

Editorial

Beyond Degree of Fibrosis- Assessment of Liver Biopsy when there is Clinical Concern for Portal Hypertension

Maryam Zenali^{1*} and Steven D Lidofsky²

¹Assistant Professor of Pathology, University of Vermont/ Fletcher Allen Hospital, USA

²Professor of Gastroenterology and Hepatology, University of Vermont/ Fletcher Allen Hospital, USA

EDITORIAL

Liver biopsy is considered the “gold standard” for assessment of liver histology. A common indication for liver biopsy is monitoring progression of fibrosis in chronic liver disorders such as viral hepatitis and nonalcoholic steatohepatitis. Liver biopsies are also used to evaluate for the presence of chronic liver disease and the extent of hepatic fibrosis when there is clinical concern for portal hypertension (e.g., gastroesophageal varices, ascites with an elevated albumin gradient) in the absence of obvious cirrhosis. To date, despite advances in imaging and identifying plethora of serological fibrosis markers, liver biopsy is a mainstay in clinical practice and the results of histological analysis has the potential to alter the management or follow up of the patients.

From a histological standpoint, several semiquantitative scoring systems, such as Ishak, Scheuer, or METAVIR, are routinely used to report the stage of hepatic fibrosis [1]. Each of these scoring systems is based solely on the extent of collagen deposition, as highlighted by Trichrome stain. Although the cut-off value for definite cirrhosis may vary between different scoring systems, the presence of septal fibrosis, regenerative nodules and/ or probable/ definitive cirrhosis will warrant strong consideration for drug therapy (in the setting of chronic viral hepatitis) [2,3] and surveillance for treatable complications of advanced liver disease (irrespective of the etiology), such as gastroesophageal varices and hepatocellular carcinoma [4,5].

Tissue adequacy and the effect of disease heterogeneity are important to consider when interpreting the biopsy results. Studies indicate a trend toward lesser degree of reported fibrosis with the shorter biopsy cores [4,6]. To ensure adequacy, several guidelines recommend greater than 6 portal tracts or greater than 15 mm length for the tissue core. A new more stringent guideline from American Association for the Study of Liver Disease suggests presence of 11 portal tracts and size of core greater than 25 mm 1 to be adequate [7]. Awareness of tissue adequacy is a critical initial step in evaluation of liver biopsy. Additionally, sampling

*Corresponding author

Maryam Zenali, Department of Pathology, University of Vermont, USA, Tel: 802-847-4290; Fax: 802-847-9644; E-mail: Maryam.Zenali@vtmednet.org

Submitted: 30 October 2013

Accepted: 23 November 2013

Published: 25 November 2013

Copyright

© 2013 Zenali et al.

OPEN ACCESS

heterogeneity – when focusing only on fibrous deposition without the effect of accompanied architectural change – has a potential to lead to clinic-pathologic misinterpretation of true extent of liver scar.

Physiologically, hepatic fibrosis is a dynamic phenomenon, which is thought to be a healing attempt in response to hepatic injury, and involves both deposition and resorption of extracellular matrix components. The interplay between these processes is governed by spatially localized activation of myofibroblastoid cells, which in turn can lead to distinct patterns of hepatic fibrosis [8,9]. Because the spatiotemporal heterogeneity of liver injury and repair may limit estimation of true fibrosis, the presence of subtle architectural and vascular alterations may provide clues to the presence of the advanced fibrosis elsewhere in the non-sampled tissue and could suggest the presence of long-standing portal hypertension.

A continuum of fibrosis extent and other parenchymal alterations has been identified in explanted cirrhotic livers. The term “hepatic repair complex”, which was coined over 10 years ago, has been used to describe vascular and architectural changes associated with fibrosis regression, which are observed in proximity to intervening areas with advanced fibrosis [10]. Familiarity with these features may provide a clue to the presence of advanced hepatic fibrosis that is not evident in the biopsy specimen and may have been missed by sampling variability. For this reason, it is our opinion that features of the hepatic repair complex, if present, should be noted in pathology reports. In particular, when significant collagen deposition is not evident on the Trichrome stain or in cases in which the clinical or radiographic data do not clearly indicate the presence of cirrhosis, histological identification of this complex can influence decisions about the need to monitor for gastroesophageal varices and hepatocellular carcinoma.

The “hepatic repair complex” is defined by the presence of several histological features, such as delicate perforated septa, thin periportal fibrous spikes, portal tract or hepatic

vein remnants, hepatocytes within portal tracts, splitting septa, aberrant parenchymal veins, minute regenerative nodules, prolapsed hepatocytes in veins, and alteration in sinusoidal caliber. Nearly identical features have been described in between fibrous bands in fully cirrhotic livers, which have been described by different investigators as a fibrosis regression phenomenon [11].

Studies from the U.S. and abroad, particularly southern Asia, report features comparable to “hepatic repair complex” in non-cirrhotic portal hypertension, also known as idiopathic portal hypertension, hepatoportal sclerosis, Banti syndrome, tropical splenomegaly, intrahepatic non-cirrhotic portal hypertension and others. General observations, in diseased pediatric and adult population both, include irregular contour of liver with vague, primarily subcapsular small nodules and microscopically, obliterative venopathy with fibrous intimal thickening, sinusoidal dilation- angiomatoid lesions of portal vein radicles, aberrant periportal vasculature, nodular regenerative hyperplasia and variable degree of fibrosis with incomplete septa. Clinically significant and sustained portal hypertension has been noted in all these patients [12-18].

The pathophysiology of disease progression in non-cirrhotic portal hypertension is not fully understood, yet the foundation is vascular (i.e., elevated pressure in the portal vein). Although some studies suggest a better long-term outcome for patients with non-cirrhotic portal hypertension than cirrhotic patients, patients with non-cirrhotic portal hypertension, like their cirrhotic counterparts, are at increased risk for developing variceal bleeding, ascities, coagulopathy, hepatic encephalopathy, spontaneous bacterial peritonitis, hepatopulmonary and hepatorenal syndrome [12-14].

In summary, as the spectrum of histological alterations in cirrhosis show features that overlap with those found in non-cirrhotic portal hypertension, familiarity with less-widely appreciated elements of the hepatic repair complex - even in absence of advanced fibrosis- is critical when evaluating biopsies to better reflect the nature of the disease and guide appropriate clinical management.

REFERENCES

- Sebastiani G, Alberti A. How far is noninvasive assessment of liver fibrosis from replacing liver biopsy in hepatitis C? *J Viral Hepat.* 2012; 19 Suppl 1: 18-32.
- European Association For The Study Of The Liver. EASL Clinical Practice Guidelines: management of chronic hepatitis B. *J Hepatol.* 2009; 50: 227-242.
- Niederau C, Hüppe D, Zehnter E, Möller B, Heyne R, Christensen S, et al. Chronic hepatitis C: treat or wait? Medical decision making in clinical practice. *World J Gastroenterol.* 2012; 18: 1339-1347.
- Everhart JE, Wright EC, Goodman ZD, Dienstag JL, Hoefs JC, Kleiner DE, et al. Prognostic value of Ishak fibrosis stage: findings from the hepatitis C antiviral long-term treatment against cirrhosis trial. *Hepatology.* 2010; 51: 585-594.
- Mendes FD, Suzuki A, Sanderson SO, Lindor KD, Angulo P. Prevalence and indicators of portal hypertension in patients with nonalcoholic fatty liver disease. *Clin Gastroenterol Hepatol.* 2012; 10: 1028-1033.
- Vuppalanchi R, Unalp A, Van Natta ML, Cummings OW, Sandrasegaran KE, Hameed T, et al Effects of liver biopsy sample length and number of readings on sampling variability in nonalcoholic Fatty liver disease. *Clin Gastroenterol Hepatol.* 2009; 7: 481-486.
- Rockey DC, Caldwell SH, Goodman ZD, Nelson RC, Smith AD; American Association for the Study of Liver Diseases. Liver biopsy. *Hepatology.* 2009; 49: 1017-1044.
- Hernandez-Gea V, Friedman SL. Pathogenesis of liver fibrosis. *Annu Rev Pathol.* 2011; 6: 425-456.
- Iwaisako K, Brenner DA, Kisseleva T. What's new in liver fibrosis? The origin of myofibroblasts in liver fibrosis. *J Gastroenterol Hepatol.* 2012; 27 Suppl 2: 65-68.
- Wanless IR, Nakashima E, Sherman M. Regression of human cirrhosis. Morphologic features and the genesis of incomplete septal cirrhosis. *Arch Pathol Lab Med.* 2000; 124: 1599-1607.
- Pattullo V, Thein HH, Heathcote EJ, Guindi M. Combining semiquantitative measures of fibrosis and qualitative features of parenchymal remodelling to identify fibrosis regression in hepatitis C: a multiple biopsy study. *Histopathology.* 2012; 61: 473-487.
- Nayak NC, Jain D, Saigal S, Soin AS. Non-cirrhotic portal fibrosis: one disease with many names? An analysis from morphological study of native explant livers with end stage chronic liver disease. *J Clin Pathol.* 2011; 64: 592-598.
- Saigal S, Nayak NC, Jain D, Kumaran V, Mohanka R, Saraf N, et al. Non-cirrhotic portal fibrosis related end stage liver disease in adults: evaluation from a study on living donor liver transplant recipients. *Hepatol Int.* 2011; .
- Siramolpiwat S, Seijo S, Miquel R, Berzigotti A, Garcia-Criado A, Darnell A, et al. Idiopathic portal hypertension: Natural history and long-term outcome. *Hepatology.* 2013; .
- Dhiman RK, Chawla Y, Vasishta RK, Kakkar N, Dilawari JB, Trehan MS, et al. Non-cirrhotic portal fibrosis (idiopathic portal hypertension): experience with 151 patients and a review of the literature. *J Gastroenterol Hepatol.* 2002; 17: 6-16.
- Sato Y, Nakanuma Y. Role of endothelial-mesenchymal transition in idiopathic portal hypertension. *Histol Histopathol.* 2013; 28: 145-154.
- Sinha A, Samanta T, Mallik S, Pal D, Ganguly S. Non-cirrhotic portal fibrosis among children admitted in a tertiary care hospital of Kolkata: a search for possible aetiologies. *J Indian Med Assoc.* 2011; 109: 889-891.
- Verheij J, Schouten JN, Komuta M, Nevens F, Hansen BE, Janssen HL, et al. Histological features in western patients with idiopathic non-cirrhotic portal hypertension. *Histopathology.* 2013; 62: 1083-1091.

Cite this article

Zenali M, Lidofsky SD (2013) Beyond Degree of Fibrosis- Assessment of Liver Biopsy when there is Clinical Concern for Portal Hypertension. *Ann Clin Pathol* 1(1): 1004.