Successful heart transplantation following melphalan plus dexamethasone therapy in systemic AL amyloidosis

Recurrence in the allograft and progression in other organs increase mortality after cardiac transplantation in AL amyloidosis. Survival may be improved after suppression of monoclonal light chain (LC) production following high dose melphalan and autologous stem cell transplantation (HDM/ASCT). However, because of high treatment related mortality, this tandem approach is restricted to few patients without significant extracardiac involvement. A diagnosis of systemic AL amyloidosis was established in a 45-year old patient with congestive heart failure related to restrictive cardiomyopathy, nephrotic syndrome, peripheral neuropathy, postural hypotension, macroglossia, and lambda LC monoclonal gammopathy. After melphalan and dexamethasone (M-Dex) therapy, which resulted in 80% reduction of serum free lambda LC, he underwent orthotopic cardiac transplantation. Two years later, he remains in a sustained hematologic remission, with no evidence of allograft or extra-cardiac amyloid accumulation. M-Dex should be considered as an alternative therapy in AL amyloid heart transplant recipients ineligible for HDM/ASCT.

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AL amyloidosis is a systemic disorder, caused by a monoclonal light chains (LC) producing clonal dyscrasia, that mainly affects the kidneys, heart, liver, and peripheral and autonomic nervous systems.[1,2] Restrictive cardiomyopathy is a severe and common manifestation of AL amyloidosis, associated with a median survival of approximately 9 months and less than 6 months once congestive heart failure is present.[3]

Cardiac transplantation in AL amyloidosis[3-10] remains controversial, because of organ shortage, recurrence of amyloid in the graft, and progression of systemic deposits. Encouraging results were recently obtained in few cases of AL amyloid cardiomyopathy, with sequential heart transplantation followed by high dose melphalan (HDM) therapy and autologous stem cell transplantation (ASCT). Providing remission of the underlying plasma cell disorder is achieved by HDM/ASCT, amyloid deposits do not recur in the allograft and extracardiac disease progression is halted, resulting in prolonged survival.[10] However, because of high treatment–related mortality associated with HDM/ASCT, this procedure is applicable only to selected cases. We report here a patient with systemic AL amyloidosis with congestive heart failure and multiple organ involvement, whose condition dramatically improved after cardiac transplantation following sustained clonal remission induced by melphalan plus dexamethasone.

Case report

A 45 year-old male patient was referred for severe hypertrophic cardiomyopathy of unknown origin discovered three years before. On admission, he complained of increasing fatigue and NYHA grade III dyspnoea. Physical examination revealed diffuse oedema, bilateral pleural effusions, macroglossia, reduced deep tendon reflexes, moderate hepatomegaly and postural hypotension without an increase in pulse rate. Nerve conduction studies confirmed bilateral sensory-motor neuropathy. ECG showed low voltage QRS complexes and atrial fibrillation. Echocardiography revealed concentric left ventricular and septal thickening (17 mm) with increased myocardial echogenicity. Left ventricular ejection fraction was reduced, with a restrictive transmitral flow pattern on doppler examination.

Biological results were: serum creatinine 0.9 mg/dL, proteinuria 2.1 g/day, total protein 56 g/L, albumin 32 g/L, calcium 2.28 mmol/L. Liver profile coagulation tests and full blood count were normal. NT-proBNP level was 10,870 ng/L (normal<300). A serum and urine monoclonal λ LC was detected. Raised serum free κ LC level (1,100 mg/L), with λ LC level of 3.1 mg/L and λ/κ ratio of 0.002 (normal range: 0.36-1) was demonstrated using the serum free LC assay (Freelite; The Binding Site, Birmingham, United Kingdom). A 10% plasma cell infiltration was found on bone marrow biopsy, without detectable amyloid deposits on the trephine.

A kidney biopsy was performed. Biopsy samples were processed for light, immunofluorescence and electron microscopy, as previously described.[11] A diagnosis of systemic AL amyloidosis was established after Congo red (Figure 1A) and immunohistochemical staining with anti-κ conjugate (Figure 1B) which confirmed diffuse mesangial and vascular AL deposits, with a typical fibrillar ultrastructural organization on electron microscopy (Figure 1C).

Chemotherapy was introduced six weeks after admission. Three courses of monthly intravenous melphalan (25 mg/m^2) plus oral dexamethasone (20 mg on days 1-4) induced a 78% decrease in serum free κ LC level (241 mg/L, λ/κ ratio 0.04). The patient was put on the waiting list for cardiac transplantation. To limit melphalan toxicity, therapy was modified to monthly oral dexamethasone alone (40 mg, days 1-4), one course of which resulted in a further decrease in serum free κ LC level to 45 mg/L (Figure 2).

Six months after initial admission, the patient underwent orthotopic cardiac transplantation from a 46 year-old donor. The intraoperative course was uneventful. Histologic examination of the explanted heart showed diffuse infiltration by κ LC amyloid deposits (Figure 1D). The immunosuppressive regimen consisted of anti-thymocyte globulins and intravenous methylprednisolone, followed by oral prednisone, cyclosporine A, and mycophenolate mofetil. Two additional courses of dexamethasone 40 mg/day, days 1 to 4, were administered at months 1 and 3 post-transplantation (Figure 2). Severe gancyclovir–resistant systemic CMV primary infection at month 4 required foscarnet therapy, fol-

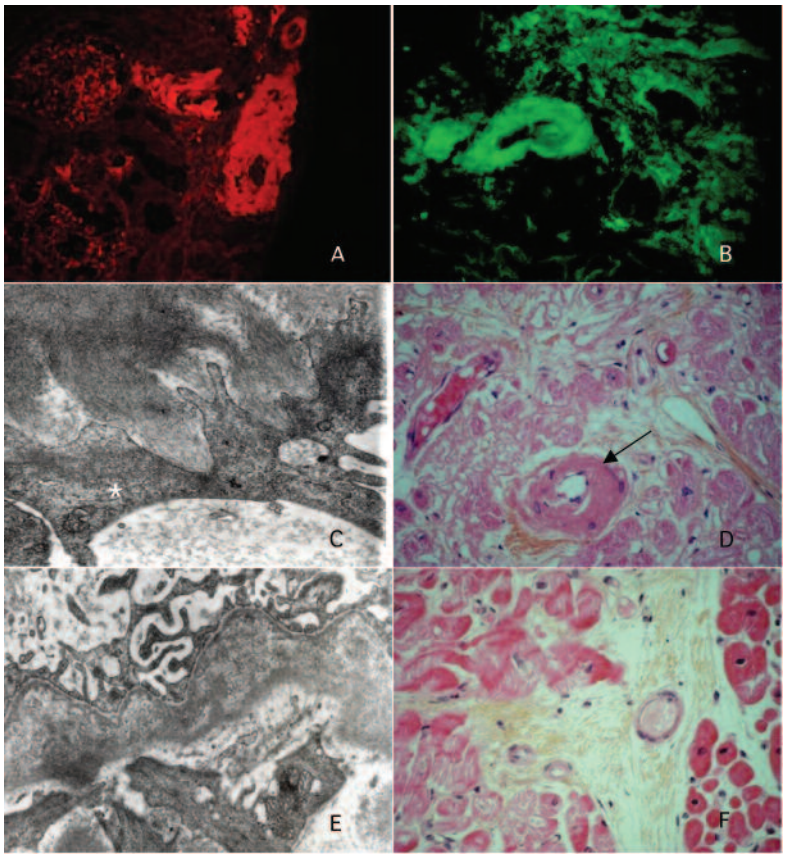


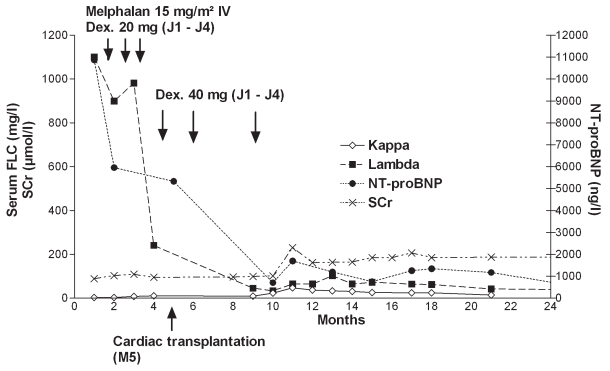
Figure 1. (A) First kidney biopsy. Ultra-violet light microscopy, Congo-red staining, original magnification x 200. Diffuse red fluorescent deposits in glomerular mesangium, interlobular arterial walls and interstitium. (B) First kidney biopsy. Immunofluorescence microscopy, original magnification x 400. Arterial and mesangial amyloid deposits were strongly stained with anti-lambda LC conjugate. No staining was observed with anti-kappa LC conjugate (not shown). (C) First kidney biopsy, electron microscopy, original magnification x 8,000. Glomerular predominant subepithelial fibrillary amyloid deposits with lysis of the lamina densa (*). Neo-production of glomerular basement membrane by podocytes or endothelial cells was not observed. (D) Endomyocardial biopsy of the explanted heart. Light microscopy, PAS staining, original magnification x 400. Parietal amorphous eosinophilic deposits in a small myocardial artery (arrow). (E) Post-treatment follow-up kidney biopsy, electron microscopy, original magnification x 8,000. Residual glomerular amyloid deposits with double contour appearance of glomerular basement membrane secondary to neo-synthesis by podocytes. Note the "vanishing" pattern of amyloid deposits which appeared less dense and contain clarified areas. (F). Graft endomyocardial biopsy, 2 years post-transplant. Light microscopy, PAS staining, original magnification x 400. No amyloid deposits were detected in myocardial interstitium and arteries. Mild infiltration by mononuclear cells.

lowed by persistent worsening of renal function probably related to combined cisclosporine and foscarnet toxicity (Figure 2). Twelve months post transplantation, serum creatinine was 2.4 mg/dL with proteinuria of 0.7 g/day. A follow-up renal biopsy showed partial regression of glomerular amyloid, with clarified deposits and neoformation of glomerular basement membranes on electron microscopic examination (Figure 1E). Two years post transplantation, physical examination was unremarkable, except for persistent moderate macroglossia. Serum creatinine was 2.1 mg/dL, total protein 65 g/L, albumin 37 g/L, serum NT-proBNP 654 ng/L and proteinuria 0.27 g/day. Liver function tests and full blood count were normal. Hematologic remission was maintained, with normal bone marrow histologic examination, absence of detectable serum and urine monoclonal component, and normal serum free κ LC level and λ/κ ratio of 39 mg/L and 0.67 respectively. Echocardiography revealed normal heart echogenicity and left ventricular ejection fraction, with septum thickness of 9 mm and no evidence of diastolic dysfunction. Neither recurrence of amyloid deposits, nor rejection, was detected on follow-up endomyocardial biopsies (Figure 1F).

Discussion

Despite growing evidence that cardiac transplantation may be life-saving in patients with end-stage AL amyloid heart disease, both the criteria of eligibility for the procedure, and the place of adjuvant therapies aimed at controlling the underlying plasma cell disorder remain unclear.

Only small multicentric series of heart transplantation in AL amyloidosis have been published.[4-10] Not only survival rates of patients grafted for amyloid cardiomyopathy are significantly lower than in the general cardiac transplant recipient population,[9] but, compared to other causes of amyloid cardiomyopathy (transthyretin amyloidosis and hereditary apolipoprotein A1 amyloidosis),



FLC: free light chain; SCr: serum creatinine

Figure 2. Follow-up of main biological parameters

patients with AL amyloidosis are at higher risk. In one series, 1 and 5 year survival rates were 86% and 64% in patients with non AL amyloid cardiomyopathy, compared to 71% and 36% in AL patients who received post-transplant chemotherapy, and only 50% and 20% in AL patients who did not receive additional chemotherapy. Among AL patients, amyloid recurred in the graft after a median of 11 months, most patients dying from progressive extra-cardiac amyloidosis.[8] In recent years, the prognosis of AL amyloidosis has been transformed with the use of HDM/ASCT. However, intensive therapy is associated with high mortality in patients with multiple organ involvement by amyloid.[12,13] In 5 AL patients, selected for the absence of clinically significant extra-cardiac amyloid, HDM/ASCT performed after cardiac transplantation resulted in survival times of 91 months and 76 months from surgery and HDM/ASCT, respectively. Three patients with sustained hematologic remission (normalization or >80% reduction in serum free LC levels) had no evidence of cardiac or extra cardiac amyloid accumulation after a follow-up of 99 months. By contrast, death related to systemic and cardiac amyloid accumulation occurred in the two patients in whom plasma cell dyscrasia failed to respond or relapsed after HDM/ASCT.[10] In the present case, we considered that the significant and symptomatic extra-cardiac amyloid deposits prohibited such a tandem approach due to the TRM risk. In patients with AL amyloidosis ineligible for HDM/ASCT, the combination of oral melphalan and high dose dexamethasone (M-Dex) is associated with a hematologic response rate of 67% (with 33% of complete response) and an organ response rate of 48%, resulting in significant survival benefit.[14] Recently, in a randomized controlled trial of 100 patients with systemic AL amyloidosis, M-Dex showed improved overall survival compared to HDM/ASCT.[15] In our patient, intermediate dose intravenous melphalan plus dexamethasone was well tolerated and induced a dramatic reduction in both serum free κ LC and NT-proBNP levels prior to heart transplantation, a factor predictive of prolonged survival in AL amyloidosis.[16] Two years after cardiac transplantation, complete hematologic remission was maintained, according to the usual criteria.[17] There was no evidence of either amyloid recurrence in the allograft or disease progression in other organs, but partial regression of glomerular amyloid fibrils.

In conclusion, this case report suggests that M-Dex may result in prolonged survival in AL amyloid patients with advanced heart failure requiring heart transplantation, by durably reducing the production of amyloidogenic LC. In patients with significant extra-cardiac involvement not eligible to HDM/ASCT, M-Dex is worth considering before cardiac transplantation. Dexamethasone dose should be reduced initially to limit the risk of severe fluid retention, particularly in patients with both cardiac and renal involvement.[18] As suggested before,[10] a rapid 80% reduction in the aberrant serum free LC concentration probably represents a predictive factor for prolonged post-operative survival and a strong argument to validate the indication of heart transplantation.

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