

**SUCCESSFUL LONG-TERM OUTCOME OF THE FIRST COMBINED HEART
AND KIDNEY TRANSPLANT IN A PATIENT WITH SYSTEMIC AL
AMYLOIDOSIS**

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Abstract

Simultaneous cardiac and renal involvement is associated with a particularly poor prognosis in patients with AL amyloidosis (AL-A). We report the first case of a successful long-term outcome of combined heart and kidney transplantation not followed by autologous stem cell transplantation in a patient with systemic AL-A. The recipient was a 46-year-old man with end-stage renal failure associated with serious cardiac involvement in the context of AL-A. Before transplantation, two courses of oral melphalan plus prednisone induced partial hematologic remission, as shown by the decrease in circulating free light chain with no improvement of renal or heart function. The patient underwent combined heart and kidney transplantation as a rescue treatment. Three years after organ transplantation, plasma cell dyscrasia remains in complete remission, with normal free lambda light chain levels and no recurrence of amyloid deposition on heart and kidney grafts. This case report demonstrates that successful long-term outcome of combined heart and kidney transplantation not systematically associated with stem cell transplantation may be considered an additional therapeutic option in AL-A patients with severe organ dysfunction and partial hematologic remission.

Introduction

Systemic AL (amyloid light chain) amyloidosis (AL-A) is a clonal plasma cell dyscrasia characterized by the synthesis of monoclonal light chains, potentially leading to the formation of beta-pleated sheets, which may be deposited in tissues, leading to progressive multiple organ failure and death (1, 2). The most common clinical presentation of AL-A includes renal involvement, characterized by nephrotic-range proteinuria, with a progressive worsening of renal function and congestive heart failure (3, 4). Cardiac dysfunction is considered to be the most important prognostic factor, patients with congestive heart failure having a median survival close to four months (5).

The optimal curative treatment for AL-A remains a matter of debate. Intravenous melphalan treatment followed by autologous stem cell transplantation (SCT) was initially reported to be the most effective treatment for eligible patients (6-8). However, a recent randomized survey in France showed that high doses of melphalan followed by autologous stem cell rescue was not superior to standard-dose melphalan plus dexamethasone treatment in terms of AL-A outcome (9). Eligibility criteria for SCT differ between hematologic centers, because this treatment is associated with high levels of mortality, which are increased by cardiac and/or renal involvement (10, 11). For this reason, most clinicians exclude this therapeutic approach in patients with severe organ dysfunction, particularly in cases of kidney and heart failure.

Recent data have suggested that the eligibility criteria for autologous SCT in patients with severe cardiac or renal involvement should be reconsidered. The therapeutic options include sequential heart transplantation and autologous SCT for patients with severe cardiac amyloid infiltration ineligible for exclusive SCT (12-15), and kidney transplantation followed by high-dose myeloablative chemotherapy and autologous SCT in patients with severely impaired kidney function considered unsuitable for SCT (16).

We report here the first case of successful combined heart and kidney transplantation as a rescue treatment for severe AL-A in a patient with end-stage renal disease and severe cardiac amyloidosis compromising short-term life expectancy. Three years after the procedure, the patient is still alive, with complete hematologic remission, having not required SCT or additional chemotherapy. No recurrence of amyloid deposition on the cardiac and renal allografts has been documented.

Case report

A 46-year-old man was referred to our nephrology department for a nephrotic syndrome in July 2004. He had no family history of amyloidosis and his relevant medical history was limited to untreated psoriatic disease. Clinical findings at admission included low blood pressure (115/70 mmHg) associated with peripheral lower limb oedema. The patient had macroglossia and spontaneous periorbital ecchymoses. Physical examination was otherwise normal. Laboratory investigations yielded the following results: urinary protein excretion of 10 g/ day and no microscopic hematuria or leukocyturia on analysis of urinary sediment. Serum albumin concentration was low, at 21 g/L. Serum creatinine concentration and creatinine clearance, as estimated with the Cockcroft and Gault formula, were 83 $\mu\text{mol/l}$ and 92 ml/min, respectively. Serum immunoelectrophoresis showed hypogammaglobulinemia (3.9g/L) with no monoclonal component. Urine immunoelectrophoresis was positive for lambda light chain (0.8 g/day). Immunonephelometric assays confirmed the presence of free light chain lambda at a concentration of 140 mg/L (normal range 5.7 to 26 mg/L) with a $\kappa:\lambda$ ratio of 0.06 (normal range 0.26 to 1.65) (17, 18). Immunological tests were negative, complement levels were in the normal range and no cryoglobulinemia was detected. Bone marrow aspirate showed the marrow to be moderately hypercellular, with normally maturing hematopoietic progenitors. Morphologically normal plasma cells that represent less than 10% of the total cells with no Congo red-stained deposits were observed on bone marrow examination. Bone X ray showed no osteolytic lesions. The renal biopsy specimen consisted of renal cortex with 16 glomeruli. Light microscopy of paraffin sections showed expansion of the mesangium by amorphous, weakly periodic acid-Schiff-positive material. Congo-red stained deposits were found both along the capillary walls in the mesangial matrix and in the arteriole wall. We detected λ light chains in direct immunofluorescence studies of renal tissue. Doppler echocardiography showed findings typical of cardiac amyloidosis, with a severe

concentric left ventricular hypertrophy (18mm) and abnormally high levels of echogenicity. Both atria were dilated and the left ventricular ejection fraction was estimated at 45%. Color Doppler analysis showed second-degree mitral valve regurgitation. Based on kidney biopsy and echocardiography results, the diagnosis of primary AL amyloidosis with cardiac and renal involvement was considered confirmed. The initial curative treatment for AL amyloidosis administered to our patient was four cycles of VAD (vincristine, adriamycin, steroids), beginning in August 2004. Unfortunately, after three courses of this chemotherapy regimen, massive gastrointestinal hemorrhage from the upper gastrointestinal tract occurred, requiring red blood cell transfusion and endoscopic treatment. Histological diagnosis confirmed the presence of an ulcerous amyloid lesion in the stomach. The patient displayed a progressive decrease in glomerular filtration rate and developed progressive dyspnea (NYHA stage IV) requiring multiple hospitalizations for acute heart failure with no decrease in circulating free lambda light chain levels after first-line chemotherapy. In November 2004, one week before the initiation of stem cell mobilization for leukapheresis to collect CD34⁺ progenitor cells, the patient was admitted in the intensive care unit for acute dyspnea due to cardiac tamponade successfully treated by surgical heart tube drainage. In December 2004, in the absence of criteria consistent with hematologic and organ responses, a second course of chemotherapy consisting of oral melphalan (8 mg/day) combined with dexamethasone (40 mg/day) administered orally on days 1 to 4 of every 28-day cycle was initiated. A partial hematologic response was observed after two courses of this chemotherapy (Fig. 1). This partial immunological response was not associated with an improvement in clinical symptoms, as demonstrated by the progressive decline of renal function, requiring chronic intermittent hemodialysis (beginning in January 2005) and the persistence of severe cardiac dysfunction on Doppler echocardiography.

The patient was considered ineligible for autologous SCT and was placed on the waiting list for heart and kidney transplantation in April 2005, with a view to performing secondary autologous SCT. An orthotopic heart transplant combined with a heterotopic kidney transplant was performed on 29th June 2005. The pretransplant panel reactive antibody (15) level was 0%. The donor was a 22-year-old woman who died from a brain hemorrhage. There were two HLA mismatches (1A, 1DR) between donor and recipient. Immunosuppression consisted of induction with antithymocyte globulin (thymoglobulin, Mérieux) for 5 days, combined with methylprednisolone during (1000 mg) and after (500 mg at 24 and 48 hours) surgery. Prednisone was initiated after extubation, with an oral dose of 1 mg/kg per day, and was progressively tapered to 0.2 mg/kg per day after two months. Mycophenolate mofetil (MMF) was administered on day 5, at a dose of 2 g per day, which was subsequently adjusted to ensure clinical safety. Tacrolimus treatment was initiated on day 3 and serum Tacrolimus trough concentrations were maintained at 8 to 10 ng/ml. Twenty-eight days after transplantation, the patient presented biopsy-proven acute heart rejection grade 3A without hemodynamic compromise or echocardiographic modification and without concomitant kidney rejection on kidney allograft biopsy. Intravenous methylprednisolone (500 mg) was administered on three consecutive days and endomyocardial biopsy 10 days later showed grade 0 rejection. The patient's subsequent recovery was uneventful and renal function at two months was defined by a serum creatinine concentration of 81 μ mol/l. Repeated searches for free lambda light chain in the serum by nephelometric immunoassays showed no recurrence of AL amyloidosis (Figure 1) and repeated heart allograft biopsies revealed an absence of amyloid deposits on the graft. In September 2005, a bone marrow examination carried out due to neutropenia and thrombopenia showed there to be no excess abnormal plasmocytes and no amyloid deposits.

We assessed intramedullary chimerism by real-time quantitative polymerase chain reaction (RQ-PCR), using the TaqMan kit and an ABI 7700 Sequence Detector (Applied Biosystems). The detection limit of the assay was 0.1%. Microchimerism was defined as the presence of 1% donor cells. No microchimerism was observed in our patient.

Three years after the procedure, echocardiography showed excellent graft function, coronarography revealed normal coronary arteries and effective kidney function (creatinine clearance calculated as 68 ml/min with the Cockcroft-Gault equation), with a urinary protein excretion of 0.12 g/day and no excess free lambda light chains in the blood. The patient is currently considered to be in complete remission, with a normal serum free lambda light chain concentration (17 mg/L). Moreover, stem cells were successfully mobilized and collected (5.59×10^6 /kg progenitor cells collected) three months after combined heart and kidney transplantation, for secondary autologous SCT in case of hematological recurrence.

Discussion

We report here for the first time the successful outcome, at 36 months, of combined heart and kidney transplantation in a patient with AL-A. This favorable outcome included complete hematologic remission, an absence of amyloid deposits in the cardiac and renal grafts and excellent renal and cardiac allograft function.

Selection of the optimal treatment remains a challenge in patients with AL-A, and solid organ transplantation has recently been identified as a therapeutic option. This approach has previously been assessed only in selected patients with AL-A, particularly those with single organ failure. However, most patients have multisystem disease or are too old to be considered suitable transplant candidates. Moreover, solid organ transplantation should be accompanied by measures to suppress the underlying clone to prevent the recurrence of amyloid deposits in the graft (19). Under such conditions, only the results of single-organ transplantation have been reported. Many studies have demonstrated the feasibility of isolated heart transplantation for cardiac AL-A (20-23). These patients had high levels of perioperative mortality due to multiple organ failure resulting from the preexisting but undiagnosed presence of deposits in other tissues. Dual heart and liver transplantation has previously been performed in systemic amyloidosis although indication was related to familial amyloidosis and no AL-A (22). In the United Kingdom, recurrent amyloid deposition (in patients with primitive AL-A) was consistently observed in the graft in the absence of additional treatment (chemotherapy and/or SCT) a median of 11 months after transplantation (range: 5 to 29.5 months) and the median survival for this group of patients was 29 months (22). Successful treatment by sequential heart transplantation and autologous SCT has been reported, this approach being developed in response to the high frequency of posttransplant disease recurrence and the risk of disease progression (12-15). Cases of cardiac amyloidosis treated

by heart transplantation followed by exclusive chemotherapy have also been reported, with an acceptable outcome (22, 24).

Renal transplantation associated with autologous SCT in patients with end-stage renal failure caused by AL-A has also recently been described (16, 25). One of these studies reported uneventful survival in all cases and a median graft survival of 7.4 years among the 21 patients undergoing renal transplantation (25). In the study by Leung, no clinical, biochemical or histological evidence of recurrence in the graft or bone marrow was detected during a mean follow-up period of 18 \pm 9 months, but recurrence in the renal graft was detected in one patient who did not undergo SCT.

This is the first case report, to our knowledge, to describe the outcome of combined heart and kidney transplantation for AL-A. Our patient displayed progressive multisystemic amyloidosis with severe renal, gastrointestinal and heart involvement despite a partial hematologic response to two courses of melphalan/dexamethasone chemotherapy with no improvement of organ function. Finally, given the major risk of rapid death due to heart and kidney failure and the high risk of death in the absence of specific treatment, combined heart and kidney transplantation seems to be the only therapeutic option available to such patients. No additional chemotherapy or SCT was carried out in our patient after renal transplantation, due to the lack of evidence of tumor activity in regular free light chain determinations by immunonephelometric assay. Early complete hematologic responses may have occurred in our patient after only two courses of melphalan- prednisone chemotherapy. Retrospectively, these two courses of treatment seem to have been sufficient to maintain prolonged remission and to abolish monoclonal light chain production. Moreover, we can not exclude that high dose of steroids used during induction therapy could have participate in the clearance of plasma cell since steroid treatment are known to induce plasma cells apoptosis. Nevertheless,

given the risk of primary hemopathy recurrence in this patient, careful follow-up will be required to detect any significant increase in free light chain concentration in the blood.

This case illustrates the feasibility of combined heart and kidney transplantation in patients with severe AL-A. Strategies of this type hold promise for the treatment of other patients with cardiac and renal amyloidosis. Extended follow-up, using a multidisciplinary approach, is required to detect recurrence of the underlying disease and for the initiation of complementary therapies, such as chemotherapy and STC.

Legend

Figure 1 Hematological follow-up before and after combined transplantation. Serum concentration of Free Light Chains (FLC) was measured by immunonephelometric assay (Lambda in black, Kappa in red)

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