Idiopathic portal hypertension in a renal transplant patient after long-term azathioprine therapy

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Summary. We report the case of a patient with renal insufficiency who was admitted for the evaluation of splenomegaly. He had received a kidney allograft 6 1/2 years ago. Treatment with azathioprine and prednisolone for immunosuppression had been discontinued 1 year before admission. The underlying cause of the splenomegaly appeared to be an idiopathic portal hypertension. Until now, this disease has been described in only 13 kidney transplant patients receiving long-term immunosuppressive therapy with azathioprine. For the first time we demonstrate that azathioprine can cause this chronic liver disease even if the drug has been withdrawn some time before. Therefore, the indication for azathioprine must be considered very carefully.

Key words: Idiopathic portal hypertension – Azathioprine – Transplant complications

With an incidence of 12.8%–49%, liver disease is a fairly frequent complication in renal transplant patients [2, 3, 10, 14, 24]. It is a significant source of morbidity and mortality especially in patients who are long-term renal allograft carriers [24]. We distinguish between preexisting liver diseases and liver injuries related to renal transplantation and immunosuppression.

Infection with the hepatitis B virus is an important example of a preexisting liver disease, because in up to 37% this infection leads to chronic aggressive hepatitis and liver cirrhosis after treatment with immunosuppressive drugs [11]. Due to the improved blood preparations and prophylactic vaccination, the number of hepatitis B surface antigen (HBsAg)-positive transplant recipients declined to 5% in more recent studies [2, 24]. The most important liver diseases acquired after renal transplantation are viral infections [4, 11, 19] or sequelae of side effects of potentially hepatotoxic drugs given in the peri- or postoperative period [2, 10, 23]. For a long time, azathioprine was used as an essential drug for the necessary immunosuppression after renal transplantation. An extremely rare side effect of long-term azathioprine therapy is the development of an idiopathic portal hypertension (IPH) with perisinusoidal fibrosis [8, 11, 15]. So far, only 13 cases have been reported. We describe another case of this disease, diagnosed 1 year after the discontinuation of azathioprine therapy.

Case report

This 55-year-old man suffered from end-stage renal insufficiency due to glomerulonephritis 7 years ago. Six years ago, he received a renal allograft, and prednisolone and azathioprine were prescribed for immunosuppressive therapy in average doses of 5 mg/day and 50 mg/day, respectively. At a routine control about 6 months later, the gammaglutamyltransferase (GGT) activity was found to be elevated up to 80 IU/l. This abnormality persisted during the following years. The transaminases and the alkaline phosphatase activities were within normal limits. The patient denied any consumption of larger amounts of alcohol. Five years later the patient became hemodialysis-dependent again because of the chronic rejection of the allograft, and treatment with azathioprine was interrupted. On this occasion, a splenomegaly was noted for the first time. One year later he was admitted for evalu-
Fig. 1. a Endosonography. Dilated portal vein (pv; diameter 15 mm) and extramural veins (arrow) as a sign of portal hypertension. The ultrasound endoscope is situated in the antrum of the stomach. b Extramural esophageal varices (arrows); A = aorta descendens.

Fig. 2. Mesentericography. The portal vein (pv) is patent but dilated; enlarged splenic vein (sv) with collaterals (c).

Physical examination. The liver was not enlarged, and the spleen was palpable 10 cm below the costal arch in the midclavicular line during deep inspiration. No jaundice and no skin signs of hepatic disease were visible.

Laboratory data. The white blood count (2800/μl) and the hemoglobin concentration (7.8 g/dl) were decreased, while the platelet count was normal (132000/μl). Elevated values were found for GGT (69 IU/l), alkaline phosphatase (497 IU/l), and leucinaminopeptidase (52 IU/l); the cholinesterase concentration was slightly diminished (3157 IU/l). Glutamate dehydrogenase, alanine and aspartate aminotransferases (ALAT, ASAT), bilirubin (0.4 mg/dl), protein as well as the protein electrophoresis results were normal.

Virological data. By the Epstein-Barr virus immunofluorescence test for immunoglobulin G was 1:320 and for immunoglobulin M, negative. Cytomegalovirus complement fixation test result was negative, as was HBAg, anti-HBs, and anti-HCV, while anti-HAV was positive.

Abdominal ultrasound. The spleen was enlarged (15 x 9 cm), while the size and echostructure of the liver were within normal limits.

Esophagogastroduodenoscopy revealed esophageal varices I.

Endoscopic ultrasound (Fig. 1). The portal vein was dilated, with a diameter of 1.5 cm. Within and beyond the wall of the duodenum, stomach, and esophagus, many dilated veins could be demonstrated.

The mesentericopportography (Fig. 2) showed a dilatation of the portal vein and collateral veins surrounding the fundus of the stomach and the esophagus.