The impact of pathologist experience on liver transplant biopsy interpretation

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We studied the impact of pathologist experience on liver transplant biopsy interpretation for cases designated 'nonspecific' by pathologists at a nontransplant center. Among 102 consecutive liver transplant biopsies from 92 patients performed at the Foothills Medical Center, 30 liver biopsies from 23 patients were designated 'nonspecific' by the local pathologist. These biopsy slides were independently reviewed by an expert in liver transplant pathology at a major US transplant center. The expert pathologist was given only the information on the original requisition. In seven biopsies from five patients, there was full agreement between the external expert and the local pathologist. In 10 biopsies from six patients, the expert concurred with the initial assessment but emphasized critical negatives such as 'no evidence of rejection or recurrent hepatitis'. A discrepant diagnosis was found in 13 biopsies from 12 patients. In five biopsies from four patients, the revised diagnoses were inaccurate due to insufficient or misleading clinical information on the requisition. In eight biopsies from eight patients, the revised diagnoses were proven to be correct by clinicopathologic correlation. Our study shows that pathology expertise helped to clarify the diagnosis in about 27% of cases, which justifies the cost of obtaining a second opinion in difficult biopsies. Misinterpretation by the expert pathologist in up to 17% of biopsies highlights the importance of direct communication between hepatologist and pathologist in order to achieve a correct diagnosis. Familiarity with those cases with relatively uncommon histology, a diligent search for subtle morphologic changes, and use of standard terminology could improve the quality of liver transplant biopsy interpretation in a nontransplant center.

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Pathological evaluation of liver allograft biopsies plays an integral role in the management of patients following liver transplantation. In certain conditions, such as liver allograft rejection, histology is regarded as the 'gold standard' because no other reliable diagnostic marker exists. 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. 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.

As liver transplantation is performed only in highly specialized tertiary care centers, a significant proportion of patients are evaluated and followed elsewhere. The clinician relies on the pathological interpretation of liver biopsy tissue to diagnose or rule out graft rejection, drug toxicity, recurrence of pretransplant diseases (eg viral hepatitis), or the development of new diseases (eg CMV hepatitis). An accurate pathological report using standard terminology and grading system is essential for patient management. However, a review of the literature, as well as data from our institution suggests that 20–30% of transplant liver biopsies are reported as 'nonspecific changes'.^{1–3} In this study, an expert liver pathologist at a major US liver transplant center independently reviewed 30 sets of liver transplant biopsies that were previously diagnosed as 'nonspecific' by pathologists at a nontransplant center. To the best of our knowledge, this is the first study that addresses the impact of pathologist experience on liver transplant biopsy interpretation. A detailed discussion of these cases with character-

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istic morphology and significant clinical implications could help to improve pathologic evaluation of liver transplant biopsies in a nontransplant center.

Materials and methods

Among 102 biopsies from 92 patients collected in a 3-year period (January 2001–March 2004), 30 biopsies from 23 patients were diagnosed as either ‘nonspecific inflammation’ or with only a microscopic description as the diagnosis. All 23 patients were seen at the Southern Alberta Liver Transplant Clinic in Calgary, Canada. This clinic follows approximately 150 patients primarily transplanted at the University of Alberta in Edmonton. Ultrasound-guided or blind needle liver biopsies (Tru-Cut 18G needles, C.R. Bard Inc, Covington, Georgia, USA) were used for sample collection. It was routine to stain eight slides in each case, including two Hematoxylin–Eosin-stained slides, and slides stained for Perls’ iron, Masson’s trichrome, Periodic Acid-Schiff either with or without diastase digestion, reticulin, and modified Shikata’s orcein. Acute allograft rejection was graded according to the International Banff Schema.¹ The primary hepatologist and local pathologist review together all liver transplant biopsy slides and exchange clinical information. Difficult biopsy slides are often sent to be reviewed by the liver transplant pathologist at the University of Alberta, where the patient received the liver transplant, however, none of these cases with ‘nonspecific’ pathologic diagnosis were reviewed by an external consultant pathologist.

All slides from these 23 patients were sent to an expert pathologist at the University of Chicago (JH) who did not perform any additional stains and obtained clinical information only from the original pathology requisition. The regular rate for consultation of \$300 per case was not charged. Following expert consultant review, demographic information and clinical data were obtained by chart review and discussion with the primary hepatologist (KWB). The cases were then classified into: (1) full agreement; (2) agreement with clarification of terminology; and (3) having a discrepant diagnosis. There was no direct impact on patient management due to the retrospective nature of the study. The potential clinical implications of revised diagnoses were assessed by the primary hepatologist based on clinicopathologic correlation.

Results

There were 23 patients (nine females and 14 males) from which 30 ‘nondiagnostic’ liver biopsies were re-reviewed. In seven biopsies from five patients, there was full agreement between the external expert and the local pathologist. In three biopsies from one patient, the original pathologic diagnoses of ‘mild nonspecific inflammation’ were revised to

‘liver tissue with normal histology’ accepting a minimum degree of inflammation as a variant of normal after transplantation. In two biopsies from one patient, the original pathology reports were ‘prominent fatty change with inflammation’ and the revised diagnoses were ‘steatohepatitis’, using a standard terminology to replace a descriptive diagnosis. In one patient transplanted for Hepatitis B with liver failure, the CT scan reported a hypoechoic mass in the liver. The biopsy diagnosis given by the local pathologist was descriptive ‘periportal fibrosis, mild focal sinusoidal dilatation and mild (grade I/IV) hemosiderosis’. The revised diagnosis was ‘no evidence of mass lesion in the biopsy tissue’, which clearly informed the hepatologist that either the lesion was not sampled or there was no lesion. There was in fact no lesion on follow-up CT scan. In one patient transplanted for hepatitis C, the biopsy diagnosis made by the local pathologist was ‘chronic passive congestion with sinusoidal dilatation’ and the revised diagnosis was ‘suggest outflow obstruction’ which was later confirmed by ultrasound. In two biopsies from a case transplanted for hepatitis B and one biopsy from a case transplanted for autoimmune hepatitis, the original diagnoses of ‘nonspecific inflammation’ were revised to ‘no evidence of rejection and no evidence of recurrent hepatitis B or autoimmune hepatitis’. The revised diagnosis emphasized the critical negatives, which reassured the hepatologist and the patient.

A discrepant diagnosis was found in 13 biopsies from 12 patients. In five biopsies from four patients (cases 9, 10, 11a, 11b, 12), the revised diagnoses were incorrect, primarily due to insufficient or misleading clinical information provided on the requisition. In eight biopsies from eight patients, the revised diagnoses were proven to be correct by clinicopathologic correlation. These cases include: early recurrent hepatitis C (case 1), fibrosing cholestatic hepatitis (case 2), evolving chronic rejection (cases 3 and 4), nodular regenerative hyperplasia (cases 5 and 6), *de novo* autoimmune hepatitis (case 7) and alcoholic cholestatic hepatitis (case 8). Results of the individual cases are presented in Table 1.

Discussion

In liver transplant patients biopsied for graft dysfunction, sufficient clinical information and detailed analysis of good quality representative biopsy material usually facilitates a specific diagnosis. However, up to 40% of protocol biopsies in patients with normal or nearly normal graft function will show a variable degree of chronic hepatitis.^{2–4} It is important to recognize that a nonspecific category may be appropriate in certain clinical situations as it prevents ‘pigeon-holing’ of biopsies and unnecessary committed therapy. If the changes are only reported as mild, this provides reassurance and may allow the clinician more time to observe and repeat

Table 1 Summary of cases with diagnostic disagreement after pathology re-review

Case no.	Age/sex	Time since transplant	Reason for transplant	Reason for biopsy	Initial pathology	Revised pathology	Clinicopathologic correlation
1	46/M	5 months	HCV, HCC	↑ LFTs	Minimal, nonspecific inflammation with focal perivenular hemosiderin deposition	Early recurrent HCV	Recurrent HCV, treated empirically by lowering immunosuppression
2	40/M	4 months	HCV	↑ LFTs	Bile stasis with patchy intralobular inflammatory foci, R/o low grade intermittent obstruction	FCH	FCH, died of acute liver failure while awaiting for second transplant
3	20/M	11 months	PSC	History of PTLD & ACR, ↑ LFTs	Chronic nonspecific inflammation	Evolving CR, recommend FK506 rescue therapy	Immunosuppression maintained at low levels due to PTLD. Episodes of ACR evolved into CR
4	30/M	11 years, 4 months	PSC, autoimmune hepatitis	↑ LFTs	Severe fibrosis, minimal mononuclear inflammatory infiltrate	Evolving CR	Radiology suggests recurrent PSC. Clinical assessment suggests possible ongoing CR. Awaiting re-transplant
5	77/M	15 years, 7 months	PSC	↑ LFTs	Focal nonspecific changes	NRH	NRH, no ACR. Died of metastatic colon cancer
6	57/F	3 years, 7 months	PCKD, liver and kidney transplant	↑ LFTs	Mild nonspecific changes, features of chronic rejection not identified	NRH	NRH. Liver enzymes normalized spontaneously, immunosuppression decreased due to PTLD
7	20/F	14 years	Unknown	No information given	Mild portal and lobular lymphocytic infiltrates, no convincing evidence of rejection	De novo AIH, suggest checking serology	Patient lost to follow-up, cannot prove or disprove the diagnosis
8	55/F	3 months	ETOH	↑ LFTs	Focal hepatocellular necrosis and hepatic vein dilation, mild steatosis	ACH	ACH, multiple admissions and for deranged liver enzymes, eventually found positive serum alcohol level
9	59/F	15 months	Cryptogenic cirrhosis	Rejection?	Minimal nonspecific inflammation, mild steatosis	Pathology cannot explain enzyme level, rule out focal lesion	Noncompliant with immunosuppressive therapy, liver enzymes improved after restarting therapy. No focal lesion
10	24/F	2 months	Hepatic adenomatosis	Rule out ACR	Mild ACR, including a component of mild hepatocellular destruction and pericentral sinusoidal dilatation	Treated ACR, recurrent HCV	Requisition stated HCV by mistake. No history of HCV infection, HCV RNA negative
11(a)	47/F	3 years, 7 months	HCV	No information given	Mild nonspecific inflammation with eosinophils, not diagnostic	Early recurrent HCV	Increased immunosuppression because cannot exclude ACR by initial interpretation. Fluctuating LFTs. Follow-up HCV RNA negative
11(b)	49/F	6 years, 2 months	HCV	No information given	Minimal nonspecific portal inflammation, sinusoidal dilation	Early recurrent HCV	Same as described in case 2
12	55/F	16 months	HBV cirrhosis	↑ LFTs	Minimal, nonspecific inflammation	Recurrent HBV	Follow-up HCV RNA negative No clinical evidence of recurrent HBV, HBV DNA and HBSAg negative

ACR, acute cellular rejection; ACH, alcoholic cholestatic hepatitis; AIH, autoimmune hepatitis; CMV, cytomegalovirus; CR, chronic rejection; FCH, fibrosing cholestatic hepatitis; HBV, hepatitis B; HBsAg, hepatitis B surface antigen; HCV, hepatitis C; LFTs, liver function tests; NRH, nodular regenerative hyperplasia; PSC, primary sclerosing cholangitis; PTLD, post-transplant lymphoproliferative disorder.

biopsy if necessary. In this study, there was full agreement between local and expert pathologist on the diagnosis of 'nonspecific inflammation' in seven biopsies from five patients. In 10/30 biopsies there was no diagnostic disagreement but the expert consultant recommended clarifying the terminology. This emphasizes the need for standard diagnostic terminology and quality improvement in pathology reporting.

In 5/30 (17%) cases, the revised diagnosis from the expert pathologist was found to be incorrect by clinicopathologic correlation. Although factors such as sampling error and tissue processing could theoretically affect the accuracy of pathologic interpretation,^{5,6} insufficient or misleading clinical information was the major cause of misinterpretation. For example, the consultant pathologist had given an erroneous diagnosis of recurrent viral hepatitis when unaware of the patient's negative viral serology. This data further highlights the importance of direct communication between hepatologist and pathologist in order to achieve a correct diagnosis.

In 8/30 (27%) cases, the revised diagnosis from the expert pathologist was proved to be correct by clinicopathologic correlation, which is likely due to the expert's increased experience in liver transplant pathology and ability to appreciate subtle pathological changes. Familiarity with the morphology and clinical implications of these discrepant diagnoses could help to improve pathologic evaluation of liver transplant biopsies in a nontransplant center.

Recurrent Hepatitis C

Hepatitis C recurrence is nearly universal after transplantation. Recurrent hepatitis C leads to chronic hepatitis and liver cirrhosis in a significant proportion of patients and lowers graft and patient survival.⁷ The difficulty for the local pathologist in diagnosing recurrent hepatitis C arises in two scenarios. The first scenario is early recurrent hepatitis C when there are only small numbers of lymphocytes in the portal tracts and lobules with occasional acidophil bodies (case 1, Figure 1a). The second scenario is a severe fibrosing cholestatic variant seen in 5% of recurrent hepatitis C.^{8,9} Pathologists unfamiliar with fibrosing cholestatic hepatitis could mistakenly interpret the relative paucity of portal infiltrates and the prominence of ductular reaction in association with lobular cholestasis as an abnormality of the bile ducts (case 2, Figure 1b). Accurate diagnosis of recurrent hepatitis C, especially the fibrosing cholestatic hepatitis variant, is important for appropriate reduction of immunosuppression and for predicting the prognosis.

Evolving Chronic Rejection

In a review of 870 consecutive primary liver transplant recipients who survived 15 days or more

following liver transplantation, the incidence of graft failure from chronic rejection was 2.4%.¹⁰ The diagnostic histologic features of chronic rejection are loss of bile ducts and obliterative arteriopathy affecting large- or medium-sized arteries.¹¹ The fact that these arteries are not usually biopsied, and that bile duct loss is not always apparent, makes it difficult for a pathologist at a non-liver transplant center to confidently diagnose chronic rejection. In a patient presenting with progressive jaundice, the following histological findings should make evolving chronic rejection a serious consideration: (1) 'dysplastic' or atrophic bile ducts featuring lymphocytic infiltration, nuclear pleomorphism, disordered polarity and focal attenuation/disruption of biliary epithelium (case 3, Figure 1c), (2) pericentral ballooning degeneration of hepatocytes, hepatocyte drop out and intimal or sinusoidal inflammation (case 4, Figure 1d), (3) cholestasis in the absence of ductular proliferation.¹¹ An early diagnosis of chronic rejection is imperative so that salvage therapy can be initiated. It is easier to diagnosis advanced classical chronic rejection but the clinical value of this is limited.

Nodular Regenerative Hyperplasia

Nodular regenerative hyperplasia is usually associated with autoimmune disease, medications and a variety of disorders. It is a common finding in late post-transplant biopsies.^{12–14} Some cases appear to be related to drug toxicity (particularly Azathioprine) or a vascular abnormality (eg portal venous insufficiency). However, in many cases no obvious cause can be found. Microscopically, nodular regenerative hyperplasia is characterized by diffuse nodularity of the liver with nodules formed by thickened liver cell plates (2–3 cells thick) with intervening atrophic parenchyma. There is no evidence of fibrosis or inflammation. The expansile architecture is best appreciated in reticulin preparations (case 5, Figure 1e). Although the clinical impact of identifying nodular regenerative hyperplasia in liver allografts may be limited, it may represent the cause of otherwise unexplained liver enzyme elevation. Awareness and identification of this entity could prevent unnecessary further investigations.

De Novo Autoimmune Hepatitis

De novo autoimmune hepatitis has been reported in patients transplanted for other reasons in both pediatric and adult populations.^{15–17} All reported cases have had high serum concentrations of immunoglobulin G and high titers of autoantibodies. Liver biopsies from these patients show portal and periportal hepatitis with lymphocytes and plasma cells, bridging collapse, and perivenular cell necrosis without changes typical of acute or chronic rejection (case 7, Figure 1f). The diagnosis requires

the incorporation of serology and morphological findings and the disease usually responds to increased immunosuppression. In our case, lack of knowledge about the patient's original liver disease, serum IgG levels, and clinical follow-up makes it impossible to exclude the differential diagnosis of viral hepatitis, adverse drug reaction or recurrence of possible original autoimmune hepatitis.

Alcoholic Cholestatic Hepatitis

It has been estimated that about 10–30% of alcoholic patients return to drinking following transplantation.^{18,19} The diagnosis is difficult when uncommon histology such as cholestasis is present, or only microvesicular steatosis is evident (case 8, Figure 1g). The characteristic changes of macrovesicular steatosis, steatohepatitis and pericentral sinusoidal fibrosis usually manifest in subsequent biopsies when the disease is more advanced (case 8, Figure 1h). Awareness of uncommon presentations and a diligent search for subtle morphological signs of alcohol-related liver damage could prevent repeated admissions/liver biopsies and allow early treatment.

Previous studies have stressed the importance of secondary re-review of medical and surgical biopsies.²⁰ In one study of 178 consecutive non-transplant liver biopsy slides provided to hepatopathology consultants, the authors identified a major discrepant diagnosis in 28% of specimens.²¹ In the year 2000, a consensus conference of expert pathologists stated that medical biopsies such as liver are so frequently misinterpreted or interpreted in a clinically nonmeaningful manner that expert reevaluations are essential.²² This is especially important in the interpretation of liver allograft biopsies. As this was a retrospective study, we were unable to determine if the revised diagnosis affected patient outcome. We are unable to comment on the potential problem of timeliness of an external review and how feasible it would be to wait for a second opinion. However, the issue of waiting could be resolved by on-line consultation with the increasing use of telepathology.²³

In summary, we have found that pathology expertise could help to clarify the diagnosis of about 27% cases that were designated 'nonspecific' by the local pathologist. Therefore, a significant proportion

of post-transplant liver biopsies which are regarded as 'nonspecific' by a general pathologist may benefit from review by an expert liver pathologist, especially when patient have clinical evidence of significant graft dysfunction. We also found that up to 17% cases were incorrectly interpreted by the expert pathologist due to insufficient or misleading clinical information on the requisition, which further highlights the importance of direct communication between hepatologist and pathologist in order to achieve a correct diagnosis. Although this was only a single institution study with a small number of cases, it has identified several case scenarios with characteristic morphology and important clinical implications. Familiarity with these relatively uncommon histological findings, a diligent search for subtle morphologic changes and the use of standard terminology could improve the quality of liver transplant biopsy interpretation in a nontransplant center.

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Figure 1 (a) Early recurrent hepatitis C. A portal tract with mild lymphocytic infiltration and an acidophil body in the adjacent parenchyma (hematoxylin–eosin, magnification $\times 400$). (b) Fibrosing cholestatic variant of recurrent hepatitis C. There is less dense portal mononuclear infiltrate than is often seen in chronic viral hepatitis. The portal area shows markedly fibrosis with fibrous strands radiate into the lobular parenchyma. Ductular proliferation in association with lobular cholestasis is evident (hematoxylin–eosin, magnification $\times 400$). (c) Evolving chronic rejection. An interlobular bile duct shows nuclear pleomorphism, hyperchromasia and distorted polarity, producing a dysplastic appearance (hematoxylin–eosin, magnification $\times 400$). (d) Evolving chronic rejection. Pericentral ballooning degeneration of hepatocytes, hepatocyte drop out and sinusoidal inflammation (hematoxylin–eosin, magnification $\times 100$). (e) Nodular regenerative hyperplasia. Expansile nodule composed of thick liver cell plates intervened by compressed atrophic liver cell plates (reticulin, magnification $\times 100$). (f) *De novo* autoimmune hepatitis. Infiltration of lymphocytes and plasmacytes in the portal tract, interface and lobular parenchyma (hematoxylin–eosin, $\times$ magnification 400). (g) Alcoholic cholestatic hepatitis. Feathery degeneration of hepatocytes and ductular proliferation in earlier biopsies. Some hepatocytes showed microvesicular steatosis. Bile plug is present in a canalicular space. (hematoxylin–eosin, magnification $\times 400$). (h) Alcoholic cholestatic hepatitis. Macrovesicular steatosis and sinusoidal fibrosis in subsequent biopsies (Masson's trichrome, magnification $\times 400$).

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