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LETTER TO THE EDITORS

Delayed diagnosis of fibrinogen Aα-chain amyloidosis after dual heart–kidney transplantation

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Dear Sir,

Besides light-chain and amyloid A amyloidosis, hereditary autosomal dominant amyloidosis is considered a rare disease. Nevertheless, it is frequently misdiagnosed [1]. Fibrinogen Aα-chain (AFib) amyloidosis involves the kidneys and causes proteinuria, hypertension, and progression to end-stage renal disease (ESRD). Isolated renal transplantation has been proposed when ESRD is reached, but it is associated with risk of recurrence and premature graft loss [2,3]. Moreover, cardiac amyloidosis has been recently described among mutated patients [4] but its precise pathogenesis remains debated [2,5]. Heart transplantation in the course of AFib amyloidosis has, to our knowledge, never been reported.

A 55-year-old smoker Caucasian male presented with a large inaugural anterior myocardial infarction in 2003 with coronary angiography showing an atherosclerotic plaque of the left anterior descending artery. Despite angioplasty and stent implantation, severe heart failure appeared (left ventricular ejection fraction = 20% with dilated left ventricle) without other echocardiographic signs suggestive of amyloid cardiopathy. Moderate renal failure [serum creatinine level (SCr) = 130 μmol/l] with proteinuria at 1.4 g/l and hypertension were contemporaneously noticed but not explored. In 2004, deterioration of kidney function (SCr = 245 μmol/l) and massive albuminuria at 6 g/day led the patient to the first nephrological assessment. Renal ultrasound evaluation revealed two small kidneys of 8 cm that did not allow renal biopsy. Family tree was unremarkable and immunological or infectious tests failed to explain this glomerulonephritis. Decline of renal and cardiac functions was prompt. He started hemodialysis at the end of 2004 and was placed on the waiting list for combined heart–kidney transplantation.

In November 2005 he received a combined heart–kidney transplant from a deceased 51-year-old male donor with no medical history. Transplantation was successful: the lowest SCr was 108 μmol/l at month 1. He received cyclosporin A, mycophenolate mofetil, and prednisone after an initial induction with anti-thymocyte globulin. At M6, a first kidney transplant biopsy (performed for SCr increased to 145 μmol/l with proteinuria at 0.7 g/day) showed chronic aspecific vascular endarteritis lesions. SCr then stabilized between 150 and 190 μmol/l with low proteinuria. Annual coronary angiographies were normal until 2009, when a nonsignificant stenosis of the right coronary artery and a mild elevation of pulmonary capillary wedge pressure (18 mmHg) were suggestive of chronic rejection. Repeated cardiac protocol biopsies revealed asymptomatic cardiac rejections grade 1R between 2007 and 2009. Repeated echocardiographs showed septum wall thickening (14 mm), an impaired relaxation pattern with restrictive profile, and a normal ejection fraction (65%). Interestingly, the septum had a granular sparkling appearance. Finally, he received a pacemaker in 2010 for repeated episodes of complete atrioventricular block.

In 2011, he was admitted for acute diarrhea secondary to intestinal cryptosporidiosis complicated by acute pre-renal failure (SCr: 625 μmol/l). He was treated by a high-volume of parenteral fluid and nitazoxanide. Despite his improved clinical status, we observed a stagnation of SCr at 260 μmol/l, without hypertension, hematuria, or proteinuria. A second renal biopsy revealed glomerular deposits of amorphous eosinophilic material without interstitial or vascular deposits. Congo red staining was positive with reddish-brown material that showed red birefringence under polarized light (Fig. 1, panels a and b). Immunofluorescence study showed no reactivity for κ and λ light-chain, AA protein, transthyretin, lysosyme, apolipoprotein, leukocyte chemotactic factor 2, and β2-microglobulin but glomerular deposits were labeled with anti-AFib antibodies. Genetic analysis confirmed a heterozygous p.E526V mutation of the AFib gene. Interestingly, careful retrospective examination of his native explanted heart also revealed mild amyloid deposits within small myocardial vessels (Fig. 1, panels c and d). However, retrospective examination of graft endomyocardial biopsies did not show amyloidosis. Our patient is currently well; Scr has stabilized at 230 μmol/l with mild proteinuria (0.5 g/day) under ACE inhibition.

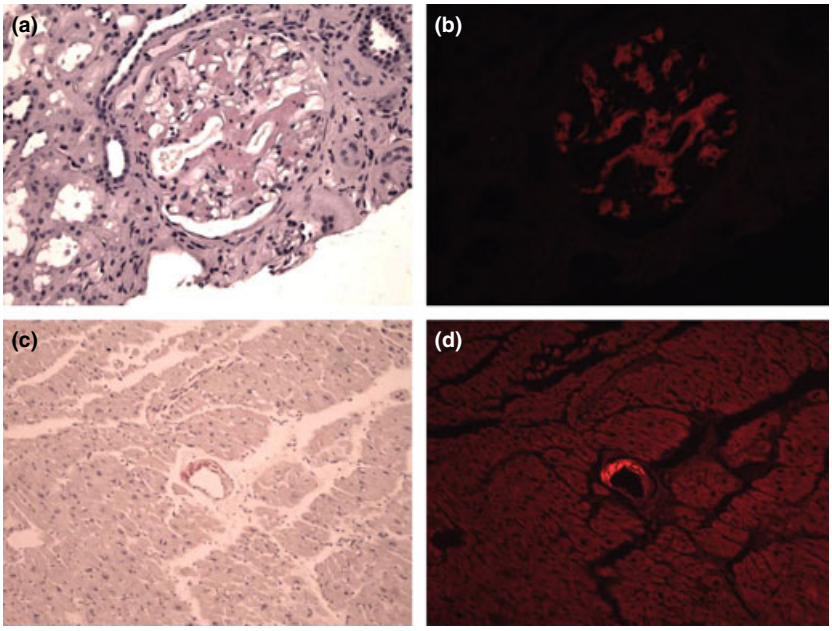

Figure 1 Renal allograft (a, b) and native cardiac (c, d) biopsies in fibrinogen Aα-chain amyloidosis. Panel a shows glomerular enlargement and endomembranous amyloid deposits. Interstitium and vessels do not contain amyloidosis (Congo red stain ×100). Panel b shows red fluorescence of the deposits on the same section. Panel c shows mild amyloid deposits in a small myocardial vessel of the native explanted heart (Congo red stain ×100). This specific coloration was tested retrospectively. Panel d shows red fluorescence of the deposits on the same section.

We thus made a retrospective diagnosis of systemic AFib amyloidosis involving kidneys and heart; it appears our case is the first report of heart–kidney transplantation in this setting. Today, recurrence is proven on transplanted kidney but only suspected on transplanted heart.

Fibrinogen Aα-chain amyloidosis recurrence after isolated kidney transplantation has been reported in nine patients, two of whom received two grafts [2,3,6–9]. Recurrence rate was 33% (4/12) in the largest cohort reported [2]. Time to recurrence is probably associated with the type of mutation. Indeed, frameshift mutation at codon 522 [3], seems to predispose to earlier recurrence (about 1 year) than p.E526V mutation (about 5 years). Even if reports are scarce, AFib amyloidosis recurrence could be a factor of poor prognosis and graft loss (8 losses/11 recurrences).

As fibrinogen production is exclusively hepatic, the only curative treatment of AFib amyloidosis is liver transplantation. Combined hepatorenal transplantation should be considered as the first therapeutic option for patients with ESRD because of (i) the frequent recurrences of AFib amyloidosis on renal transplants, then premature transplant losses, (ii) the relatively early onset of AFib amyloidosis-related ESRD, and (iii) the risk of systemic evolution of the disease. Thirteen cases of hepatorenal transplantation have been reported [3,4,8,9]. In the largest cohort, six of nine patients (66%) are alive with good liver and renal functions without recurrence [4]. If liver transplantation is contraindicated, isolated kidney transplantation could be considered but risk of recurrence should be individually evaluated.

Cardiac involvement of AFib amyloidosis has been recently identified. In the cohort of 22 AFib patients [4], 52% had abnormal echocardiographic findings suggestive of amyloid cardiomyopathy (with 3/4 positive endomyocardial biopsies) and 54% had parasympathetic dysfunction with bradycardia. Prevalence of coronary atherosclerotic disease was also high (68%). This cardiac involvement implies the need for screening. In the present case, even if endomyocardial biopsies were negative, ultrasound findings and repeated episodes of complete atrio-ventricular block after graft suggest cardiac recurrence. In the setting of AFib amyloidosis involving the heart, combined heart–liver, or combined heart–liver–kidney transplantation could be discussed [10].

In conclusion, the importance of determining the original kidney disease before graft is emphasized here. The diagnosis of systemic AFib amyloidosis at the time of discovery of proteinuria would have led us to discuss combined heart–liver transplantation or heart–liver–kidney transplantation.

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