

Case report

Aged Budd-Chiari syndrome attributed to chronic deep venous thrombosis with alcoholic liver cirrhosis

YUJIN HOSHIDA¹, SUSUMU YAMAKADO¹, KEI SHINOKI¹, TSUKASA TAKEUCHI¹, TOSHIHIKO NAGAI¹, YUSUKE HYAKUNA², and YUJI ITOH³

¹Division of Gastroenterology, Tokyo Metropolitan Tama Geriatric Hospital, 1-7-1 Aoba-cho, Higashimurayama, Tokyo 189-8511, Japan

²Division of Surgery, Tokyo Metropolitan Tama Geriatric Hospital, Tokyo, Japan

³Division of Pathology, Tokyo Metropolitan Tama Geriatric Hospital, Tokyo, Japan

Abstract: Budd-Chiari syndrome is a rare disease, but there are many known causes. Recent studies showed that it can be an acquired lesion resulting from thrombosis in some elderly patients. We report a 74-year-old man with Budd-Chiari syndrome attributed to chronic deep venous thrombosis and alcoholic liver cirrhosis. When he was aged 45 years, stasis ulcers of the lower extremities appeared. Cerebral infarction and left hemiparesis occurred at age 71. Ultrasonography, venacavography, and three-dimensional-magnetic resonance imaging on admission demonstrated total obstruction of the inferior vena cava with several massive thrombi and developed collateral vessels. Although the etiology of the thrombosis remained obscure, we made some speculative assumptions that chronic disseminated intravascular coagulation (which is frequently observed in cirrhosis) or hereditary coagulopathy could be involved, from his familial history of thrombotic phenomena and a severe deficiency of clotting inhibitors. Despite the high mortality of untreated Budd-Chiari syndrome reported in previous studies, this patient had been alive for about 30 years from the suspected onset.

Key words: Budd-Chiari syndrome, alcoholic liver cirrhosis, deep venous thrombosis, elderly

Introduction

Budd-Chiari syndrome (BCS) is an uncommon disorder caused by obstruction of hepatic venous outflow.^{1,2} There are a number of known causes of BCS, such as tumors, thrombosis, and congenital fibrous diaphragm or web across the vena cava.² In Japan, primary membranous obstruction of the inferior vena cava (IVC) was

considered the main cause of BCS. However, in recent studies, it has been reported that BCS can be an acquired lesion resulting from thrombosis in some patients.³ In these patients, congenital or acquired coagulation disorders were frequently noted. The prognosis of untreated BCS is considered to be very poor.⁴⁻⁶ We report an elderly man with BCS attributed to chronic deep venous thrombosis (DVT) with alcoholic liver cirrhosis whose survival period from onset was estimated to be about 30 years.

Case report

A 74-year-old man was admitted to our hospital for evaluation of sudden disturbance of consciousness in September, 1996. When he was 35 years old, liver dysfunction was identified, but he refused any medical follow-up. At age 45, stasis ulcers of the lower extremities appeared. Cerebral infarction and left hemiparesis occurred at age 71. He had been drinking heavily—approximately 240 g of ethanol a day from age 20 to age 60 years, then gradually reducing to 10 g per day until admission. Physical examination revealed spider angiomas of the skin, palmar erythema, uprising venous dilatation on the abdomen, stasis dermatitis of bilateral crural skin, and clubbed fingers. Laboratory tests gave the following results: leukocyte count, $8.9 \times 10^3/\text{mm}^3$; erythrocyte count, $380 \times 10^4/\text{mm}^3$; hemoglobin, 14.0 g/dl; platelet count, $6.0 \times 10^4/\text{mm}^3$; aspartate aminotransferase (AST), 23 IU/l; alanine aminotransferase (ALT), 8 IU/l; lactate dehydrogenase (LDH), 228 IU/l; alkaline phosphatase (ALP), 159 IU/l; γ -glutamyl transpeptidase (GTP), 52 IU/l; albumin, 3.0 g/dl; total bilirubin, 3.3 mg/dl; direct bilirubin, 0.7 mg/dl; prothrombin time, 14.1 s (control, 11.5–13.5 s); activated partial thromboplastin time, 41.1 s (control, 22.9–35.2 s); fibrinogen, 398 mg/dl (control, 200–400); ammonia, 197 $\mu\text{g}/\text{dl}$; alpha-fetoprotein (AFP), <10 ng/ml; des-

Reprint requests to: Y. Hoshida

Received: September 14, 1998 / Accepted: April 16, 1999

gamma-carboxyl prothrombin (DCP), 13.1 AU/ml; IgG, 2217 mg/dl; IgA, 479 mg/dl; IgM, 211 mg/dl. Serum α 1 protease inhibitor and ceruloplasmin levels were normal. Antinuclear and anti-pyruvate dehydrogenase (PDH) antibodies were negative. Results of serological tests for hepatitis A, B, C, and G viruses were all negative. Tests for Epstein-Barr virus and cytomegalovirus infection were also negative. Electrocardiogram was normal. Upper gastrointestinal endoscopy revealed esophageal varices and mild portal hypertensive gastropathy. Colonoscopy revealed multiple tubulovillous adenomas. On ultrasonography, irregular surface of the liver, hypertrophy of the lateral segment of the left hepatic lobe, multiple small gallstones in the gallbladder, and mild splenomegaly were noted. In addition, hepatic veins and the hepatic portion of the IVC were obscure. At this time, he was diagnosed with hepatic encephalopathy as a complication of liver cirrhosis, and his condition was improved by intravenous branched-chain amino acid infusions. However, asymptomatic cholecystolithiasis was also present.

Physical findings such as crural stasis dermatitis and uprising venous dilatation on the abdomen, which could not be explained only by portal hypertension, together with the findings of ultrasonography, suggested vena caval involvement. Venocavography demonstrated total obstruction of the IVC just above the renal veins, thrombotic occlusion of the right common iliac vein and left internal iliac vein, and several massive thrombi in the IVC (Fig. 1). Three-dimensional-magnetic resonance imaging also revealed total obstruction and kinking of the IVC (Fig. 2). On dynamic helical computed tomography, several collateral circulations were observed, e.g., bilateral ascending lumbar veins to the azygos vein, and the great saphenous vein to the superficial epigastric and circumflex iliac veins (Fig. 3). Transarterial portography via the superior mesenteric artery showed patent portal venous flow and developed hepatofugal collaterals such as that to the left gastric vein. At this time, he was diagnosed with BCS with DVT. The presence of multiple DVTs suggested the existence of a coagulation disorder. Additional hemostatic data were then obtained: fibrin split products (FSPs), 367 ng/ml (normal, <100); D-dimer, 1177 ng/ml (normal, <1000); antithrombin III-antigen, 13.0 mg/dl (normal, 23–34); antigenic activity, 58% (normal, 79%–121%); protein C antigen, 27% (normal, 70%–150%); antigenic activity, 18% (55%–140%); activated protein C (APC) resistance ratio, 2.60 (normal, \geq 2); protein S antigen, 61% (normal, 65%–135%); antigenic activity, 35% (normal, 60%–150%); α 2-plasmin inhibitor, 3.4 mg/dl (normal, 4.0–6.0); antigenic activity, 56% (normal, 13%–135%); plasminogen, 4.7 mg/dl (normal, 7.0–13.0); antigenic activity, 37% (normal, 73%–135%); α 2-plasmin inhibitor-plasmin complex, 3.6 μ g/ml (nor-



Fig. 1. Venocavography demonstrated total obstruction of the inferior vena cava, the right common iliac vein, and the left internal iliac vein. Several massive thrombi were observed



Fig. 2. Three-dimensional magnetic resonance imaging (maximum intensity projection method) demonstrated total obstruction and kinking of the inferior vena cava just above the renal vein

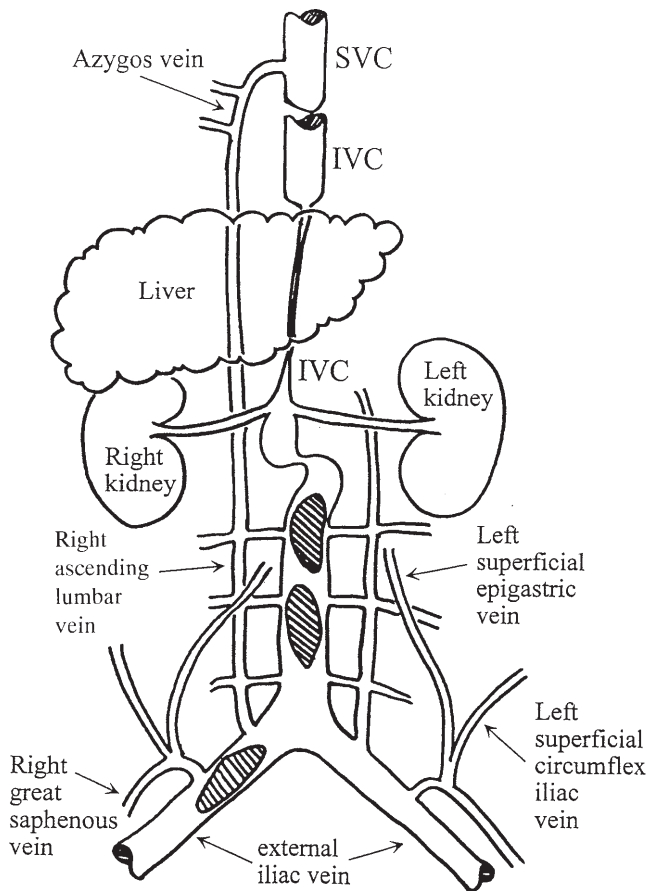


Fig. 3. Schematic presentation of venous collateral circulation reconstructed from the finding of dynamic helical computed tomography. *Shaded areas*, thrombus. *SVC*, superior vena cava; *IVC*, inferior vena cava

mal, ≤ 0.8); thrombin-antithrombin III complex, 13.1 ng/ml (normal, < 3.0); factor II, 42% (normal, 62%–127%); factor V, 45% (normal, 50%–150%); factor VII, 34% (normal, 65%–135%); factor VIII-related antigen, $\geq 200\%$ (normal, 50%–150%); factor IX, 42% (normal, 60%–140%); factor X, 34% (normal, 23%–34%). Lupus anticoagulant and anti-cardiolipin antibodies were negative.

The patient died of acute cholecystitis accompanied by septic shock in December, 1996. Pathological findings at autopsy demonstrated micronodular liver cirrhosis with the presence of hyaline bodies and chronic congestion of the liver (Fig. 4), spleen, and kidneys. Histologically, hepatic congestion, with zone 3 sinusoidal distension arising from occlusion of the entry of hepatic veins to the IVC, was observed (Fig. 5). The hepatic portion of the IVC was occluded 6.5 cm in length, with organized thrombi of varying age (Fig. 6). Phlebosclerosis with calcification in the IVC and thrombotic occlusion of the left common iliac vein were observed. Just below the occluded lesion, localized cal-

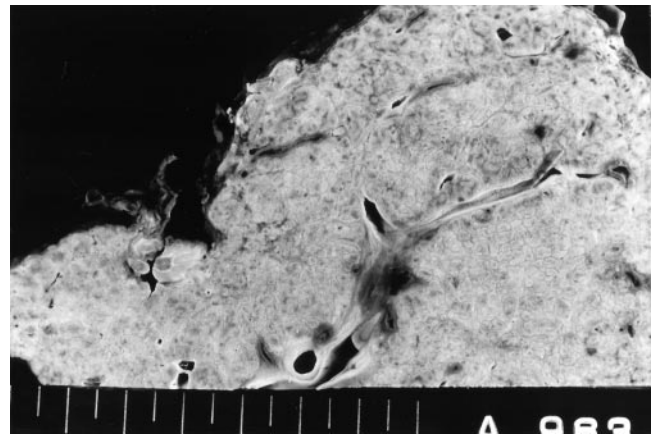


Fig. 4. Cut surface of the liver at autopsy demonstrated micronodular liver cirrhosis with chronic congestion

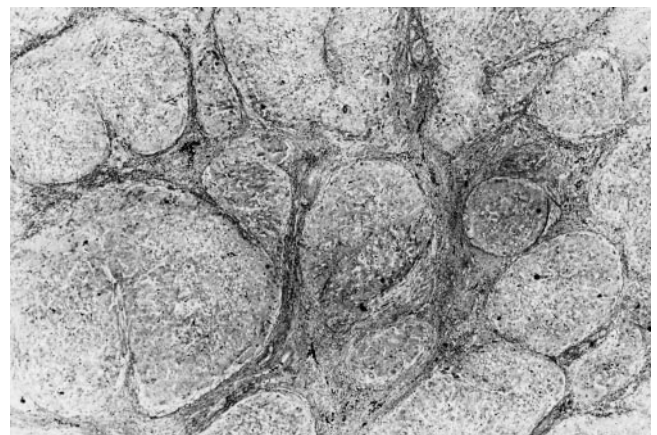


Fig. 5. Histological section of the liver showed hepatic congestion with zone 3 sinusoidal distension and pooling. Azan, $\times 8$

cification of the IVC was observed. Orifices of hepatic veins were recognized only as small depressed regions on the wall of the IVC (type 2 BCS; according to Sugiura,⁷ a relatively common pattern in Japan).

Discussion

BCS is a disorder caused by hepatic venous outflow obstruction (HVOO) and is rarely observed in daily clinical practice. According to Okuda et al,⁸ the number of patients with BCS was estimated to be about 300 (prevalence of 2.4/million), with about 20 new cases occurring every year in Japan. The average age at the time of the first medical visit was 36.4 years (range, 10–72 years) in men and 46.5 years (range, 16–75 years) in women. The average period from suspected onset was

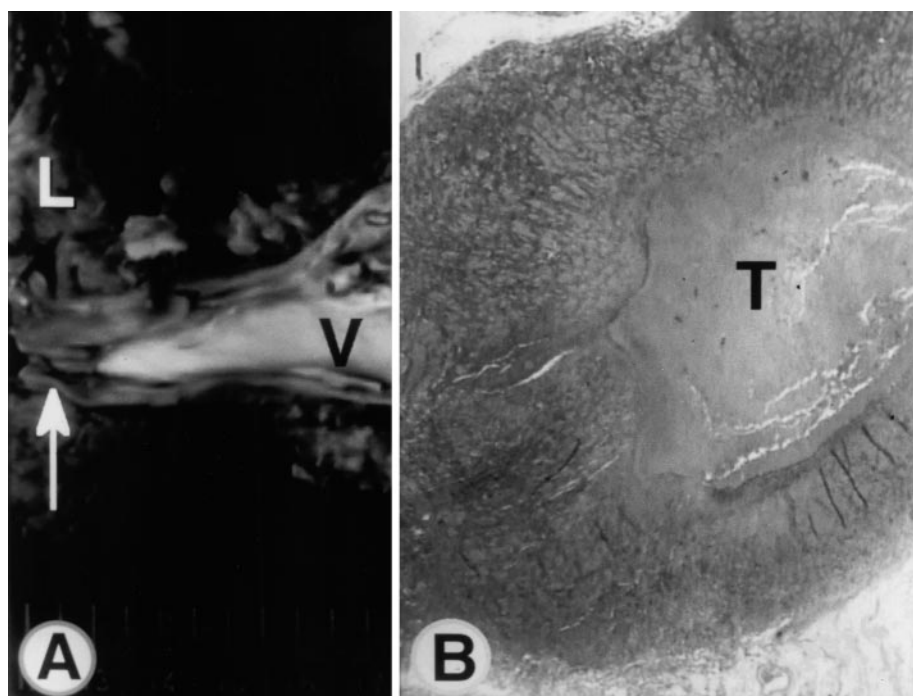


Fig. 6A,B. Hepatic portion of the IVC. **A** Total obstruction of the IVC (*arrow*). **B** Phlebosclerosis with calcification in the hepatic portion of the IVC and total obstruction with organized thrombus (*T*). *L*, liver; *V*, inferior vena cava. Elastica van Gieson, $\times 4$

6.6 years.⁸ In a histopathological study of 17 autopsy cases by Kage et al.³ the oldest patients were a 66-year-old man, and a 72-year-old woman.

The nature of HVOO is variable⁹ and there are geographic variations. In the United States and Western countries, thrombosis with apparent pathogenesis is the most common cause of HVOO. Previously reported conditions that predispose to thrombosis are myeloproliferative disorders such as polycythemia vera and essential thrombocytosis, including preclinical stage,¹⁰ and abnormal clotting tendencies due to deficiencies of antithrombin III,¹¹ protein C,^{12,13} or protein S,¹⁴ blood constituents that protect against thrombosis. Oral contraceptive use,¹⁵ the presence of lupus anticoagulant¹⁶ and anticardiolipin antibodies,¹⁷ paroxysmal nocturnal hemoglobinuria (PNH),¹⁸ and factor V Leiden mutation¹⁹ also predispose to thrombosis. Less well documented associations were reported, such as ulcerative colitis,²⁰ Behcet's disease,²¹ fat overload syndrome,²² idiopathic granulomatous venulitis,²³ and pregnancy. Tumors or caudate hypertrophy due to chronic HVOO, with caval compression and hepatic abscess or cyst directly obstructing major hepatic veins were also reported.¹ In Africa and Asia, primary membranous obstruction of the IVC (MOVC), such as weblike stenosis or occlusion, is frequently observed and it is considered endemic.^{3,24} Although congenital so-called MOVC was regarded as the major cause of Japanese

BCS,⁸ only about 10% of the cases have identifiable etiologies. A recent study by Kage et al.³ suggested that it was an acquired lesion after thrombosis in some patients with late age onset. Regarding the etiology of BCS in our patient, chronic DVT was considered to be the most likely etiology from the findings of X-ray examination and autopsy.

To clarify the etiology of DVT, additional hemostatic data were obtained, allowing us to make some speculative assumptions. Elevated levels of FSPs and D-dimers, and normal fibrinogen level suggested a chronic intravascular hypercoagulable condition similar to disseminated intravascular coagulation (DIC), which is frequently observed in cirrhotic patients. Similarly, despite low levels of $\alpha 2$ -plasmin inhibitor and plasminogen, due to reduced synthesis in the cirrhotic liver, elevated levels of $\alpha 2$ -plasmin inhibitor-plasmin complex and thrombin-antithrombin III complex were observed, possibly reflecting the existence of thrombosis and chronic thrombolysis. Broad depression of plasma clotting factors and inhibitors, except for factor VIII, was compatible with impaired protein synthesis in the uncompensated cirrhotic liver. However, it is usually thought that depressed levels of clotting inhibitors in liver disease are not associated with thrombotic complications,^{25,26} and the very severe deficiency of clotting inhibitors, such as protein C, S, and AT III, suggested the presence of masked hereditary coagulopathy. As for

the patient's familial history, his older brother died after a long course of myocardial infarction and cerebral infarction, and his son suffered cerebral infarction at the age of 40. However, their sera and the sera of other, living, siblings could not be investigated, so it was unclear whether this conjecture was right. Factor V Leiden mutation was ruled out, with the result of a normal APC ratio. Further, regarding the rare condition of PNH occasionally found in association with venous thrombosis, diagnostic tests such as the Ham test and sugar water test were not performed. But there was no clear evidence of abnormal hemolysis, such as abnormal red cells, hemoglobinuria, hemosiderinuria, and elevated levels of LDH. So the probability of PNH was thought to be negligible. According to Chedid et al.,¹⁷ anticardiolipin antibodies, which are strongly associated with thromboembolic phenomena, were present in the serum of patients with alcoholic liver disease. In our patient, these antibodies were negative, despite his history of alcohol drinking.

In regard to the etiology of liver cirrhosis, metabolic diseases such as α 1 protease inhibitor deficiency, hemochromatosis, and Wilson's disease were ruled out. There was no evidence of viral hepatitis or autoimmune disease, such as primary biliary cirrhosis or autoimmune hepatitis. Thus, alcohol abuse was considered to be the most likely etiology. Furthermore, chronic liver congestion after the formation of the IVC occlusion could have contributed to the progression of liver cirrhosis. As for the reasons to explain why the hepatic portion of the IVC was obstructed, several possibilities, such as mechanical injury, stasis of blood flow, and infection of the IVC (perhaps long ago) have already been offered.³ Finally then, it was considered that the long course of the disease made the mechanism complicated.

Some studies have reported the poor prognosis of patients with untreated BCS.⁴⁻⁶ In the study of McCarthy et al.,⁴ overall mortality of BCS was 57% (medical treatment, 86%; surgical treatment, such as side-to-side portacaval shunt, 31%). Reported causes of death are liver failure, variceal bleeding, and hepatocellular carcinoma.¹ In our patient, the diagnosis of BCS was made almost incidentally and from the history of physical findings, the occlusion of the IVC was estimated to have begun about 30 years previously. The reason for this patient having been alive for such a relatively long period, despite frequent episodes of thrombotic phenomena, was unclear. But it was considered that the developed venous collaterals decompressed the caval pressure and led to a mild form of BCS without some major symptoms such as abdominal pain and ascites.

Acknowledgments. We thank Dr. Y. Suzuki of the Division of Gastroenterology, Toranomon Hospital, Tokyo, for his kindly advice and assistance.

References

1. Reynolds TB. Budd-Chiari syndrome. In: Schiff ER, editor. Diseases of the liver. 7th ed. Philadelphia: JB Lippincott; 1993. p. 1091-8.
2. Schwartz ME. Diseases of the hepatic blood vessels. In: Haubrich WS, editor. Bockus gastroenterology. 5th ed. Philadelphia: WB Saunders; 1995. p. 2381-92.
3. Kage M, Arakawa M, Kojiro M, Okuda K. Histopathology of membranous obstruction of the inferior vena cava in the Budd-Chiari Syndrome. *Gastroenterology* 1992;102:2081-90.
4. McCarthy PM, van Heerden JA, Adson MA, Schafer LW, Wiesner RH. The Budd-Chiari syndrome. Medical and surgical management of 30 patients. *Arch Surg* 1985;120:657-62.
5. Maddrey WC. Hepatic vein thrombosis (Budd Chiari syndrome). *Hepatology* 1984;4:44S-6S.
6. Ishibe R, Maruko M, Tabata D, Toyohira H, Furuzono K, Nishimura A, et al. Membranous obliteration of the inferior vena cava in the hepatic portion—postmortem study of a rapidly deteriorated aged case. *Nippon Geka Gakkai Zasshi (J Jpn Surg Soc)* 1990;91:290-2.
7. Sugiura M. Etiology and symptoms of the portal system. In: Kimoto S, editor. Current surgery no. 40 (in Japanese). Tokyo: Nakayama; 1970. p. 72-85.
8. 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 Hepatol* 1995;22:1-9.
9. Ludwig J, Hashimoto E, McGill DB, van Heerden JA. Classification of hepatic venous outflow obstruction: ambiguous terminology of the Budd-Chiari syndrome. *Mayo Clin Proc* 1990;65:51-5.
10. Valla D, Casadevall N, Lacombe C, Varet B, Goldwasser E, Franco D, et al. Primary myeloproliferative disorder and hepatic vein thrombosis. A prospective study of erythroid colony formation in vitro in 20 patients with Budd-Chiari syndrome. *Ann Intern Med* 1985;103:329-34.
11. Das M, Carroll SF. Antithrombin III deficiency. An etiology of Budd-Chiari syndrome. *Surgery* 1985;97:242-6.
12. Sugano S, Suzuki T, Makino H, Yanagimoto S, Nishio M, Onmura H, et al. Budd-Chiari syndrome attributed to protein C deficiency. *Am J Gastroenterol* 1996;91:777-9.
13. Bourliere M, Le Treut YP, Aronoux D, Castellani P, Bordigoni L, Maillot A, et al. Acute Budd-Chiari syndrome with hepatic failure and obstruction of the inferior vena cava as presenting manifestation of hereditary protein C deficiency. *Gut* 1990;31:949-52.
14. D'Angelo A, Bigano-D'Angelo S, Esmon CT, Comp PC. Acquired deficiencies of protein S: protein S activity during oral anticoagulation, in liver disease, and in disseminated intravascular coagulation. *J Clin Invest* 1988;81:1445-54.
15. Lewis JH, Tice HL, Zimmermann HJ. Budd-Chiari syndrome associated with oral contraceptive steroids: review of treatment of 47 cases. *Dig Dis Sci* 1983;28:673-83.
16. Pomeroy C, Knodell RG, Swaim WR, Arneson P, Mahowald ML. Budd-Chiari syndrome in a patient with the lupus anticoagulant. *Gastroenterology* 1984;86:158-61.
17. Chedid A, Chadawala KR, Morgan TR, Moritz TE, Mendenhall CJ, Hammond JB, et al. Phospholipid antibodies in alcoholic liver disease. *Hepatology* 1994;20:1465-71.
18. Valla D, Dhumeaux D, Babany G, Hillon P, Rueff B, Rochant H, et al. Hepatic vein thrombosis in paroxysmal nocturnal hemoglobinuria. A spectrum from asymptomatic occlusion of hepatic venules to fatal Budd-Chiari syndrome. *Gastroenterology* 1987;93:569-75.
19. Fickert P, Ramschak H, Kenner L, Hoefler G, Hinterleitner TA, Petritsch W, et al. Acute Budd-Chiari syndrome with fulminant hepatic failure in a pregnant woman with factor V leiden mutation. *Gastroenterology* 1996;111:1670-3.
20. Brinson RR, Curtis WD, Schuman BM, Mills LR. Recovery from hepatic vein thrombosis (Budd-Chari syndrome) complicating ulcerative colitis. *Dig Dis Sci* 1988;33:1615-20.

21. Bismuth E, Hadenque A, Hammel P, Benhamou JP. Hepatic vein thrombosis in Behcet's disease. *Hepatology* 1990;11:969-74.
22. Haber LM, Hawkins EP, Seilheimer DK, Saleem A. Fat overload syndrome. An autopsy study with evaluation of the coagulopathy. *Am J Clin Pathol* 1988;90:223-7.
23. Young ID, Clark RN, Manley PN, Groll A, Simon JB. Response to steroids in Budd-Chiari syndrome caused by idiopathic granulomatous venulitis. *Gastroenterology* 1988;94:503-7.
24. Simson IW. Membranous obstruction of the inferior vena cava and hepatocellular carcinoma in South Africa. *Gastroenterology* 1982;82:171-8.
25. Arousseau MH, D'Angeli JL, Josso F. Antithrombin III versus prothrombin in liver cirrhosis. *Haemostasis* 1981;10:104-7.
26. Epstein DJ, Berjum PW, Bajaj SP, Rapaport SI. Radioimmunoassays for protein C and factor X: plasma antigen levels in abnormal hemostatic states. *Am J Clin Pathol* 1984;82:573-81.