protocol allograft biopsies may also be

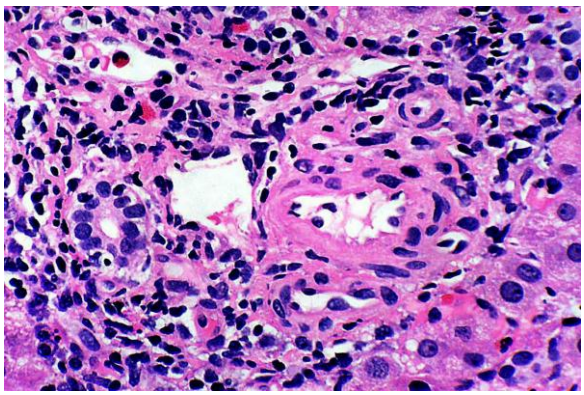

Figure-4: Liver allograft biopsy with classical acute cellular rejection (at 4 weeks): The portal tract shows a mixed portal infiltrate comprising activated lymphoid cells, neutrophils and eosinophils. The damaged interlobular bile duct shows cytoplasmic vacuolation and intraepithelial lymphocytes. No portal venous endotheliitis is present in this tract. (H&E stain, original magnification x 400).

necessary in patients who are no longer on immunosuppressants (IMS). Up to 20% of selected liver allograft recipients can maintain good long-term graft function when immunosuppression is withdrawn[45]. Although the factors determining success are not completely elucidated, there has been some

suggestion that immunophenotyping the lobular inflammation in liver histology can provide a guide to the likelihood of successful withdrawal of IMS[46]. Protocol biopsies after withdrawal of IMS may provide early evidence that IMS should be reinstituted, although the relevant studies have yet been undertaken.

In summary, protocol liver biopsies appear to provide useful clinical information both at time-zero as well as in the later years post-transplant, and may be important in improving long term outcomes of patients as the length of graft survival increases.

CONCLUSION

The pathologist contributes to the liver transplant team at multiple time points. The histopathologist is like a puppet master, maneuvering the strings and co-ordinating multiple facets of the case to roll out a meaningful story. Clinical findings are sufficient in most cases to guide patient management, and the advent of new non-invasive technologies may reduce the need for liver biopsies; however, the integration of histologic findings with clinical and radiologic findings is still key to optimizing patient outcomes.

CONFLICT OF INTEREST

This study has no conflict of interest to declare by any author.

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