Other full case

Ten-year follow-up after autologous stem cell transplantation of a patient with immunoglobulin light-chain (AL) amyloidosis with deposits in the heart, liver and gastrointestinal tract

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Summary

The prognosis in amyloid light chain (AL)-amyloidosis and multiorgan involvement is poor, with a high-treatment-related mortality after high-dose melphalan and autologous stem cell transplantation (HDM/SCT). Some patients, however, might benefit from the therapy. We report a case of cardiac AL-amyloidosis with multiorgan involvement where the progressive cardiomyopathy was halted after successful treatment with HDM/SCT in 2001. The patient is in an excellent cardiac condition with a good quality of life, receiving treatment with angiotensinogen receptor blockers and a flexible diuretics regimen at follow-up after 10 years.

BACKGROUND

Immunoglobulin light-chain (AL)-amyloidosis is a plasma cell disorder in which, tissue deposition of the immunoglobulin light-chain may lead to multiple organ dysfunction.^{1–3} The main clinical features associated with AL-amyloidosis are nephrotic syndrome, cardiac failure, hepatomegaly and sensorimotor neuropathy. An M-component is sometimes observed in conjunction with both monoclonal gammopathy of unknown significance and multiple myeloma. The median survival time from diagnosis for patients with primary AL-amyloidosis is about 2 years,³ with a substantially worse prognosis for patients with cardiac involvement.^{4–5} The first reports of patients in whom AL-amyloidosis was treated with high-dose melphalan and autologous stem cell transplantation (HDM/SCT) appeared during the mid-1990s,^{6–7} and were soon followed by studies of larger cohorts of AL patients.^{8–9} Patients with renal insufficiency and nephrotic syndromes responded best,^{10–11} while those with multiple organ failures did worse, with high treatment-related mortality.^{8–9}

Later, publications concluded that, the prognosis for patients with cardiac failure was particularly poor after HDM/SCT,^{12–14} and it was agreed that, severe cardiac involvement should constitute a contraindication to SCT.¹⁵ The use of cardiac biomarkers in conjunction with echocardiography and clinical assessment is now recommended for prognostic stratification and choice of therapy.^{15–17} The introduction of the new highly effective and less toxic multiple myeloma drugs bortezomib and lenalidomide, with or without dexamethasone, has changed the perspective for treatment of AL-amyloidosis.^{18–23} Only early results with these new and promising drugs have been published, with relatively short follow-up periods. We would like, therefore, to report our experience with a patient with cardiac AL-amyloidosis with multiorgan involvement treated with HDM/SCT in 2001. This patient remains in a stable clinical

condition with an excellent quality of life after 10 years. The patient developed collagenous colitis 18 months after the SCT, details of which have been reported earlier.²⁴

CASE PRESENTATION

A healthy 52-year-old woman experienced chest pain in 1993. A coronary angiogram showed no abnormalities. Despite this, she was prescribed aspirin. No further cardiac symptoms were observed until February 1997, when she was admitted to the emergency ward with acute chest pain, melena and severe anaemia (Hb 61 g/l). Myocardial infarction was ruled out. Blood pressure was normal. The ECG showed left ventricular hypertrophy.

Gastroscopy revealed a large ulceration in the fundus region surrounded by exuberant erythematous coarse nodular or folding mucosa, which is histologically described as ‘hyperplasiogenic polyps without dysplasia’. It was considered that the ulcer was due to the medication with aspirin. The chest pain subsided after treatment with red blood cell transfusions and omeprazol. A check up by gastroscopy 2 months later, showed that, the ulcer had healed. *Helicobacter pylori* was detected and eradicated, but the appearance of the mucosa stayed the same.

Echocardiography in 1997 showed that, the septum and posterior left ventricular walls were severely enlarged, 17 and 19 mm, respectively. The left ventricle diameter was normal. The left ventricular mass was high, calculated to be 190 g/m² according to the Penn formula. The ejection fraction was low, 40–50% and there was pronounced diastolic dysfunction. No abnormalities in the aortic outflow tract or the valves were found. (figure 1)

The patient still complained of uncharacteristic chest pain, and thus an exercise test was carried out, and a myocardial scintigram and a dobutamine stress echocardiogram were recorded. None of these investigations showed any signs of coronary insufficiency. Spasm angina was

Figure 1 Echocardiographic short axis (A), and parasternal view (B), showing left ventricular wall hypertrophy.

suspected, and the patient was prescribed calcium channel blockers. This had a good effect on the chest pain.

Ulcerative colitis was diagnosed in 1998. The patient responded well to steroids and remained stable on mesalazine treatment. Blood tests showed slightly increased levels of transaminases and alkaline phosphatase. Other liver function tests, serum and urine immunoelectrophoresis were all normal. Liver biopsy showed mild portal and intra-acinar, unspecific inflammation and a granuloma-like lesion.

After 2 years in a relatively stable condition, the patient was admitted with acute dyspnoea in March 2000. Chest x-ray showed signs of pulmonary congestion. A CT scan did

not reveal any signs of pulmonary embolism. The echocardiogram was still pathological with advanced concentric left ventricular hypertrophy, and the ejection fraction had fallen to 30–35%. Blood pressure remained normal, 110/75 mm Hg. The symptoms were interpreted as systolic and diastolic heart failure, and the patient responded well to diuretics. Treatment with angiotensinogen receptor blockers was started. The echocardiographic picture with characteristic variations in echodensity was strongly suggestive of cardiac amyloidosis. Biopsies from the rectal mucosa and abdominal fat aspirate stained with Congo red were negative, but a subsequent myocardial biopsy in June 2000 revealed a picture typical of amyloidosis (figure 2).

Figure 2 Myocardial biopsy with amyloid (red) deposits. Congo red stain $\times 250$.

Review of all previous organ biopsies revealed heavy deposits of AL-amyloid distributed diffusely in vessel walls, both in the gastric submucosa and in the granuloma of the liver, while only minor amyloid deposits in a few vessels were present in the submucosa of the large intestine. The haematological work-up in August 2000 showed a normal haemoglobin value and peripheral blood cell counts and a normal serum electrophoresis with no M-component. Urine electrophoresis revealed moderate albuminuria (0.5 g/l) and a relative overweight of λ -type light chains over κ -type, 45 and 46 mg/l, respectively. Bone marrow examination showed normal cellularity with less than 5% plasma cells. There were no signs of myeloma. A slight increase of the number of λ -positive cells was evident by immunophenotyping, but Congo red staining did not reveal any amyloid deposits in the bone marrow. The findings were compatible with AL-amyloidosis with λ -chain depositions, involving multiple organs including the heart, stomach, large intestine, liver and possibly also the kidney.

A few case reports and some smaller studies led to the suggestion in the mid-1990s that, (HDM/SCT) could improve the clinical course of advanced AL-amyloidosis.^{8,9} After informed patient consent, treatment according to the then current myeloma protocol was started. This included induction chemotherapy with four courses of VAD (vincristine, adriamycin and betamethasone), followed by HDM/SCT. Due to intermittent symptoms of heart failure, the use of corticosteroids was restricted to the first week of each course. After two courses of VAD, urine electrophoresis showed no albuminuria and a normal excretion of light chains, while a bone marrow biopsy showed an increased number of λ -positive plasma cells, with amyloid deposits now chiefly restricted to the area around the stroma. Consequently, the chemotherapy regimen was changed

to VACP (etoposide, adriamycin, cyclophosphamide and betamethasone). After the first course of VACP, the patient had an episode of febrile neutropenia. No other major adverse events occurred during the induction phase. Stem cells were collected from peripheral blood after the second VACP course, with the support of filgrastim Granulocyte colony-stimulating factor. A total of $8.2 \times 10^6/\text{kg}$ cluster of differentiation 34-positive cells were harvested and cryopreserved, and later used after HDM ($100 \text{ mg}/\text{m}^2$ i.v.) therapy in March 2001.

The patient has now been followed for 10 years after the HDM/SCT, and has remained prone to heart failure. Cardiac condition, otherwise, has been excellent, on treatment with angiotensinogen receptor blockers and a flexible diuretics regimen. Regular echocardiographic controls have shown a relatively unchanged picture, with no signs of progression of the left ventricular hypertrophy. The systolic ejection fraction has varied from 35% to normal, and the pronounced diastolic dysfunction has persisted: N-terminal-pro B-type natriuretic peptide was slightly elevated to 1217 pg/ml in November 2010. The latest exercise test showed normal working capacity, a 24-hour ECG showed no arrhythmia, and the patient has been able to take up golf again.

Collagenous colitis was diagnosed in 2003, 18 months after treatment.²⁴ The ulcerative colitis was in remission at that time, and microscopy showed restored crypt architecture with minor amyloid deposits in the small submucosal vessels. The patient developed a mild exacerbation of ulcerative colitis in 2007, and this responded well to corticosteroids followed by maintenance therapy with 5-acetylsalicylic acid (5-ASA). Gastroscopy undertaken also in 2007 revealed macroscopically normal mucosa in the antrum region and in the lower part of the corpus, while exuberant erythematous coarse nodules and folds in the fundus

and part of the corpus were still present. Microscopically, amyloid deposits were still present in the small vessels in the antrum and fundus. 5-ASA was discontinued in the autumn of 2009; the patient subsequently developed loose stools. The endoscopic picture was still normal but microscopy revealed a picture of collagenous colitis.

Levels of alkaline phosphatase and other serum markers of liver function have remained normal, as the level of serum creatinine. Serum and urine electrophoresis shows normal results. Bone marrow investigations performed 2 years after the transplant, and again in 2010, showed remaining slight amyloid deposits by Congo red staining, and a small subpopulation of monoclonal λ -positive plasma cells by flow cytometry. The percentages of plasma cells did not exceed 5% in either of the two marrow samples. Analysis of serum free light chains in 2010 showed normal values for both κ and λ -chains, and a normal κ/λ a-ratio.

DISCUSSION

We describe a case of AL-amyloidosis with multiorgan manifestation, including cardiac involvement. The patient was successfully treated with HDM/SCT 10 years ago. Diagnosing amyloidosis is often a clinical challenge. Manifestations may mimic other diseases, such as hypertrophic cardiomyopathy, inflammatory bowel disease, ischaemic colitis and myeloma. Our patient probably suffered from a long history of cardiac disease, and the episode of chest pain in 1993 might have been her debut symptom. An echocardiogram revealing severe left ventricular hypertrophy with varying echodensity, in the absence of hypertension and valvular disease, led us to suspect AL-amyloidosis. Although traditional biopsies were obtained and initially found negative, we preceded with a myocardial biopsy, which was diagnostic. Systemic amyloidosis with multiorgan involvement became obvious after scrutinising previously obtained biopsies, which showed amyloid deposits in the stomach, large intestine, liver and bone marrow.

At the time of diagnosis, HDM/SCT had only recently been reported to be of benefit in advanced cases of AL-amyloidosis that otherwise, had a dismal prognosis, in particular, in cases with cardiac involvement.^{8 9} It appeared as time progressed, that patients with cardiac failure did worse than initially hoped from HDM/SCT, with a high rate of treatment-related mortality. HDM/SCT was, therefore, not recommended for patients with multiorgan involvement and severe cardiac failure.^{8 14 25} However, given the poor prognosis in these cases, later studies suggested that the overall survival in AL-amyloidosis could be improved by HDM/SCT also in cases with a poor prognosis, particularly when haematological remission was achieved.^{4 26} The long-term outcome of 80 patients with AL-amyloidosis treated with HDM/SCT showed a median survival of 57 months, with 23% of the patients living longer than 10 years.²⁷ Our case apparently achieved a stable disease with remaining microscopical signs of AL-amyloidosis in the stomach, gut and bone marrow, and echocardiographic signs of an increased left ventricular mass and diastolic dysfunction, but with no clonal free light chains in the serum. Even though some earlier reports have shown regression of the amyloid deposits,²⁸ this is not a prerequisite for a good clinical response.^{29 30} The outcome in this case

supports two recent case reports^{28 31} that have also shown beneficial clinical effects of HDM/SCT in selected cases of advanced AL-amyloidosis with multiple organ dysfunction and cardiac failure. Cardiac biomarkers were not available when our patient was treated, but clinically and echocardiographically, she suffered from severe cardiac failure, and she would therefore probably not have been treated with HDM/SCT today.¹⁵ Nevertheless, HDM/SCT has improved the patient's long-term clinical condition with no signs of progressive disease, despite signs of AL-amyloidosis deposits being present in most organs.

Learning points

- HDM/SCT can halt progressive cardiomyopathy in AL-amyloidosis. Complete remission is not required for prolonged survival.

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Competing interests None.

Patient consent Not obtained.

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