Combined cardiac and liver transplantation for the treatment of familial amyloidosis

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A 55-year-old white man presented with weight loss and diarrhea in 2002. An extensive workup, including colonoscopy and gastrointestinal biopsy, led to a diagnosis of familial transthyretin amyloidosis (Appalachian variant). The patient had a steady decline over the next 2 years, including progressive weakness, peripheral neuropathy, and wasting. Because of the clinical progression, he underwent evaluation for liver transplantation. During this workup, an echocardiogram demonstrated right ventricular enlargement,

pulmonary pressures in excess of 50 mm Hg (based on tricuspid regurgitation), a small pericardial effusion, and an increased echogenicity of the myocardium (*Figure 1*). These findings were consistent with cardiac amyloid.

Right heart catheterization demonstrated a mean right atrial pressure of 12.1 mm Hg. The other pressures were as follows (mm Hg): right ventricular, 56/14; pulmonary arterial, 54/25, with a mean of 38; pulmonary capillary wedge, 23.4; right ventricular end diastolic, 12; and left ventricular end diastolic, 26. The cardiac output was 5.2 L/min, and the cardiac index was 2.5 L/min/m². The overall ejection fraction was 55% without wall motion abnormalities. A vasodilator challenge (Nipride) was performed to evaluate for the presence of reversible pulmonary hypertension. With infusion of Nipride, the patient's pulmonary arterial pressure decreased from 54/25 to 43/18 mm Hg, and the mean pressure decreased from 38 to 32 mm Hg, suggesting that the pulmonary hypertension was reversible.

Left heart catheterization demonstrated coronary arteries without significant atherosclerosis. Six biopsy specimens of myocardium from the right ventricular septum were obtained percutaneously using fluoroscopic guidance. Five of these were sent for Congo red staining and microscopy (*Figure 2*). A single sample was sent for electron microscopy (*Figure 3*). The biopsy findings confirmed the presence of cardiac amyloid.

In the setting of reversible pulmonary hypertension, liver transplantation was felt to be potentially curative for this type of amyloidosis (1, 2), and the patient was evaluated and accepted for a combined heart and liver transplantation. The patient tolerated posttransplant immunosuppression well with tacrolimus, mycophenolate, daclizumab, and corticosteroids. He was discharged to a rehabilitation center 2 weeks after surgery. Although he was doing well from a transplant standpoint, 2 months after surgery he died from complications unrelated to either his underlying illness or the transplant itself. His death appeared to be secondary to a pulmonary embolism while he

Figure 1. Echocardiogram demonstrating increased echogenicity of the myocardium in (a) the parasternal long and (b) four-chamber views. A small pericardial effusion is noted (arrows). (c) Mitral valve inflow demonstrates “pseudonormalization” of velocities, suggestive of restrictive cardiomyopathies. (d) Tissue Doppler confirms this, by demonstrating low velocities during myocardial relaxation.

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Figure 2. The right ventricular endocardial biopsy specimen after Congo red staining. The (a) “apple-green birefringence” and (b) light pink homogeneous deposits (arrow) are consistent with amyloid.

was at a skilled nursing facility for rehabilitation. No autopsy was performed.

DISCUSSION

Amyloidosis, first named in 1854 by Rudolph Virchow (3), is characterized by multiple organ infiltration with fibrillar proteins described as amyloid deposits. These deposits cause mechanical disruption in the organs they invade (4). The disease is classified as primary (immunoglobulin light-chain derived), secondary (chronic infectious or inflammatory disease related), or hereditary (usually autosomal dominant). Regardless of classification, the disease process is often systemic and involves more than one organ system.

Confirmation of this diagnosis requires biopsy of involved tissue in order to demonstrate the protein deposition. After Congo red staining, tissues with amyloid deposits show “apple-green birefringence” under polarized light. The characteristic fibrillar structure can also be demonstrated by electron microscopy. Twenty-four distinct proteins have been demonstrated to form beta-pleated sheet amyloid fibrils. Identification of the specific protein causing amyloidosis in a particular patient is helpful since amyloid proteins of diverse origins have similar physical properties when examined by Congo red staining, electron microscopy, or x-ray diffraction (5, 6).

Familial amyloidotic polyneuropathy (FAP) is a hereditary autosomal dominant form of amyloidosis. In general, it is a late-onset disorder that progresses slowly, potentially causing polyneuropathies, cardiomyopathies, and nephropathies, as well as gastrointestinal and/or ocular involvement (5). It is most often caused by a structurally abnormal protein called transthyretin (TTR), which is made up of polypeptide chains synthesized by the liver (7). This protein is deposited in multiple organs, ultimately causing organ failure and death.

Figure 3. Electron micrograph demonstrating the classic appearance of amyloid fibrils within the myocardium.

FAP accounts for approximately 10% of patients with amyloidosis (8). Multiple variants of FAP have been identified to date. The patient reported here had the Appalachian variant, which is notable for a single amino acid substitution of alanine for threonine at the 60th codon (Thr60Ala) of the FAP prealbumin (TTR) molecule (9). More than 80 mutants of TTR have been described (6). Variants of FAP tend to manifest in different ways. For example, the Iowa variant is characterized by the development of lower limb neuropathy, nephrotic syndrome, and peptic ulcer disease, whereas the Appalachian type is associated with late-onset cardiomyopathy and polyneuropathy (7, 10).

Medical treatment has been limited to organ dysfunction palliation, including pacemakers for cardiac dysfunction and dialysis for renal failure. In the past 15 years, liver transplant has become not only a treatment but the only potential cure for FAP. Since the abnormal TTR protein is produced mainly in the liver, transplanting a normal liver should halt accumulation of the mutated TTR molecule. This prevents further deposition of the abnormal protein and tends to halt further progression of the disease. Posttransplantation studies show the mutant TTR amyloid levels in serum to become almost undetectable (1, 2). The first orthotopic liver transplantation for FAP was performed in 1990 in Sweden (1, 11). Now, over 500 FAP patients have had orthotopic liver transplants with cadaver or living donors, with 5-year survival rates between 60% and 77% (12–15). There is some evidence of potential reversibility of the polyneuropathy; other evidence indicates that the process is arrested and stabilized (6, 14, 16).

TTR-type amyloidosis is an accepted indication for orthotopic liver transplantation, but cardiac amyloidosis can paradoxically progress even after the transplant procedure (17–19). This progression of cardiac dysfunction has been noted to occur in transplanted patients even as deposition in other organs stabilizes or regresses (17, 19). One theory is that the variant TTR in the myocardium may act as a nidus for subsequent deposition of normal wild-type TTR even after liver transplantation. This has been called the “seeding” hypothesis. After enough variant

TTR deposition occurs, deposition of wild-type TTR might be accelerated. This seems especially true in the heart, in which there is an inherent tendency for wild-type TTR to deposit. In patients with cardiomyopathy due to FAP, the proportion of wild-type to mutated TTR can be up to 50% (19, 20).

In amyloid patients with known mutations that are associated with cardiomyopathy, liver transplantation prior to development of cardiac dysfunction can potentially avoid this complication. However, in patients who have already developed significant cardiomyopathy, wild-type amyloid can continue to deposit, negating the benefit of the liver transplantation. Combined heart and liver transplants have been performed in these patients (6). Only patients with FAP variants that are associated with cardiomyopathy should be considered for combined heart-liver transplantation.

Our patient developed a severe cardiomyopathy secondary to FAP; therefore, it appeared that a combined heart and lung transplantation would provide him with the most benefit. Very few of these procedures have been performed to date for FAP. As more combined heart and lung transplants are performed, the benefit of this approach can be better defined.

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