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ORIGINAL ARTICLE

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Liver transplantation as rescue treatment in a patient with primary AL kappa amyloidosis

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Abstract Although involvement of the liver is common in systemic amyloidosis, clinical manifestations of hepatic dysfunction and liver biochemical abnormalities are often absent or only mild. Here we report on a patient with primary amyloidosis and rapid development of liver failure, who was successfully treated by liver transplantation. The patient is a 61-year-old Swedish man who was admitted to the local hospital for spontaneous rupture of the spleen. Before admission, he had suffered from diffuse upper abdominal discomfort, diminished appetite, and had lost 15 kg in 6 months. Shortly after splenectomy, he developed cholestatic liver failure with moderate hepatomegaly, jaundice, ascites and hyponatremia. Over a period of 3 weeks his liver failure progressed, renal function deteriorated rapidly, and he developed encephalopathy. Liver transplantation was performed on the 35th day after splenic rupture. Histological examination revealed extensive deposits of amyloid in the spleen and liver. N-terminal amino acid sequence analysis of the amyloid protein, purified from the patient's native liver, revealed an AL protein of kappa I-type origin. The postoperative course was uncomplicated, apart from one episode of sepsis and one course of treatment for acute rejection. He was discharged from hospital with normal liver function and good kidney function. One year after surgery, he was in good condition, with normal liver function. However, a liver biopsy taken at the same time showed de novo amyloid deposits in the grafted liver. We conclude that liver transplantation may be indicated as a life-saving procedure in rapidly progressing hepatic amyloidosis with cholestatic jaundice, although the underlying disease has not changed.

Key words Primary amyloidosis · Splenic rupture · Liver transplantation

Abbreviations *AL* Amyloidosis light chain-associated amyloidosis · *LTx* Liver transplantation · *TTR V30M* Transthyretin mutation, a substitution of methionine for valine at position 30

Introduction

Immunoglobulin light-chain-associated (AL) amyloidosis is characterized by extracellular deposition of insoluble fibrillar monoclonal light chains. A pathological process of amyloid deposition in tissues leads to organ failure and may be fatal if allowed to progress [46]. The most common amyloid syndromes involve renal failure, heart failure, carpal tunnel syndrome, and peripheral neuropathy [12]. Splenic rupture is an unusual complication of systemic amyloidosis, associated with high mortality [30, 37]. Although the liver is frequently in-

volved in systemic AL amyloidosis, clinically dominant hepatic amyloidosis is uncommon [10]. Involvement of organs has often been considered as a contraindication for organ transplantation since it is a systemic disease and amyloid deposition will develop in the organ allograft. Despite these concerns, several centers have performed heart [15, 17, 21] and kidney [19, 25, 31, 45], transplantations for AL amyloidosis with good intermediate-term results in some patients. Allogeneic bone-marrow transplantation for AL amyloidosis has also been reported to lead to complete clinical recovery after 3 years [13]. Although amyloid deposits are often present in the spleen and liver, we report in this paper a rare case of severe AL amyloidosis, causing rupture of the spleen and rapid deterioration of liver function, successfully cured with liver transplantation.

Case report

A 61-year-old Swedish man was admitted to a regional hospital for abdominal pain associated with jaundice and a feeling of faintness that had continued over a period of a few days. His past medical history included hypercholesterolemia and hypertension, and his only medication was an angiotensin-converting enzyme inhibitor. He had lost 15 kg a few months before he developed pain and had suffered from intermittent abdominal discomfort, unrelated to meals, for a few weeks. He had no history of abdominal trauma.

On admission to the regional hospital, he was sallow and showed signs of shock. His abdomen was distended and he had an enlarged liver and a tender spleen on palpation. The findings on physical examination were otherwise normal, without peripheral edema or stigmata of liver disease. Laboratory tests on admission revealed a hemoglobin of 90 g/l, and he was therefore given a transfusion with whole blood. Computed tomography of the abdomen confirmed the presence of hepatosplenomegaly. It also showed the presence of blood around the spleen and along the anterior of the liver. The chest X-ray and electrocardiogram were normal. Preliminary diagnosis of spontaneous rupture of the spleen with intra-abdominal hemorrhage was made.

Laboratory tests revealed the following: negative alfa-fetoprotein (1.5 μg/l, ref. < 19 μg/l), negative hepatitis A, B and C markers, hypoalbuminemia (14 g/l, ref. 37–48 g/l) and glomerular proteinuria on urine analysis (0.6 g/day). Urinary immunoelectrophoresis, performed on a 24-h urine sample, showed albuminuria 52 mg/day (ref. < 30 mg/day), but no monoclonal proteins.

On laparotomy, several liters of old and fresh blood were present in the upper abdomen, presumably the result of moderate bleeding from a laceration of the anterior surface of the spleen, which was enlarged and hard. The spleen and an accessory spleen, which was also hard, were excised. No lymphadenopathy was seen in the abdomen that would have suggested a lymphoproliferative disorder, and there was no evidence of any other intra-abdominal pathology. The liver was slightly enlarged and wedge biopsy was taken from its left lobe. Postoperatively, there were no signs of persistent intra-abdominal hemorrhage.

Histological examination of the spleen showed diffuse deposits of amyloid with green birefringence after staining with Congo red. On biopsy, the architecture of the liver was normal, but amyloid deposits were also found, mainly around vessels. Mild fatty changes and mild cholestasis were also present.

There were no signs of lymphoma or sarcoidosis. A radiological examination and a bone-marrow biopsy were performed to exclude multiple myeloma. The X-ray of the skeleton was negative, and the bone-marrow biopsy revealed a normal number of plasma cells. No Bence-Jones protein was found in the urine, and there was no detectable immunoglobulin kappa M band in plasma electrophoresis. No Howell-Jolly bodies were seen in the peripheral blood smear, which was interpreted as a normosplenic blood picture. DNA analysis, using the PCR technique, was negative for TTRV30 M mutation (familial amyloidotic polyneuropathy, Portuguese/Swedish type).

The patient's subsequent clinical course showed progressive deterioration in hepatic function with increasing total biliribin up to 693 μmol/l (ref. < 26 μmol/l), alkaline phosphatase higher than 105 ukat/l (ref. < 0.80 ukat/l), and albumin level 15 g/l. Deterioration of the kidney function was moderate with creatinine 188 μmol/l (ref. < 120 μmol/l) and sodium level decreased to 125 mmol/l (ref. 136–146 mmol/l).

On day 35 after splenectomy, the patient underwent transplantation with a whole liver graft of about the same size as that of the recipient from an ABO-identical female donor. The native hepatectomy was performed, using a conventional technique and an extracorporeal venovenous bypass. The biliary anastomosis was carried out by end-to-end choledochocholedochostomy. Post-transplant immunosuppression comprises: a triple regimen with tacrolimus, azathioprine, and prednisolone. The postoperative course was uncomplicated, apart from one episode of sepsis 10 days after transplantation, and one course of treatment for acute rejection 2 weeks after transplantation. The patient was discharged from the hospital 4 weeks after transplantation with normal liver function and good kidney function.

Histological sections of the native liver confirmed the diagnosis of amyloidosis with extensive amyloid deposits. The portal tracts were widened by these deposits, and there was a mild bile duct proliferation. Deposits were also present in the lobules along the liver cell plates and around central veins, together with focal atrophy of the hepatocytes. Cholestasis, mainly intracanalicular, was also seen. The diagnosis of amyloidosis was made before liver transplantation, but the more detailed investigations were performed after hepatectomy of the patient's native liver.

To type the amyloid specifically, amyloid fibrils were extracted from a small piece (about 100 mg) of the liver. Enzyme-linked immunosorbent assay of dissolved fibrils [40] revealed reactivity with two antisera against AL protein of the kappa type. The fibrils were also dissolved and subjected to sodium dodecylsulfate polyacrylamide gel electrophoresis. The proteins were then electrotransferred to a PVDF membrane, and N-terminal amino acid sequence-analysis of a major amyloid fibril protein was performed, as described [23, 39], revealing the N-terminus of an AL protein of kappa I type (Fig. 1).

After transplantation, the patient was closely followed-up regarding renal, liver-, and heart function. No other organ biopsies were taken. Chemotherapy was not added to the post-transplant treatment protocol.

One year after surgery, the patient was in good condition and fully enjoying life. The liver tests were good with total bilirubin 3.0 μmol/l and alkaline phosphatase 4.0 ukat/l. A liver biopsy, performed at this time, showed normal liver structure. However, sparse de novo amyloid deposits were seen with Congo red staining in polarized light along the liver trabecule in the portal tracts (Fig. 2). Renal function tests at the 1-year check-up showed slow deterioration with GFR 45 ml/min per 1.73 m^2 (postoperatively 49 ml/min 1.73 m^2) and increasing serum creatinine level up to 131 μmol/l.

During the second postoperative year, the patient developed immunosuppression-related diabetes mellitus and osteoporosis.

Fig. 1 N-terminal amino acid sequence of AL protein BGZ compared to that of kappa immunoglobulin light-chain AG. (Residues in *parentheses* were not fully verified; *X* not identified residue; * deletion)

	5	10	15	20	25	30	35	40
AL-BGZ	X I Q M T Q S P S S L S A S V G D K V T I T (C) X A S Q G I T D Y L N (W Y) Q Q K X							
BJ-AG				R		D N H		* P

His diabetes mellitus was well controlled with insulin. The liver function tests were stable with total bilirubin 6.1 μmol/l and alkaline phosphatase 7.1 ukat/l, but renal function was further reduced with increasing creatinine level up to 161 μmol/l. The albumin level was low at 34 g/l because of severe albuminuria 3320 mg/l (ref. < 25 mg/l), which had progressed since transplantation.

Discussion

Some degree of hepatic involvement is usually present in both primary (AL) and secondary (AA) forms of systemic amyloidosis, but clinically dominant liver amyloidosis is relatively rare. In systemic AL amyloidosis, monoclonal plasma cells produce monoclonal immunoglobulin light chains that polymerize into non-degradable beta-pleated sheet fibrils [34]. Amyloid fibrils accumulate in the extracellular space, replacing and destroying normal tissues. This monoclonal population of plasma cells may be derived from a malignant clone (myeloma-associated AL) or from a small nonproliferative population of plasma cells (plasmacellular dyscrasia) [11, 28, 29]. In the present case, because of the absence of lytic bone lesion and hypercalcemia, we could not make a diagnosis of multiple myeloma [11]. Although our patient must have had plasma cell dyscrasia, no monoclonal component was detected in the serum and urine. AL-kappa-type amyloidosis may have a slow clinical course, sometimes associated with marked hepatomegaly [4, 27, 42], but there is no definite correlation between the clinical course and the type of light chain making up the fibril. It has to be stressed that AL amyloidosis is a systemic type of amyloidosis, and liver transplantation alone does not eliminate the source of amyloid production. This is in contrast to familial amyloidotic polyneuropathy, in which almost 95 % of amyloid is produced by the liver.

Systemic AL amyloidosis is progressive; it causes major morbidity and is usually fatal. Most organs may be affected by it, but involvement of the kidneys and heart usually causes serious symptoms, which results in death. In our patient, renal function deteriorated perioperatively. After transplantation, it continued to deteriorate slowly, with rising creatinine levels and albuminuria [44]. No signs of cardiac failure before or after transplantation were detected by physical or laboratory examinations of our patient. However, this does not exclude the presence of amyloid deposits. Although involvement of the liver is common in systemic amyloidosis, little or no clinical evidence of hepatic dysfunction or abnormalities in liver chemistries can be detected [10, 28]. Weight loss, early satiety, weakness, abdominal bloating, and hepatomegaly are suggestive clinical signs

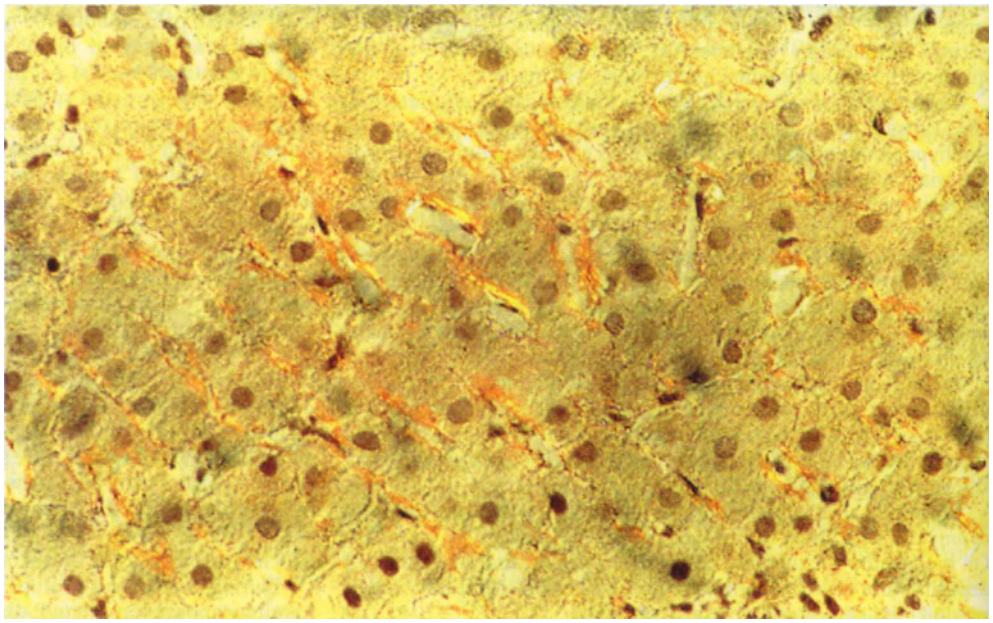

Fig. 2 Representative section of a needle biopsy from the graft 1 year after transplantation. De novo AL amyloid is seen along the sinusoids in the liver parenchyma (*yellow-red*). Congo red staining, in partial polarization (× 500)

of hepatic involvement in primary amyloidosis [10]. Hyperlipidemia also has been described as the first biochemical manifestation of primary hepatic amyloidosis [1]. Our patient was treated for hyperlipidemia over a period of 7 years before he showed signs of a deterioration in liver function and required a transplantation.

The mechanism of the spontaneous rupture of the spleen in amyloidosis is unclear. It is generally thought to be caused by rapid expansion of the splenic capsule, which has become rigid because of amyloid deposits and then ruptures [8, 37, 48]. Fragility of the vascular red pulp from amyloid infiltration of the blood vessel walls [2, 24, 32, 35, 37], and coagulation abnormalities including factor X deficiency and prothrombin time prolongation [26, 50], may also be contributory factors.

In patients with centrilobular cholestasis, amyloid is mainly deposited in the periportal area where it interferes with passage of bile from the small intrahepatic bile ducts to the septal bile duct [20, 36, 38, 43]. This was true of our patient.

Complications of hepatic amyloidosis are rarely of clinical importance. Splenomegaly, ascites, portal hypertension, and varices have been reported, without evidence of worsening an already poor prognosis [22]. The survival of patients with liver involvement in amyloidosis is no different from that of other patients with amyloidosis [12]. However, when complicated by cholestatic jaundice, the prognosis is even less satisfactory [38]. The levels of alkaline phosphatase tend to increase as the cholestatic picture worsens. These patients have a uniformly poor prognosis, as death occurs within a few months after the onset of jaundice [5, 14, 41]. This picture is seen only in patients with primary amyloidosis and, to our knowledge, it has not been reported in association with AA or various familial forms of amyloidosis.

In the literature, the median survival of patients with a premortem diagnosis of primary hepatic amyloidosis is about 9 months, and projected 5- and 10-year survival rates are 13% and 1%, respectively [10]. In particular, median survival rates of 1.8 and 3.3 months are reported in patients presenting with a total bilirubin level exceeding 1.5 mg/dl and alkaline phosphatase more than four times the normal [10]. The prognosis is very poor in cases of cholestatic acute liver failure in hepatic amyloidosis [5, 33, 49], especially when it is associated with rupture of the spleen and/or the liver [3, 37]. In these cases, liver transplantation may be the only life-saving treatment, and it has been successfully performed in cases of spontaneous, massive hepatic hemorrhage [16]. However, the authors report a lack of correlation of the prognosis with the size of the liver, the results of laboratory tests, or the degree of amyloid deposition [8].

Regression of hepatic AL amyloidosis has been reported with normalization of liver size and function after the treatment of amyloidosis [7, 9, 12]. This may not correlate with histological resolution of the amyloid. However, it has been shown that hepatic AL-amyloid deposition undergoes substantial regression after cytotoxic therapy [18], and some patients survive more readily when they undergo chemotherapy similar to that given in multiple myeloma [6]. There is no specific treatment that causes the resolution of amyloid deposits with certainly, but therapy that reduces the supply of amyloid fibril precursor proteins can improve survival rates and preserve organ function. In AL amyloidosis, the aim of the treatment is to suppress the underlying B-cell clone, and this suppresses production of the amyloid fibril precursor protein [47]. In cases such as ours, this can be difficult to achieve since the disease develops very rapidly when cholestatic jaundice occurs. Many patients die before benefits of the therapy are realized. In our patient, liver and spleen amyloidosis were prominent features, while the other organs were clinically much less involved (good cardiac function and stable renal function), and no biopsies of other organs than the spleen and the liver were taken. Chemotherapy was not added to the post-transplant treatment protocol. Recurrent amyloidosis in the graft is a well-documented event in renal allograft recipients undergoing transplantation for amyloid renal disease. Recurrence of amyloid deposits in the renal grafts also occurs in rheumatic disorders and AL amyloidosis. Prior to this case, no de novo AL or AA amyloid deposits have been reported in liver grafts.

Because survival of the patients with hepatic amyloidosis and cholestatic jaundice is poor, liver transplantation is a life-saving procedure in rapidly progressing hepatic amyloidosis of extrahepatic origin, even if the underlying disease does not change. The experience with this treatment in AL amyloidosis is limited. However, compared to earlier reports on patients suffering from hepatic amyloidosis with cholestatic jaundice, the outcome in our patient was favorable in the short term. We found no rapid deterioration of the transplanted liver due to amyloid deposits. Several years of follow-up will be necessary before we can evaluate the long-term effect of liver transplantation for this disease.

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