Acknowledgements

References

[1] Gurakan F, Kocak N, Yuce A, Ozen H. Extrahepatic portal venous obstruction in childhood: etiology, clinical and laboratory findings and prognosis of 34 patients. Acta Paediatr Jpn 1997;39:595-600.

[2] Bhandarkar PV, Sreenivasa D, Mistry FP, Abraham P, Bhatia SJ. Profile of extrahepatic portal venous obstruction in Mumbai. J Assoc Phys India 1999;47:791-4.

[3] Kawamata H, Kumazaki T, Kanazawa H, Takahashi S, Tajima H, Hayashi H. Transjugular intrahepatic portosystemic shunt in a patient with cavernomatous portal vein occlusion. Cardiovasc Intervent Radiol 2000;23:145-9.

[4] Bayraktar Y, Balkanci F, Kayhan B, Ozenc A, Arslan S, Telatar H. Bile duct varices or 'pseudo-cholangiocarcinoma sign' in portal hypertension due to cavernous transformation of the portal vein. Am J Gastroenterol 1992;87:1801-6.

[5] Guimaraes H, Castelo L, Guimaraes J, et al. Does umbilical vein catheterization to exchange transfusion lead to portal vein thrombosis? Eur J Pediatr 1998;157:461-3.

[6] Lim GM, Jeffrey RB, Ralls PW, Marn CS. Septic thrombosis of the portal vein: CT and clinical observations. J Comput Assist Tomogr 1989;13:656-8.

[7] Rehan VK, Cronin CM, Bowman JM. Neonatal portal vein thrombosis successfully treated by regional streptokinase infusion. Eur J Pediatr 1994;153:456-9.

[8] Schmutz GR, Benko A, Billiard JS, Fournier L, Peron JM, Fisch-Ponsot C. Computed tomography of superior mesenteric vein thrombosis following appendectomy. Abdom Imaging 1998;23:563-7.

[9] Crowe A, Taffinder N, Layer GT, Irvine A, Nicholls RJ. Portal vein thrombosis in a complicated case of Crohn's disease. Postgrad Med J 1992;68:291-3.

[10] Ando H, Kaneko K, Ito F, Seo T, Watanabe Y, Ito T. Anatomy and etiology of extrahepatic portal vein obstruction in children leading to bleeding esophageal varices. J Am Coll Surg 1996;183:543-7.

[11] Egesel T, Buyukasik Y, Dundar SV, Gurgey A, Kirazli S, Bayraktar Y. The role of natural anticoagulant deficiencies and factor V Leiden in the development of idiopathic portal vein thrombosis. J Clin Gastroenterol 2000;30:66-71.

[12] Amitrano L, Brancaccio V, Guardascione MA, et al. Inherited coagulation disorders in cirrhotic patients with portal vein thrombosis. Hepatology 2000;31:345-8.

[13] Bayraktar Y, Balkanci F, Kayhan B, et al. Congenital hepatic fibrosis associated with cavernous transformation of the portal vein. Hepato-Gastroenterology 1997;44:1588-94.

[14] Tanaka M, Wanless IR. Pathology of the liver in Budd-Chiari syndrome: portal vein thrombosis and the histogenesis of veno-centric cirrhosis, veno-portal cirrhosis, and large regenerative nodules. Hepatology 1998;27:488-96.

[15] Nakanuma Y, Tsuneyama K, Ohbu M, Katayanagi K. Pathology and pathogenesis of idiopathic portal hypertension with an emphasis on the liver. Pathol Res Pract 2001;197:65-76.

[16] Bayraktar Y, Balkanci F, Kansu E, et al. Cavernous transformation of the portal vein: a common manifestation of Behcet's disease. Am J Gastroenterol 1995;90:1476-9.

[17] Khuroo MS, Yattoo GN, Zargar SA, et al. Biliary abnormalities associated with extrahepatic portal venous obstruction. Hepatology 1993;17:807-13.

[18] McCormick A, Chronos N, Burroughs AK, McIntyre N, McLaughlin JE. Pancreatic pseudocyst causing portal vein thrombosis and pancreatico-pleural fistula. Gut 1990;31:561-3.

[19] Lohr JM, Kuchenreuter S, Grebmeier H, Hahn EG, Fleig WE. Compression of the common bile duct due to portal-vein thrombosis in polycythemia vera. Hepatology 1993;17:586-92.

[20] Ishikawa M, Koyama S, Ikegami T, et al. Venous tumor thrombosis and cavernous transformation of the portal vein in a patient with gastric carcinoma. J Gastroenterol 1995;30:529-33.

[21] Denninger MH, Chait Y, Casadevall N, et al. Cause of portal or hepatic venous thrombosis in adults: the role of multiple concurrent factors. Hepatology 2000;31:587-91.

[22] Ohbu M, Okudaira M, Watanabe K, Kaneko S, Takai T. Histopathological study of intrahepatic aberrant vessels in cases of noncirrhotic portal hypertension. Hepatology 1994;20:302-8.

[23] Agnihotri N, Bhusnurmath SR, Narasimhan KL, Dilawari JB, Majumdar S, Kaur U. Experimental extrahepatic obstruction of portal vein: documentation of histopathological alterations in liver and extrahepatic tissues. J Gastroenterol Hepatol 1996;11:971-7.

[24] Ohno Y, Shiga J, Mori W. Selective segmental hepatic necrosis produced by the Shwartzman mechanism in rabbits. Virchows Arch A Pathol Anat Histopathol 1989;416:75-80.

[25] Roth RI. Hemoglobin enhances the production of tissue factor by endothelial cells in response to bacterial endotoxin. Blood 1994;83:2860-5.

[26] Hoffman M, Cooper ST. Thrombin enhances monocyte secretion of tumor necrosis factor and interleukin-1 beta by two distinct mechanisms. Blood Cells Mol Dis 1995;21:156-67.

[27] Omokawa S, Asanuma Y, Koyama K. Evaluation of hemodynamics and hepatic mitochondrial function on extrahepatic portal obstruction in the rat. World J Surg 1990;14:247-53.

[28] De Gaetano AM, Lafortune M, Patriquin H, De Franco A, Aubin B, Paradis K. Cavernous transformation of the portal vein: patterns of intrahepatic and splanchnic collateral circulation detected with Doppler sonography. AJR Am J Roentgenol 1995;165:1151-5.

[29] Terada T, Takegoshi T, Doishita K, Nakanuma Y. Histological study of intrahepatic cavernous transformation in a patient with primary myelofibrosis and portal venous thrombosis. Virchows Arch A Pathol Anat Histopathol 1988;412:339-45.

[30] Oikawa H, Masuda T, Sato S, et al. Changes in lymph vessels and portal veins in the portal tract of patients with idiopathic portal hypertension: a morphometric study. Hepatology 1998;27:1607-10.

[31] Tang L, Tanaka Y, Marumo F, Sato C. Phenotypic change in portal fibroblasts in biliary fibrosis. Liver 1994;14:76-82.

[32] Masuda T, Oikawa H, Sato S, Satodate R, Suzuki K, Sato S. Distinguishing small lymph vessels in the portal tracts of human liver from portal veins by immunohistochemistry for alpha smooth muscle actin. Int Hepatol Commun 1996;4:277-82.

[33] Kobayashi S, Nakanuma Y, Matsui O. Intrahepatic peribiliary vascular plexus in various hepatobiliary diseases: a histological survey. Hum Pathol 1994;25:940-6.

A comparative histological and morphometric study of vascular changes in idiopathic portal hypertension and alcoholic fibrosis/cirrhosis

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Aim: To examine the pathological changes of hepatic arteries in idiopathic portal hypertension (IPH) which is characterized by the obliteration of the intrahepatic portal vein branches and presinusoidal portal hypertension.

Methods and results: Liver specimens (biopsied or surgically resected) from 20 patients with IPH, 20 patients with alcoholic fibrosis/cirrhosis (AF/C) and 20 histologically normal livers were used. The vascular lumina of arterial and venous vessels in portal tracts were morphometrically evaluated by an image analysis system. The ratio of portal venous luminal area to portal tract area (portal venous index) of IPH and that of AF/C were significantly reduced compared with normal liver. The portal venous index for IPH was significantly lower than that for AF/C. The ratio of hepatic arterial luminal area to portal tract area for AF/C was significantly higher than that in normal liver; however, that for IPH was similar to normal. The peribiliary vascular plexus was increased in AF/C but not in IPH. In AF/C, the number of mast cells and macrophages known to be the source of angiogenic substances was significantly increased in the portal tract compared with normal liver, while in IPH it was not increased.

Conclusions: In AF/C, a reduction in portal venous lumen was associated with an increase of hepatic arterial lumen and of angiogenesis-related cells in portal tracts. However, such compensatory arterial changes were not evident in IPH, and this compensatory failure may be a feature of IPH.

Introduction

A decrease of the portal venous inflow into the liver is always and immediately associated with a compensatory increase of hepatic arterial flow in man and experimental animals.[1–4] This increase is recognizable by imaging and haemodynamic studies.[1–4] This compensation may be associated with arterio-portal (A-P) shunts and/or an increase or dilatation of hepatic arterial branches. A-P shunts mainly involve the pre-existing peribiliary vascular plexus.[5,6]

Idiopathic portal hypertension (IPH) is characterized by presinusoidal portal hypertension due to intrahepatic, presinusoidal portal venous block.[7–9] Histologically, portal fibrosis, phlebosclerosis and the obliteration of

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small portal vein branches in portal tracts and abnormal blood vessels in the hepatic lobules are features of IPH.[8-12] Terada et al.[12] reported that inlet portal venules in addition to conducting veins were decreased in IPH. However, there has been no detailed histological examination of hepatic arteries in IPH.

In this study, we histometrically measured the respective areas of hepatic arterial lumina and of portal venous lumina within peripheral portal tracts in IPH, alcoholic fibrosis/cirrhosis (AF/C) and normal control livers. In addition, the distribution and density of activated macrophages and mast cells in the portal areas were examined, because these cells are known to produce angiogenic substances such as basic fibroblast growth factor (bFGF), vascular endothelial growth factor (VEGF), matrix metalloproteinase (MMP) and nitric oxides.[13-15]

Materials and methods

LIVER TISSUE PREPARATION

The liver specimens from 20 cases of IPH (five needle and 15 wedge liver biopsies) were obtained from the file of hepatobiliary diseases in our laboratory and affiliated hospitals. In all cases, other causes of portal hypertension such as cirrhosis, extrahepatic portal venous obliteration and congenital hepatic fibrosis were excluded.[8] As controls, we used 20 cases of normal liver and 20 cases of AF/C (wedge biopsy or surgically resected liver specimens) with a comparable age and sex distribution to the IPH cases.

These liver tissues were fixed in 10% neutral buffered formalin and embedded in paraffin. More than 20 serial sections, 4 μm in thickness, were cut from each paraffin block, some of which were processed for H&E, elastic van Gieson (EVG), Mallory's azan, Gomori's reticulin and orcein staining. The remaining sections were used for immunohistochemistry.

ANATOMICAL CLASSIFICATION OF THE INTRAHEPATIC BILE DUCT AND PORTAL VEIN

The peripheral areas of the liver are known to be most affected in IPH.[8,9] In this study, the small and medium-sized portal tracts in the subcapsular areas were mainly examined. In these portal tracts, the interlobular and septal bile ducts are identifiable, the external calibre of the former being <80 μm and that of the latter >80 μm. The septal bile ducts have their own fibrous wall, while the interlobular bile ducts do not.[15,16] The small portal veins are defined as those running parallel to the interlobular bile ducts and the medium-sized

veins as portal veins lying parallel to the septal bile ducts.

MORPHOMETRIC ANALYSIS OF PATHOLOGICAL BLOOD VESSELS IN THE PORTAL TRACTS

To categorize histologically portal veins and hepatic arteries, serial sections were immunostained using anti-CD31 monoclonal antibody (clone JC/70 A; Dako, Glostrup, Denmark) and anti-alpha-smooth muscle actin (α-SMA) monoclonal antibody (clone 1A4; Dako). With the help of H&E and EVG-stained sections, CD31+ blood vessels with strong α-SMA expression in the wall were categorized as hepatic arteries and those with weak α-SMA expression in the wall as portal veins. Lymph vessels in portal tracts and 'abnormal vessels' in the hepatic lobules with thin walls[13] and without CD31 and α-SMA expression were excluded from the morphometric analysis.

At ×200 magnification, a microscopic image was captured from three selected portal tracts in each of 13 normal livers, 13 cases of AF/C, and 13 cases of IPH, by a digital camera (Olympus, DP-50; Tokyo, Japan) and exported to the image analyser (NIH image) (Figure 1). In all these cases, at least three complete portal tracts were identifiable. The summed luminal area of portal vein(s) (PV) and that of hepatic arteri(es) (HA) in each portal tract and the area of the portal tract (PT) were outlined and calculated, respectively. Then, the portal venous index (PV/PT) and the hepatic arterial index (HA/PT) were calculated in each portal tract and the mean and SD of these indices were calculated in the three individual groups, respectively. The former reflects the relative volume of portal vein in the portal tract and the latter that of hepatic artery.

EVALUATION OF PERIBILIARY VASCULAR PLEXUS (PVP)

Our previous study showed that the PVP is well developed around the septal bile ducts.[6] In this study, the PVPs near the septal bile ducts, which were frequently available in the wedge liver biopsies, were evaluated as follows. At least one septal bile duct with a fibrous wall was seen in 15 cases of IPH, 15 cases of AF/C, and 15 cases of normal liver. First, the total number of microvessels of PVPs near the septal bile duct was counted in each specimen. In normal liver, the mean number of these microvessels around the septal bile duct and its SD was 15.0 ± 3.8. So, the number in IPH and AF/C ranging from 11.2 to 18.8
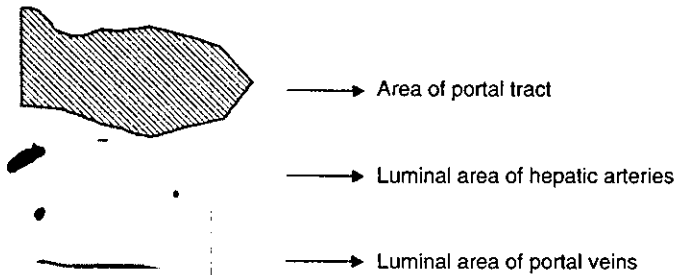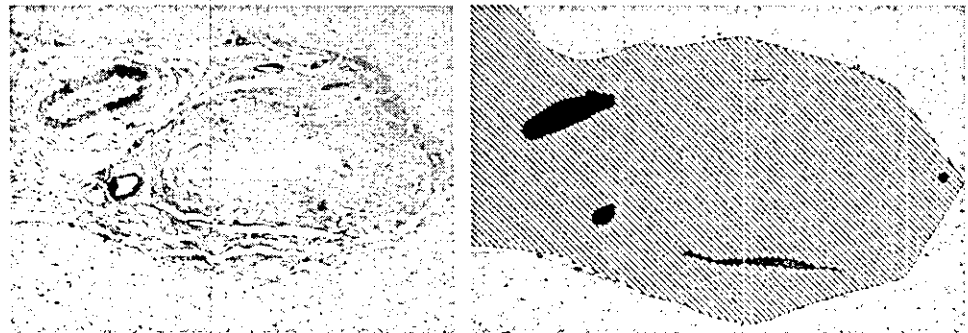
Figure 1. The luminal area of hepatic arteries and portal veins as well as the area of the portal tract are shown schematically and analysed by digital camera and image analyser (see text).

was regarded as 'normal', and a number <11.2 as 'less than normal' and >18.8 as 'more than normal'.

DETECTION OF MAST CELLS AND MACROPHAGES IN THE PORTAL TRACTS

Activated macrophages and mast cells were surveyed immunohistochemically in the portal tracts of 20 cases of IPH, AF/C and normal livers, respectively. CD68 (clone KP-1; Dako) was used for the detection of macrophages, and tryptase (clone AA1; Dako) for the detection of mast cells. Mast cells and CD68+ cells were counted in all complete portal tracts of each specimen and the average number per portal tract was calculated (mast cell index and macrophage index).

IMMUNOHISTOCHEMISTRY

After deparaffinization and following standard microwave treatment[17] the sections were incubated in the serum-free protein block reagent (Dako, Carpinteria, CA, USA) for 30 min. They were then incubated with mouse monoclonal antibody against CD31, mouse monoclonal antibody against α-SMA, mouse monoclonal antibody against human tryptase and mouse monoclonal antibody against human CD68 at a pertinent dilution overnight at 4°C. After a PBS wash, Envision-PO (Dako) was applied at room temperature for 1 h. After another wash and a benzidine reaction, the sections were lightly counter-

stained with haematoxylin. Replacement of each primary antibody with PBS resulted in negative staining.

STATISTICAL ANALYSIS

Intergroup comparisons were made by the Fischer's exact test and the Kraskal–Wallis test, and the difference was considered significant when P-values were < 0.05.

Results

HISTOPATHOLOGY AND MORPHOMETRIC ANALYSIS OF PORTAL VEINS AND HEPATIC ARTERIES

In IPH, small portal veins constantly showed luminal narrowing and/or obliteration. In addition, medium-sized portal veins frequently showed intimal and medial thickening (phlebosclerosis) and occasionally recanalization, though such findings were rare in AF/C. In IPH, hepatic arteries numbered one to several per portal tract, they showed intimal thickening to various degrees and their lumina were narrowed, while the numbers of hepatic arteries in portal tracts and fibrous septa were increased in AF/C. In EVG staining, irregularity of the elastic laminae of arteries was observed here and there in IPH, but such findings were not constant in AF/C.

The portal venous index for IPH (1.6 ± 0.2) was significantly lower than that for AF/C (9.1 ± 1.8) and
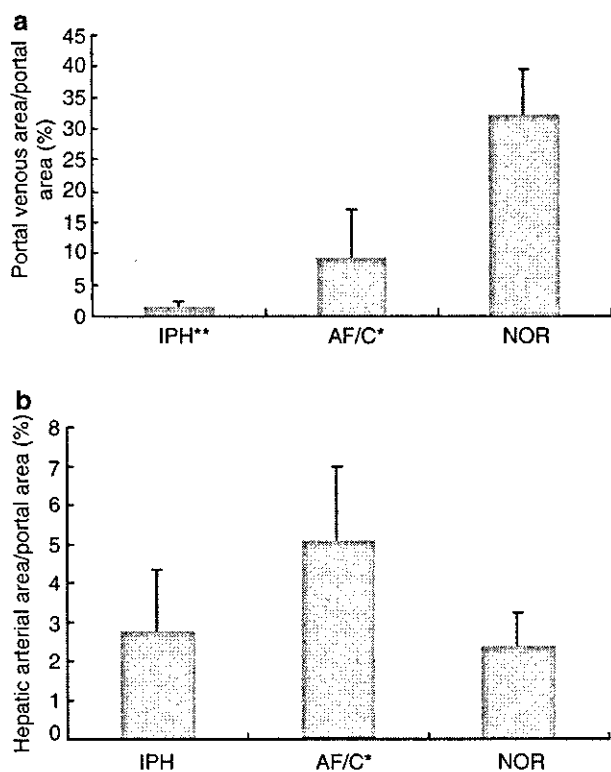
Figure 2. a, The portal venous index (mean ± SD) for idiopathic portal hypertension (IPH) (12 cases, 1.6 ± 0.2), alcoholic fibrosis/cirrhosis (AF/L) (12 cases, 9.1 ± 1.8) and normal livers (NOR) (12 cases, 32.0 ± 1.7). *P < 0.05 compared with the value for NOR; **P < 0.05 compared with the value for AF/C and that for NOR, respectively. b, The hepatic arterial indices of IPH (12 cases, 2.8 ± 0.4), AF/L (12 cases, 5.1 ± 0.4) and normal livers (NOR) (12 cases, 2.3 ± 0.2) are shown. *P < 0.05 compared with the value for IPH and NOR, respectively.

normal liver (32.0 ± 1.7) (Figure 2a). The hepatic arterial index in IPH (2.8 ± 0.4) was almost equal to that of normal liver (2.3 ± 0.2), while the index for AF/C (5.1 ± 0.4) was significantly higher than that for IPH and normal liver (Figure 2b).

THE NUMBER OF MICROVESSELS OF PVP AROUND SEPTAL BILE DUCTS

The number of microvessels of PVP was significantly higher in AF/C (23.5 ± 9.1) than in IPH (12.0 ± 6.1) and normal liver (15.0 ± 3.8) (Figure 3). In addition, 9/15 (60%) cases of IPH belonged to the 'less than normal' group, while only 2/15 (13.3%) cases of IPH belonged to the 'more than normal' group. In AF/C, 9/15 (60%) cases belonged to the 'more than normal' group, while only 1/15 (6.7%) belonged to the 'less than normal' group.
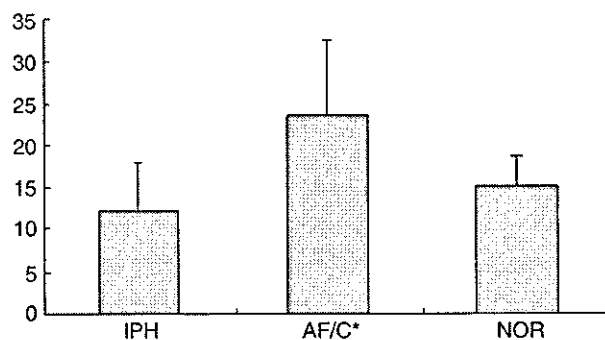

Figure 3. The number of microvessels of peribiliary vascular plexus (PVP) around the septal bile duct (mean ± SD, 15 ducts) in idiopathic portal hypertension (IPH) (12.0 ± 6.1), alcoholic fibrosis/cirrhosis (AF/C) (23.5 ± 9.1) and normal liver (NOR) (15.0 ± 3.8).
*P < 0.05 compared with the value for IPH and NOR, respectively.

DISTRIBUTION OF MAST CELLS AND MACROPHAGES IN PORTAL TRACTS

In normal and IPH livers, a few mast cells were located near small vessels and occasionally bile ducts (Figure 4a). However, in AF/C a variable number of mast cells was observed in enlarged portal tracts (Figure 4b). The mast cell index for IPH (5.5 ± 1.7) was almost equal to that in normal livers (5.5 ± 1.2), whilst for AF/C (19.4 ± 3.8) it was significantly higher than in IPH and normal liver (Figure 4c).

In normal liver and IPH, there were CD68+ mononuclear cells in the sinusoids (Kupffer cells) and few in portal tracts (activated macrophages) (Figure 5a). In AF/C, many CD68-positive cells were observed in the sinusoids and enlarged portal tracts (Figure 5b). The macrophage index in the portal tract of IPH (3.7 ± 0.6) was almost equal to that of normal liver (4.0 ± 0.9), whilst for AF/C (11.9 ± 1.9) it was significantly higher than in IPH and in normal liver (Figure 5c).

Discussion

In chronic liver disease with portal hypertension, haemodynamic studies have shown that the blood flow in hepatic arteries and other splanchnic arteries is increased.[18,19] In IPH, splanchnic arterial flow, particularly splenic arterial flow, is markedly increased, though the hepatic arterial flow or luminal size is only slightly increased or actually decreased.[20] While portal venous inflow to the liver increases slightly in IPH, there is extensive obliteration of the small portal branches responsible for sustained presinusoidal hypertension.[8,21]
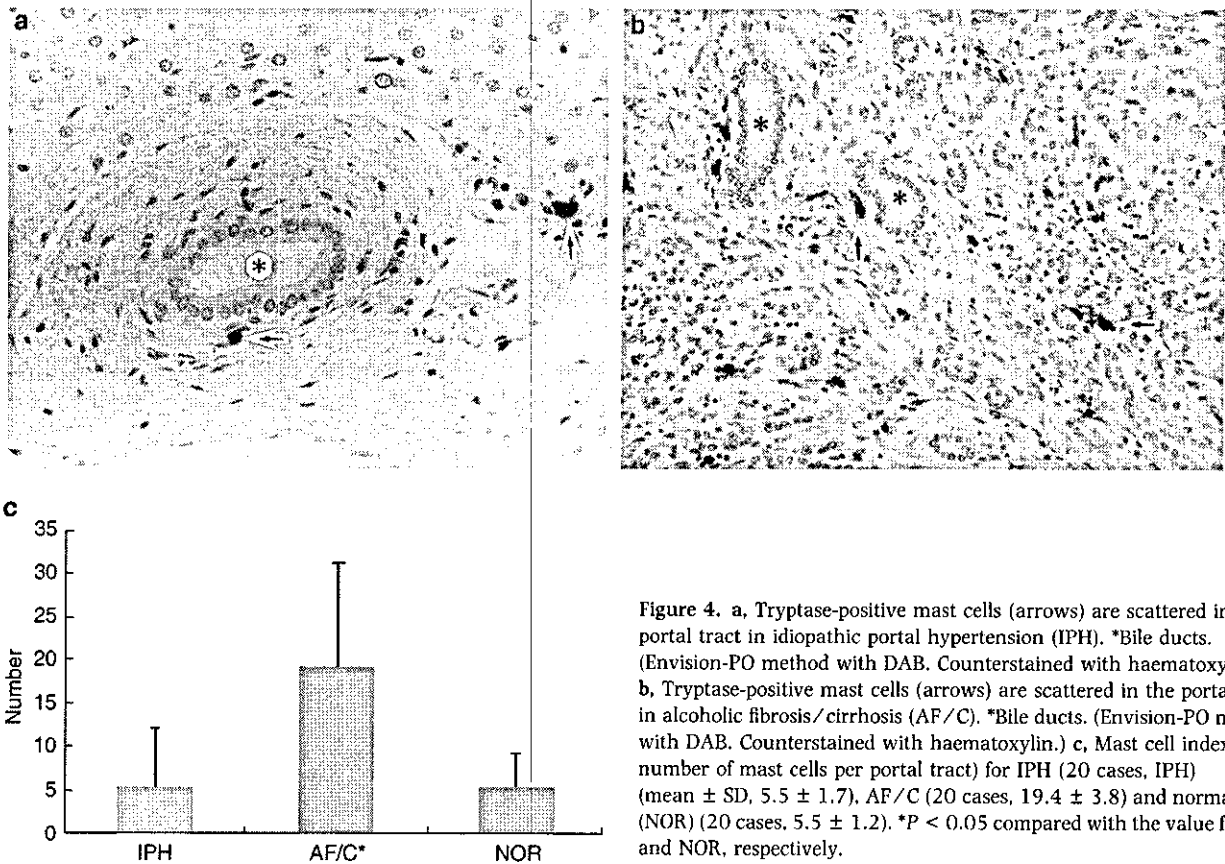
Figure 4. a, Tryptase-positive mast cells (arrows) are scattered in the portal tract in idiopathic portal hypertension (IPH). *Bile ducts. (Envision-PO method with DAB. Counterstained with haematoxylin.) b, Tryptase-positive mast cells (arrows) are scattered in the portal tract in alcoholic fibrosis/cirrhosis (AF/C). *Bile ducts. (Envision-PO method with DAB. Counterstained with haematoxylin.) c, Mast cell index (the number of mast cells per portal tract) for IPH (20 cases, IPH) (mean ± SD, 5.5 ± 1.7), AF/C (20 cases, 19.4 ± 3.8) and normal liver (NOR) (20 cases, 5.5 ± 1.2). *$P < 0.05$ compared with the value for IPH and NOR, respectively.

In the present study, we focused on the portal tracts, particularly in the subcapsular peripheral regions of the liver, which are those both selectively affected in IPH and generally sampled by biopsy needles. First, we measured the luminal area of portal veins (portal venous index) and of hepatic arteries (hepatic arterial index) relative to the area of the portal tract on the assumption that the luminal area of these blood vessels reflects their blood flow volume.[22] In AF/C, the portal venous index was reduced, probably due to portal fibrosis, whereas the hepatic arterial index was increased. The increased arterial blood flow may compensate for the reduction of portal blood flow to keep the total hepatic blood inflow constant. In contrast, in IPH, in spite of a marked reduction of the portal venous index, the hepatic arterial index was not increased. This finding and hepatic arteriographic studies[21] suggest that an arterial perfusion comparable to that in normal liver was retained in IPH in spite of a marked reduction in portal venous flow. Haemodynamic studies have shown that A-P shunts are negligible in IPH.[18,19] The present study has shown that PVP, a route for A-P shunts in the liver,[5,6] is increased in AF/C but not in IPH, supporting the above-mentioned haemodynamic studies. Thus, IPH can be regarded as a disease with a compensatory failure of hepatic arteries in spite of marked reduction of portal venous inflow in the liver. In this context, IPH livers, particularly in the subcapsular peripheral areas, are prone to be in an ischaemic state due to both portal venous as well as hepatic arterial disturbance, leading to atrophy or even loss of the peripheral hepatic parenchyma.[9]

There are several possible explanations for the compensation failure of hepatic arterial inflow in IPH. One is that in IPH, portal sclerosis with dense elastic fibre deposition may prevent mechanical dilatation of pre-existing arteries or arterioles in the portal tract and around the bile duct.[9,20] Another possibility is that angiogenesis caused by angiogenic factors does not develop properly in IPH. Mast cells and activated macrophages, which are known to secrete angiogenic substances such as bFGF and VEGF, are strong regulators of angiogenesis in the liver.[5,14,18–23] In normal liver, few mast cells and macrophages were seen in the portal tract. In AF/C, the numbers of mast cells and macrophages were significantly increased. However, in IPH the numbers of both types of cell were equal to
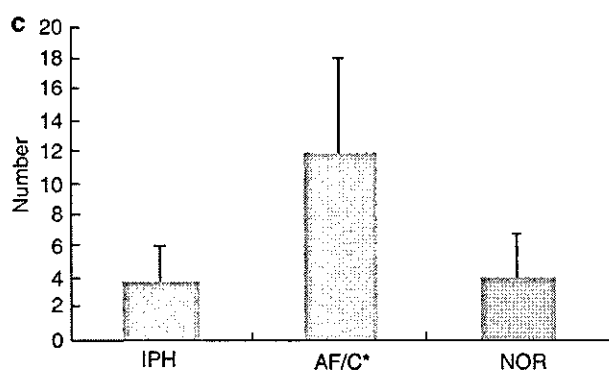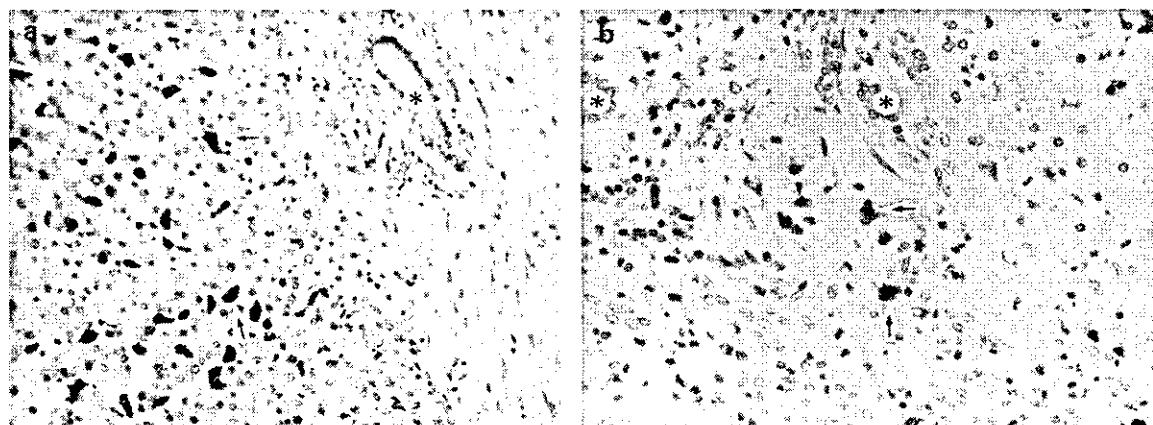
Figure 5. a, CD68+ Kupffer cells (arrows) are seen in the sinusoids, while CD68+ macrophages are rare in the portal tracts in idiopathic portal hypertension (IPH). *Bile duct. (Envision-PO method with DAB. Counterstained with haematoxylin.) b, Many CD68+ cells (arrows) were seen in the portal tract as well in the sinusoid in alcoholic fibrosis/cirrhosis (AF/C). *Bile duct. (Envision-PO method with DAB. Counterstained with haematoxylin.) c, Macrophage index (the number of CD68+ macrophages per portal tract) for IPH (20 cases, IPH) (mean ± SD, 3.7 ± 0.6), AF/C (20 cases, 11.9 ± 1.9) and normal liver (NOR) (20 cases, 4.0 ± 0.9). *P < 0.05 compared with the value for IPH and NOR, respectively.

those in normal liver, suggesting that recruitment of mast cells and macrophages in the portal area did not occur. Adhesion molecules and chemokines, which are expressed in endothelial cells and biliary epithelial cells as well as various mononuclear cells,[24-26] may not be turned on for the migration of macrophages and mast cells.

In conclusion, increased and dilated hepatic arterial branches were not seen in portal tracts of IPH with a marked reduction of portal vein lumen. Not only the portal venous obliteration but also hepatic arterial disturbance may cause a sustained ischaemic state in the liver in IPH. The absence of an increase in inflammatory cells expressing angiogenic substances in addition to dense portal elastofibrosis may explain the poor arteriogenesis in IPH.

Acknowledgements

References

1. Itai Y, Moss AA, Goldberg HI. Transient hepatic attenuation difference of lobar or segmental distribution detected by dynamic computed tomography. Radiology 1982; 144; 835–839.

2. Matsui O, Takashima T, Kadoya M et al. Segmental staining on hepatic arteriography as a sigh of portal vein obstruction. Radiology 1984; 152; 601–606.

3. Nagino M, Nimura Y, Kamiya J et al. Immediate increase in arterial blood flow in embolized hepatic segments after portal vein embolization: CT demonstration. Am. J. Roentgenol. 1998; 171; 1037–1039.

4. Itai Y. Hemodynamics in and around the liver. In Okuda K ed. Hepatobiliary diseases, 1st edn. Oxford: Blackwell Science, 2001; 228–246.

5. Koda W, Harada K, Tsuneyama K et al. Evidence of the participation of peribiliary mast cells in regulation of the peribiliary vascular plexus along the intrahepatic biliary tree. Lab. Invest. 2000; 80; 1007–1017.

6. Kobayashi S, Nakanuma Y, Matsui O. Intrahepatic peribiliary vascular plexus in various hepatobiliary diseases: a histological survey. Hum. Pathol. 1994; 25; 940–946.

7. Aikat BK, Bhusnurmath SR, Chhuttani PN, Mitra SK, Dutta DV. The pathology. of noncirrhotic portal fibrosis. Hum. Pathol. 1979; 10; 405–418.

8. Okuda K, Nakashima T, Okudaira M et al. Liver pathology of idiopathic portal hypertension. Comparison with non-cirrhotic portal fibrosis of India. Liver 1982; 2; 176–192.

9. Nakanuma Y, Tsuneyama K, Ohbu M, Katayanagi K. Pathology and pathogenesis of idiopathic portal hypertension with an emphasis on the liver. *Pathol. Res. Pract.* 2001; 197; 65–76.

10. Nakanuma Y, Hoso M, Sasaki M *et al.* Histopathology of the liver in non-cirrhotic portal hypertension of unknown aetiology. *Histopathology* 1996; 28; 195–204.

11. Ohbu M, Okudaira M, Watanabe K, Kaneko S, Takai T. Histopathological study of intrahepatic aberrant vessels in cases of noncirrhotic portal hypertension. *Hepatology* 1994; 20; 302–308.

12. Terada T, Hoso M, Nakanuma Y. Microvasculatures in the small portal tracts in idiopathic portal hypertension. A morphological comparison with other hepatic diseases. *Virchows Arch.* 1989; 415; 61–67.

13. Qu Z, Liebler JM, Powers MR *et al.* Mast cells are a major source of basic fibroblast growth factor in chronic inflammation and cutaneous hemangioma. *Am. J. Pathol.* 1995; 147; 564–573.

14. Sunderkotter C, Steinbrink K, Goebeler M, Bhardwaj R., Sorg C. Macrophages and angiogenesis. *J. Leuk. Biol.* 1994; 55; 410–422.

15. Nakanuma Y, Hoso M, Sanzen T, Sasaki M. Microstructure and development of the normal and pathologic biliary tract in humans, including blood supply. *Microsc. Res. Tech.* 1997; 38; 552–570.

16. Nakanuma Y, Ohta G. Histometric and serial section observations of the intrahepatic bile ducts in primary biliary cirrhosis. *Gastroenterology* 1979; 76; 1326–1332.

17. Cattoretti G, Pileri S, Parravicini C *et al.* Antigen unmasking on formalin-fixed, paraffin-embedded tissue sections. *J. Pathol.* 1993; 171; 83–98.

18. Ohnishi K, Chin N, Sugita S *et al.* Quantitative aspects of portal-systemic and arteriovenous shunts within the liver in cirrhosis. *Gastroenterol.* 1987; 93; 129–134.

19. Ohnishi K, Sato S, Pugllese D *et al.* Changes of splanchnic circulation with progression of chronic liver disease studied by echo-Doppler flowmetry. *Am. J. Gastroenterol.* 1987; 82; 507–511.

20. Okuda K. Noncirrhotic portal hypertension. In Okuda K ed. *Hepatobiliary diseases,* 1st edn. Oxford: Blackwell Science, 2001; 287–314.

21. Arai K, Matsui O, Kadoya M *et al.* MR imaging in idiopathic portal hypertension. *J. Comput. Assist. Tomogr.* 1991; 15; 405–408.

22. Oikawa H, Masuda T, Sato S *et al.* Changes in lymph vessels and portal veins in the portal tract of patients with idiopathic portal hypertension: a morphometric study. *Hepatology* 1998; 27; 1607–1610.

23. Yamashiro M, Kouda W, Kono N *et al.* Distribution of intra-hepatic mast cells in various hepatobiliary disorders. An immuno-histochemical study. *Virchows Arch.* 1998; 433; 471–479.

24. Tsuneyama K, Yasoshima M, Hiramatsu K *et al.* A putative role for eotaxin and RANTES in primary biliary cirrhosis: eosinophilic infiltration and damaged bile ducts. *Hepatol. Res.* 1999; 16; 68–77.

25. Yasoshima M, Nakanuma Y, Tsuneyama K, Van de Water J, Gershwin ME. Immunohistochemical analysis of adhesion molecules in the microenvironment of portal tracts in relation to aberrant expression of PDC-E2 and HLA-DR on the bile ducts in primary biliary cirrhosis. *J. Pathol.* 1995; 175; 319–325.

26. Tsuneyama K, Harada K, Yasoshima M *et al.* Monocyte chemo-tactic protein-1, -2, and -3 are distinctively expressed in portal tracts and granulomata in primary biliary cirrhosis: implications for pathogenesis. *J. Pathol.* 2001; 193; 102–109.

Editorial

Budd-Chiari syndrome and hepatocellular carcinoma

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Recurrence of hepatocellular carcinoma 102 months after successful eradication and removal of membranous obstruction of the inferior vena cara
TAKAMURA M, ICHIDA T, YOKOYAMA J, et al.

Budd-Chiari syndrome (BCS) refers to a disorder associated with symptoms of portal hypertension due to occlusion and/or stenosis of the hepatic veins or the inferior vena cava at its hepatic portion. BCS is idiopathic in some cases but of known etiology in other cases.

BCS has geographical characteristics. Thrombotic occlusion of the hepatic veins is common in Europe and the United States, and the causes are known in many cases. In contrast, in Japan[1-3] and developing countries such as South Africa,[4] India,[5] and Nepal,[6] the majority of BCS patients are idiopathic and show membranous obstruction of the inferior vena cava (MOVC) at its hepatic portion.[3] Hepatocellular carcinoma (HCC) is one of the major complications in BCS, and it is of interest that patients with MOVC are more frequently complicated by HCC.

Regarding frequency of BCS in the total number of HCC patients, the results of studies of numerous patients in Japan and South Africa are as follows. Of the total 2982 HCC patients surveyed by the Liver Cancer Study Group of Japan between 1986 and 1987, 0.10% developed HCC against the background of BCS. Kew et al.[4] in South Africa reported that the frequency of MOVC was 6 (3.6%) in 166 blacks with HCC. In the total HCC patients, the frequency of HCC developing against the background of BCS seems low.

The incidence of HCC associated with MOVC in Japan varies according to different authors. In 1968, Nakamura et al.[2] reported a high incidence (41%) of combined MOVC and HCC, whereas Okuda et al.[1] reported a low HCC incidence of 10 (6.4%) in 156 MOVC patients during a 15-year follow-up. One (6.7%) of the 15 cases of MOVC we studied was complicated by HCC.[3]

Kew et al.[4] surveyed the literature on MOVC in South Africa, and found a high incidence of MOVC

complicated by HCC in 57 (43.5%) of 131 cases including their own cases. Six (11%) of 54 MOVC patients in India[5] and 7 (4.7%) of 150 MOVC patients in Nepal[6] were reported to be complicated by HCC.[6] Thus, although the incidence of HCC complicating MOVC varies greatly according to country and author, many articles emphasize the association between the two conditions.

The reported characteristics of patients with BCS associated with MOVC are that HCC develops at a younger age and has a poorer prognosis compared with that in HCC patients with no MOVC.

The mechanism of hepatocarcinogenesis in MOVC is unknown. It has been postulated that prolonged congestion due to MOVC causes hepatocellular necrosis and regeneration over many years, thereby increasing the sensitivity of liver cells to carcinogens. The frequency of HCC associated with MOVC varies according to region in South Africa, suggesting the involvement of environmental carcinogens.[4] Also, the possible involvement of viral hepatitis is debatable. No reports have emphasized the involvement of hepatitis B virus (HBV) in the development of HCC in MOVC. Simson[7] reported that the hepatitis B surface antigen (HBsAg)-positivity rate in MOVC patients complicated by HCC in South Africa was 22.2%, which was higher than that (8.7%) in the control group; however, because the HBsAg-positivity rate in the total HCC patients was 33.7%, Simson[7] speculated that HBV was not significantly involved in hepatocarcinogenesis. Similarly, in Japan, Okuda et al.[1] reported that the HBsAg-positivity rate was as low as 1 in 10 MOVC patients complicated by HCC.

Because few or no studies have investigated the involvement of hepatitis C, an important subject of future study will be the clarification of the HCV infection rate in BCS patients complicated by HCC.

Against what background hepatic lesions does HCC develop in BCS? No reports have described detailed histopathological findings of hepatic lesions in the non-

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cancerous region. The background lesions appear to be cirrhosis in the majority of patients in Japan. Okuda et al.[1] reported that, of the 10 BCS patients complicated by HCC, 8 had cirrhosis, 1 congestive liver, and 1 liver fibrosis. In the above-mentioned South African cases,[4] congestive liver or congestive hepatic fibrosis, and not cirrhosis, was described. It would be interesting to know whether the noncancerous region has the histological features of both congestive hepatic lesions and viral hepatitis, or of either. Although this has not been fully documented, there have been cases, including those reported in this issue by Takamura et al.[8] in which the involvement of hepatitis viruses is unlikely in the presence of typical chronic congestive hepatic lesions in the noncancerous region. From the histological point of view, chronic hepatic congestion alone can be a risk factor for HCC. It is also clear that HCC does not necessarily develop on the basis of cirrhosis, but can arise from a state of mild congestive hepatic fibrosis. It should be borne in mind that even patients with BCS of long disease duration and congestive hepatic fibrosis are at risk for HCC. Therefore, it seems important to recanalize the obstructed hepatic veins and inferior vena cava promptly to relieve hepatic congestion, and to follow patients as having a risk factor of not only occurrence but also recurrence of HCC.[8]

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References

1. Okuda H, Yamagata H, Obata H, Iwata H, Sasaki R, Imai F, et al. Epidemiological and clinical features of Budd-Chiari syndrome in Japan. J Hepatology 1995;22:1–9.
2. Nakamura T, Nakamura S, Aikawa T, Suzuki O, Onodera A, Karoji N. Obstruction of the inferior vena cava in the hepatic portion and the hepatic veins. Angiology 1968;19:479–98.
3. Kage M, Arakawa M, Kojiro M, Okuda K. Histopathology of membranous obstruction of the inferior vena cava in the Budd-Chiari syndrome. Gastroenteology 1992;102:2081–90.
4. Kew MC, McKnight A, Hodkinson J, Bukofzer S, Esser JD. The role of membranous obstruction of the inferior vena cava in the etiology of hepatocellular carcinoma in Southern African blacks. Hepatology 1989;9:121–5.
5. Dilawari JB, Mambery P, Chawla Y, Kaur U, Bhusnurmath SR, Malhotra HS, et al. Hepatic venous flow obstruction (Budd-Chiari syndrome): experience with 177 patients and a review of the literature. Medicine 1994;73:21–36.
6. Shrestha SM, Okuda K, Uchida T, Maharjan KG, Shrestha S, Joshi BL, et al. Epidemicity and clinical picture of liver disease due to obstruction of the hepatic portion of the inferior vena cava in Nepal. J Gastroenterol Hepatol 1996;11:170–9.
7. Simson IW. Membranous obstruction of the inferior vena cava and hepatocellular carcinoma in South Africa. Gastroenterology 1982;28:233–5.
8. Takamura M, Ichida T, Yokoyama J, Matsuda Y, Nomoto M, Aoyagi Y. Recurrence of hepatocellular carcinoma 102 months after successful eradication and removal of membranous obstruction of the inferior vena cava. J Gastroenterology 2004;39:681–4.