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CASE REPORT

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Recurrence of Budd–Chiari syndrome after liver transplantation in paroxysmal nocturnal hemoglobinuria

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Abstract Venous thrombembolism is a major complication of paroxysmal nocturnal hemoglobinuria (PNH). Often, veins of a typical localization are afflicted, resulting in cerebral, mesenteric, or hepatic venous thrombosis. We present a patient who received an orthotopic liver graft for chronic Budd–Chiari syndrome in 1988. PNH was the only thrombophilic predisposition identified in this patient. After transplantation, he repeatedly suffered from hemorrhage. Subsequently, the patient discontinued prophylactic anticoagulation nearly 10 years after transplantation. Within 6 months Budd–Chiari syndrome recurred, but stabilized after anticoagulation therapy with low-molecular-weight heparin was reinstituted. The patient is clinically stable 14 years after receiving the liver graft. Eleven cases of relapsing Budd–Chiari syndrome have been reported in the literature. Of these, four patients suffered from PNH. All patients transplanted for PNH-associated Budd–Chiari syndrome in these reports suffered from either major bleeding or thrombosis. In conclusion, patients afflicted with PNH appear to be at high risk of incurring complications after liver transplantation.

Keywords Budd–Chiari syndrome · Liver transplantation · Paroxysmal nocturnal hemoglobinuria · PNH · Thrombophilia

Introduction

Thrombotic obstruction of the hepatic veins (Budd–Chiari syndrome) is a rare disorder that may lead to hepatic failure requiring liver transplantation. According to the European Liver Transplant Registry, 391 of 39,399 European patients (1.0%) were transplanted for Budd–Chiari syndrome between January 1988 and December 2001 (http://www.eltr.org/).

The underlying causes of hepatic venous thrombosis are variable. Up to 80% of patients suffer from myeloproliferative disorders [1]. Thrombophilic diathesis due to alterations of single factors within the coagulation cascade is also well recognized, and deficiency of coagulation inhibitors (e.g., antithrombin III, protein C, protein S) as well as dysfunction of clotting factor control (e.g., factor V Leiden mutation) have been described [2]. In many patients a combination of both hematologic and thrombophilic factors is found.

Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired clonal disorder affecting early hematopoetic progenitor or stem cells. Mutations within the PIG-A

gene [3, 4, 5] lead to a deficiency in the assembly of the glycosylphosphatidylinositol (GPI) anchor for the attachment of membrane proteins. Due to the lack of CD55 and CD59 molecules at the cell surface, erythrocytes in particular become sensitized to non-specific activation of the alternative complement cascade [6], resulting in a characteristic clinical picture of intravascular hemolysis. Thrombembolic complications affect about 40% of PNH patients. They predominantly occur in the hepatic veins, the portal and the splenic vein. Other sites of predilection for thrombosis in PNH are cerebral and skin veins.

Ten to 20% of patients with Budd–Chiari syndrome suffer from PNH [7]. On the other hand, more than 10% of deaths in patients with PNH are related to hepatic vein thrombosis [8, 9]. Herein, we present a patient with PNH who developed a relapse of hepatic venous thrombosis after liver transplantation.

Case report

In 1986 at the age of 28 years, the male patient developed recurrent upper gastrointestinal ulcers. Transaminases started to increase. Nine months later ascites developed, which was controlled well by diuretics. Angiography revealed Budd–Chiari syndrome with thrombosis of the small hepatic veins predominantly of the right liver lobe. Additional causes of chronic liver disease were excluded (viral hepatitis, autoimmune hepatitis, metabolic liver disease). Anticoagulation was withheld due to pronounced thrombocytopenia and persistent gastric erosions. In December 1987, ascites recurred massively. Upper gastrointestinal endoscopy revealed stage-III esophageal varices. Using Doppler ultrasound, complete obliteration of the right hepatic vein was detected, while the middle and left hepatic vein still showed some residual flow in the central area with no detectable flow in the periphery. Liver function was severely impaired: prothrombin time was 51% of that of controls (INR 1.59), albumin was 32 g/l, and bilirubin 149 µmol/l (8.8 mg/dl). Because of the progressive clinical course, the patient was evaluated for liver transplantation.

In February 1988, bleeding from esophageal varices developed. One week later the patient received a liver graft by means of the standard orthotopic technique without intraoperative complications. Explant pathology confirmed the diagnosis of Budd–Chiari syndrome with severe cholestasis and focal areas of cirrhosis. Immunosuppression was started on cyclosporine, prednisolone, azathioprine, and antithymocyte globulin. Postoperatively, the course was complicated by three severe bleeding episodes, all at sites of prior interventions and each requiring surgical repair (left axillary vein due to veno-venous bypass, upper vena cava anastomosis, right jugular vein due to central venous catheter). The patient developed cholestasis due to stenosis of the bile duct anastomosis, requiring surgical reconstruction (end-to-side) 1 month after OLT. Cyclosporine and prednisolone were used for long-term immunosuppression. The patient developed mild chronic renal failure. To allow for lower cyclosporine doses, azathioprine was initiated 3 years after OLT. Two years later, azathioprine had to be stopped due to the development of thrombocytopenia. Since the discontinuation of prednisolone 9 years after OLT, the patient was kept on single immunosuppression with cyclosporine.

Due to the bleeding complications, prophylactic anticoagulation was initiated with a 12-month delay after liver transplantation. Oral anticoagulation with phenprocoumon (a coumadin derivative) was started in February 1989. Twelve months later, the patient developed a chronic subdural hematoma with headaches, seizures, and motoric aphasia. Thus, phenprocoumon prophylaxis had to be stopped. The hematoma was removed surgically. The patient's neurological function recovered completely within a 4-month period. After removal of the subdural hematoma, prophylactic anticoagulation with low-molecular-weight heparin was started (Certoparin, daily dose: 3000 IU anti-Xa, equivalent to 18 mg of the 1. LMW heparin standard).

In March 1997, the patient discontinued heparin medication. Six months later a routine sonographic examination revealed a partial portal vein thrombosis. The right hepatic vein was completely occluded. The middle and left hepatic veins were partially occluded, with some residual flow. Apart from moderate abdominal discomfort, the patient was clinically free of major symptoms. The patient was immediately anticoagulated with standard heparin (PTT between 60 and 80 s). After 2 weeks of therapy, the portal and hepatic venous flow started to improve. Therapy was switched to low-molecular-weight heparin (Certoparin, daily dose: 6000 IU anti-Xa, equivalent to 36 mg of the 1. LMW heparin standard). Repeated ultrasound examinations showed complete recanalization of the portal vein by December 1998. Thrombosis of the right hepatic vein persisted, while flow in the left and middle hepatic veins was compensated for by atypical collaterals (Fig. 1). The patient was followed up until September 2002 and is alive and well without further progression of Budd–Chiari syndrome.

After liver transplantation, mild anemia and thrombocythemia persisted. Lactate dehydrogenase was continuously elevated at moderate levels (Fig. 2). Hemolysis was confirmed by a strongly decreased serum haptoglobin concentration (0.06 g/l, normal range 0.27–1.39 g/l). Finally, the diagnosis of PNH was confirmed by flow-cytometric analysis of GPI-linked proteins on blood cells [10] in October 1997 (Fig. 3). During follow-up, the proportion of GPI-deficient cells did not change significantly. In the initial phase after liver transplantation, thrombocytes were substituted due to severe thrombocytopenia. Three years after liver transplantation, thrombocyte counts had nearly normalized when azathioprine was started. This led to a drop in thrombocyte counts, which did not recover after cessation of azathioprine treatment (Fig. 2).

A concomitant myeloproliferative or myelodysplastic disorder was excluded by several bone marrow biopsies before and after liver transplantation (07/87, 05/88, 12/97). However, there was mild hypoplasia of myelopoiesis without clear signs of dysplasia. The

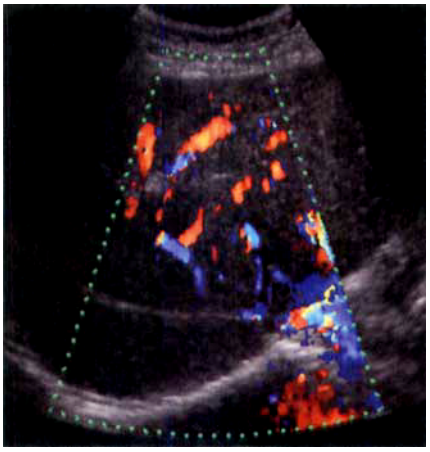

Fig. 1 Color Doppler ultrasound image of the right liver lobe. Subcostal view showing (1) a scar formation located at the place of the completely obliterated right hepatic vein, (2) residual flow in the middle and left hepatic veins, and (3) atypical collateral flow

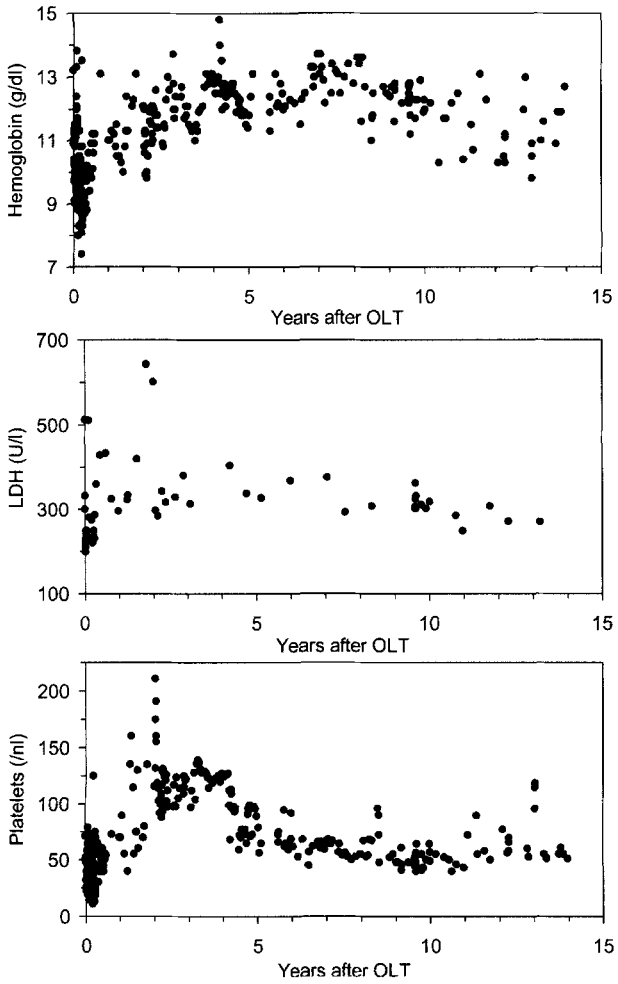

Fig. 2 Hemoglobin concentration, serum lactate dehydrogenase (*LDH*) activity, and platelet counts during follow-up after liver transplantation

alkaline leukocyte phosphatase index was normal. A cytogenetic analysis confirmed a normal male karyotype (46, XY) without clonal chromosomal abnormalities in 11 metaphases.

Prior to liver transplantation, antithrombin-III deficiency had been excluded. After liver transplantation, the patient was screened for plasmatic coagulation disorders. Factor II and V Leiden mutations were excluded. Alterations of resistance for activated protein C were not detected. Activities of antithrombin III, protein C, and protein S were normal. Dysfibrinogenemia was excluded. Antibodies against cardiolipin were negative, and prothrombin time was not prolonged.

Discussion

We describe a patient with PNH complicated by Budd–Chiari syndrome requiring liver transplantation. No additional thrombophilic risk factor was detected. The clinical course after transplantation was initially complicated by several bleeding episodes that delayed the application of prophylactic anticoagulation. Once started, phenprocoumon therapy had to be stopped due to the development of a subdural hematoma. Prophylactic anticoagulation was switched to low-molecular-weight heparin, which was temporarily stopped by the patient. During that period, he developed recurrent Budd–Chiari syndrome and portal vein thrombosis.

PNH presented with low-level hemolysis and anemia. No hemolytic crises occurred. One prominent feature in this case were the recurrent postoperative bleeding episodes under standard prophylactic anticoagulation with coumarin derivatives. In contrast, portal and hepatic vein thrombosis recurred shortly after anticoagulation was stopped completely. This demonstrates a remarkably narrow individual therapeutic range for anticoagulation. Later, the patient developed progressing thrombocytopenia and leukopenia.

Recurrent Budd–Chiari syndrome is a rare complication after liver transplantation. In our own experience, the presented case was one of three relapses in 51 patients transplanted for Budd–Chiari syndrome (partially published in [11]). A literature review estimated the relapse frequency for Budd–Chiari syndrome after OLT to be 4% [12]. To our knowledge, 11 patients including ours were reported in whom Budd–Chiari syndrome recurred after liver transplantation [12, 13, 14, 15, 16, 17]. Four of these 11 patients (36%) suffered from PNH. In four patients the underlying disease was not known. Three patients suffered from myeloproliferative disorders. Most cases of recurrence were associated with periods of insufficient anticoagulation.

In contrast to the high frequency of PNH in relapsing Budd–Chiari syndrome after liver transplantation, PNH is relatively rare as an underlying disease for Budd–Chiari syndrome requiring liver transplantation. The reported patient was one of two patients suffering from PNH among the 51 patients transplanted for Budd–Chiari syndrome at our center. Similar data were published from Pittsburgh, Cambridge, and Berlin where 1/23, 0/26, and 1/16 transplanted patients, respectively, were found to be PNH-positive [13, 14, 16]. Therefore, the total frequency of diagnosed PNH in patients after liver transplantation for Budd–Chiari syndrome may be estimated to be 3–4%. This leads to the impression that PNH is overrepresented among patients with recurrent Budd–Chiari syndrome. Two patients have been described who developed both portal venous thrombosis as well as hepatic artery thrombosis after transplantation for Budd–Chiari syndrome with underlying PNH. One patient died, the other required re-transplantation [13, 18]. Furthermore, we are not aware of a single PNH patient after liver transplantation who did not develop major splanchnic thrombosis during long-term follow-up. We therefore conclude that the risk either of recurrence of Budd–Chiari syndrome or of other major splanchnic thrombosis is particularly high in PNH patients, if adequate anticoagulation is not maintained.

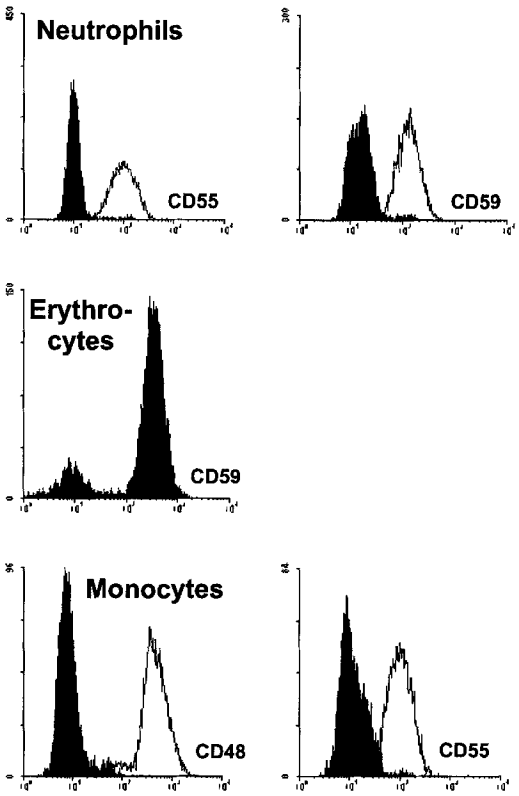

Fig. 3 Flow-cytometric analysis of GPI-linked proteins on blood cells of the patient described. Histograms representing the relative proportions of deficient cells (*shaded black*) and regular cells (*not shaded*) are shown for $CD15^+$ neutrophils (CD55, CD59), glycophorin$^+$ erythrocytes (CD59), and $CD64^+$ monocytes (CD48, CD55)

Additionally, the risk of recurrence of Budd–Chiari syndrome in PNH patients appears to be higher than in patients with other underlying hematological disorders like myeloproliferative diseases (e.g., essential thrombocythemia, polycythemia vera).

The mechanism of thrombosis in PNH especially at atypical sites is still unknown. Apart from the release of strongly prothrombogeneic cytoplasmic constituents of red blood cells due to intravascular hemolysis, such a mechanism is merely a matter of speculation. On the other hand, molecular similarities of clonal expansion in PNH with myeloproliferative diseases such as polycythemia vera might lead to a shared consequence [19]. It has been suggested that the expansion of the GPI-deficient clone in PNH is the result of cytotoxic NK lymphocytes capable of distinguishing between normal cells and those carrying the GPI-deficient phenotype [20]. In such a scenario, NK cells might also be toxic to endothelial cells, resulting in a higher risk of thrombosis [21].

Coumadin derivatives are recommended as thrombosis prophylaxis in PNH [9]. As observed in the presented case, therapeutic doses may result in major bleeding episodes. Hemorrhage is known as a major cause of death in PNH patients, accounting for nearly 20% of all deaths [8]. In the case of our patient, we successfully used low-molecular-weight heparin to prevent and treat thrombosis.

Glucocorticoids are recommended to decrease complement activation in PNH [22, 23]. Unfortunately, the effect varies between patients. One may speculate that double immunosuppression including prednisolone might be preferable in complicated cases of PNH after liver transplantation. The therapeutic efficacy of this approach can be monitored by serum lactate dehydrogenase activity.

The spontaneous prognosis of PNH is unfavorable [8, 9]. About 25% of the patients will eventually develop pancytopenia. An association with aplastic anemia and progression to acute leukemia have been reported [24]. However, patients suffering from PNH aplasia syndrome appear to have a better prognosis in terms of thrombembolic complications [9]. The only curative option for PNH so far is bone marrow transplantation (BMT). One case has been published in which Budd–Chiari syndrome resolved after BMT [25]. For our patient, an HLA-identical relative has been identified as a potential donor for BMT.

In conclusion, we believe that Budd–Chiari syndrome with underlying PNH should not lead to exclusion from liver transplantation. Nevertheless, these patients are at high risk either for recurrence of BCS or the development of other major splanchnic thrombosis after OLT. It is therefore mandatory to maintain life-long anticoagulation, which has to be monitored closely to avoid hemorrhage. Especially in young patients, allogeneic hematopoietic stem cell transplantation should be considered.

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