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Case Report

Progression from idiopathic portal hypertension to incomplete septal cirrhosis with liver failure requiring liver transplantation

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We report the case of a 30-year-old male patient suffering from what was initially thought to be end-stage cryptogenic cirrhosis with portal hypertension and liver failure, who underwent liver transplantation. Histological examination of the surgical specimen showed incomplete septal cirrhosis. At the age of 17 this patient had presented pancytopenia and splenomegaly, which were treated by splenectomy. The surgeon discovered portal hypertension. Re-examination of the wedge liver biopsy taken at this time revealed features of idiopathic portal hypertension.

This case clearly shows that incomplete septal cirrhosis may be a late manifestation of idiopathic portal hypertension. The presence of sinusoidal dilatation and peliosis as well as early evidence of fibrosis which are already visible on the initial biopsy and are still present on the late specimen, are indirect evidence of a continuous process which ultimately led to incomplete cirrhosis with liver failure.

Key words: **Hepatoportal sclerosis; Idiopathic portal hypertension; Light liver microscopy.**

In 1966, Popper (1) introduced the term "incomplete septal cirrhosis" (ISC), which represents a type of macronodular cirrhosis in which thin and often incomplete septae demarcate larger, rather inconspicuous nodules. In 1988, Sciot et al. (2) reviewed a series of cases. The following histological features appeared to be characteristic: parenchymal nodularity, thin incomplete septae, hypoplastic portal tracts, an increase in the number of venous channels, abnormal spacing between portal tracts and veins, crowding of reticulin fibers between adjacent zones of hypoplastic parenchyma, hyperplasia of hepatocytes and dilatation of sinusoids.

On histological and clinical grounds, incomplete septal cirrhosis resembles idiopathic portal hypertension (IPH), nodular regenerative hyperplasia and partial nodular transformation. In these conditions, obliterative portal venopathy resulting in heterogeneity of the portal blood supply to the parenchyma has been suggested as a pathogenic mechanism (3–6).

Despite the fact that clinical symptoms are different from cirrhosis (a higher incidence of bleeding varices, low incidence of ascites, absence of encephalopathy), the survival curve was similar to that of macronodular cirrhosis with a 5-year survival rate of 75 and 72% and a 10-year rate of 54 and 57%, respectively (3). This is markedly lower than the survival rate observed in non-cirrhotic portal hypertension (7,8).

We report a case of end-stage chronic liver failure of unknown origin in which the patient underwent liver transplantation. Graft pathology showed areas of incomplete cirrhosis. Retrospective analysis revealed that this patient suffered from IPH.

Case Report

A white male patient born in 1956 was admitted to the Liver Transplant Unit in 1990 for end-stage chronic liver failure and underwent transplantation in December of the same year. He was suffering from jaundice,

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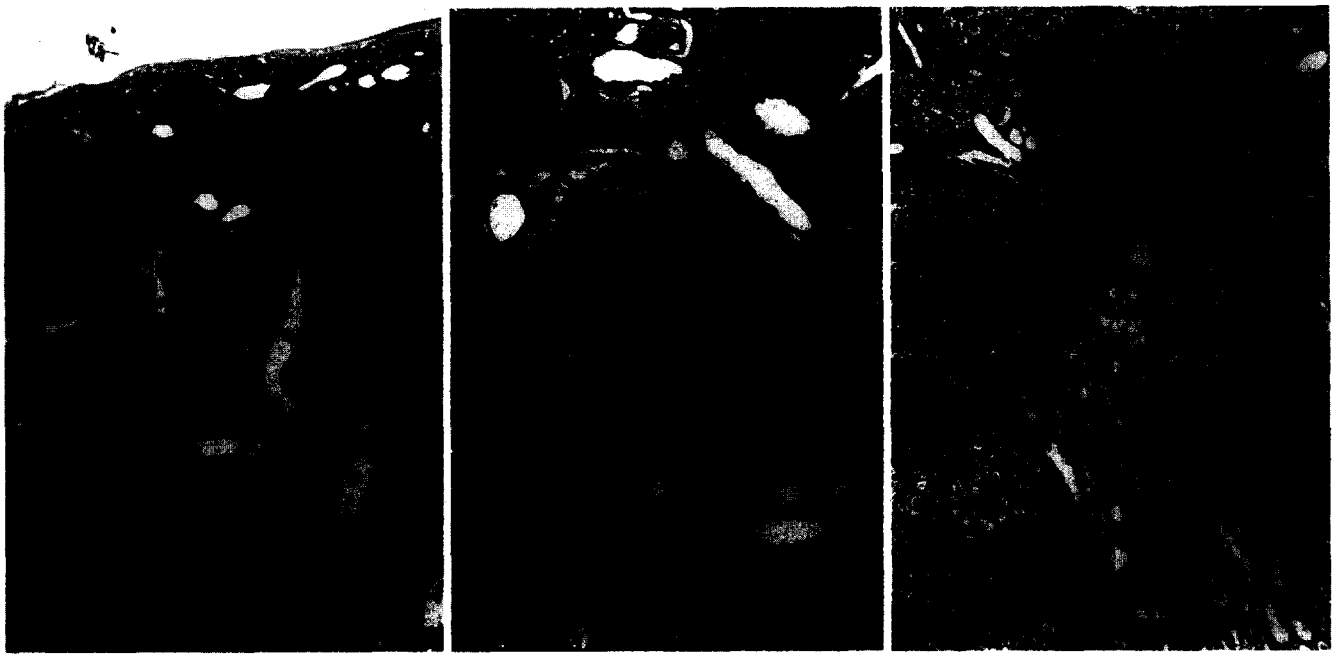

Fig. 1. Various views at low magnification of the heterogeneous lesions which can lead to a diagnosis of idiopathic portal hypertension and incomplete septal cirrhosis: an increased number of veins (star) in the parenchyma (a), fibrosed portal tracts, periportal angiomatosis, approximation of portal tracts (b), irregular thickness of fibrous bands surrounding nodules (c), arciform form of fibrous bands (b, c), thin septae (a, b). Underneath the capsule (a), not visible at this magnification, there is an irregular band of necrosis (arrowhead). (Explanted liver. H&E. a, b, c, original magnification: ×6.)

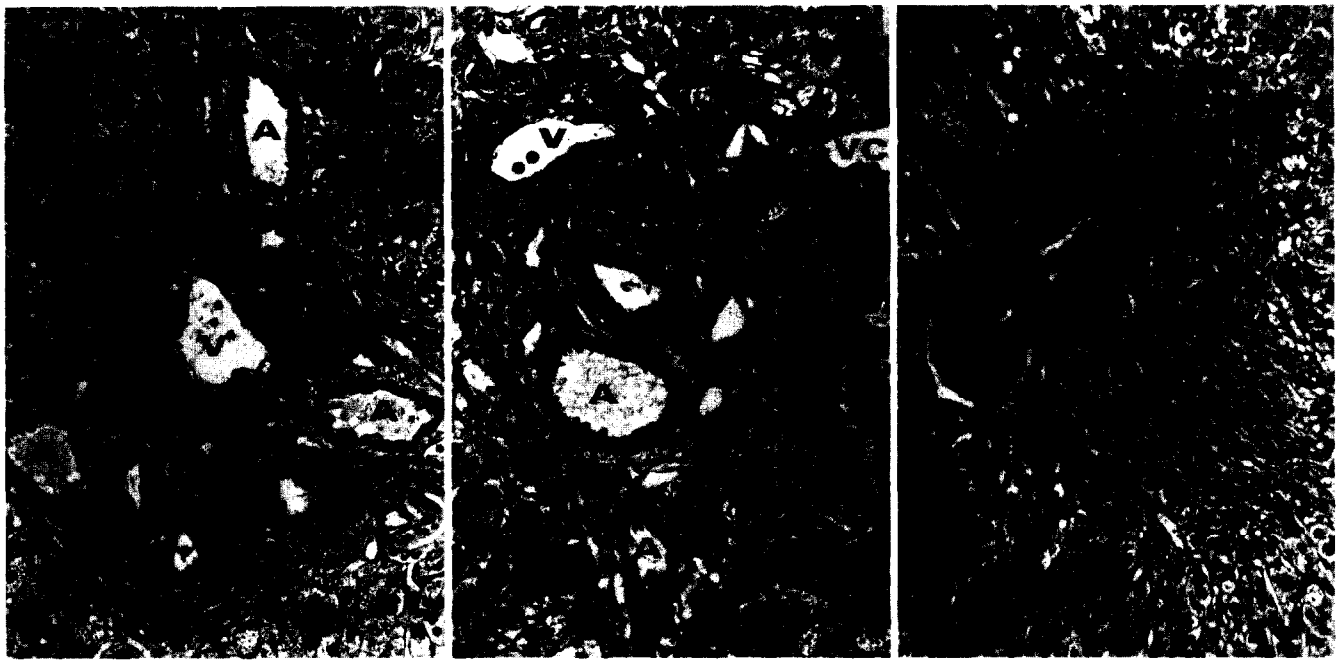

Fig. 2. Different aspects of fibrous portal tracts: (a) sclerosis of portal vein (V) in a fibrosed portal tract with three arteries (A); (b) abnormal intralobular venous channels (VC) abutting onto a fibrosed portal tract containing two arteries (A) and a small vein (V), and the fibrosed remnant of a vessel (arrowhead). (c) fibrosed portal tract (PT) in which identification of vessels is almost impossible; major inflammatory reaction and ductular proliferation. Note swollen hepatocytes in the periportal region (thick arrow). (Explanted liver, H&E, original magnification: a ×40, b ×60, c ×31.)

ascites, and encephalopathy. He had never suffered from bleeding. Liver tests gave the following results: bilirubin: 154 μmol/l (N<20 μmol/l), aspartate aminotransferase (ASAT): 125 IU/l (N<40 IU/l), alanine aminotransferase (ALAT): 56 IU/l (N<40 IU/l), PT: 42% (N>80%), Factor V: 59% (N>80%), alkaline phosphatase: 388 IU/l (N<120 IU/l). The patient had, 1 year earlier, undergone a routine check up which had shown bilirubin 36 μmol/l, ASAT 72, ALAT 46 and alkaline phosphatase 170. Complete examination at that time had revealed portal hypertension, esophageal varices (grade 3), wedge hepatic vein pressure 31 cmH_2O, gradient 24 cmH_2O, and cirrhosis on the liver biopsy. Investigation of possible etiologies, including alcohol, drugs, viruses (B, D, C), immune disorders, and metabolic disorders (Wilson, α1 anti-trypsin, hemochromatosis), was negative. There was no history of arsenic absorption or of exposure to vinyl chloride, "Bordeaux mixture" nor of excessive intake of vitamin A. Liver CT scan and indirect angiography showed no tumors or thrombosis of the portal vein or branches.

In 1976, the patient had undergone splenectomy to treat severe pancytopenia. The surgeon had noticed that the liver was rather small and mildly irregular and that there was portal hypertension. A wedge liver biopsy performed during surgery was interpreted as portal fibrosis. From 1976 to 1989, the patient had been in good health.

Three years later after liver transplantation, the patient is well and has returned to work.

Liver Pathology

Explanted liver

The liver weighed 1070 g and was atrophic, whitish, but with a noticeable red hypertrophic zone in part of the left lobe. On sections, these pale and reddish zones were clearly visible although there was no obvious systematization.

Modifications of portal tracts and extraportal vascular abnormalities with associated inflammation and disturbances of lobular architecture constituted the principal anomalies. These varied considerably from one area to another (Fig. 1). There were in many portal tracts numerous sections of veins, capillaries and lymphatic vessels (Fig. 1a, b), together with evidence of phlebosclerosis (Fig. 2a), and approximation of portal tracts or hepatic veins (Fig. 1a, b), all of which contributed to give the impression of a shrunken liver. Some fibrous portal tracts contained large arteries, which contrasted with the small vessels found in the place of a true portal vein (Fig. 1, 2). At the most, portal tracts contained only fibrous tissue with remnants of bile ducts and inflammatory elements (Fig. 2c). Occasional abnormal venous channels could be seen in the immediate vicinity of portal tracts (Fig. 2b).

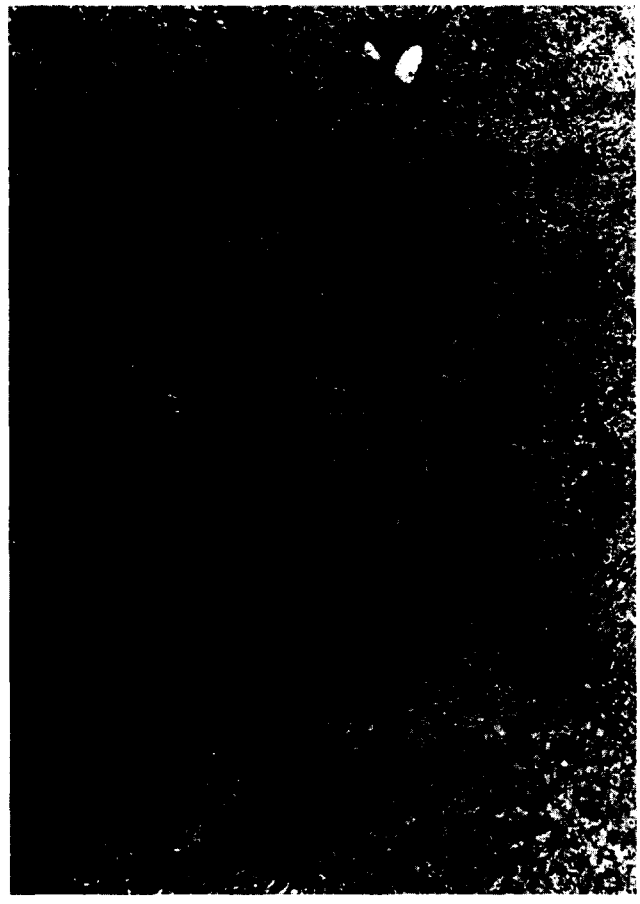

Fig. 3. Reddish area. Dilatation of sinusoids with extravasation of red blood cells and atrophic hepatocytes. These dilated sinusoids appear to parallel septae (arrowhead) radiating from veins and surround a fibrosed portal tract (PT) (see Fig. 2c). (Explanted liver, H&E, original magnification ×12.)

Vascular necrotic areas bridged portal tracts or branches of the hepatic vein in the subcapsular space. This vascular bridging often consisted of thin-walled blood vessels resembling capillaries and venules, engorged with erythrocytes, lymphocytes, plasma cells and other inflammatory cells (not shown). Some well-defined nodules could be observed, mainly underneath capsule, as well as zones of ill-defined nodularity with some nodules smaller than a lobule and some the size of several lobules (Fig. 1c). Nodules were partly separated by thin collagenous septae and occasionally by thick bands of arciform fibrosis (Fig. 1c). Well-defined nodules contained on their periphery large clear hepatocytes, some prenecrotic (Fig. 2c, 3). There was no evidence of cholestasis. Hepatic veins were often fibrotic. Rare areas of nodular regenerative hyperplasia

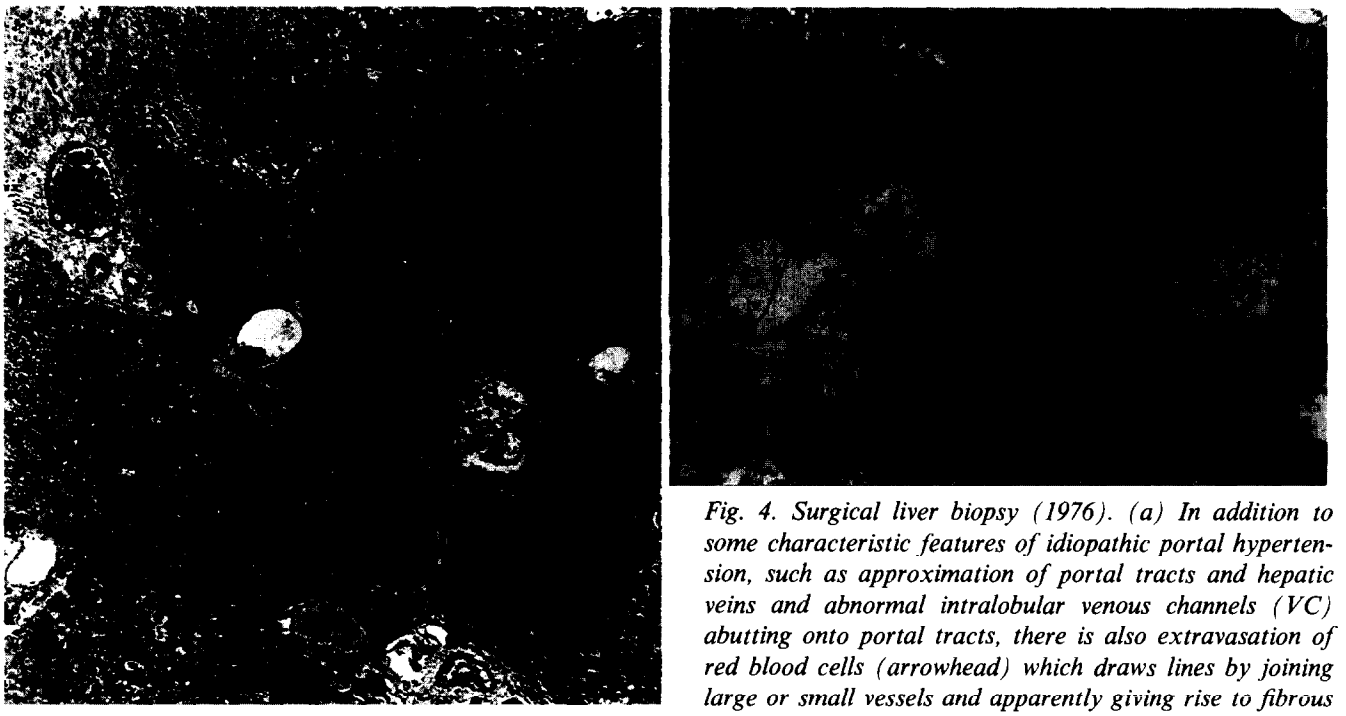

Fig. 4. Surgical liver biopsy (1976). (a) In addition to some characteristic features of idiopathic portal hypertension, such as approximation of portal tracts and hepatic veins and abnormal intralobular venous channels (VC) abutting onto portal tracts, there is also extravasation of red blood cells (arrowhead) which draws lines by joining large or small vessels and apparently giving rise to fibrous septae. (b) This portal tract partly seen at the bottom of the micrograph (a) contains numerous enlarged capillaries (C) in a loose fibrotic tissue. (Masson's trichrome, original magnification: a ×16, b ×30.)

could be seen (reticulin stain, not shown). In necrotic and peliotic areas, hepatocytes were loaded with iron (Perl's stain, not shown).

In specimens sampled in red areas, there was less evidence of vascular necrosis and fewer areas with fibrous bands than in whitish areas. Sinusoids were sometimes dilated and surrounded by atrophic bands of hepatocytes forming occasional peliotic areas containing inflammatory cells (Fig. 3). Lines of sinusoidal dilatation seemed to follow septae between vessels and give rise to the emergence of fibrous bands (Fig. 3).

Wedge liver biopsy (1976)

Portal tracts appeared enlarged by star-like fibrosis and contained numerous abnormal venous lumens. Some portal veins showed thickened walls; in somes cases venous channels abutted directly onto hepatocytic plates. There were also some peliotic areas surrounding septae (Fig. 4).

Discussion

Idiopathic portal hypertension (also known as hepatoportal sclerosis) can be defined as a clinical disorder of unknown cause, typically associated with splenomegaly and anemia in the absence of conditions that are known to cause portal hypertension (9). Liver pathology in severe cases is very characteristic, provided specimens are large enough, since lesions are extremely heterogeneous (2,10–12). This diagnosis should be borne in mind in the presence of: (a) numerous venous structures of varying size in the vicinity of a portal tract (periportal angiomatosis), (b) an increased number of veins in the parenchyma next to a septum, (c) a fibrosed peripheral portal tract with phlebosclerosis of some portal branches or even portal radicles beyond recognition, and (d) an approximation of portal tracts and perihepatic veins, particularly towards the capsule. The prognosis for IPH is generally good if variceal bleeding can be controlled (8,9). A certain number of cases of hepatic failure have, however, been reported.

Although this is still a confused and confusing area, some authors have considered ISC to be a late manifestation of IPH (3) and would place ISC on the border of the spectrum of cirrhotic liver disease on an interface with vascular disorders (2,3,13). Morphological criteria are the same for both disorders, except for the presence of parenchymal nodularity in ISC. The generally good prognosis for ISC has recently been challenged. The prognosis is, in effect, similar to that of macronodular cirrhosis (3).

The progression from IPH to ISC with liver failure requiring orthotopic liver transplantation has not been re-

ported. This case shows that ISC can be a late manifestation of IPH. The lesions described in our case, however, are far more severe than in the case described by Sciot (2), with areas indistinguishable from advanced micronodular cirrhosis raising the possibility that some unknown complicating factors hastened the fibrosis and possibly the hepatic failure. There appears to be little doubt, if we review all the pathologic abnormalities, that IPH is a vascular and probably a portal and/or sinusoidal and/or hepatic venous disorder. The approximation of portal tracts and of hepatic veins is a sequela of vascular collapse. In our case, vascular necrosis bridging portal tracts and hepatic veins was clearly visible, as were peliotic lesions which could represent the first obvious manifestation of this collapse. Portal tracts often presented, even on the same specimen, the two extreme characteristics of vascular disorder: (a) dilatation of venous vessels as a consequence of either an increase in blood flow or a blockage, or of both and (b) the ultimate disappearance of portal vessels preceded by phlebosclerosis of the vein, leaving in its place a fibrous scar with some proliferation of bile ductules. Even arteries, once hypertrophied, can disappear, causing atrophy of bile ducts. The presence of abnormal venous channels, a hallmark of this disease, can be interpreted as an attempt to form new portal veins. This lesion has been observed in rats with congenital portocaval shunt (14). The vascular origin of this disease is corroborated by the presence of some areas of nodular regenerative hyperplasia (7,11,15), a disease thought to be due to a heterogeneity in blood supply (6). The disease can be mild with some periportal angiomatosis and fibrosed portal tracts, or extremely severe with thick bands of collagens encircling cirrhotic nodules. The prognosis for ISC should remain reserved, particularly if evolutive lesions of vascular necrosis bridging portal tracts or hepatic veins, or peliosis, are discovered. Lesions observed on the 1976 liver biopsy were already severe.

It has been said that IPH is a very rare disease in western society (8,9). One center alone has, however, registered 47 cases of ISC over a period of 20 years (3). The absence of reported cases of liver transplantation in decompensated ISC would suggest that this disease has often been classified as cirrhosis.

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