Hepatic vein lesions in alcoholic liver disease: retrospective biopsy and necropsy study

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SUMMARY Obliteration of the terminal hepatic venules with perivenular fibrosis (phlebosclerosis) is a well recognised feature in alcoholic liver disease. Veno-occlusive lesions with intimal obliteration of hepatic veins and a lymphocytic phlebitis of hepatic veins may also be present. We looked for these lesions in 256 liver biopsies and 50 livers obtained at necropsy from patients with alcoholic liver disease. Phlebosclerosis was a universal finding in alcoholic hepatitis and cirrhosis and showed increasing severity with progressive liver injury. Veno-occlusive lesions, however, were found in only 25 of 256 (9.8%) of biopsies and 11 of 50 (22%) of livers obtained at necropsy, showing alcoholic hepatitis or cirrhosis: lymphocytic phlebitis was found in 10 of 256 (3.9%) and two of 50 (4%), respectively. Moreover, veno-occlusive lesions were generally mild. The prevalence of veno-occlusive lesions and lymphocytic phlebitis was considerably less than has been previously documented. Phlebosclerosis may have a different mechanism and be a more important contributory factor in progressive liver injury.

The histological features of alcoholic liver disease have been reviewed in several recent publications. The presence of hepatic vein lesions, however, has been little emphasised. Edmondson et al emphasised the importance of the obliteration of hepatic vein branches by a process of perivenular fibrosis. In their review of alcoholic liver disease Baptista et al noted that the venous radicles eventually become obliterated in alcoholic hepatitis and may, consequently, be difficult to identify. Venous occlusion by a process of intimal proliferation was noted by Patrick and McGee, but Popper et al considered this lesion to be rare and seldom of substantial functional importance. Goodman and Ishak, however, in a retrospective necropsy study showed these veno-occlusive lesions in 25 of 48 (52.1%) cases of alcoholic hepatitis and in 103 of 139 (74%) cases with established alcoholic cirrhosis. In addition, they reported on the universal prevalence of perivenular phlebosclerotic lesions in both hepatitis and cirrhosis and described a lymphocytic phlebitis in eight (16.7%) cases with alcoholic hepatitis.

In this retrospective study we reviewed a series of 256 liver biopsies and 50 livers obtained at necropsy from patients with alcoholic liver disease: we specifically looked for hepatic vein lesions as defined by Goodman and Ishak.

Material and methods

The material comprised 256 liver biopsies submitted to the department of pathology at this hospital over five years (from 1977 to 1982). This was a consecutive series selected on the basis of: histological diagnosis; a documented clinical history of alcohol abuse; and clinical exclusion of any other known cause of liver injury. There was a male to female ratio of 1.56:1 with a mean age at the time of biopsy of 51·1 years (range 20–76) and 51·8 (range 31–76), respectively.

Liver tissue obtained after death was examined from a similarly selected group of 50 cases, comprising 37 men and 13 women (mean age 56·3 and 58·3 years, respectively). Thirty eight (78%) of the patients had died from complications related to their liver disease; the proximate causes of death in eight of the remaining patients were: acute pancreatitis (3), pneumonia (3), fungal septicaemia (1), and Gram negative peritonitis (1). In the final four death was attributed to congestive cardiac failure (rheumatic heart disease (2), congestive cardiomyopathy (1), and cor pulmonale (1)): in all four cases there was established cirrhosis, but cardiac failure was not thought to have been a major contributor to the liver disease.

Sections (5 μm) from all specimens were routinely stained with haematoxylin and eosin, Masson's trichrome, Gordon and Sweet's reticulin, Shikata's

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Fig. 1a  Moderate (grade 2+) veno-occlusive lesion with accompanying phlebitis and perivenular fibrosis in alcoholic hepatitis. (Masson's trichrome.) × 300. (b) Serial section stained with Shikata's orcein showing presence of intimal proliferation within elastic lamina. × 300.

orcein, periodic acid Schiff (before and after diastase treatment), and Perls's reaction. In selected cases additional sections were stained with elastic van Gieson.

Vascular lesions were assessed according to the criteria of Goodman and Ishak:

Veno-occlusive lesions  These were characterised by intimal proliferation and fibrosis occurring within the elastic lamina of the vein radicles, ranging from mild (1+), intimal thickening with one third occlusion, through to moderate (2+), with two thirds occlusion, to severe (3+), when there was more than two thirds occlusion to complete obliteration (Figs. 1 and 2). Individual cases were scored on the basis of the most severe lesion present.

Phlebosclerosis  This consisted of compression of

Fig. 2  Severe (grade 3+) veno-occlusive lesion in cirrhotic liver affecting interlobular vein and tributary. Necropsy series. (Elastic van Gieson.) × 140.

Fig. 3  Mild (grade 1+) phlebosclerosis in alcoholic hepatitis. (Elastic van Gieson.) × 180.
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Fig. 4a Obliterative lesion in hepatic vein branch in cirrhotic liver at necropsy (Hamatoxylin and eosin.) × 375. (b) Elastic tissue admixed with collagen in obliterative lesion. (Elastic van Gieson.) × 375.

hepatic vein radicles by perivenular fibrosis and was graded as: mild (1+), perivenular fibrosis with minimal compression of the vein lumen (Fig. 3); moderate (2+), more marked fibrosis and compression of the vein lumen; severe (3+), complete obliteration of the vein radicle with extensive perivenular fibrosis (Fig. 4). Individual cases were also scored on the basis of the most severe lesion present.

Lymphocytic phlebitis was defined as the presence of an inflammatory infiltrate, predominantly lymphocytic, within the walls of hepatic vein branches (Figs 1a and 5). Spillover of neutrophil polymorphs from foci of hepatocyte necrosis in the perivenular zone was excluded.

Results

The biopsy cases were classified as follows: fatty liver (71), fatty liver with pericellular or perivenular fibrosis, or both (20), alcoholic hepatitis (82), and cirrhosis (83). Of the 83 cases of cirrhosis, 76 showed evidence of continuing active alcoholic hepatitis. Cirrhosis was present in 44 livers obtained at necropsy and alcoholic hepatitis in six.

The Table summarises the incidence of hepatic vein lesions in the various subgroups. Veno-occlusive lesions were found in only one case of fatty liver, although they were present in 13 (15.8%) of the 82 biopsy specimens with alcoholic hepatitis and in 12 (14.4%) of those with cirrhosis; they were generally mild (1+). Phlebosclerotic lesions were much more common; lesions were found in 20 (22%) of the 91 cases with fatty liver and in all but one instance they were of mild degree and concomitant with mild pericellular fibrosis. When we compared the subgroups with alcoholic hepatitis with those with cirrhosis, the severity of the phlebosclerotic lesion was greater in the group with cirrhosis; 65 of 83 (78%) were severe (3+) compared with four of 82 (5%) in the group with alcoholic hepatitis. A lymphocytic phlebitis occurred in eight (9.7%) of the 82 cases of alcoholic hepatitis and in two (2.4%) of the cases of

Fig. 5 Mild lymphocytic phlebitis affecting interlobular vein in established cirrhosis. (Haematoxylin and eosin.) × 280.
cirrhosis.

In the necropsy group veno-occlusive lesions were seen in three of six (50%) of those with alcoholic hepatitis but were present in only eight of 44 (18%) of the cirrhotic livers. Phlebosclerosis was universally present and severe lymphocytic phlebitis was rare.

**Discussion**

Edmondson noted that obliterator sclerosis of hepatic veins and perivenular sinusoids was a feature of alcoholic hepatitis and termed this "sclerosing hyaline necrosis." This phlebosclerosis has subsequently been referred to in several other accounts of alcoholic liver disease, but its prevalence, pathogenesis, and its possible contribution to the progression of the liver injury have remained uncertain. Furthermore, in some accounts distinction has been drawn between phlebosclerosis and veno-occlusive lesions. The veno-occlusive lesions resemble those described by Bras et al in their classical studies of pyrollizidine related liver disease. Goodman and Ishak in their retrospective necropsy study also distinguished between phlebosclerosis and veno-occlusive lesions, finding phlebosclerosis in all their cases of alcoholic hepatitis or alcoholic cirrhosis and veno-occlusive lesions in 52% and 74%, respectively. The authors also described a lymphocytic phlebitis, which was found much less often.

In this study we looked for hepatic vein lesions as defined by Goodman and Ishak. The veno-occlusive lesions were readily identified and usually affected the larger hepatic vein branches. The prevalence of these lesions was, however, considerably less than that noted by Goodman and Ishak.

The histological diagnosis of phlebosclerosis presented some difficulties. In sections stained with haematoxylin and eosin it was often difficult to identify hepatic vein radicles within areas of fibrous scarring that topographically corresponded to the venular and perivenular zones. Residual elastic lamina, however, could usually be shown within these areas on either the orcein stain or the elastic van Gieson stain (Fig. 4). In a small number of biopsies some hepatic vein branches showed features of intimal veno-occlusion as defined by Goodman and Ishak but accompanied by perivenular adventitial fibrosis. Possibly, progression of both the intimal proliferation and the adventitial fibrosis could have produced a totally obliterator lesion which we then regarded as being phlebosclerotic. Nakamura et al showed transitions between veno-occlusive and phlebosclerotic lesions in cirrhosis on serial sectioning.

The pathogenesis of veno-occlusion and phlebosclerosis in alcoholic liver disease is unclear. These conditions may represent direct toxic injury to vascular endothelium in a manner similar to that proposed for lesions seen with certain toxins and chemotherapeutic agents. Veno-occlusive disease produced by pyrollizidine alkaloids, however, may be related to injury at the sinusoidal level with subsequent damage to both endothelial cells and hepatocytes. There is a consequent decrease in hepatic vein flow and a narrowing in the luminal diameter to a size appropriate for the reduced blood flow. In cirrhotic livers studied after death by Nakamura et al focal veno-occlusive lesions were found in 75–90%, and the incidence and morphology of the lesions seemed to be similar irrespective of the aetiological type of the cirrhosis—that is, alcoholic, primary biliary, posthepatitic, or cryptogenic. They suggested that these focal lesions represented a secondary response to a reduced blood flow, the reduction resulting from microvascular disturbance by fibrous scarring or nodular regeneration, or both.

Although such an explanation could apply to the veno-occlusive lesions which we saw in this study, we believe that the phlebosclerotic lesions represent a different form of injury. They were seen at a stage of alcoholic fatty liver in which there was no evident swelling of the liver cells and when reduction in venous flow seemed improbable. These early lesions were accompanied by a mild degree of pericellular

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**Table: Prevalence of hepatic vein lesions in subgroups of alcoholic liver disease**

<table>
<thead>
<tr>
<th></th>
<th>Veno-occlusive lesions</th>
<th>Phlebosclerosis</th>
<th>Lymphocytic phlebitis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mild moderate severe</td>
<td>Mild moderate severe</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>( % )</td>
<td>( % )</td>
<td>(%)</td>
</tr>
<tr>
<td>Fatty liver (n = 71)</td>
<td>1 0 0</td>
<td>1 (1-4)</td>
<td>0</td>
</tr>
<tr>
<td>Fatty liver with fibrosis (n = 20)</td>
<td>0 0 0</td>
<td>19 1 0</td>
<td>20 (100)</td>
</tr>
<tr>
<td>Alcoholic hepatitis:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biopsy (n = 82)</td>
<td>9 3 1</td>
<td>13 (15-8)</td>
<td>41 35 4</td>
</tr>
<tr>
<td>Necropsy (n = 6)</td>
<td>0 1 2</td>
<td>3 (30)</td>
<td>0 3 3</td>
</tr>
<tr>
<td>Cirrhosis:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biopsy (n = 83)</td>
<td>9 3 0</td>
<td>12 (14-4)</td>
<td>1 17 65</td>
</tr>
<tr>
<td>Necropsy (n = 44)</td>
<td>2 4 2</td>
<td>8 (18-1)</td>
<td>0 0 44</td>
</tr>
</tbody>
</table>

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fibrosis, which is being increasingly recognised as an early component of liver disease induced by alcohol and which, indeed, may progress to cirrhosis without an intervening stage of alcoholic hepatitis.15–17

It seems likely to us that the early phlebosclerotic lesion is part of the fibrosis induced by alcohol, which commences in the perivenular zone and which may be the very earliest evidence of incipient and progressive liver injury. It is evident from our results that the severity of the phlebosclerosis increases with progressive liver injury and may of itself be important in the further evolution of the disease.

References


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