Case Report

Recovery of acute renal failure and nephrotic syndrome following autologous stem cell transplantation for primary (AL) amyloidosis

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Introduction

Primary AL amyloidosis is a plasma cell dyscrasia characterized by the deposition of monoclonal immunoglobulin light-chain protein. The latter forms insoluble fibrils with β-pleated sheet configuration within a variety of tissues, resulting in severe organ dysfunction and poor outcome. In patients with primary AL amyloidosis, cyclic treatment with melphalan and prednisone improves by ~2-fold median survival from 8 to 18 months [1]. However, this regimen affords no benefit on renal survival, while kidney involvement occurs in 48–82% of patients [1,2]. The most common renal manifestations include nephrotic-range proteinuria and progressive renal failure that ultimately require dialysis support in one-third of all cases [3]. To break down the production of the amyloidogenic immunoglobulin by the underlying B-cell clone and stop tissue deposition, dose-intensive melphalan with autologous blood stem cell support is currently under evaluation in primary AL amyloidosis [4].

We report the case of a 50-year-old woman with primary AL amyloidosis who experienced a complete recovery of both nephrotic syndrome and protracted anuric renal failure after high-dose melphalan and autologous blood stem cell transplantation (SCT).

Case

The patient was referred to our centre for lower limb oedema, a 5 kg weight loss, and syncope the day before admission. On physical examination, supine blood pressure was 112/74 mmHg dropping to 98/75 mmHg, while standing, without an increase in pulse rate. Non-infiltrative purpura of abdominal skin and hepatomegaly were also found. During hospitalization, she experienced bloody diarrhea.

Initially, her serum creatinine was 89 μmol/l. On serum protein electrophoresis, albumin was 19 g/l and a 3 g/l monoclonal component (M-protein) was detected. Immunofixation characterized the peak as a monoclonal IgA lambda. The 24-h urinary protein excretion reached 6.4 g, consisting of albumin (56%), the M-component (20%) and free lambda light-chains. Serum calcium concentration was 1.9 mmol/l, blood haemoglobin was 14 g/dl. Bone marrow aspiration failed to demonstrate excess of abnormal plasmaocytes and skeletal X-rays were normal.

Renal biopsy disclosed glomerular amyloidosis with positive deposits for Congo red staining in the mesangium and along the capillary walls. There was no deposit along the tubules nor in blood vessel walls. By immunofluorescence study, intense glomerular staining was found with an anti-λ serum. Staging of AL amyloidosis demonstrated peripheral neuropathy and included tilt-test that confirmed autonomic failure. Biopsies showed involvement of both upper and lower gastrointestinal tract by AL amyloidosis. Echocardiography demonstrated left ventricular hypertrophy (septum wall thickness, 11 mm) and diastolic dysfunction. One month after admission, an ischaemic stroke related to paroxystic atrial fibrillation occurred. Anticoagulation was started and neurological deficit resolved within a few days. A diagnosis of primary AL amyloidosis was made with renal, cardiac, neurological and digestive involvement.

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After counseling, the patient decided for high-dose melphalan and autologous peripheral blood SCT. Granulocyte colony stimulating factor was initiated for stem cell mobilization at 10μg/kg/day for 5 days. Leukapheresis was then successfully performed, collecting $7.25 \times 10^{6}$/kg CD34⁺ progenitor cells. Two weeks later, the patient underwent conditioning with high-dose melphalan (200 mg/m²) followed by autologous stem cell infusion 2 days later (referred to as day 0). On day 8, while related treatment toxicities were limited to mild leucopenia (700 leukocytes/mm³) and grade III mucositis, the patient developed rapidly progressive multi-organ failure including acute respiratory distress syndrome and anuria, related to a septic shock (Figure 1). Treatment associated positive end expiratory pressure mechanical ventilation, i.v. pressor support (epinephrine), continuous veno-venous haemodiafiltration and broad-spectrum antibiotherapy. No causative microorganism was isolated. Epinephrine was required until day 14. On day 22, she was extubated and haemodiafiltration was switched to periodic haemodialysis.

From day 49, she recovered from renal failure and serum creatinine dropped to 80 μmol/l on day 58. The nephrotic syndrome persisted: proteinuria was 5.8 g/day while serum albumin was 17 g/l. By serum and urinary protein immunoelctrophoresis, neither the M-component nor free lambda light-chains could be detected. On day 86, serum creatinine and albumin were 70 μmol/l and 20 g/l, respectively. The patient was discharged with 5 mg of lisinopril for nephroprotection and 2 mg of acenocoumarol.

Six months after engraftment, 24-h urinary protein output was 1.25 g, without monoclonal component in serum or urine. Serum creatinine was 90 μmol/l, while assessment of glomerular filtration rate by EDTA clearance was 33 ml/min/1.73 m². Complete remission of the nephrotic syndrome was achieved by 15 months post-SCT. On last follow-up, 3 years post-transplantation, serum creatinine was 103 μmol/l and serum albumin was 42 g/l. There was no detectable M-protein in blood or urine. Autonomic failure and left ventricular diastolic dysfunction assessed by echocardiography stabilized. Gastrointestinal symptoms remained unchanged.

Discussion

Survival remains unsatisfactory in primary AL systemic amyloidosis. Two studies have shown that combination of oral melphalan and prednisone as compared with colchicine resulted in a significant albeit small increase in median survival from 8 to 18 months in one study [1] and from 6 to 12 in the other [2]. Autologous SCT was introduced with the assumption that eradication of the culprit clone would completely stop the production of the amyloidogenic immunoglobulin, and subsequent tissue deposits. In a recent overview of published series, 62% of patients entered complete haematologic response following SCT [4]. However, treatment-related mortality ranged from 21 to 39% according to the different series, thus making it necessary to select the patients eligible for transplantation [4]. Early
mortality is best predicted by the extent of amyloid organ involvement. In two early trials, the 100-days survival rate in patients with two or fewer affected organs reached 81%, as compared with 31% in patients with three and more systems involved ($P < 0.01$) [5,6]. Additional prognostic factors of mortality include cardiac amyloid deposition and a pre-SCT increase of serum creatinine level, which is also predictive of acute renal failure early post-procedure.

Our patient was a middle-aged woman with rapidly progressive multi-system amyloidosis involving kidney, heart, gastrointestinal tract and nervous system. Being aware of the prognosis of her disease and the risks of the treatment, she elected dose-intensive melphalan and blood SCT. While on aplasia she developed septic shock and multi-organ failure including anuria, and required dialysis for 6 weeks before recovery. A complete haematological response was achieved. On mid-term, the nephrotic syndrome went on complete remission, while mild renal failure persisted and extra-renal involvement stabilized.

The renal course deserves two comments. (i) To our knowledge, no other patient with AL renal amyloidosis necessitating dialysis support for 6 weeks eventually recovered good renal function. Acute renal failure carries very poor prognosis in the patients with AL amyloidosis. In patients who necessitate dialysis support, the median survival time from the start of haemodialysis in only 8.2 months [3]. (ii) Resolution of the nephrotic syndrome was obtained following haematological remission achieved by SCT. This reinforces the relationship between the haematological and the renal responses. As shown by Dember et al. [7] renal benefits can be expected following successful SCT. Among 50 patients who survived >12 months after SCT, she pointed out that 71% of the patients achieving haematologic response met the criteria of renal response, as compared with 11% of haematologic non-responders. Also, 68% of haematologic responders maintained a creatinine clearance at 75% of the baseline value and only 8% of patients progressed to dialysis up to 4 years of follow-up. Of note, remission of nephrotic syndrome usually occurs despite persistence of glomerular amyloid deposits [8]. In contrast, while anecdotal reports documented complete resolution of AL amyloidosis-related nephrotic syndrome and improvement of renal failure after many years of melphalan-prednisone therapy [9], Kyle et al. [1] found no difference regarding the renal response nor the need for dialysis support in a prospective trial comparing melphalan-prednisone and colchicine.

For our patient, despite poor prognosis factors including four-organ systems involvement and because of a rapidly progressive course, dose-intensive therapy was the unique approach to obtain prompt eradication of the plasmacytic clone and stop the progression of amyloid disease. This intuition is consistent with a recent randomized trial where survival of the patients did not benefit from two cycles of oral melphalan-prednisone before SCT, as compared with immediate treatment by SCT [10]. That latter approach mostly benefited to the patients with cardiac involvement, who carry the highest risk of early death. Reduction of melphalan dosing (to 140 or 100 mg/m²) may also result in a similar rate of haematologic response and improvement of organ involvement, with lower morbidity and mortality rates [4]. Such individualization of the treatment, based on a risk-adapted approach may extend indications of SCT to patients otherwise considered ineligible.

In sum, this report highlights how autologous SCT may apply to the patients with primary AL amyloidosis and severe multi-system involvement. Furthermore, resolution of acute renal failure and nephrotic syndrome are achievable, with long-term stabilization of kidney dysfunction.

**Conflict of interest statement.** None declared.

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