Hepatitis C and bile duct loss

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Abstract

Aim—To assess whether bile duct loss is associated with the bile duct damage induced by chronic hepatitis C.

Methods—Sections were examined from 171 liver biopsy specimens from patients with chronic hepatitis C, 98 biopsy specimens from patients with chronic hepatitis B, 25 postmortem specimens from patients with no evidence of liver disease, and 23 patients who underwent protocol liver biopsy at the time of cholecystectomy.

Results—The bile duct:portal tract ratio for the hepatitis C group was 0.89, for the hepatitis B group was 0.93 and for the two control groups was 0.96 and 0.90, respectively. The ratio was lower in the hepatitis C group than in the other three. In no case of chronic hepatitis C was the ratio less than 0.60. In the hepatitis C group greater bile duct loss was seen in cirrhotic patients.

Conclusions—Hepatitis C is associated with bile duct loss and this was related to the stage of the disease. However, in the cases studied this did not reach what is generally considered to be significant (that is, greater than 50% of portal tracts lacking bile ducts). This does not preclude a contributory effect of hepatitis C to bile duct loss in the presence of other risk factors, especially in liver transplant recipients.

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Ludwig *et al*¹ coined the term idiopathic adulthood ductopaenia to describe a condition characterised by morphological demonstration of decreased numbers of bile ducts in liver biopsy specimens (present in less than 50% of portal tracts), unknown aetiology and adult age of onset. They considered that age alone distinguished these cases from infantile paucity of intrahepatic bile ducts.² It was emphasised that this was a diagnosis of exclusion and that other diseases which could produce a morphologically identical picture include: primary biliary cirrhosis, sarcoidosis, sclerosing cholangitis, drug induced liver disease, graft versus host disease, and hepatic allograft rejection. A number of similar cases have been published subsequently.^{3,4}

As cytomegalovirus infection has been associated with a paucity of intrahepatic bile ducts⁵ and because non-A, non-B hepatitis⁶ and more recently hepatitis C^{7,8} have been associated with bile duct damage, viruses have been suggested

as potential causes of this condition. Indeed, one recent study of the pathology of hepatitis C reported a very high frequency of bile duct damage and even bile duct loss.⁹ However, the bile duct loss was not documented fully. The objective of this study was to investigate the changes in bile duct numbers seen in a large series of patients with hepatitis C to ascertain whether there was an association between this condition and bile duct loss.

Methods

One hundred and eighty three liver biopsy specimens from patients with serologically confirmed chronic hepatitis C were examined. Twelve biopsy specimens contained less than three portal tracts and were excluded from the study because they were considered too small for assessment. Haematoxylin and eosin, diastase periodic acid Schiff, haematoxylin van Gieson, and orcein stained sections from the remaining 171 biopsy specimens were examined. We also examined 98 biopsy specimens from hepatitis B positive patients. Postmortem liver sections were obtained from 25 patients with no clinical history or histological evidence of liver disease. These were used as the first control group. The second control group was made up of 23 patients who underwent protocol liver biopsy at the time of cholecystectomy. All 23 patients had normal liver function tests at the time of surgery and the biopsy specimens were assessed as having normal histology.

The percentage of portal tracts containing bile ducts was defined using the criteria of Nakanuma and Ohta.¹⁰ Portal tracts were identified by the presence of an artery (with a lumen >35 μ m) and bile ducts as biliary structures with lumina of >25 μ m. The latter included both interlobular and septal bile ducts but excluded marginal ductules. This method of identifying portal areas allowed cirrhotic livers to be included in this study.

Statistical analysis was carried out using the χ^2 test on the C-Stat package (Cherwell Scientific Publishing).

Results

HEPATITIS C

Of the 1373 portal tracts examined, interlobular or septal bile ducts were found in 1223—that is, the bile duct:portal tract ratio was 0.89. The range was 0.60 (6/10) to 1.38 (11/8). In no case was there histological evidence of chronic cholestasis, with swelling of periportal hepatocytes containing Mallory's hyaline or copper associated protein. In portal tracts which lacked bile ducts there was no suggestion that there had been fibrous obliteration of bile ducts.

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Table 1 Bile duct:portal tract ratios in liver biopsy specimens from patients with chronic hepatitis B and C with and without cirrhosis. Results are expressed as range (number of cases)

	Hepatitis B		Hepatitis C	
	No cirrhosis	Cirrhosis	No cirrhosis	Cirrhosis
Bile duct:portal tract ratio	0.89–1.10 (69)	0.85–1.11 (29)	0.69–1.38 (112)	0.60–1.22 (59)

HEPATITIS B
Of the 1368 portal tracts examined, 1273 contained bile ducts giving a bile duct:portal tract ratio of 0.93. The range was 0.85–1.11.

CONTROLS
In the postmortem control group 207 portal tracts were examined and contained 199 bile ducts, giving a ratio of 0.96. The range was 0.80–1.13. In the cholecystectomy control group 173 portal tracts were examined and contained 155 bile ducts, giving a ratio of 0.90; range 0.89–1.11.

There was no significant difference between the number of bile ducts per portal tract in either of the control groups and patients with hepatitis B ($0.5 > p > 0.25$). The difference between the number of bile ducts per portal tract in patients with hepatitis C and each of the control groups and the hepatitis B group was statistically significant ($p < 0.001$ in each case).

Table 1 summarises the relation between bile duct loss and stage. In the case of hepatitis B there was no statistically significant difference between those patients with cirrhosis and those without. With hepatitis C there was a difference between the non-cirrhotic and cirrhotic groups, with bile duct numbers being significantly lower in the latter ($0.01 < p < 0.05$). There was a correspondingly significant difference in bile duct numbers between the cases of cirrhosis resulting from hepatitis B and hepatitis C infection ($0.001 < p < 0.01$).

Discussion

We have demonstrated a small but statistically significant decrease in the number of bile ducts in patients with chronic hepatitis C compared with controls and patients with chronic hepatitis B. Although our control group was based on postmortem material it is unlikely that this would have biased our analysis significantly and in any case there was a significant difference between the hepatitis B and C groups. It should be noted that there was no evidence of chronic cholestasis or fibrous obliteration of bile ducts in any of the cases examined. Although the difference between the control and hepatitis B groups is not significant the slight decrease in the number of bile ducts per portal tract is interesting in view of the observation of Lefkowitz *et al.*⁷ These authors found bile duct damage in 9.8% of cases of chronic hepatitis B although this was significantly less than in cases of hepatitis C (31.2%). The bile duct loss in the cases of hepatitis C was significantly greater in the cirrhotic as

opposed to the non-cirrhotic livers. No such difference was seen with hepatitis B. This suggests that bile duct loss in hepatitis C is an ongoing process and increases with chronicity.

The accepted definition of significant ductopaenia is that less than 50% of the portal tracts contain bile ducts.¹¹ This definition was originally applied to liver transplant pathology but has now been used in identifying cases of idiopathic adult ductopaenia.¹ It has been expanded to include cases with slightly greater than 50% bile ducts but with widespread severe active bile duct damage.³ The lowest percentage seen in our study was 69%, which is well above this value. It is generally accepted that it is necessary to have an aggregate of 20 portal tracts to assess the number of bile ducts adequately in an individual patient.¹¹ Although we did not have enough biopsy specimens from individual patients to apply this criterion, the large number of specimens examined and the fact that the lowest percentage was 60% means that significant ductopaenia must be very rare in chronic hepatitis C.

In our experience, although lymphocytic infiltration of bile ducts associated with minor epithelial degeneration is relatively common in chronic hepatitis C, a destructive cholangiopathy is extremely rare. Although Bach *et al* found both bile duct damage and bile duct loss in 91% of cases, they did not provide sufficient data to document these claims adequately.⁹ Other studies have found this to be much less common. Scheuer *et al*⁸ found significant damage in only 6% and less severe damage in 17% of cases. However, one careful study demonstrated bile duct damage in one third of cases.¹² In this study bile duct damage was defined as variable epithelial damage such as cytoplasmic swelling, vacuolation and acidophilia, nuclear pleomorphism and loss of nuclear polarity. It was noted that some, but not all, of the damaged bile ducts were embedded in lymphoid aggregates. This study concluded, however, that bile duct loss was rare in chronic hepatitis C.

All of the histopathological studies of hepatitis C carried out previously have provided qualitative information about bile duct pathology but not the quantitative data which are necessary to address the relation between hepatitis C and idiopathic adult ductopaenia. The results of the present study suggest that hepatitis C is associated with minor but statistically significant bile duct loss and that it is a potential cause of this condition, although this must be very rare. It may, however, be significant in the patients with end stage hepatitis C who undergo liver transplantation. A univariate analysis found that these patients with recurrent hepatitis C were at increased risk of chronic rejection (ductopaenic rejection) compared with patients who received transplants for other liver diseases, including hepatitis B.¹³ In a case report an acute vanishing bile duct syndrome has been related to interferon- α therapy for recurrent hepatitis C in a liver transplant recipient.¹⁴ It has even been suggested that granulomatous destruction of bile ducts after liver transplantation

may, in certain cases, be caused by hepatitis C rather than recurrent primary biliary cirrhosis.¹⁵

- 1 Ludwig J, Wiesner RH, LaRusso NF. Idiopathic adulthood ductopenia. A cause of chronic cholestatic liver disease and biliary cirrhosis. *J Hepatol* 1988;7:193-9.
- 2 Bruguera M, Llach J, Rodes J. Nonsyndromic paucity of intrahepatic bile ducts in infancy and idiopathic ductopenia in adulthood: the same syndrome? *Hepatology* 1992;15:830-4.
- 3 Faa G, Van Eyken P, Demelia L, Vallebona E, Costa V, Desmet VJ. Idiopathic adulthood ductopenia presenting with chronic recurrent cholestasis. *J Hepatol* 1991;12:14-20.
- 4 Zafrani ES, Metreau JM, Douvin C, Larrey D, Massari R, Reynes M, et al. Idiopathic biliary ductopenia in adults: a report of five cases. *Gastroenterology* 1990;99:1823-8.
- 5 Finegold MJ, Carpenter RJ. Obliterative cholangitis due to cytomegalovirus: a possible precursor of paucity of intrahepatic bile ducts. *Hum Pathol* 1982;13:662-5.
- 6 Poulsen H, Christoffersen P. Abnormal bile duct epithelium in liver biopsies with histological signs of viral hepatitis. *Acta Pathol Microbiol Scand Sect* 1969;76:383-90.
- 7 Leffkowitz JH, Schiff ER, Davis GL, Perrillo RP, Lindsay K, Bodenheimer HC Jr, et al. Pathological diagnosis of chronic hepatitis C: a multicenter comparative study with chronic hepatitis B. The Hepatitis Interventional Therapy Group. *Gastroenterology* 1993;104:595-603.
- 8 Scheuer PJ, Ashrafzadeh P, Sherlock S, Brown D, Dusheiko GM. The pathology of hepatitis C. *Hepatology* 1992;15:567-71.
- 9 Bach N, Thung SN, Schaffner F. The histological features of chronic hepatitis C and autoimmune chronic hepatitis: a comparative analysis. *Hepatology* 1992;15:572-7.
- 10 Nakanuma Y, Ohta G. Histometric and serial section observations on the intrahepatic bile ducts in primary biliary cirrhosis. *Gastroenterology* 1979;76:1326-32.
- 11 Ludwig J, Wiesner RH, Batts KP, Perkins JD, Krom RA. The acute vanishing bile duct syndrome (acute irreversible rejection) after orthotopic liver transplantation. *Hepatology* 1987;7:476-83.
- 12 Kaji K, Nakanuma Y, Sasaki M, Unoura M, Kobayashi K, Nonomura A, et al. Hepatic bile duct injuries in chronic hepatitis C: histopathologic and immunohistochemical studies. *Mod Pathol* 1994;7:937-45.
- 13 Hoffmann RM, Gunther C, Diepolder HM, Zachoval R, Eissner HJ, Forst H, et al. Hepatitis C virus infection as a possible risk factor for ductopenic rejection (vanishing bile duct syndrome) after liver transplantation. *Transplant Int* 1995;8:353-9.
- 14 Dousset B, Conti F, Houssin D, Calmus Y. Acute vanishing bile duct syndrome after interferon therapy for recurrent HCV infection in liver-transplant recipients. *N Engl J Med* 1994;330:1160-1.
- 15 Farges O, Bismuth H, Sebach M, Reynes M. Granulomatous destruction of bile ducts after liver transplantation: primary biliary cirrhosis recurrence or hepatitis C virus infection? *Hepatology* 1995;21:1765-7.