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Review Article

Importance of Liver Biopsies during Liver Transplantation

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Abstract

Liver biopsy remains the "gold standard" to evaluate the histological abnormalities that are undetectable by serological, biochemical, and radiological methods. Liver biopsy might play an important role in diagnosis the problem. A variety of other histopathological abnormalities have also been reported among apparently healthy living donors. Here, we present the time, the size, the technique and the histological analysis of liver biopsies during liver transplantation.

Keywords: *Liver Biopsy; Donor Biopsy; Time Zero Liver Biopsy; Liver Transplantation*

Introduction

Although most causes of elevated liver enzymes can be determined, or at least suspected, on the basis of a careful history and laboratory tests, histological assessment remains the gold standard for most liver diseases [1]. The diagnosis and management of liver disease patients is based on the liver biopsy and it has long been considered to be an integrant step for proper diagnosis [2]. Certainly, besides helping to confirm the diagnosis, a preoperative liver biopsy in potential living donors may reveal an occult liver condition leading to exclusion from donation [3]. Assessment of these histological changes is crucial because of their impact on the outcome of the transplant program. Hepatic steatosis is considered a criterion for marginality because it is an important risk factor for early post-transplant liver dysfunction. The moderate degree of macrovesicular steatosis is proved to be evidence of a high risk of graft non-function [4].

Times of Liver biopsies

Pre-transplant liver biopsy: This type of liver biopsy is indicated in living donor liver transplant. The preoperative liver biopsy in potential living donors may reveal an occult liver condition leading to exclusion from donation [3].

Per operative liver biopsy: This type of liver biopsy is called Time-zero biopsies sampled after graft revascularization predicts adverse clinical outcomes after liver transplantation.

Post-liver transplant biopsy: This type of liver biopsy is indicated when there is post-transplant unclear complication.

Size of liver biopsy

It is recommended that the size of the biopsy wedge be 1.5 cm x 1.5 cm, alternately a 2 cm long, 0.2cm in diameter true-cut biopsy needle can be used [5].

Technique of liver biopsy

1. **True-Cut needle biopsies**: True-Cut needle biopsies were obtained during operation after complete implantation of the allograft. The handling of the liver is associated with subcapsular injury and inflammation, and therefore may be misinterpreted as predicting preservation injury but the subcapsular region was not expected to be sampled by the True-Cut biopsies [6].
2. **Sub capsular wedge biopsy**: Sub capsular wedge biopsy specimens of liver allograft were taken intraoperatively after complete revascularization of the allograft. They are taken instead of tru-cut needle biopsies to avoid tru-cut needle biopsy related complications such as bleeding.

Histopathological analysis of liver biopsies

Pre-transplant liver biopsy

Abnormal histopathological findings which might be detected in donor biopsy.

Non-alcoholic fatty liver disease (NAFLD)

NAFLD is defined as fat accumulation in the liver exceeding 5% to 10% by weight, but it is estimated practically as the percentage of fat-laden hepatocytes observed by light microscopy [7]. The disease includes a spectrum of hepatic pathology that ranges from simple, bland steatosis to steatosis plus features of cellular injury, including necrosis, hepatocyte ballooning and inflammatory infiltrate (i.e. non-alcoholic steatohepatitis (NASH), which may or may not be associated with increased liver fibrosis. In some patients, NASH progresses to advanced fibrosis, cirrhosis with their consequent complications of liver failure and hepatocellular carcinoma [7]. In most LDLT programs, the maximal acceptable amount of steatosis in the donor liver varies and ranges from 10% - 30% [8]. It remains controversial whether potential donors with mild macrosteatosis (up to 30% steatosis) should be denied from donation [9].

Schistosomiasis

Simple presence of Schistosoma eggs in liver tissue is not a contraindication for liver donation especially when the treatment of Schistosomiasis is possible during the preoperative evaluation of the donor [10,11]. On the other hand, some studies reported that the histological finding of granulomatous reactions with Schistosoma eggs in preoperative liver biopsy samples was a contraindication for liver donation [3,12].

Other histopathological abnormalities

Abnormal histologic findings, other than steatosis, have also been reported. Ryan., *et al*. [5] reported that 38% of potential donors exhibited other abnormal histologic findings other than hepatic steatosis. Those varied from triaditis (a conventional term to describe portal inflammation) to increased hepatic iron and granuloma also chronic hepatitis, fibrosis of unclear etiology and abnormal vascular pattern.

Per operative liver biopsy (Time Zero biopsy)

Abnormal histopathological findings in time zero biopsy include: Hepatocyte ballooning degeneration, steatosis, cholestasis, presence of apoptotic bodies, bile plugs, neu¬trophilic infiltration and central confluent necrosis. These changes are evaluated and graded according to the following criteria:

- Ballooning degeneration: was defined as hepatocellular swelling, vacuolization of the cytoplasm and cytoplasmic clumping of filamentous eosinophilic material. The grading of ballooning degeneration was divided into present or absent [13].
- Micro-vesicular steatosis: was defined as presence of many tiny cytoplasmic droplets, in hepatocyte and was divided into the following categories 0% (negative), 1% - 10% (mild), more than 11% (sever) [14].
- Macro-vesicular steatosis: means presence of a single large droplet in hepatocyte and was divided into the following categories: 0% - 4% (negligible), 5% - 33% (mild), 34% - 66% (moderate), more than 67% (severe) [14].
- Hepatocellular cholestasis: hepatocyte discoloration by brown pigmented material and indicate of retention of biliary material in hepatocytes and was divided into Present or absent [14].

- Bile plug, is defined as retention of bile in a distended bile canaliculus.
- Apoptotic cells were identified by cytoplasmic shrinkage and eosinophilia, chromatin condensation and karyorrhexis [14].

Interpretation of histopathological findings in Time zero biopsy

Neutrophilic infiltration and Hepatocyte necrosis

The degree of lobular neutrophilic infiltrate and hepatocyte necrosis on postreperfusion biopsy specimens during the OLT procedure reflect the degree of IRI [15]. Kocbiyik., et al. [16] observed that the histological features on postreperfusion biopsy specimens did not appear to be related, except neutrophilic infiltration of the liver parenchyma and hepatocellular necrosis, which were both related to initial poor function whether assessed by presence or grade. The combined presence of sinusoidal neutrophilia and hepatocellular necrosis in the post biopsy specimen strongly correlates with the development of IRI in the early postoperative period [17].

Steatosis

The histological features of reperfusion injury (neutrophilic infiltrate and hepatocyte necrosis) were distinct from simple steatosis as independent predictors of graft outcome.

Subcapsular changes

The manipulation of the liver during surgery is associated with subcapsular fingerprint injury and inflammation and therefore may be misinterpreted as predicting preservation injury [6]. Subcapsular neutrophilic infiltration (a sign of surgical hepatitis) was not considered of value in indicating preservation injury [16].

Other changes

The size and site of por¬tal congestion, ballooning degeneration, bilirubinostasis, and bile plug revealed no significant correla¬tion with early postoperative graft recovery [14].

Post-liver transplant biopsy

Abnormal histopathological findings in post-liver transplant biopsy is important for diagnosis.

Primary non-function (PNF)

The exact cause(s) of this life-threatening event is unknown. It is likely that some of the metabolic/immunological events associated with ischaemia/reperfusion injury contribute to PNF in some way, but there is no direct correlation. Clinical parameters include profound coagulopathy despite administration of fresh frozen plasma, hepatic encephalopathy and aspartate aminotransferase (AST) values more than 5000 IU. Biopsy findings include ischaemic cholangiopathy and necrosis. Mortality approaches 100% if PNF persists longer than 36 - 48 hours, and re-transplantation is the only effective treatment [18].

There is a variant of PNF called primary or initial poor function in which the clinical and laboratory findings are similar to PNF but less extreme. This is often related to rejection, infection or hepatotoxic drugs and resolves when the underlying cause is appropriately treated [19].

Acute rejection

Acute cellular rejection, characterised by biopsy findings of mixed portal inflammation, endothelialitis, bile duct damage and occasional eosinophils in portal tracts, is accompanied by varying degrees of hepatic dysfunction. It occurs most commonly in the first 4 - 8 weeks post-transplantation, but is also common during the first year. Modern immunosuppression regimens result in most acute cellular rejection episodes being successfully reversed, usually following administration of increased steroid doses, addition of a second agent or occasionally lymphocytotoxic antibodies [20].

Chronic rejection

The current literature suggests the rate is now between 2% and 5% and suggests that improved immunosuppression along with better preservation techniques is responsible for the improvement. Histological features include bile duct atrophy and portal tract loss with concomitant arteriopathy or obliterative arteritis. There may or may not be mononuclear cell infiltration. Chronic rejection does not usually respond to increases in immunosuppression [21]. Recent publications have suggested involvement of donor-specific HLA antibodies in the pathogenesis of chronic liver allograft rejection and reported that antibody-depleting therapy (plasmapheresis, intravenous immunoglobulin, rituximab) can salvage 'at-risk' grafts that had not responded to increases in traditional immunosuppression [22].

Conclusion

Liver biopsy remains the "gold standard" to evaluate the histological abnormalities in liver tissue in both donor and recipient which could not diagnosed by laboratory and radiological examination.

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