Transpl Int (1994) 7: 115–119

ORIGINAL ARTICLE

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Liver transplantation for Budd-Chiari syndrome – palliation or cure?

Received: 8 April 1993
Accepted: 19 May 1993

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Abstract This report documents two cases of Budd-Chiari syndrome (BCS) with essential thrombocytosis and antithrombin (AT) III deficiency as underlying etiological factors. Orthotopic liver transplantation was successfully performed in both patients but with different therapeutic intention. In the patient with essential thrombocytosis, hepatic transplantation only relieved the symptoms of the predisposing thrombogenic condition; it did not cure the underlying disorder. Prophylactic long-term anticoagulation, as well as adjuvant therapy for the causative disease, remained necessary. On the other hand, in the patient with AT III deficiency, liver transplantation was curative, resulting in complete reconstitution of serum AT III activity with resolution of the hypercoagulable state postoperatively. Thus, depending on the underlying etiology, liver transplantation for BCS can be considered as palliative, necessitating long-term adjuvant therapy, or as curative, with correction of a metabolic defect.

Key words Liver transplantation, Budd-Chiari syndrome ~~Budd-Chiari syndrome~~

Introduction

Budd-Chiari syndrome (BCS) and venous occlusive disease (VOD) are rare clinical entities characterized by hepatic venous outflow obstruction. While BCS is caused by obstruction of the major hepatic veins or the inferior vena cava (IVC), VOD describes the occlusion of central or sublobular intrahepatic veins. Both diseases may present acutely and be rapidly progressive or in a more chronic course with ascites, hepatomegaly, and abdominal pain as the initial symptoms. BCS and VOD often occur in patients with a predisposition to thrombosis. In recent years, a large number of etiological factors have been identified, such as myeloproliferative disorders, oral contraceptives, and hemostatic abnormalities. The prognosis for patients with BCS or VOD is determined by complications of portal hypertension or, less frequently, hepatic failure.

Therapeutic attempts vary from conservative medical concepts to liver transplantation (LTX) [1, 9, 11, 15–17, 19]. Therapy with diuretics and anticoagulation has been reported to be valuable in relieving ascites or limiting the progression of thrombosis. Such treatment may succeed when hepatic venous obstruction is incomplete, though this is a very rare event. In a small number of patients with acute onset of BCS, thrombolytic therapy may be successful [12]. Decompressive portal-systemic shunts are the most frequent surgical procedures in BCS. Conflicting reports have appeared regarding the long-term progression of liver disease [1, 2, 25]. Proponents report the reversal of severe pathological changes in the liver after portacaval shunt, whereas other groups describe the progression of fibrosis [14, 17]. In end-stage liver disease, orthotopic LTX represents the treatment of choice.

However, removal of the cirrhotic liver in hepatic transplantation may not cure the underlying hypercoagulable state. Recurrence of hepatic vein thrombosis after LTX has been described and the use of prophylactic anticoagulation has been proposed [3, 23].

We present the eventful history of two patients with different etiologies of hepatic venous outflow obstruction who underwent liver transplantation. It is the purpose of this report to describe the symptomatic and causative as-

pects of the treatment in BCS, to discuss the necessity of adjuvant therapy, and to point out that, depending on the underlying disease, orthotopic LTX may represent either a palliative or a curative therapeutic approach.

Case reports

Case 1

A 12-year-old girl with acute onset of abdominal pain, nausea, hepatomegaly, and abdominal distension was admitted for further examination in July 1990. At that time, liver enzymes were as follows: SGOT 875 U/l, SGPT 1075 U/l, and alkaline phosphatase 270 U/l. Sonography showed hepatosplenomegaly, ascites, and a rarefaction of the hepatic veins. A computer tomography scan revealed a large, tumorous mass in the right liver lobe, while cavography demonstrated extrinsic compression of the inferior vena cava. Her blood count revealed a hematocrit of 51.8% and platelets of 440000/mm^3. Bone marrow biopsy confirmed the diagnosis of an essential thrombocytosis. Initially, the patient was thought to suffer from a malignoma, but sonography and cavography were highly suggestive of a BCS. Therapy with diuretics and anticoagulants was started without any consequent improvement. Liver function deteriorated rapidly and, for a short period, the patient became encephalopathic. A few days later, the patient underwent an urgent orthotopic LTX. The graft function was satisfactory initially, but on the 4th postoperative day renal failure developed with pulmonary and hemodynamic insufficiency, leading to severe cardiovascular shock. Assuming that these changes were caused by an acute rejection with hepatic necrosis and graft failure, an exceptional procedure with total hepatectomy, in order to remove the necrotic liver, and a portacaval end-to-side shunt were performed, which led to immediate hemodynamic stabilization [20]. The next day, an ABO blood group-incompatible graft was transplanted in combination with splenectomy. Two weeks later repeated acute rejection required a third liver transplantation. The postoperative course after the third LTX was complicated by several intra-abdominal hemorrhages and by platelet counts greater than three million. Hydroxyurea was, therefore, administered for myelosuppression. Initially after LTX, prophylactic anticoagulation was performed using heparin for more than 1 year, later followed by coumarin. Myelosuppressive therapy with hydroxyurea has been continued and platelet counts have decreased to normal ranges (422000/mm^3). The patient has been well for almost 2.5 years after LTX and has returned to school. Ongoing therapy consists of FK 506 and steroids for immunosuppression and hydroxyurea in combination with coumarin for prophylaxis of recurrent BCS.

Histological examination of the recipient's liver showed dilatation of the sinusoids and extensive centrilobular congestion with confluent areas of hepatic necrosis involving almost all zones of the hepatic lobules. The liver veins were completely obstructed by acute thrombosis. The portal tracts, however, revealed only very slight changes and were surrounded by a border of intact liver parenchyma (Fig. 1).

The first explanted graft showed signs of moderate to severe acute rejection with prominent vascular changes and secondary ischemic parenchymal damage. The second graft demonstrated severe blastoid infiltration of the portal tracts, probably representing acute rejection.

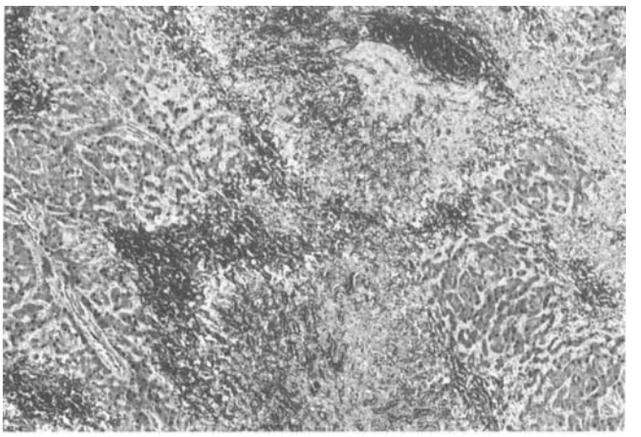

Fig. 1 Confluent areas of acute centrilobular congestion with acute thrombosis and hepatocyte necrosis (H & E, ×40)

Case 2

A 23-year-old man presented with abdominal pain and bloody diarrhea. At laparotomy he was found to have mesenteric venous thrombosis with partial infarction of the small bowel requiring resection of the afflicted parts. Two months later increased liver enzymes were noted and the AT III activity was found to be below 70%. Therapy with heparin and AT III substitution was started. Eight months later the patient was readmitted because of jaundice and abdominal distension. Complete thrombosis of the inferior vena cava and portal vein and obstruction of the major liver veins were demonstrated with magnetic resonance imaging. Sonography was also suggestive of BCS. Endoscopy revealed esophageal and cardia varices. The therapy with heparin and AT III was continued and finally changed to oral anticoagulation with coumarin. Two months later the patient experienced upper gastrointestinal bleeding that could be managed by endoscopic sclerosing. At that time, cavography showed a slight recanalization of the IVC, whereas thrombosis of the portal vein was still present. About one year later the patient acquired an acute hepatitis B infection, leading to rapid and severe deterioration of his liver function and requiring hepatic transplantation. Intraoperatively, signs of portal hypertension and portal vein thrombosis were found. Immunosuppression was attained with cyclosporin, steroids, and azathioprine. The function of the transplanted liver was normal and the patient was discharged in good condition 6 weeks after LTX. The patient has been well for almost 5 years and has returned to work.

In the immediate postoperative period, prophylactic anticoagulation was achieved with heparin and, afterwards, continued with coumarin. Since serum AT III activity was in the normal range (>100%) after LTX, long-term anticoagulant therapy was discontinued.

The explanted liver was 25 × 23 × 11 cm and weighed 1970 g. Liver parenchyma showed complete micronodular cirrhosis with a network of fibrous tissue and massive cholestasis. The major hepatic veins were completely occluded. There was phlebosclerosis of the IVC and of the portal vein with a partly recanalized thrombus.

Histological examination demonstrated thickened or obstructed centrilobular veins with adjacent scarred tissue or hepatic cell necrosis. The portal tracts, however, revealed only slight fibrotic changes with normal bile ducts. Various areas showed prominent sinusoid dilatation and massive hemostasis. Specimens taken from a major hepatic vein confirmed complete obliteration by scar tissue (Fig. 2).

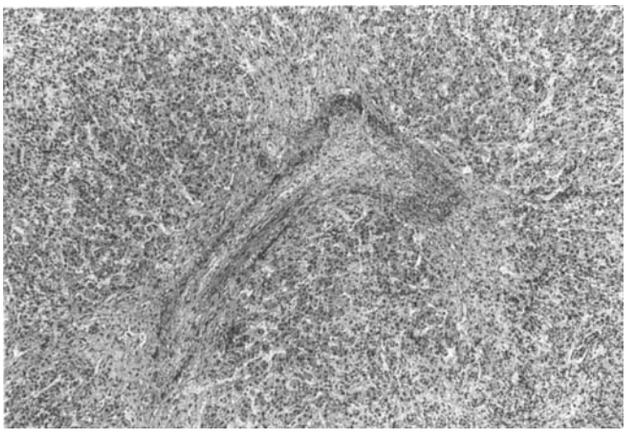

Fig. 2 Small hepatic vein occluded by an organized thrombus surrounded by a network of fibrous tissue and areas of chronic sinusoid dilation with complete cirrhosis (H & E, ×25)

Discussion

Several diseases and predisposing conditions have been associated with BCS. In 30%–50% of the cases, however, the origin of the syndrome remains undetermined, and in children an even higher rate of unknown causes has been reported. The frequency of different etiological factors shows geographic variations. In Japan and the Orient, a membraneous web in the inferior vena cava is the most often established origin, whereas in western countries myeloproliferative disorders represent a common cause of BCS [1, 7, 15, 24].

The mechanism of hepatic vein thrombosis due to primary myeloproliferative disorder is based on high blood viscosity or an increased platelet count. The absence or – as seen in our case – only slight expression of peripheral blood count changes, typical of a myeloproliferative disorder, can be explained by two different mechanisms. First, hepatosplenomegaly may lead to decreased production or increased destruction of blood cells with a consequent iron deficiency. Second, polycythemia vera or portal hypertension may result in an increased plasma volume. Both pathological alterations may mask typical findings in the peripheral blood. Thus, the need for a bone marrow biopsy and close follow-up of blood counts becomes obvious [24].

Abnormalities of hemostatic mechanisms leading to hypercoagulation are increasingly being recognized. An AT III deficiency, which may occur as an acquired or hereditary autosomal dominant transmitted syndrome, is a well-documented cause of BCS [5, 6, 13].

In cases with hereditary AT III deficiency, the liver is incapable of synthesizing sufficient amounts of antithrombin. This disorder is characterized by recurrent thromboembolic events, and a fatal outcome may result from pulmonary embolism, thrombosis of critical vessels, or disseminated intravascular coagulation (DIC) [7]. Mesenteric veins are a rare but typical location of thrombosis due to AT III deficiency [26]. Once thromboembolism has occurred, anticoagulation therapy should be started and continued indefinitely because of the unpredictable occurrence of further thromboembolic complications. Heparin plus AT III concentrate are used for acute therapy. Oral coumarin has been reported to provide effective prophylaxis and should be administered indefinitely [5, 6].

The clinical presentation of BCS is very unspecific and variable with a broad spectrum from fulminant hepatic failure to chronic liver disease. By far the most frequent appearance of BCS is as a subacute illness with painful hepatomegaly and ascites [1, 15, 18]. The two cases reported here were at both ends of this spectrum. In the case of the young girl with essential thrombocytosis, there was biochemical and histological evidence of extensive hepatic cell necrosis with marked elevation of serum transaminase consistent with an acute hepatic failure. By contrast, micronodular cirrhosis with regenerative nodules and esophageal varices in the young man with AT III deficiency represented the chronic form of BCS.

The course of patients suffering from BCS depends on the rapidity and extent of occlusion of the hepatic venous outflow tract but, in general, the prognosis without treatment is poor. Spontaneous reversal of hepatic vein thrombosis is extremely rare. Many untreated patients die from hepatic failure, bleeding esophageal varices, or other complications associated with portal hypertension and chronic liver disease [1, 9, 11, 15]. Accordingly, the goals in the treatment of BCS are prevention of further thrombosis, portal decompression, and reduction of ascites.

While there is discussion about the most effective therapy in early BCS, orthotopic LTX is the treatment of choice in the fulminant or chronic form with end-stage liver disease [1, 9, 10, 16, 19]. Jamieson et al. report on 26 patients with BCS who underwent 28 liver transplantations with 1-, 3-, and 5-year actuarial survival rates of 69.2%, 69.2%, and 49.7%, respectively [10]. However, one noteworthy aspect of LTX for BCS is the underlying hypercoagulable state, which might cause recurrence of hepatic vein thrombosis [23]. Furthermore, there are various reports of thromboembolic events after LTX in patients with BCS. Campbell et al., therefore, demanded adjuvant anticoagulation with heparin and coumarin after LTX. They report on 17 patients with a 3-year survival rate of 88% without any recurrence of hepatic vein thrombosis. Nonfatal hemorrhagic complications occurred in 44% of their patients. Despite anticoagulation, five patients suffered from thrombotic complications with two associated deaths [3]. This reveals the thrombogenic state of patients with BCS, and the advantages of using heparin and coumarin for long-term prophylaxis seem to

outweigh the increased risk of bleeding complications. In cases of myeloproliferative disorder, however, this therapeutic management is not directed towards the underlying hematologic defect and exposes the patient to the disadvantages of anticoagulation. Additional therapy with hydroxyurea or acetyl salicylic acid is a more rational therapeutic approach. Goldstein et al. even suggest this strategy after LTX for idiopathic hepatic vein thrombosis [8].

In our own clinical experience with LTX for hepatic venous outflow obstruction, we have not observed any recurrence of BCS [21]. Based on this experience, we also agree on the necessity of routine, prophylactic anticoagulation after LTX. Our protocol consists of formal full anticoagulation with heparin initially, followed by coumarin. In cases of underlying myeloproliferative disease or with platelets greater than 500000 cells/mm^3, acetyl salicylic acid and hydroxyurea are given additionally.

In patients with BCS due to a myeloproliferative disorder, hepatic transplantation is only a palliative therapy; it may even be regarded as a contraindication, e.g., in paroxysmal nocturnal hematuria [22]. The underlying disease is not treated; only the symptoms are relieved and adjuvant therapy remains obligatory. By contrast, LTX is curative for BCS caused by a defect that is localized in the liver. If BCS is secondary to a genetic AT III or protein C deficiency or related to another protein synthesized in the liver, then hepatic transplantation may be curative. The successful treatment of a patient with homozygous protein C deficiency has been reported [4]. In these patients hepatectomy removes the predisposition to thrombosis, and prophylactic anticoagulation may not be required. With regard to the major objective of LTX as effective therapy for BCS, the underlying etiology plays a significant role. In cases with myeloproliferative disorders lifelong anticoagulation with or without cytoreductive drugs will be essential to prevent recurrent BCS, whereas genetic defects that cause protein deficiencies may be cured by LTX.

References

1. Bismuth H, Sherlock DJ (1991) Portasystemic shunting versus liver transplantation for the Budd-Chiari syndrome. Ann Surg 214: 581–589
2. Cameron JL, Herlong HF, Sanfey H, Boitnott J, Kaufman SL, Gott VL, Maddrey WC (1983) The Budd-Chiari syndrome: treatment by mesenteric-systemic venous shunts. Ann Surg 198: 335–346
3. Campbell DA, Rolles K, Jamieson N, O'Grady J, Calne R (1988) Hepatic transplantation with perioperative and long term anticoagulation as treatment for Budd-Chiari syndrome. Surg Gynecol Obstet 166: 511–518
4. Casella JF, Bontempo FA, Markel H, Lewis JH, Zitelli BJ, Starzl TE (1988) Successful treatment of homozygous protein C deficiency by hepatic transplantation. Lancet I: 435–437
5. Cosgriff TM, Bishop DT, Hershgold EJ, Skolnick MH, Martin BA, Baty BJ, Carlson KS (1983) Familial antithrombin III deficiency: its natural history, genetics, diagnosis and treatment. Medicine 62: 209–220
6. Das M, Carroll SF (1985) Antithrombin III deficiency: an etiology of Budd-Chiari syndrome. Surgery 97: 242–245
7. Gentil-Kocher S, Bernard O, Brunelle F, Hadchouel M, Maillard JN, Valayer J, Hay JM, Alagille D (1988) Budd-Chiari syndrome in children: report of 22 cases. J Pediatr 113: 30–38
8. Goldstein R, Clark P, Klintmalm G, Husberg B, Gonwa T, Stone M (1991) Prevention of recurrent thrombosis following liver transplantation for Budd-Chiari syndrome associated with myeloproliferative disorders: treatment with hydroxyurea and aspirin. Transplant Proc 23: 1559–1560
9. Halff G, Todo S, Tzakis AG, Gordon RD, Starzl TE (1990) Liver transplantation for the Budd-Chiari syndrome. Ann Surg 211: 43–49
10. Jamieson NV, Williams R, Calne R (1991) Liver transplantation for Budd-Chiari syndrome, 1976–1990. Ann Chir 45: 362–365
11. Klein AS, Sitzmann JV, Coleman J, Herlong FH, Cameron JL (1990) Current management of the Budd-Chiari syndrome. Ann Surg 212: 144–149
12. McCarthy PM, Heerden JA van, Adson MA, Schafer LW, Wiesner RH (1985) The Budd-Chiari syndrome: medical and surgical management of 30 patients. Arch Surg 120: 657–662
13. McClure S, Dincsoy HP, Glueck H (1982) Budd-Chiari syndrome and antithrombin III deficiency. Am J Clin Pathol 78: 236–241
14. Millikan WJ, Henderson JM, Sewell CW, Guyton RA, Potts JR, Cranford CA, Cramer AR, Galambos JT, Warren WD (1985) Approach to the spectrum of Budd-Chiari syndrome: which patients require portal decompression? Am J Surg 149: 167–176
15. Mitchell MC, Boitnott JK, Kaufman S, Cameron JL, Maddrey WC (1982) Budd-Chiari syndrome: etiology, diagnosis and management. Medicine 61: 199–218
16. Oldhafer KJ, Ringe B, Wittekind C, Pichlmayr R (1990) Budd-Chiari syndrome: portacaval shunt and subsequent liver transplantation. Surgery 107: 471–474
17. Orloff MJ, Girard B (1989) Long term results of treatment of Budd-Chiari syndrome by side to side portacaval shunt. Surg Gynecol Obstet 168: 33–41
18. Powell-Jackson PR, Ede RJ, Williams R (1986) Budd-Chiari syndrome presenting as fulminant hepatic failure. Gut 27: 1101–1105
19. Putnam CW, Porter KA, Weil R, Reid HAS, Path MRC, Starzl TE (1976) Liver transplantation for Budd-Chiari syndrome. JAMA 236: 1142–1143
20. Ringe B, Pichlmayr R, Lübbe N, Bornscheuer A, Kuse E (1988) Total hepatectomy as temporary approach to acute hepatic or primary graft failure. Transplant Proc 20 [Suppl 1]: 552–557
21. Ringe B, Oldhafer K, Lang H, Laas J, Link H, Pichlmayr R (1992) Optimal treatment of Budd-Chiari syndrome (BCS) – conventional surgery or liver transplantation? HPB Surgery 5 [Suppl]: 14

22. Schmid T, Sandbichler P, Pernthaler H, Vogel W, Kunz F, Schmid K, Margreiter R (1989) Multiple venous thrombosis with recurrence of Budd-Chiari syndrome after liver transplantation for paroxysmal nocturnal hematuria. Clin Transplant 3: 194–197
23. Starzl TE, Iwatsuki S, Thiel DH van, Gartner JC, Zitelli BJ, Malatack JJ, Schade RR, Shaw BW Jr, Hakala TR, Rosenthal JT, Porter KA (1982) Evolution of liver transplantation. Hepatology 2: 614–636
24. Valla D, Casadevall N, Lacombe C, Varet B, Goldwasser E, Franco D, Maillard J-N, Pariente EA, Leporrier M, Rueff B, Muller O, Benhamou J-P (1985) 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 103: 329–334
25. Vons C, Smadja C, Bourstyn E, Szekely A-M, Bonnet P, Franco D (1986) Results of portal systemic shunts in Budd-Chiari syndrome. Ann Surg 203: 366–370
26. Wilson C, Walker ID, Davidson JF, Imrie CW (1987) Mesenteric venous thrombosis and antithrombin III deficiency. J Clin Pathol 40: 906–908