

Case Report

Late recovery of renal failure after autologous haematopoietic stem cell transplantation for multiple myeloma: a report of two cases

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Abstract

Acute renal failure is a frequent feature in patients with multiple myeloma (MM). MM-related renal insufficiency may improve after autologous haematopoietic stem cell transplantation (autoHSCT) even in patients initially requiring dialysis. Herein, we report on two unusual cases of late improvement in renal function occurring over more than 5 years after autoHSCT for MM. Clinicians must be aware that slow and progressive improvement in renal function may occur over years in patients with MM-associated renal failure. Our data underline the need for an aggressive treatment, including autoHSCT, in MM patients presenting with severe renal dysfunction.

Keywords: multiple myeloma; haematopoietic stem cell transplantation; renal disease

Introduction

Acute renal failure is a frequent feature at diagnosis of multiple myeloma (MM). It is present in 20–55% of patients with a newly diagnosed MM [1,2], among whom 2–3% require dialysis [3]. Renal impairment is a poor prognostic factor in patients with MM as it is associated with an increased morbidity and early mortality rates. However, patients with renal insufficiency are eligible for high-dose chemotherapy and autologous haematopoietic stem cell transplantation (autoHSCT). Indeed, autoHSCT-associated morbidity and mortality rates are not increased in these patients compared to those with normal renal function [4–6]. Moreover, MM-related renal insufficiency may improve after autoHSCT even in patients initially requiring dialysis. Renal function recovery usually occurs in the first months following autoHSCT (median 1.6–4 months) [2].

Here, we report on two unusual cases of late improvement in renal function after autoHSCT for MM.

Case reports

Case 1

A 57-year-old woman with a history of cervix carcinoma and pulmonary tuberculosis was diagnosed with stage III B lambda light chain MM in January 2003. She initially presented with acute renal failure. At that time, laboratory tests showed: serum creatinine (SCr) 673 $\mu\text{mol/L}$, glomerular filtration rate (GFR) estimated according to MDRD formula at 6 mL/min/1.73 m², calcaemia 2.28 mmol/L, albuminaemia 33 g/L, haemoglobin 7.9 g/dL and platelets 125 000/mm³. On serum immunofixation, a monoclonal lambda light chain (4 g/L) was detected with the presence of Bence–Jones proteinuria (BJP) (1.18 g/day). MRI revealed diffuse vertebral osteolytic lesions. Bone marrow aspiration showed 50% dystrophic plasma cells. The diagnosis of MM was made.

Despite oral and intravenous sodium bicarbonate intake, her renal function did not improve and she was started on haemodialysis, three times weekly. Initial treatment of MM consisted in five courses of vincristine–adriamycin–dexamethasone (VAD) chemotherapy with near complete remission (no plasma paraprotein detected, BJP 0.09 g/day). Three months after MM diagnosis renal function partially improved allowing the reduction of haemodialysis dose to two sessions per week.

On June 2003, autoHSCT was performed after high-dose melphalan (200 mg/m²); complete remission was obtained. In September 2005, BJP increased to 0.6 g/day without reappearance of plasma paraprotein. Second-line chemotherapy with thalidomide (100 mg/day) and dexamethasone (40 mg/day 4 days a month) was started. After 11 months of treatment, patient started complaining of neuropathy. BJP had decreased to 0.07 g/day and no monoclonal component was detectable in the plasma. Thalidomide was stopped.

Following autoHSCT, renal function slowly and continuously improved (Figure 1). On July 2007, 56 months

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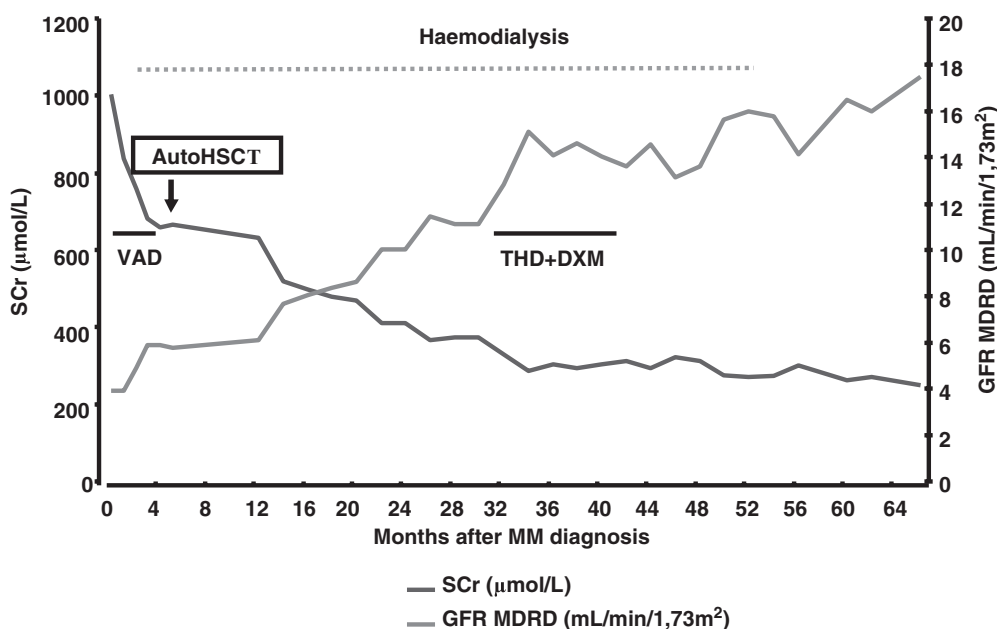


Fig. 1. Patient 1. Evolution over time of serum creatinine (SCr) ($\mu\text{mol/L}$) and glomerular filtration rate (GFR) estimated using the simplified MDRD equation (mL/min/1.73 m^2). Haemodialysis was started immediately after multiple myeloma (MM) diagnosis. Haemodialysis dose was decreased in March 2003 and subsequently stopped in July 2007. Autologous haematopoietic stem cell transplantation (autoHSCT) was performed in July 2003 after five courses of vincristine–adriamycine–dexamethasone (VAD) chemotherapy. The patient received second-line chemotherapy with thalidomide (THD) and dexamethasone (DXM) between September 2005 and August 2006.

after MM diagnosis, haemodialysis was discontinued (SCr $280 \mu\text{mol/L}$, GFR at $15.86 \text{ mL/min/1.73 m}^2$). As of last follow-up in July 2008, the patient remains independent of dialysis and renal function is still improving (SCr $256 \mu\text{mol/L}$, GFR $18 \text{ mL/min/1.73 m}^2$).

Case 2

A 56-year-old woman with no medical history was admitted in our nephrology department on March 2003 for acute renal failure. Laboratory tests showed SCr $576 \mu\text{mol/L}$ (GFR estimated at $7 \text{ mL/min/1.73 m}^2$), serum calcium 2.43 mmol/L , haemoglobin 8.4 g/dL and platelets $364\,000/\text{mm}^3$. Renal ultrasonography was normal. Plasma immunofixation revealed the presence of an IgA lambda monoclonal component. Lambda light chains were also detected in the urine (0.10 g/day). No bone lesions were detected. Bone marrow aspiration revealed 93% of dystrophic plasma cells. The diagnosis of IgA lambda MM was made. A renal biopsy showed tubular necrosis, some cast with giant cells (Figure 3) and by immunofluorescence linear fixation of anti-lambda and anti-IgA antisera along the glomerular basement membrane and tubular basement membrane. It was finally recognised as the association of a cast nephropathy and a Randall syndrome.

She was treated with five courses of VAD chemotherapy. However, no remission was obtained (plasma paraprotein 10 g/L , BJP 1.6 g/day). Second-line chemotherapy with five courses of oral melphalan (12 mg/day for 4 days/month) and dexamethasone was performed and was followed by a near complete remission (no detectable serum paraprotein, BJP at 0.09 g/day). Subsequently, the patient underwent

an autoHSCT after high-dose melphalan (140 mg/m^2) on January 2004.

At the time of autoHSCT, SCr had stabilized around $450 \mu\text{mol/L}$ (GFR at $9 \text{ mL/min/1.73 m}^2$). Six months later, autoHSCT started to improve gradually (Figure 2). At last follow-up on September 2008, 66 months after MM diagnosis, the patient was still in complete remission (no detectable paraprotein in plasma, BJP $< 0.10 \text{ g/d}$) and SCr was $240 \mu\text{mol/L}$ (GFR at $19 \text{ mL/min/1.73 m}^2$).

Discussion

Management of MM-associated renal insufficiency is a crucial issue as renal dysfunction is a poor prognosis factor leading to an increased morbidity and early mortality rate. In contrast, patients in whom renal function recovers have a survival rate similar to patients without MM-associated renal insufficiency [7]. Renal function recovers in 20–73% of patients with MM-associated renal failure and in 34–43% of patients who undergo autoHSCT. Most interestingly, recovery from dialysis-dependent renal failure occurs in up to one-fourth of patients with MM undergoing autoHSCT [8]. Predictive factors for renal recovery include severity and duration of renal failure, serum calcium level and amount of BJP. Renal function usually improves in the first months following autoHSCT with a median time to renal recovery ranging from 1.6 to 4 months [2,9,10]. To our knowledge, the latest renal function recovery reported in the literature occurred 16 months after autoHSCT for MM [2].

Herein, we report two unusual cases of late and slow improvement in renal function occurring over more than

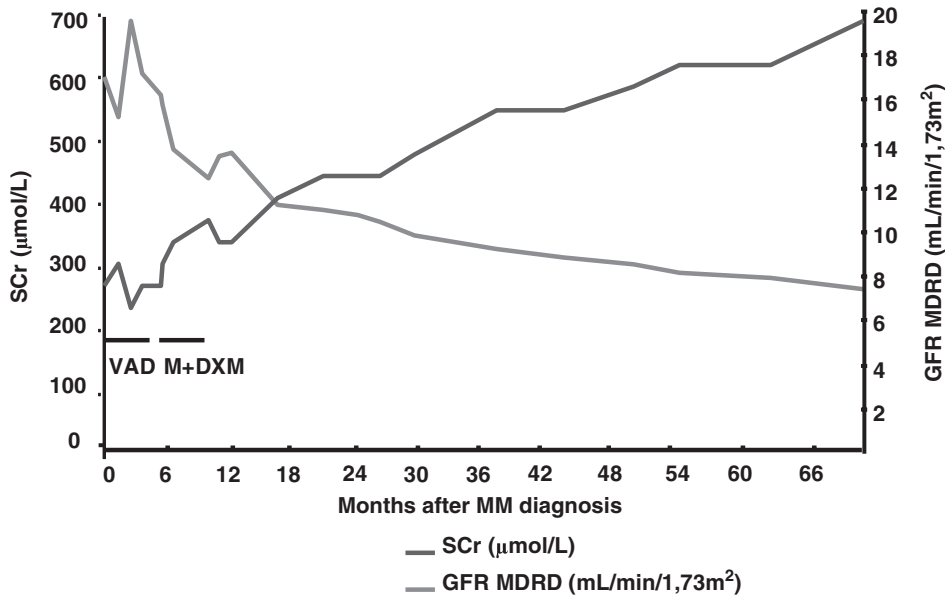


Fig. 2. Patient 2. Evolution over time of serum creatinine (SCr) ($\mu\text{mol/L}$) and glomerular filtration rate (GFR) estimated using the simplified MDRD equation ($\text{mL/min}/1.73 \text{ m}^2$). Autologous haematopoietic stem cell transplantation (autoHSCT) was performed in January 2004 after vincristine–adriamycin–dexamethasone (VAD) and melphalan–dexamethasone (M+DXM) chemotherapy.

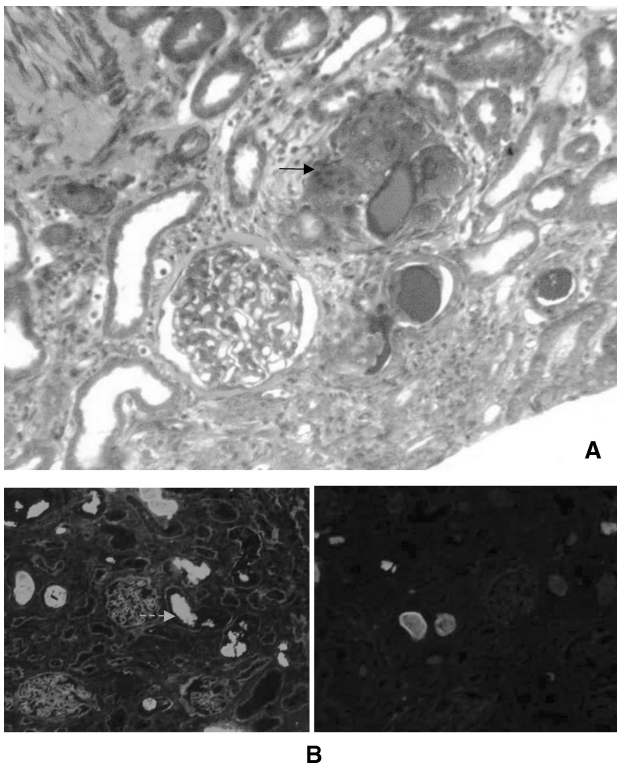


Fig. 3. Kidney biopsy in patient 2. (A) Light microscopy (Masson's trichrome, $\times 250$). The presence of tubular cells necrosis and one intratubular cast surrounded by macrophages and giant cells (arrow). (B) Immunofluorescence study ($\times 50$). Left panel: intratubular casts were positive for anti-IgA (not shown) and anti-lambda light chain staining (dashed arrow). Lambda light chains were also detected along the glomerular and tubular basement membranes. Right panel: kappa light chain staining was negative along the glomerular and tubular basement membranes and faintly positive in rare tubular casts.

5 years in two patients who underwent autoHSCT for MM. Both patients presented initially with severe MM-associated acute renal failure and one patient required long-term dialysis. Following various MM treatments including autoHSCT, renal function improved gradually in both patients and chronic haemodialysis was discontinued in one patient. MM-associated renal failure is usually related to acute tubular injury due to myeloma cast nephropathy. More rarely, it may be due to Randall syndrome or amyloidosis. Even though the kidney biopsy was only performed in the second patient, the diagnosis of myeloma cast nephropathy associated is highly likely in the first patient. The improvement of renal function over several years is not typical of acute tubular necrosis recovery. The latter probably accounts for the initial partial improvement of renal function noted in the first 3 months in both patients.

Slow progressive renal function recovery in our patients may be due to the aggressive treatment of MM including autoHSCT. Obtaining MM complete remission led to the arrest of monoclonal component secretion thus preventing further intra-tubular precipitation of free monoclonal light chains. However, one cannot exclude that autoHSCT may have contributed to the recovery of renal function through the regeneration of damaged renal tissues. Controversial and contrasted data regarding the impact of haematopoietic stem cells on organ regeneration, including the kidney, have been reported. Several authors have pointed out the lack of specificity of most techniques usually used to detect chimeric cells derived from stem cells in various organs [11,12]. Moreover, the number of chimeric cells detected is usually nonsignificant. However, stem cells may contribute indirectly to tissue regeneration through paracrine mechanisms leading to the recruitment of organ-resident cells [13]. Furthermore, experimental models of acute as well as chronic renal disorder have suggested that mobilization of

stem cells may hasten renal function recovery [14]. No definite conclusions can be drawn regarding the implication of stem cells in renal repair. However, the slow and significant improvement over several years of renal function in the two patients presented herein raises once again the issue of stem cell in organ regeneration.

In all, clinicians must be aware that slow and progressive improvement in renal function may occur over years in patients with MM-associated renal failure. These data may suggest the need for an aggressive treatment in MM patients presenting with severe renal dysfunction in the setting of MM.

Conflict of interest statement. None declared.

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