Liver International 2004: 24: 452–456
Printed in Denmark. All rights reserved

Liver International
DOI: 10.1111/j.1478-3231.2004.0989.x

Clinical Studies

Incomplete septal cirrhosis: an enigmatic disease

Schinoni MI, Andrade Z, de Freitas LAR, Oliveira R, Paraná R. Incomplete septal cirrhosis: an enigmatic disease.
Liver International 2004: 24: 452–456. © Blackwell Munksgaard 2004

Abstract: Incomplete septal cirrhosis is a form of macronodular cirrhosis characterized by fine and incomplete septa, which delimit rudimentary regeneration nodules. Its etiopathogeny is uncertain and is associated with various diseases such as regenerative nodular hyperplasia, idiopathic portal hypertension, and partial non-cirrhotic nodular transformation, as well as with progression and regression of cirrhosis of any etiology. Few studies are available in the literature describing the clinical and biological characteristics of incomplete septal cirrhosis. *Goal:* The objective of the present descriptive study was to study this entity in the city of Salvador, Bahia, Brazil, and to compare the histopathological, biological and clinical data obtained with those reported in the specialized literature. *Materials and Methods:* We reviewed eight cases of incomplete septal cirrhois of varieties etiologies. Hepatitis C, autoimmune hepatitis, alcoholic liver disease and criptogenic liver disease were present in our cases. Fibrosis progression as well as cirrhosis regression could be identified in these patients. *Conclusions:* We concluded that Incomplete septal cirrhosis is not a disease itself but it could be considered as a stage of progression and regression of liver fibrosis.

Maria I. Schinoni[1], Zilton Andrade[2], Luiz A.R. de Freitas[2], Rubem Oliveira[1] and Raimundo Paraná[1]

[1]CPgMS-Federal University of Bahia, Bahia, Brazil, [2]CPqGM-Oswaldo Cruz Foundation, Bahia, Brazil

Key words: etiology – histopathology – incomplete septal cirrhosis

Maria Isabel Schinoni, Av. Juracy Magalhães, Jr No. 2096, Sala 510 Salvador, Bahia 41920.000, Brazil.
Fax: 5571.3594980
e-mail: unif@svn.com.br

Received 2 October 2003,
accepted 17 May 2004

Incomplete sepal cirrhosis (ISC), described by Popper (1) in 1966, represents the macronodular type of cirrhosis in which fine and incomplete septa delineate rudimentary regeneration nodules. ISC was initially correlated to the 'post-hepatitis' type of cirrhosis or type III in the classification proposed by Gall (2) and to type B in the classification of Miyake (3). The histological characteristics of ISC are: hypoplastic portal tracts, increase in venous channels, abnormal space between portal tracts and veins, accumulation of reticulin between adjacent zones of hyperplastic parenchyma with dilated sinusoids, and hepatocyte hyperplasia with two- or three-cell-thick plaques. It is important to point out that, among the histopathological entities, ISC is the one in which the finding of sepal fibrosis (fibrosis that starts from the portal space connecting it to other portal spaces or to the centrolobular veins) is most prominent.

The role of histopathology is crucial in the diagnosis of this entity. Several investigators have reported that a surgical hepatic biopsy or a liver biopsy obtained at autopsy is more sensitive for the diagnosis than a needle biopsy. Some of them consider mandatory staining techniques for reticulin and collagen to define diagnosis (4).

The etiopathogic pathways of ISC are uncertain, since this entity having been described in patients with hepatitis B and C virus infection (5), alcoholism (5), intoxication with vasculotoxic chemicals such as arsenic (6), and also in relatives (7), indicating a possible hereditary nature.

The pathogenesis is also unknown. The hypothesis that has been raised was related to alterations in intrahepatic blood flow leading to an unequal blood supply to the hepatic parenchyma, promoting atrophy and hepatocellular damage.

In most reported cases of ISC, the clinical picture was silent and in patients who presented some signs or symptoms of liver disease, anemia and thrombocytopenia were the most relevant findings.

The most controversial point about ISC concerns the evolution and prognosis of the disease. Many authors consider it to be the final stage of

Abbreviations: ALT, alanine transaminase; ANA, anti-nuclear antibodies; Anti-HAV IGg, hepatitis A antibody; Anti-HCV, hepatitis C antibody; ASMA, anti-smooth muscle antibodies; AST, aspartate transaminase; HbsAg, hepatitis B antigen; IBD, inflammatory bowel disease.

an entity known as idiopathic portal hypertension (4, 8, 9), while others have postulated that ISC may be a stage of regression of cirrhosis (10, 11).

In view of the lack of consistent epidemiological, clinical and biological data concerning ISC in Brazil, studies are needed for a better understanding of this entity. We report here cases collected in the city of Salvador, Bahia, Brazil, at referral centers for the study of liver diseases in Northeastern Brazil.

Marerials and methods

We conducted a retrospective descriptive study of series of ISC cases diagnosed over the last 6 years at three referral centers for the study of liver disease in Salvador, Northeastern Brazil. The main objective was to study the histopathological, biological and clinical features of our cases of ISC.

The study involved a survey of the records of the laboratory of pathological anatomy of the University Hospital of Bahia, Aliança Hospital and Laboratory of Experimental Pathology and Cell Biology of the Research Center Gonçalo Moniz of the Oswaldo Cruz Foundation in Salvador city, Northeastern Brazil.

We surveyed the autopsy reports and the reports concerning needle or surgical liver biopsies containing descriptions compatible with ISC dignosis (fine fibrous septa and incomplete nodules) or already confirmed diagnosis. If the liver biopsy description suggested the possibility of ISC, the slide was selected for a protocol review.

Two expert pathologists reviewed the selected slides at the Oswaldo Cruz Foundation who further selected the slides that fulfilled the diagnostic criteria of ISC.

The patients whose histopathological diagnosis did not establish ISC in a categoric manner or whose clinical history was incomplete were excluded from the study.

The clinical, biological and histological variables were analyzed using the SPSS software Chicago, IL, USA, with a study of the frequencies, means and standard deviation.

Results

A total of 99 liver biopsy slides obtained from January 1995 to December 2001 were reviewed. The diagnosis of ISC was confirmed in 11 of these slides (11.11%), although only eight had a complete file record.

The data listed below were considered to be the most relevant for each case.

Case 1

A 68-year-old Caucasian male, an alcoholic consuming around 20 g alcohol per day, presented the liver palpable 4 cm below the right costal margin. No signs of chronic liver disease were present. The biopsy demonstrated the presence of fine and long fibrous septa originating from enlarged portal spaces and dissecting the hepatic parenchyma in various directions, completely or incompletely surrounding irregular portions of hepatic tissue. The circumscribed portions of the parenchyma occasionally formed regeneration nodules or maintained a normal trabecular structure. There were some focal points of inflammation inside the fibrous tissue with small accumulations of mononuclear inflammatory cells. The hepatocytes were of regular size.

Case 2

A 19-year-old Caucasian female with a familiar history of chronic hepatitis, history of choluria, jaundice, increased transaminase levels, positive autoantibodies and diarrhea with blood and mucus, was submitted to a liver biopsy and colonoscopy, with a diagnosis of idiopathic ulcerative recto colitis and chronic hepatitis of autoimmune etiology. Because of the difficulty in controlling inflammatory bowel disease, the patient was submitted to colectomy and to a new liver biopsy 4 years later, which was compatible with ISC. The biopsy showed sections of a subcapsular liver fragment with architecture altered by the presence of parenchymatous nodules of varying sizes fully or partially delimited by fine fibrous septa. Small portal spaces were recognizable in these septa. In some nodules, there was a disproportion between the number of central veins and the portal spaces. The inflammatory component was minimal, with no histological evidence of activity in the process.

Case 3

A 64-year-old Caucasian female with an ultrasonographic incidentally was showing echogenic alterations of the liver parenchyma, liver palpable 3 cm below the right costal margin, with no signs of chronic liver disease. She had slightly increased transaminase levels. She was negative for B/C virus or autoantibodies. She also had normal ceruloplasmin, serum ferritin and iron, and normal lipid profile. She was referred to a cryptogenic hepatitis outpatient clinic. A liver biopsy showed a moderate inflammatory infiltrate with the presence of fine septa that penetrated the hepatic parenchyma, surrounding incomplete nodules.

Case 4

A 20-year-old Caucasian male presented alterations of the hepatic profile in routine exams. Ultrasonography demonstrated hepatosplenomegaly with no physical signs of chronic liver disease. The patient had negative for B/C virus or autoantibodies, and copper and iron levels were normal. The patient was submitted to a liver biopsy. The histological findings were portal spaces enlarged by star-like fibrosis with formation of fibrous septa in the parenchyma. Proliferations of bile ductules and small or absent branches of the portal vein were observed in the portal spaces. In the interface with the parenchyma, some dilated vessels with thin walls were observed.

Case 5

A 54-year-old Caucasian male had a diagnosis of diabetes mellitus type 2 and hypertriglyceridemia, with alterations in hepatic profile and an ultrasound report of hepatic steatosis. He consumed 40 g of alcohol per day. He hadn't signs of chronic liver disease. He also presented elevated serum iron and ferritin levels motivating a liver biopsy with a suspicion of hemochromatosis, which was not confirmed. Abdominal tomography was performed during an episode of abdominal pain, revealing thrombosis of the proximal portion of the superior mesenteric vein coinciding with partial thrombosis of the portal vein. The liver biopsy revealed steatohepatitis with fine septal fibrosis eventually surrounding large nodules. The morphological picture showed ISC and steatohepatitis.

Case 6

A 63-year-old Caucasian male with positive serology for hepatitis C virus who reported a consumption of 20–50 g of alcohol per day. He had no signs of chronic liver disease or portal hypertension. Histology revealed areas with nodules of various sizes delimited by fine and incomplete septa. Dense inflammatory infiltrate surrounding bile ducts were detected in the portal spaces, with vacuolar damage to the lining epithelium. Mild steatosis with a moderate iron overload was observed. The hepatocytes were of regular size and aspect. There was mild necroinflammatory periportal and paraseptal activity. Chronic hepatitis of probable C virus etiology was diagnosed, evolving to histological signs of ISC.

Case 7

A 15-year-old Caucasian male was submitted to laparoscopy in the presence of acute abdominal pain. Hepatic changes suggestive of chronic disease were visualized and a liver biopsy was obtained. One of his grandfathers had autoimmune hepatitis. He was icteric, his liver was palpable 2 cm below the right costal margin, and he had acne and palmar erythema. Autoantibodies and viral serology were negative, and urinary copper was normal. The biopsy revealed fibrous enlargement of portal spaces and the formation of parenchymal septa, which tended to surround in part nodular portions of hepatic tissue.

Case 8

A 43-year-old Caucasian female with positive serology for hepatitis C virus, genotype 1b, was treated with interferon-α and ribavirin for 6 months, with no sustained response. The biopsy revealed large nodules delimited by fine septa, some of them incomplete, at times forming a spur that ended abruptly inside the nodule. There was minimal steatosis and inflammation with minimal signs of activity, but with leukocyte accumulation of moderate intensity in portal space. No iron overload was observed.

Table 1 summarizes the clinical history, Table 2 the findings of clinical examination, and Table 3 the laboratory data obtained at the time of biopsy. Figures 1–3 are representative slides of the cases.

Discussion

In the present study, we reviewed 99 liver biopsies obtained at autopsy or during surgery or with a needle whose description suggested ISC. We detected 11 cases of confirmed incomplete septal cirrhosis (11.11%), but only eight could be included.

Data reported by Wanless (12) in a study of 2500 liver biopsies revealed a 1.4% frequency of ISC. Another study conducted in Belgium by Nevens et al. (8) detected a 0.74% frequency (98 cases) of ISC in 13 300 liver biopsies. The discrepancy among these results may be explained by different approaches to the search for samples from the cases of this entity, with different sources of histological specimens being considered for analysis. In our study we selected cases with liver biopsy description compatible with ISC.

Demographically, all the patients in our study had a Caucasoid phenotype, and mean age was 43 ± 22 years. Five were males and three were females, in agreement with other series in which the male sex prevailed (8, 13).

In our series, four patients had presented hepatitis before evolution to ISC, patient number 2 had autoimmune hepatitis accompanied by inflammatory bowel disease and presented high

titers of autoantibodies (anti-nuclear antibodies (ANA), anti-smooth muscle antibodies (ASMA)); a first biopsy obtained during the phase of diagnosis of autoimmune hepatitis led to a diagnosis of hepatic cirrhosis with intense portal and lobular activity. This patient responded to treatment with prednisone and azathioprine. A second biopsy obtained 4 years later, during colectomy, was found to be compatible with ISC with no inflammatory activity. We should emphasize the excellent response to immunosuppression.

Considering that azathioprine can be a cause of nodular transformation of the liver, with regenerative nodular hyperplasia and incomplete septal cirrhosis being a manifestation of the latter (12), we cannot rule out this etiologic hypothesis. On the other hand, the absence of vascular damage typical of azathioprine toxicity and the clinical and biochemical responses to treatment suggest that ISC was the result of regression of fibrosis after resolution of hepatic aggression.

The third case had a diagnosis of asymptomatic cryptogenic hepatitis. The diagnosis of ISC was made 6 months after the first visit in order to clarify the laboratory signs of hepatic aggression. The patient had no antecedents of parenteral exposure and all known viral etiologies were ruled out because she participated in a research protocol on cryptogenic hepatitis.

Case number 6 was an asymptomatic carrier of C virus, genotype 1b, with a history of alcohol ingestion of about 40 g/day. Case number 8 was another patient with hepatitis C, genotype 1a, with a history of hepatitis 20 years before. She consumed 20 g of alcohol per day. Both patients presented two risk factors for the evolution of hepatic fibrosis, i.e., hepatitis C virus and alcohol ingestion. In a biopsy for treatment control, the first patient presented a picture of chronic virus hepatitis C evolving to ISC, the second had a previous biopsy showing only chronic hepatitis. In a later sample this patient already presented ISC. Cases of hepatitis C evolving to ISC have been reported by different authors, with findings of different stages of macronodular cirrhosis in the same specimen (4, 10). On the other hand, this patient was abstaining from alcohol, a fact that might have influenced the development of ISC possibly, as hepatic regeneration after stopping alcohol aggression.

Case number 5 was the only one with a history of diabetes type 2 and hypertriglyceridemia, with an ultrasound picture compatible with hepatic steatosis 2 years before the liver biopsy was taken. The histopathologic study demonstrated ISC. In this case there was another risk factor for progression of fibrosis since the patient reported an alcohol ingestion exceeding 50 g/day. On this basis, it became difficult to confirm whether the hepatic aggression originated from diabetes type 2 and insulin resistance (NASH) or from alcoholism.

Another important fact concerning this patient and probably the one most related to the etiopathogeny of ISC, was that the patient had signs and symptoms compatible with thrombosis in a superior mesenteric vein coinciding with partial thrombosis of the portal vein. In some reports of ISC cases, apparently without portal thrombosis, when the liver was studied macroscopically, portal thrombosis was detected (14).

The clinical variables considered in our study were those present at the time when the liver biopsy was taken. Most patients presented no symptoms and their hepatic laboratory profile were normal or slightly abnormal, in agreement with literature reports (7, 8).

Of the total number of liver biopsies with a diagnosis of ISC, six were obtained by laparoscopic surgery or laparotomy and two with a needle. All cases presented the two most important characteristics of ISC, with fine incomplete septa surrounding hepatic regeneration nodules, features that were detected in all cases reported in the literature (4, 10, 15). Additional findings were: enlarged portal spaces due to fibrosis, small portal spaces, and disproportion between the number of central veins and portal spaces, also described in ISC.

For the histopathological work-up, surgical biopsies should be preferred since the diagnosis of ISC seems to be underestimated in material obtained with a needle.

Considering the first description of ICS by Popper, some other authors tried to better define this entity, but reports are conflicting.

Nakanuma et al. (16), re-evaluated 107 liver biopsy with non-cirrhotic portal hypertension in Japan. The classical features of ISC were described in 25 cases, but overlap features were observed in patients with partial nodular transformation (PNT) and in true idiopathic portal hypertension (IPH).

The authors concluded that portal venous obliteration may be a remark of this condition and they suggested that PNT and ISC comprise a family of non-cirrhotic disease and could be considered different stages of the same disease (16).

In our cases, only one patient is in agreement with the Nakanuma et al.' study. This could be explained by different selection criteria. While Nakanuma et al. selected patients with non-cirrhotic portal hypertension, we selected patients with cirrhosis diagnosis in which the slide description suggested

ISC. This fact triggered the inclusion of a broad spectrum of liver disease in our study.

In a recent study, Ibarrola and Colina (17), reported nine cases of non-cirrhotic portal hypertension. The authors described the high degree of heterogeneity of histopatological features in these cases. Only three of them could be considered as having a defined diagnosis. Between these patients only one comprises diagnostic criteria for pure ISC. Remarkably, hilar portal thrombosis and other vascular abnormalities were described in many cases.

The authors concluded that in non-cirrhotic portal hypertension the histopatological findings were an abnormal remodeling of the liver related to vascular abnormalities (17).

Again, this study had a complete different selection criteria if compared with our study. As we selected patients without knowing their clinical diagnosis, we observed a variety of conditions in which vascular abnormalities were not present.

In conclusion, ISC is a histopathological entity caused by different etiologies and probably related to the process of evolution or involution of hepatic fibrosis. It does not seem to be a liver-specific disease. Moreover, ISC in this study was clearly related to a stage of fibrosing liver disease of different etiologies.

References

1. Popper H. What are the major types of hepatic cirrhosis? In: Ingelfinger F, Relman A, Finland M, eds. Controversy in Internal Medicine. Philadelphia: Saunders, 1966; 223–43.
2. Gall E A. Post-hepatitic, postnecrotic and nutritional cirrhosis. Am J Pathol 1960; 36: 241–71.
3. Nakashima T, Okuda K, Kojiro M, et al. Pathology of hepatocellular carcinoma in Japan, 232 consecutive cases autopsied in ten years. Cancer 1983; 51: 863–77.
4. Sciot R, Staessen D, Van Damme B, et al. Incomplete septal cirrhosis: histopathological aspects. Histopathology 1988; 13: 593–603.
5. Biolac-Sauge P, Le Bail B, Bernard P H, et al. Hepatoportal sclerosis. Semin Liver Dis 1995; 15(4): 329–39.
6. Guha Mazunder D N, Das Gupta J. Arsenic and non-cirrhotic portal hypertension. J Hepatol 1999; 11(1): 80–5.
7. Barnett J, Appelman H, Moseley R. A familial form of incomplete septal cirrhosis. Gastroenterology 1992; 102: 674–8.
8. Nevens F, Staesen D, Sciot R, et al. Clinical aspects of incomplete septal cirrhosis in comparison with macronodular cirrhosis. Gastroenterology 1994; 106: 459–63.
9. Bernard P-H, Le Bail B, Cransac M, et al. Progression from idiopathic portal hypertension to incomplete septal cirrhosis with liver failure requiring liver transplantation. J Hepatol 1995; 22: 495–9.
10. Wanless I, Nakashima E, Sherman M. Regression of human cirrhosis. Morphologic features and the genesis of incomplete septal cirrhosis. Arch Pathol Lab Méd 2000; 124: 1599–607.
11. Lemos I, Baptista A, Andrade Z. Histopatologia da cirrhose hepática em regressão. In: Anais da Reunião Anual de Iniciação Científica CPQ-GM. 2002; 31.
12. Wanless I. Micronodular transformation (nodular regenerative hyperplasia) of the liver: a report of 64 cases among 2,500 autopsies and a new classification of benign hepatocellular nodules. Hepatology 1990; 11(5): 787–97.
13. Dumortier J, Boillot O, Chevallier M, et al. Familial occurrence of nodular regenerative hyperplasia of the liver: a report on three families. Gut 1999; 45(2): 280–94.
14. Hillarie S, Bonte E, Denninger M-H, Casadevall N, Cadranel J-F, Lebrec D, et al. Idiopathic non-cirrhotic intrahepatic portal hypertension in the West: a reevaluation in 28 patients. Gut 2002; 2: 275–80.
15. Okuda K, Nakashima T, Okudaira M, Kage M, Yoshifumi A, Omata M, et al. Liver pathology of idiopathic portal hypertension. Comparison with non- cirrhotic portal fibrosis of India. Liver 1982; 2: 176–92.
16. Nakanuma Y, Hoso M, Sasaki M, Terada T, Katayanagi K, Nomomura A, et al. Histopathology of the liver in non-cirrhotic portal hypertension of unknown aetiology. Histopathology 1996; 28(3): 195–204.
17. Ibarrola C, Colina F. Cllinicopathological features of nine cases of non-cirrhotic portal hypertension: current definitions and criteria are inadequate. Histopathology 2003; 42: 251–64.