Case Reports

Title:

Acute deterioration of Idiopathic Portal Hypertension required Living Donor Liver Transplantation: A case report

Running title:

LDLT for idiopathic portal hypertension

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Abstract

Case reports of severe IPH requiring liver transplantation are very rare. We report the case of a 65-year-old woman who was diagnosed as having idiopathic portal hypertension (IPH). At the age of 60 years, her initial symptom was hematemesis due to ruptured esophageal varices. Computed tomography of the abdomen showed splenomegaly and a small amount of ascites without liver cirrhosis. She was diagnosed as having IPH and followed-up as an outpatient. Five years later, she developed symptoms of a common cold and rapidly progressive abdominal distension. She was found to have severe liver atrophy, liver dysfunction and massive ascites. Living donor liver transplantation was then performed and her postoperative course was uneventful. Histopathological findings of the explanted liver showed collapse and stenosis of the peripheral portal vein. The areas of liver parenchyma were narrow while the portal tracts and central veins were approximate one another, leading to a diagnosis of IPH. There was no liver cirrhosis. The natural history of refractory IPH could be observed in this case. Patients with end stage liver failure due to severe IPH can be treated by liver transplantation.

Introduction

Idiopathic portal hypertension (IPH) is a relatively rare disease, and it has been reported mostly in patients from Japan [1)]. Most IPH patients have a good prognosis with treatment for their esophagogastric varices, but some IPH cases develop end-stage liver failure despite various medical treatments[2-11)]. Such end-stage liver failure is an indication for liver transplantation, but details of such cases have not been fully reported in the literature. We treated a patient with severe IPH who required living donor liver transplantation (LDLT); this case allows one to observe the natural history of severe refractory IPH.

Case Report

A 65-year-old woman who had been followed-up for IPH at our hospital developed abdominal distension. At the age of 60 years, the patient presented with sudden hematemesis and was taken to a nearby hospital. On emergent upper gastrointestinal endoscopy, the ruptured esophageal varices were successfully ligated. Subsequently, the patient was transferred to our hospital.

On admission, her vital signs (heart rate, blood pressure, respiratory rate, and body temperature) were stable. On physical examination, her abdomen was soft, flat, and non-tender. Her spleen was palpable, but her liver was not palpable. She did not have encephalopathy. The patient denied any history of blood transplantation, alcohol abuse, or medications. Laboratory data showed pancytopenia (hemoglobin, 9.4g/dL; platelet count, 4.5 x $10^4/\mu$ L; and white blood cell count, 1,300 / μ L). Liver and renal function tests and electrolytes were normal. Her prothrombin time was slightly prolonged (73%). Hepatitis B surface antigen, hepatitis C virus antibody, and anti-mitochondoria antibody were all negative.

Computed tomography of the abdomen showed splenomegaly, incomplete extrahepatic portal vein thrombus, and a slight volume of free peritoneal fluid, but no hepatomegaly, liver cirrhosis, or liver tumors (Fig. 1A). The gastrointestinal tract, gallbladder, pancreas, kidneys, and genital organs were unremarkable. There was no obstruction of the extrahepatic portal vein or the inferior vena cava. Upper gastrointestinal endoscopy showed persistent esophageal varices.

The patient had portal hypertension that consisted of esophageal varices, splenomegaly, and pancytopenia. Liver function was completely normal at laboratory data, and liver cirrhosis was not found on imaging diagnosis, though liver biopsy was not performed.

Obstruction of the extrahepatic portal vein and the inferior vena cava, hematological malignancies, or other known diseases was ruled out. IPH was diagnosed, and she was followed routinely at our hospital as an outpatient during which she was prescribed propranolol and warfarin. Her condition remained quite stable and uneventful for five years.

At the age of 65 years, she developed symptoms of the common cold and rapidly progressive abdominal distension. At that time, laboratory data showed anemia (hemoglobin, 7.5 g/dL), but normal platelet and white cell counts. Serum aspartate aminotransferase, alanine aminotransferase, and total bilirubin levels were normal. Her serum albumin level was decreased to 2.6 g/dL. Her prothrombin time was 44%, which was drastically prolonged, despite vitamin K administration. She also had acute renal failure (blood urea nitrogen, 61 mg/dL; and serum creatinine, 3.8 mg/dL). Computed tomography showed massive ascites, and volumetry showed that her liver was atrophic, with only 44% of the volume of that 5 years earlier (Fig. 1B). Extrahepatic portal vein thrombus which was found 5 years earlier was disappeared. The Child-Pugh score was 11 points, and the model of end-stage liver disease (MELD) score was 23 points. She was diagnosed as having non-reversible, end-stage liver failure, and she underwent liver transplantation.

At laparotomy, she had 15 L of free intraperitoneal fluid. The liver was extremely atrophic; the resected whole liver weight was only 620g. An extended left lobe liver graft, weighting 400 g, was transplanted from her husband. The graft weight standard liver volume rate was 36.8%. A total splenectomy was also performed. The patient’s postoperative course was uneventful, and she was discharged at 50 days after surgery. Five months after transplantation, the patient developed enterocolitis caused by

cytomegalovirus infection; she died from peritonitis following perforation of the small intestine.

The explanted liver at the time of the LDLT was atrophic with a wavy surface. On histopathology, there was collapse and stenosis of the peripheral portal vein (Fig. 1C). The areas of liver parenchyma had become narrow so that the portal tracts and central veins were approximate one another. The entire specimen showed narrowing of the liver parenchyma, which was especially severe near the capsule. Inflammatory cells collection and dilated abnormal vessels were seen around the portal tracts. There were no pseudolobules or bridging folds. The histopathological findings were compatible with IPH. There was no liver cirrhosis or evidence of malignancy.

Discussion

Portal hypertension is usually caused by liver cirrhosis, but some cases of portal hypertension occur without cirrhosis. Sinusoidal portal hypertension of unknown etiology is regarded as IPH clinically. When diagnosing IPH, one must rule out liver cirrhosis, obstruction of the extrahepatic portal vein and the inferior vena cava, blood diseases, parasitic diseases, granulomatous hepatic disease, congenital liver fibrosis, chronic viral hepatitis, primary biliary cirrhosis, and other known diseases.[12)] IPH has been found in 2.1% to 2.6% of livers at autopsy.[13, 14)] IPH is associated with a spectrum of histological lesions, including incomplete septal cirrhosis, nodular regenerative hyperplasia, and partial nodular transformation.[14-16)] The lesions show some degree of uneven fibrosis but may coexist in the same liver. In our case, typical findings of incomplete septal cirrhosis, nodular regenerative hyperplasia, or partial nodular transformation were not seen. The pathogenesis of IPH is unclear, but it can occur in association with a variety of developmental, vascular, collagen vascular, or biliary tract diseases.[6, 8, 11)] Renal failure with or without transplantation and the toxic effects of some drugs may be related to IPH.[5, 8, 10, 11)] Common symptoms of IPH include splenomegaly, pancytopenia, gastrointestinal bleeding, ascites, and encephalopathy.

IPH patients can be treated by the usual approaches: a) chronic medical therapy, along with balloon tamponade and vasoactive drugs for bleeding esophageal varices; b) endoscopic variceal ligation and sclerotherapy for both chronic and acute treatment; and c) portosystemic shunt procedures (portocaval, mesocaval, or radiological) or devescularization surgery.[8)] In general, IPH dose not progress to liver cirrhosis or hepatocellular carcinoma. The prognosis for IPH patients is mostly good, if the gastrointestinal bleeding can be controlled. However, some IPH cases progress to

end-stage liver failure.

In our case, the patient developed symptoms of the common cold and rapidly progressive abdominal distension. Collagen diseases and autoimmune disorders are known as associated with IPH.[10, 11] Immune system plays a role in IPH, so infection may be one of progressive factors for IPH. Though decrease of hepatic blood flow is considered to relate to IPH progression, it is unclear whether decrease of hepatic blood flow affected acute deterioration in this case.[11] Portal vein thrombus is one of causes for decrease of hepatic blood flow, but it was not found in operation and explanted liver specimen.

Some IPH patients who are resistant to all other therapies may be successfully treated with orthotopic liver transplantation (OLT). Several case reports dealing with OLT for severe IPH are summarized in Table 1 [2-11]. Taking into account these previous reports and the present, there were 40 patients (30 men, 10 women) with a mean age at transplantation of 45.5 years (range: 20-65 years). Gastrointestinal varices, splenomegaly, and ascites were commonly seen in severe IPH patients who required OLT, but these symptoms are common in IPH (Table 2). No specific symptoms characterize severe IPH. Eleven patients were treated for varices, seven with sclerotherapy and four with endoscopic variceal ligation, and 9 patients underwent pretransplantation porto-systemic shunting procedures (6 transjugular intrahepatic porto-systemic shunts and 3 mesocaval shunts) (Table 3). The time between the clinical manifestations of portal hypertension and liver transplantation ranged from 2 months to 14 years, with a mean of 4.6 years. Patients underwent OLT because of rapidly progressive, life-threatening complications of portal hypertension and liver disease and the inefficacy of surgical or radiological porto-systemic shunting. Combined liver and

renal transplantation is performed in patients with associated severe renal failure.[5, 8, 10] Most patients with severe IPH in the literature were well following OLT. Four patients died in the early posttransplantation period, due to herpes zoster encephalitis, suicide, sudden rupture of an unsuspected splenic aneurysm, and pneumonia.[2, 8, 11] Three patients showed evidence suggestive of recurrent with IPH in the graft liver. One patient developed symptoms one year after OLT;[11] 2 patients were asymptomatic, though their liver biopsy findings after OLT suggested recurrence.[8, 11]

Making a pretransplantation diagnosis of IPH is difficult; 23 of the 40 patients with IPH were clinically believed to have cirrhosis, based on the clinical presentation, the pretransplantation biopsy findings, or the radiological images. The diagnosis was made only after post-transplant examination of the explanted liver. In cases who died from what appeared to be liver cirrhosis clinically, some had hidden IPH. In cases with symptoms of severe portal hypertension without liver dysfunction, IPH should be considered.

In conclusion, appropriate treatment can provide IPH patients with a good prognosis, but some patients with IPH develop end-stage liver failure. Some patients who are clinically diagnosed as having cryptogenic cirrhosis may have IPH. Patients with severe IPH who are resistant to other therapies may be good candidates for OLT, after which a favorable outcome can be expected.

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Figure Legends

Fig. 1: A. Computed tomography at the time of the first admission shows splenomegaly and incomplete extrahepatic portal vein thrombus (arrow). No liver cirrhosis or liver tumor is seen. B. Computed tomography 5 years after the first admission shows massive ascites and a very atrophic liver. C. Histopathological findings show collapse of the peripheral portal vein. Inflammatory cells and dilated abnormal vessels are seen near the portal tract (Hematoxylin and eosin stain).

Table 1 summary of case reports with severe IPH required liver transplantation

author	year	cases	gender	age at LT	diagnosis before LT	span between manifestation and LT	explanted liver weight	pathological diagnosis	prognosis
McDonald[2)]	1990	1	male	47	cirrhosis	10 years	973g	NRH	died (4 months)
Le Bail[3)]	1990	1	male	48	recurrent HCC Alagille syndrome	N / A	N / A	HCC NRH	well
de Sousa[4)]	1991	1	female	24	multiple liver tumors	1 year	2,970g	NRH Budd-Chiari synd.	well
Elariny[5)]	1994	1	female	44	cirrhosis	3 years	1,850g	NRH	well
Nadir[6)]	1994	2	male 1 female 1	60 (55-64)	cirrhosis 2	4 years (4-4 years)	N /A	NRH 2	all well
Bernard[7)]	1995	1	male	34	cirrhosis	14 years	1,070g	ISC	well
Loinaz[8)]	1998	4	male 4	35 (25-41)	NRH 1 cirrhosis 1 nodular liver 1 chronic liver disease 1	0.5 years (2 months-1 year)	1,100g (110-2,400g)	NRH 3 partial nodular transformation	died 2 (1, 3 months) recurrence 1 (7 years)
Radomski[9)]	2000	4	male 3 female 1	46 (39-55)	cirrhosis 4	7.7 years (4-13 years)	N / A	NRH 4	all well
Dumortier[10)]	2001	8	male 8	45 (20 - 63)	IPH 8	4.5 years (3-10 years)	1,045g (630-1,520g)	ISC 5 NRH 3	all well
Krasinskas[11)]	2005	16	male 11 female 5	47 (31-64)	cirrhosis 13 azathioprine-associated liver injury 2 NRH 1	4.3 years (1-11 years)	1,100g (600-1,550g)	NRH 15 ISC 9	died 1 (5 months) recurrence 2 (3.5, 7 months)
our case		1	female	65	IPH	5 years	620g	IPH	died (5 months)
total		40	male 30 female 10	45.5 (mean)		4.6 years (mean)	1,150g (mean)		

HCC, hepatocellular carcinoma; IPH, idiopathic portal hypertension; ISC, incomplete septal cirrhosis; NRH, nodular regenerative hyperplasia; LT, liver transplantation
N / A no available

Table 2 symptoms before liver transplantation in literatures

	Number of patients (%)
Gastrointestinal varices	33(83)
Splenomegaly	26(65)
Ascites	24(60)
Gastrointestinal bleeding	15(38)
Encephalopathy	11(28)
Cytopenia	6(15)
Hepatopulmonary syndrome	3(8)
Liver atrophy	1(3)
Retroperitoneal collateral rupture	1(3)
Pleural effusion	1(3)
Hepatomegaly	1(3)
Recurrent HCC	1(3)
Bacterial peritonitis	1(3)

HCC, hepatocellular carcinoma

Table 3 treatments before liver transplantation in literatures

	Number of patients (%)
sclerotherapy	7(18)
Transjugular intrahepatic porto-systemic shunts	6(15)
endoscopic variceal ligation	4(10)
mesocaval shunt	3(8)
splenectomy	3(8)
tumorectomy for HCC	1(3)

HCC, hepatocellular carcinoma

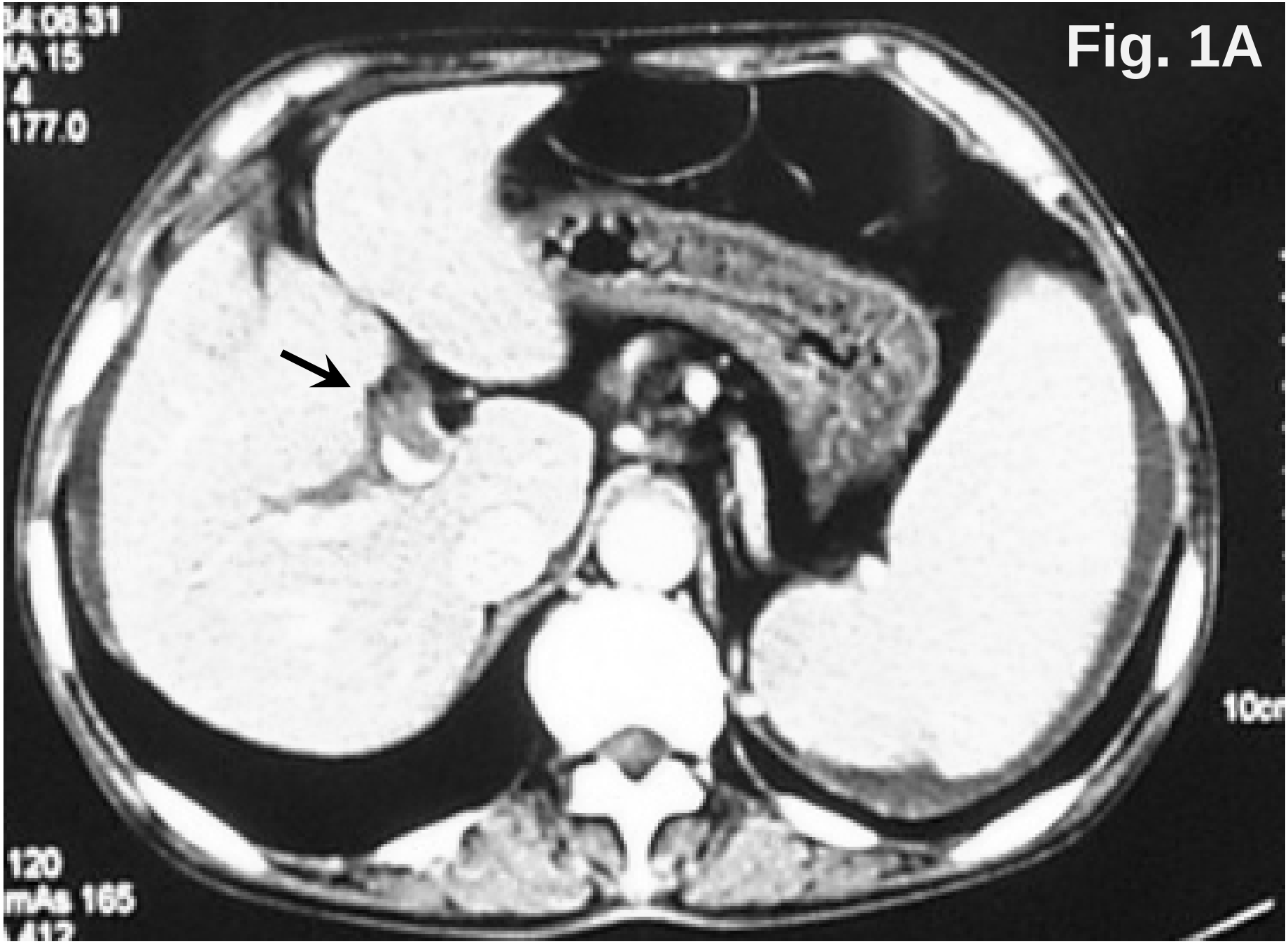
Fig. 1A

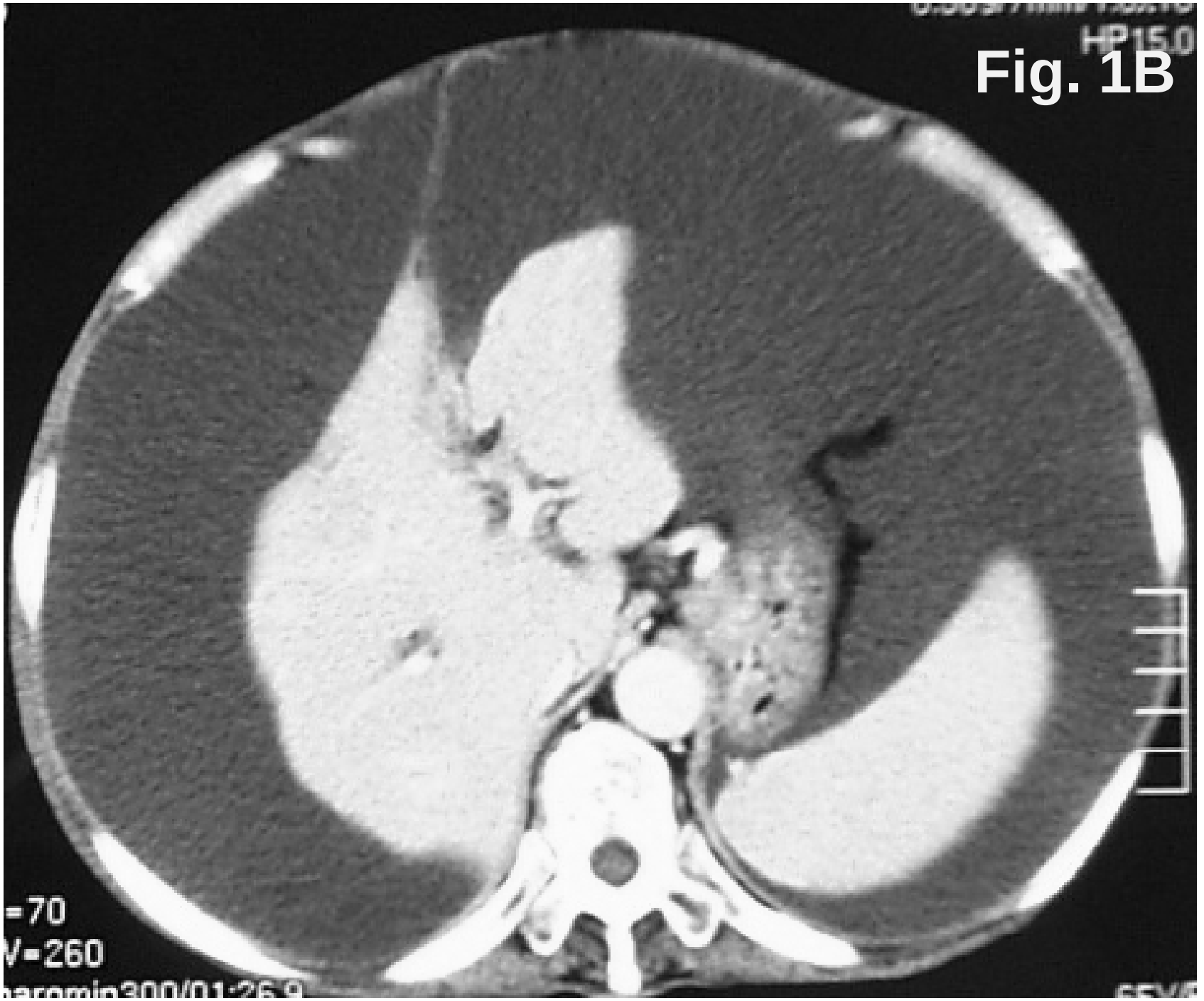

Fig. 1B

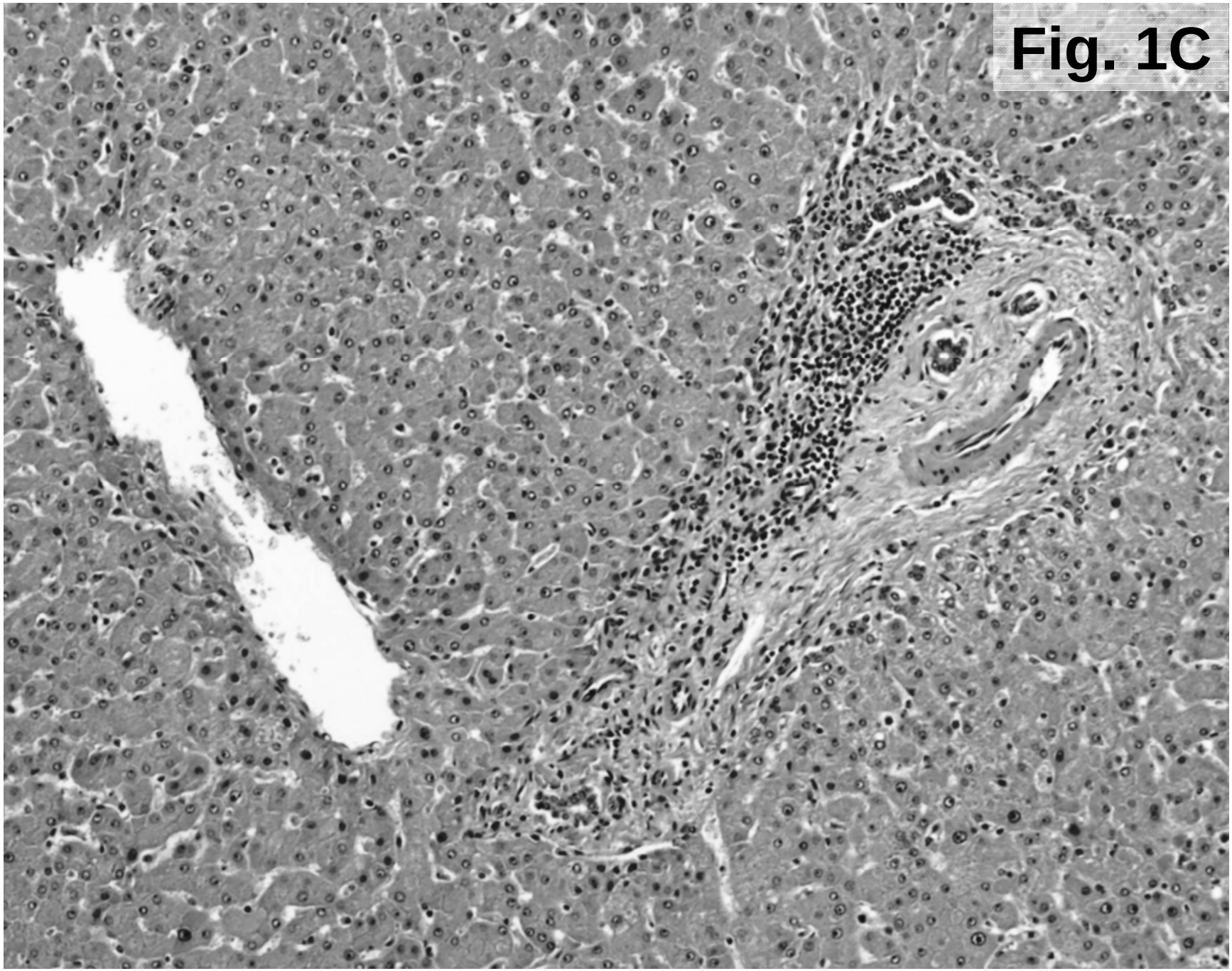

Fig. 1C