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Clinical Aspects of Incomplete Septal Cirrhosis in Comparison With Macronodular Cirrhosis

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Background/Aims: **Incomplete septal cirrhosis (ISC) is a form of macronodular cirrhosis characterized by slender, incomplete septa that demarcate inconspicuous nodules. Its clinical features have not been investigated in a large series. The aims of this study were to review the clinical symptoms and evolution of ISC in 42 patients.** ***Methods:*** **Forty-two patients with at least one liver biopsy strongly suggestive of ISC were selected for the study covering a period between 1968 and 1987. Data for these patients were compared with the evolution of 49 patients with classical macronodular cirrhosis after chronic active hepatitis type B or C.** ***Results:*** **Possible etiological factors for ISC were alcohol abuse, arsenic treatment, and hepatitis B infection. In three cases, a genetic factor could not be excluded. Patients with ISC had significantly lower serum concentrations of transaminases and bilirubin at diagnosis. Compared with macronodular cirrhosis, bleeding varices were more frequent (57% vs. 22%) in ISC. Ten-year survivals in the ISC and the macronodular cirrhosis groups were 54% and 57%, respectively.** ***Conclusions:*** **ISC represents a relatively stable burnt-out form of macronodular cirrhosis with an unusually high incidence of variceal bleeding. This could be explained by a superimposed insufficiency of the portal vascular supply.**

The macronodular type of cirrhosis is subdivided into two subforms. One is the postnecrotic type, in which the liver is coarsely scarred with obvious macronodules surrounded by broad fibrous septa. The second is the incomplete septal form, characterized by slender and often incomplete septa that demarcate large, rather inconspicuous nodules. The latter type was first described by Popper in 1966.[1] The clinical features of incomplete septal cirrhosis (ISC) have never been investigated in a large series. Therefore, we analyzed the clinical characteristics of 42 patients with ISC diagnosed between 1968 and 1987 in a retrospective study. Histopathological aspects have been described in detail in a separate report.[2]

Materials and Methods

Between 1968 and 1987, 98 of 13,300 liver biopsy specimens were characteristic or suggestive of ISC. These specimens were evaluated according to a histological scoring system based on the presence of the following morphological features: parenchymal nodularity, thin incomplete septa, hypoplastic portal tracts, increase in venous channels, abnormal spacing between portal tracts and veins, crowding of reticulin fibers, hyperplastic hepatocytes, and dilated sinusoids. For the purpose of the present clinical study, only 42 patients, 27 male (64%) and 15 female (36%), were selected. For them, at least one liver biopsy specimen was considered highly probable (n = 26) or suggestive of ISC (n = 16) (categories I and II of reference 2).

Clinical data for these 42 patients were obtained from the patient records. In 1989, 26 patients were still alive and 23 of them were seen in our outpatient clinics. At these visits, values of liver enzymes, hepatitis B serology, and C antibodies (first-generation Ortho ELISA system; Ortho, Raritan, NJ) were assessed. An ultrasound examination of the liver was performed in all 23 patients, and esophagogastroscopy was performed in 20 of them.

The outcome of the 42 patients with ISC was compared with the evolution of a group of 49 patients, 30 male (61%) and 19 female (39%), with classical macronodular, viral hepatitis–related cirrhosis (MNC), who were followed up during the same period. Liver biopsy specimens of these patients were characterized by the presence of obvious macronodules, surrounded by broad fibrous septa. MNC had resulted from a chronic hepatitis B infection in 37 patients and from chronic hepatitis C in the 12 others. For both groups of patients, ISC and MNC, time of entry in the study was the moment of histological diagnosis of cirrhosis.

Statistical analysis of the differences in symptoms and complications between the two groups was examined using Fisher's Exact Test. Differences in the laboratory data were analyzed with the Wilcoxon Mann–Whitney and the two-sample *t* test. Survival estimates were calculated by the Kaplan–Meier method; overall mortality as well as liver-related death were used as end points. All calculations were performed with the statistical package SAS.[3]

Abbreviations used in this paper: ISC, incomplete septal cirrhosis; MNC, macronodular cirrhosis.

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Table 1. Major Presenting Characteristics, Clinical Features, and Total Number of Complications in Patients With ISC and MNC

	ISC (%) (n = 42)	MNC (%) (n = 49)	P^a
Presenting symptoms and signs	27 (64)	1 (2)	<0.001
Portal hypertension			
Bleeding esophageal varices	23 (55)	0 (0)	<0.001
Thrombocytopenia or splenomegaly	4[b] (10)	1 (2)	0.177
Jaundice	6 (14)	18 (37)	0.018
Serum transaminase levels >2× upper limit	3 (7)	26 (53)	<0.001
Incidental finding	6 (14)	2 (4)	0.137
Ascites	0 (0)	2 (4)	0.497
Clinical features at diagnosis	0	36	
Median time period between appearance of symptoms and diagnosis of cirrhosis (*mo*)			
Esophageal varices	28[c] (72)	15[c] (35)	<0.001
Bleeding varices	23 (55)	3 (6)	<0.001
Clinically significant ascites	6 (14)	8 (16)	1.000
Child–Pugh classification	30 (71)	26 (53)	0.057
A			
B	11 (26)	16 (33)	0.646
C	1 (2)	7 (14)	0.065
Complications	24 (57)	11 (22)	0.001
Bleeding varices			
Ascites[d]	8 (19)	17 (35)	0.106
Spontaneous bacterial peritonitis	1 (2)	2 (4)	1.000
Hepatorenal syndrome	0 (0)	2 (4)	0.497
Encephalopathy[e]	0 (0)	7 (14)	0.014
Hepatocellular carcinoma	0 (0)	6 (12)	0.029
IgA glomerulonephritis	0 (0)	3 (6)	0.025

IgA, immunoglobulin A.
[a]Fisher's Exact Test, two-tailed.
[b]In general, thrombocytopenia (<100,000/μL) was observed at the initial examination in 18 patients; 14 of them presented with bleeding varices.
[c]Endoscopy or radiography was performed in 39 patients with ISC and in 43 patients with MNC. Percentages are expressed in relation to the number of patients examined for the presence of varices.
[d]Clinically significant ascites, requiring diuretic treatment.
[e]Postshunt encephalopathy excluded.

Results

Presenting Symptoms and Signs

At diagnosis, the mean ± SD age of the patients with ISC was 42.8 ± 18.6 years (range, 3–75). There were three children below the age of 10 years. One of them had had history of recurrent variceal bleeding since the age of 2. In two 8-year old children with persistent elevation of transaminase levels, a chronic hepatitis B infection was shown by serology and histological examination.

Symptoms and signs at the first presentation of liver disease and at the time of histological diagnosis of cirrhosis are given in Table 1. Most patients with ISC (64%) had bleeding esophageal varices and/or hypersplenism and thrombocytopenia. In contrast, patients with MNC mainly presented with jaundice or persistent elevation of serum transaminase levels. At the time of histological diagnosis of liver cirrhosis, endoscopic or x-ray examination of the upper gastrointestinal tract was performed in 39 of the patients with ISC. Twenty-three of them had bleeding varices. Corresponding values for patients with MNC were significantly lower. Of the 23 ISC patients with bleeding esophageal varices, 16 belonged to the Child A group. At the time of diagnosis, clinically significant ascites that needed diuretic therapy was equally present in both groups. In 2 patients with ISC, ascites developed later on (Table 1). Possible risk factors for the development of ascites in these 8 patients with ISC consisted of an episode of variceal bleeding (n = 6), a child B status (n = 5), the presence of a portal vein thrombosis (n = 4), and histological evidence of chronic

hepatitis B infection (n = 2). In the MNC group, ascites was present at diagnosis in 8 patients; ascites developed in 9 cases during further follow-up (Table 1).

Liver test results were similar in both groups except for lower bilirubin values in ISC. The median (range) values for ISC and MNC, respectively, were as follows: bilirubin, 0.87 mg/dL (0.20–3.66) vs. 1.15 mg/dL (0.35–5.10), $P = 0.006$; aspartate aminotransferase, 17 U/L (7–84) vs. 53 U/L (11–406), $P = 0.001$; and alanine aminotransferase, 17 U/L (6–159) vs. 68 U/L (14–535), $P = 0.001$.

Possible Etiological Factors

Based on histology and immunohistochemistry, a specific etiology of the cirrhosis was only found in four biopsy specimens: three hepatitis B infections and one alcoholic liver disease. However, on clinical grounds, in 7 patients, ISC could possibly be related to alcohol abuse of at least 100 g of alcohol per day (taken as beer) for more than 10 years. Five other patients had been treated for psoriasis with arsenic (Fowler's solution) during 2–15 years. Three patients with negative staining for hepatitis B surface antigen (HBsAg) and hepatitis B core antigen (HBcAg) in the liver specimen had anti-HBs and anti-HBc in serum. One patient had been treated with prednisone and azathioprine because of an antinuclear and anti–smooth muscle antibody–positive autoimmune chronic hepatitis. In 4 patients, a clinical diagnosis of chronic non A non B hepatitis had been suggested. Stored sera of these patients were negative for hepatitis C antibodies.

Follow-up

Sixteen patients with ISC (38%) have died. In 10 of them (24%), mortality was directly related to the liver disease. One patient died of spontaneous bacterial peritonitis, whereas death was related to variceal hemorrhage in 9 others. Four died during a variceal bleeding episode, whereas 5 patients died of post-shunt liver insufficiency between 3 and 57 months after portosystemic shunt surgery.

In the 26 patients who have survived, median follow-up was 104 months (range, 31–204 months). At the end of the follow-up period, nearly all survivors had remained in the same Child class as that observed at the time of diagnosis, except for 3 patients who progressed from class A to B and 1 patient from class B to C. In 1 of the 19 patients who had not bled by the time of diagnosis, variceal hemorrhage developed during further follow-up. Of the 26 survivors, 10 did not have endoscopic evidence of varices at the time of diagnosis of ISC. In 6 of them, absence of varices was confirmed by esophagogastroscopy at the last control examination, whereas the 4 others had no evidence of variceal bleeding during the follow-up period but lacked endoscopic confirmation.

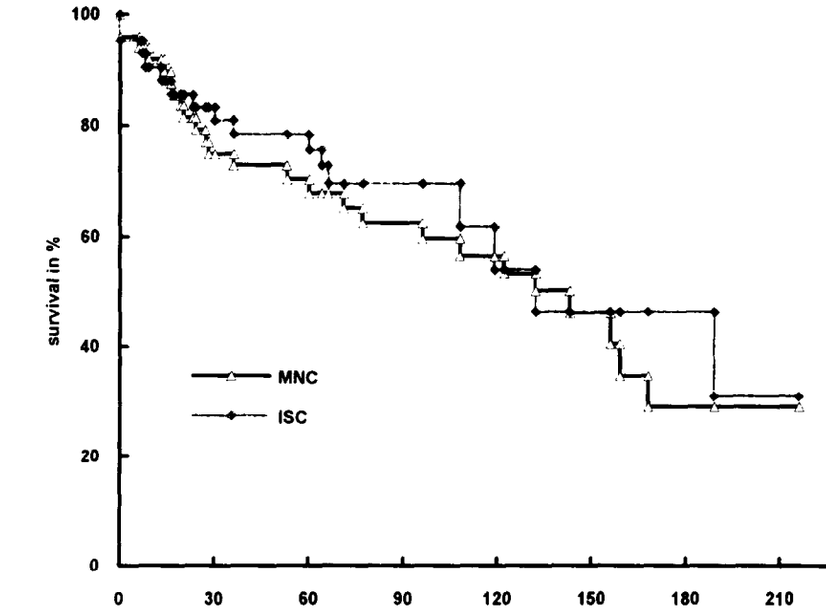
Variceal bleeding was treated by portosystemic shunting in 19 patients. The shunt operation was performed in relation to the first bleeding episode in 6 patients and to recurrent bleeding in the 13 others. Seven of these 19 patients had initially been treated by endoscopic variceal sclerotherapy, which was, however, followed by severe recurrent variceal bleeding within 1–3 months after the start of sclerotherapy. Nine of the 19 patients who underwent portosystemic shunting (47%) died: 2 died within the first postoperative days, 3 died within 1 year, and 4 died later. The median survival of the 10 patients who are alive after portosystemic shunting is 96 months (range, 57–160 months); none of them has developed recurrence of bleeding. The mean portal pressure for 15 patients in whom it was measured intraoperatively was 39.6 ± 8.4 cm H_2O.

Mortality Rates

The final outcome of the 42 patients with ISC was compared with the evolution of 49 patients with MNC. Mean age of the ISC and the MNC group was 42.8 ± 18.6 and 53.4 ± 12.4 years (±1 SD), respectively, whereas the mean duration of follow-up was 79 and 86 months, respectively. Complications related to the two types of macronodular cirrhosis are given in Table 1. The overall survival curves for both groups are shown in Figure 1. No significant differences between the two groups could be found ($P = 0.59$, Wilcoxon). The Kaplan–Meier survival estimates for liver related deaths also showed no significant differences between both groups ($P = 0.85$, Wilcoxon). Ten-year survival rates in the ISC and the MNC patients were 54% and 57%, respectively.

Discussion

ISC has been considered to run an indolent course with well-preserved liver functions but with portal hypertension and gastrointestinal bleeding as major complications.[4] The etiology of this type of cirrhosis is obscure.[4–6] In the 42 patients in our study, histological features indicative of a specific etiology were only found in four biopsy specimens. This supports Popper's initial description that histological indicators of the original offender are usually absent.[1] On a clinical basis, ISC could often be related to treatment with arsenic and to long-term alcohol abuse. Recently, four family members with ISC without any evidence of chronic illness or of any exposure to specific drugs or chemicals were described,[7]



months	0	30	60	90	120	150	180	210	240
MNC	49	34	28	21	17	7	2	1	0
ISC	42	34	28	14	6	4	3	0	0

Figure 1. Survival function estimates (Kaplan–Meier) of a group of 49 patients with classical MNC and a group of 42 patients with ISC. The numbers of patients remaining in the sample at the given time points are shown beneath the figure.

suggesting a common environmental or even genetic etiological factor. It is noteworthy that, in our series, three patients with ISC had congenital diseases such as Noonan's syndrome and mitochondrial myopathy and a disorder characterized by congenital cataract and mental retardation.

Our patients most frequently presented with bleeding esophageal varices and/or hypersplenism and only mild or no abnormalities of liver test results. Overt portal hypertension occurred in the absence of a previous history of long-standing liver disease. This is in contrast to the patients with MNC, who had a median history of liver disease of 36 months before the diagnosis of cirrhosis. Variceal hemorrhage was not a feature of end-stage liver disease, because 70% of our patients with variceal bleeding belonged to Child class A. The high number of failures of variceal sclerotherapy necessitating shunt surgery, the high portal venous pressure, and the high total mortality related to variceal hemorrhage were indicative of the severity of the portal hypertension complicating ISC. The clinical evolution of the surviving patients was characterized by an almost unchanged Child index at the end of the follow-up period. Furthermore, at least 10 patients did not have varices at the time of diagnosis and did not develop varices or had no evidence for variceal bleeding during further follow-up. Both of these findings further support our concept that ISC represents a burnt-out, hyperregenerative form of liver cirrhosis.[2]

Taking into account the histological and clinical aspects, ISC seems to resemble a number of liver diseases, such as idiopathic portal hypertension or noncirrhotic portal fibrosis,[8–13] nodular regenerative hyperplasia,[9,14–15] partial nodular transformation,[9,16–18] and chronic schistosomiasis.[19] These entities are also characterized by portal hypertension with only mild abnormalities of liver test results. Their pathogenesis is uncertain but seems to be related to an obliterative venopathy of the intrahepatic portal vein radicles. ISC primarily results from liver cell necrosis with minimal collapse and fibrosis and with predominant regeneration.[1,2] However, a portal vascular insufficiency seems to be superimposed on these pathogenic factors. The miniature size of portal tracts and phlebosclerotic lesions in larger portal tracts may lead to a deficient portal blood supply to the parenchyma.[2] As such, ISC could be placed at the "edge" of the spectrum of cirrhotic liver diseases linking the group of cirrhotic conditions with the vascular diseases.[20]

The prognosis of idiopathic portal hypertension is much better than that of liver cirrhosis.[10,11] In the series of Okuda et al.,[11] 10-year survival from the time of diagnosis was 77% for idiopathic portal hypertension in contrast to 29% for cirrhosis. In our series, no difference was found between the ISC and MNC groups. A direct comparison between ISC and noncirrhotic portal fibrosis could not be made because of our limited experience with the latter group of patients. Kingham et al.[13] reported a median survival rate of about 30 years in a group of 59 cases with noncirrhotic portal hypertension. By contrast,

the median survival rate in our ISC group was 11 years. The 5-year survival of our shunted patients was 63%, which is far below the reported 5-year survival of approximately 90% in noncirrhotic portal fibrosis.[12,15] ISC thus seems to behave more like classical MNC. The evolution of ISC may follow a heterogeneous pattern, varying from a stable, uncomplicated condition to a liver disease with severe portal hypertension but with good response to decompressive shunt surgery, or to a real cirrhotic condition with evolution to liver failure after shunt surgery for bleeding varices.

In conclusion, ISC represents a characteristic pathological and clinical entity within the broad spectrum of liver cirrhosis. The histological picture with parenchymal nodules and septa, albeit often very vague and inconspicuous, as well as the overall survival curve, which is similar to that of a MNC control group, indicate that ISC is indeed a genuine cirrhosis. However, portal hypertension is far more important in the ISC group. In our opinion, ISC can best be placed at the edge of the spectrum of cirrhotic liver disease linking the group of cirrhotic conditions with the "vascular diseases."

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