

Rapidly progressive renal and hepatic failure in AL-amyloidosis: bortezomib and steroid support in a young woman two months after delivery

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ABSTRACT

Introduction: The epidemiology of amyloidosis is not well known and its diagnosis is difficult, due to unspecific early clinical manifestations. Amyloidosis is considered when organ failure occurs. Renal, cardiac and hepatic involvement usually occurred despite therapy. Presenting this case report, we aimed to underline the need of new treatments for amyloidosis.

Materials and Methods: We describe a 41 years old woman admitted to the hospital with proteinuria (1280 mg/24h) and rapid deterioration of renal function (serum creatinine from 0.8 to 1.6 mg/dL). Autoantibodies, immunoglobulin and C3/C4 were negative. A renal biopsy showed the presence of AL-Amyloidosis with k-light chains deposition at immunofluorescence. Subsequently, the patient showed nephrotic syndrome onset (proteinuria 4000 mg/24h with albuminuria 3400 mg/24h) and increased rates of cholestasis with hepatomegaly and hepatic failure.

Results: This case is very interesting because renal involvement was the initial presentation of amyloidosis and rapid progressive renal and hepatic failure was subsequently observed; its management was challenging from the clinical approach to the final diagnosis and treatment.

Discussion: Treatment with bortezomib and dexamethasone gave a complete hematological response but renal function was not improved.

Conclusions: In terms of organ response, it is necessary to develop new strategies to counteract the progressive organ failure due to amyloid deposition.

ABBREVIATIONS

AL-amyloidosis, light chain amyloidosis; GFR, glomerular filtration rate; HDM, high dose melphalan; SCT, stem cell transplantation; sCr, serum creatinine; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, Gamma-glutamyl transferase; AP, alkaline phosphatase; INR, International Normalized Ratio; BNP, B-type natriuretic peptide; HDM/SCT, high-dose melphalan followed by autologous stem cell transplantation.

INTRODUCTION

Amyloidosis is a rare disease with higher prevalence in adult males; its diagnosis is difficult because of the absence of early manifestations and specific signs. Disease includes a heterogeneous group of pathological features characterized by the extracellular deposition of fibrillar proteinaceous material in various tissues and organs in particular renal glomeruli with an estimated prevalence ranging from 2.7% to 4% of renal biopsies¹. The marked selective proteinuria (albuminuria), usually reported, reflects the main glomerular deposition that characterizes this kind of damage. Amyloidosis is defined light chain amyloidosis (AL) when the protein fibrils derived from the variable region of the light chain, usually lambda chains deposits^{2,3}. The most common manifestations of AL-amyloidosis are related to the involvement of kidney, heart and liver⁴. The symptoms depend on the organs affected by the accumulation of amyloid.

The goal of treatment is eradication of the monoclonal plasma cell population and suppression of the pathologic light chains, which can result in organ improvement and extend patient survival.

Standard treatment approaches include oral melphalan and prednisone, even if only a quarter of patients achieved a hematologic response to this treatment and the median survival was only 12-18 months⁵. In fact, a progressive glomerular filtration rate (GFR) reduction with cardiac involvement and increased in liver size usually occurred despite therapy. In this context, high dose melphalan (HDM) followed by autologous hematopoietic stem cell transplantation (SCT) has shown to be effective in reducing clonal disease and circulating light chains improving kidney function in AL-amyloidosis nephropathy⁶ and is not associated to the numerous side effects related to chemotherapy. Recently, therapeutic strategies may include novel agents such as immunomodulatory drugs or proteasome inhibitors, in particular bortezomib, in patients not eligible for SCT.

MATERIALS AND METHODS

We have studied a 41 years old woman admitted to the Department of Clinical Medicine, Nephrology and Dialysis Unit, Policlinico Umberto I of Rome, in December 2011 due to recent onset of proteinuria and rapid deterioration of renal function (serum creatinine – sCr from 0.8 to 1.6 mg/dL during the last 2 months). She had a child 2 months before admission and during that period she didn't present proteinuria but only high blood pressure. She did not refer nephrotoxic drugs assumption but frequent episodes of epistaxis. On admission in our Nephrology Department she was afebrile and hydrated in appearance without any peripheral edema, she had mild heart murmur with blood pressure 150/85 mmHg and heart rate 75 bpm; the rest of physical examination was negative. Laboratory tests showed anemia with haemoglobin 10 g/dL, red blood cells $3560 \times 10^3/\text{mm}^3$ and serum iron 100 mg/dL, hypercholesterolemia and hypertriglyceridemia with cholesterol level 260 mg/dL and triglyceride level 300 mg/dL, white blood cells $5680/\text{mm}^3$, platelets $230 \times 10^3/\text{mm}^3$, glucose 84 mg/dL, blood urea nitrogen (BUN) 14.5 mg/dL, uric acid 5 mg/dL, serum sodium 140 mEq/L, serum potassium 4.3 mEq/L, serum calcium 9.5 mg/dL, serum phosphate 4 mg/dL, serum protein 6.5 g/dL, aspartate aminotransferase (AST) 15 U/L, alanine aminotransferase (ALT) 17 U/L, coagulation test and serum protidogram were normal. Blood gas analysis was

normal. Urinalysis: pH 6.5, specific gravity 1015, red blood cells absent. The 24 h urine volume was 2 liters with proteinuria 1280 mg/24 h. Renal ultrasonography excluded ureteral obstruction and showed kidney normal size. We suspected an autoimmune disease but ANA, dsDNA, c/p-ANCA, ENA antibodies were negative and IgG/A/M, C3, C4 were in the normal range. Furthermore TSH, FT3, FT4, markers of hepatitis B and C viruses resulted in normal range. We performed a renal biopsy which showed global glomerular deposition of pale eosinophilic acellular weakly PAS-positive material deposited in the mesangial region and along capillaries, obliteration of capillary lumen and patent bowmans' space (Figure 1); this material was Red Congo positive (Figure 2) and immunofluorescence shows conspicuous mesangial accumulations of AL amyloid that stain with anti-Kappa light chains antiserum (Figure 3).

RESULTS

Two months after delivery, our patient presented a rapid deterioration of renal function with nephrotic syndrome and deterioration of liver function associated to hepatomegaly: sCr 2.0 mg/dL, BUN 40.5 mg/dL, albumin 3.0 mg/dL, total bilirubin 1.9 mg/dL, AST 200 U/L, ALT 150 U/L, Gamma-glutamyl transferase (GGT) 50 U/L, alkaline phosphatase (AP) 25 U/L, International Normalized Ratio (INR) 1.5, 24h urine test showed proteinuria 4000 mg/24 h with albuminuria 3400 mg/24 h and immunoelectrophoresis showed abnormal zone of restriction in kappa light chain, suggesting Bence-Jones protein, free kappa type (Figure 4); hepatic ultrasound showed diffuse coarse echo and hypoechoic pattern with hepatomegaly; renal ultrasound showed normal kidney size with increase of parenchymal echogenicity, mildly reduced cortical thickness and resistance indices increased bilaterally. At the same time, cardiac biomarkers increased showing a possible extent of cardiac involvement, even if echocardiogram was negative: troponin T 30 ng/L (normal values in woman 0-14 ng/L) provided a quantitative assessment of cardiac damage, B-type natriuretic peptide (BNP) and NT-proBNP resulted increased and indicated cardiomyocyte stress⁷.

The patient was treated with bortezomib 1.3 mg/m² biweekly associated with dexamethasone.

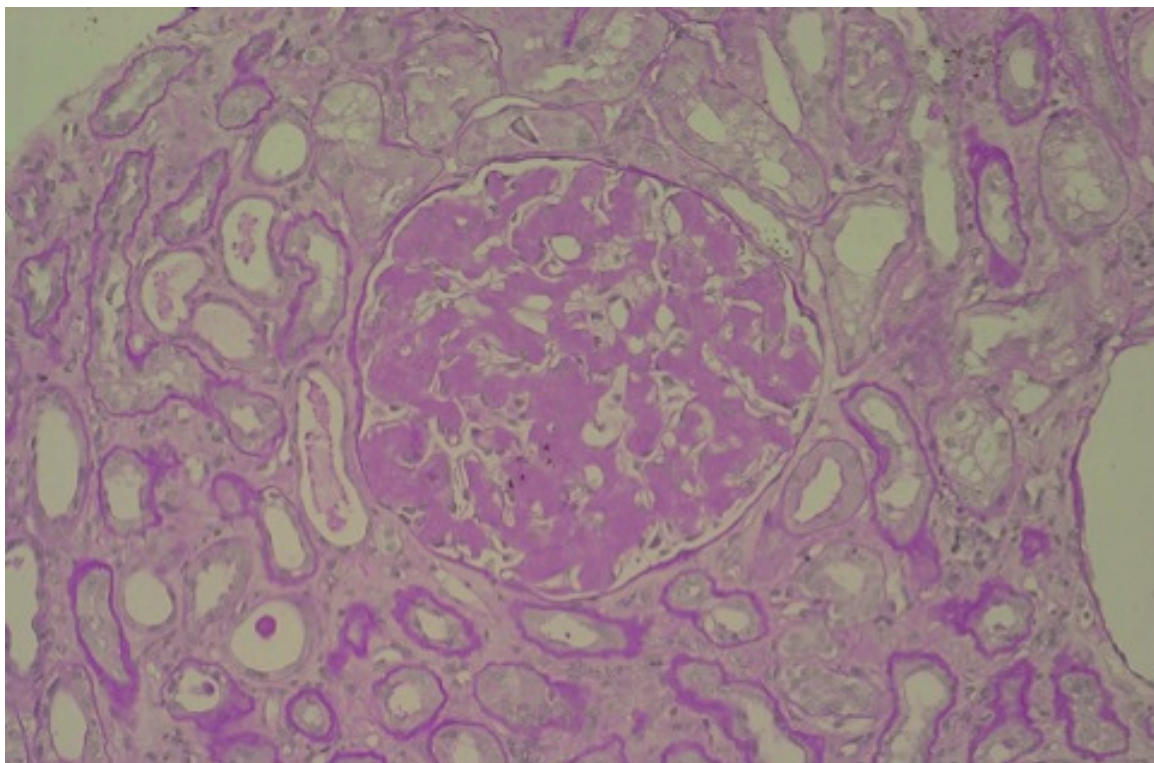


Figure 1. Extensive glomerular deposition of amorphous material. PAS 200x

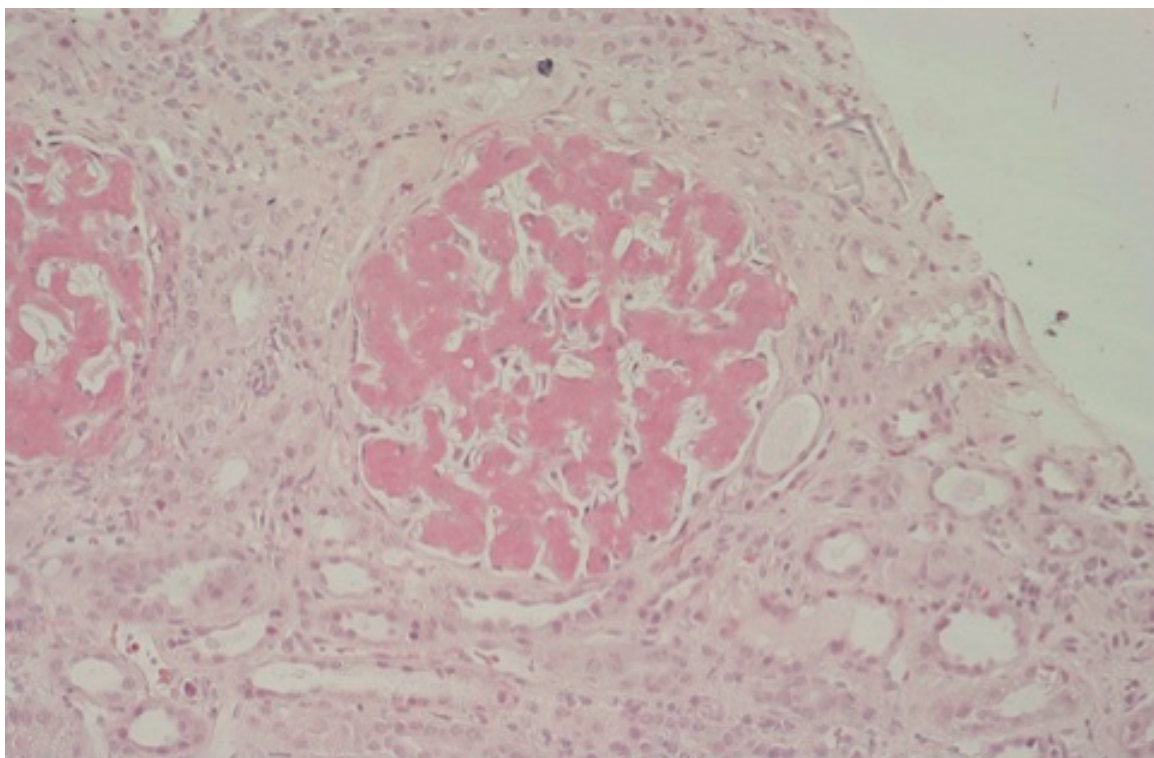


Figure 2. The glomerulus stain with Congo red. 200x.

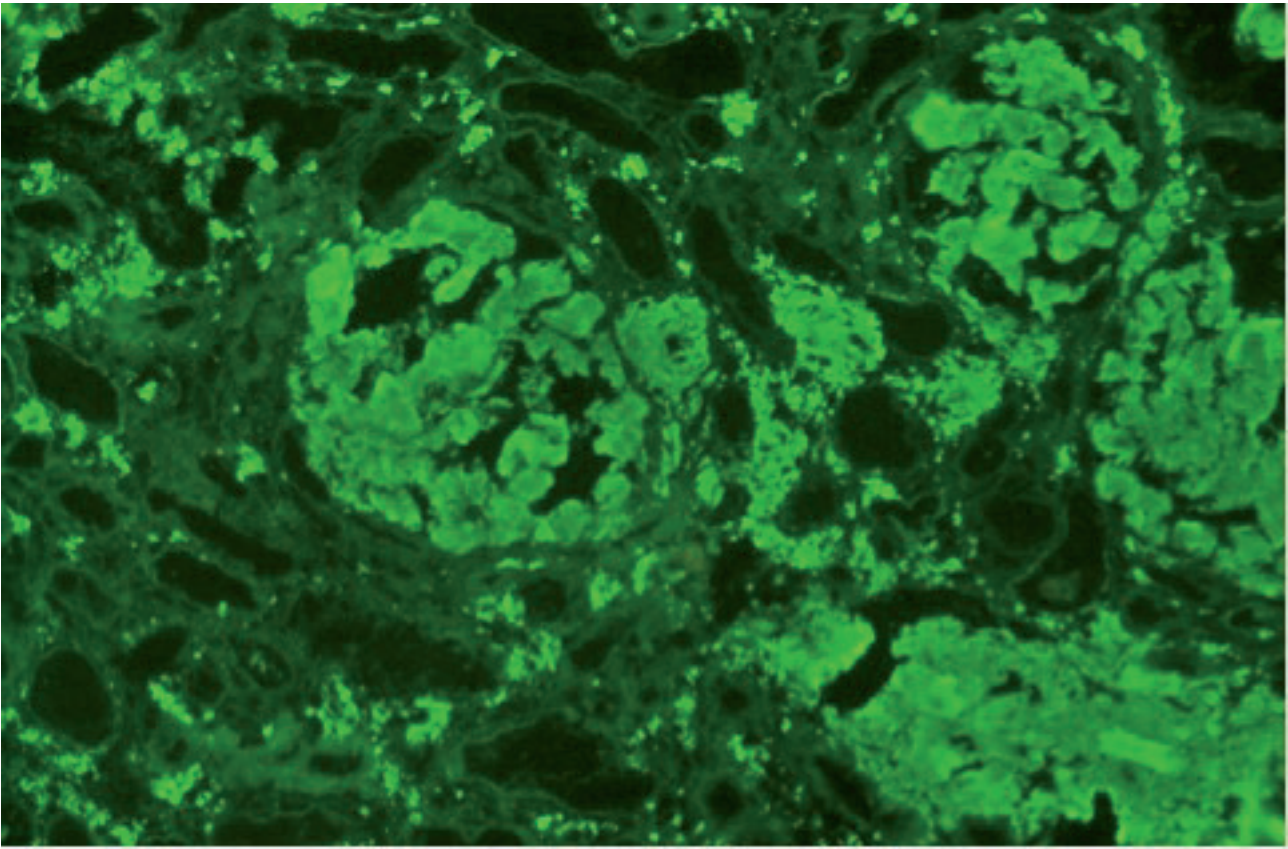


Figure 3. Immunofluorescence shows conspicuous mesangial accumulations of AL amyloid that stain with anti-Kappa light chains antiserum.

The treatment led to a mild clinical improvement and rapid hematological response (1 month) with good tolerance of therapy. Complete hematological response was defined on the basis on the International Society for Amyloidosis criteria as negative serum and urine immunofixation electrophoresis, normal serum free light chain ratio and < 5% clonal plasma cells on bone marrow studies⁸. However, patient showed a sustained worsening of renal function with a progressive GFR reduction until 20 ml/min; therefore she has been referred to a predialysis satellite unit.

DISCUSSION

The epidemiology of AL-amyloidosis is not well known because it is a rare entity difficult to recognize, due to the unspecific early clinical manifestations of the disease. The hypothesis of AL-amyloidosis is only considered when specific organ failure occurs. Clinical/organ involvement were defined by the consensus report from the 10th International Symposium on Amyloid and Amyloidosis as demonstration by biopsy of affected organ or

biopsy at an alternate site to confirm the histologic diagnosis of amyloidosis: fine-needle abdominal fat aspirate and/or biopsy of the minor salivary glands, rectum, or gingiva⁹. In our case the unusual nephrologic onset consisting of hypertension and nephrotic proteinuria in young woman after pregnancy imposed the renal biopsy that finally defined the diagnosis of AL-amyloidosis. Renal biopsy demonstrated the amyloid glomerular deposition consists of kappa light chains, while lambda light chains are observed more frequently. The marked selective proteinuria, mainly represented by albumin (about 80%), expresses the main glomerular damage typical of fibrillar amyloid deposition¹⁰. Moreover, a rapid progressive renal and hepatic failure was simultaneously observed, and renal amyloid deposition was restricted to the glomeruli, whereas myocardium was not involved initially.

Subsequently cardiac involvement occurred despite therapy and cardiac biomarkers were increased. In fact, several studies suggest that Troponin I or T provide a quantitative assessment of cardiac damage and are independently associated

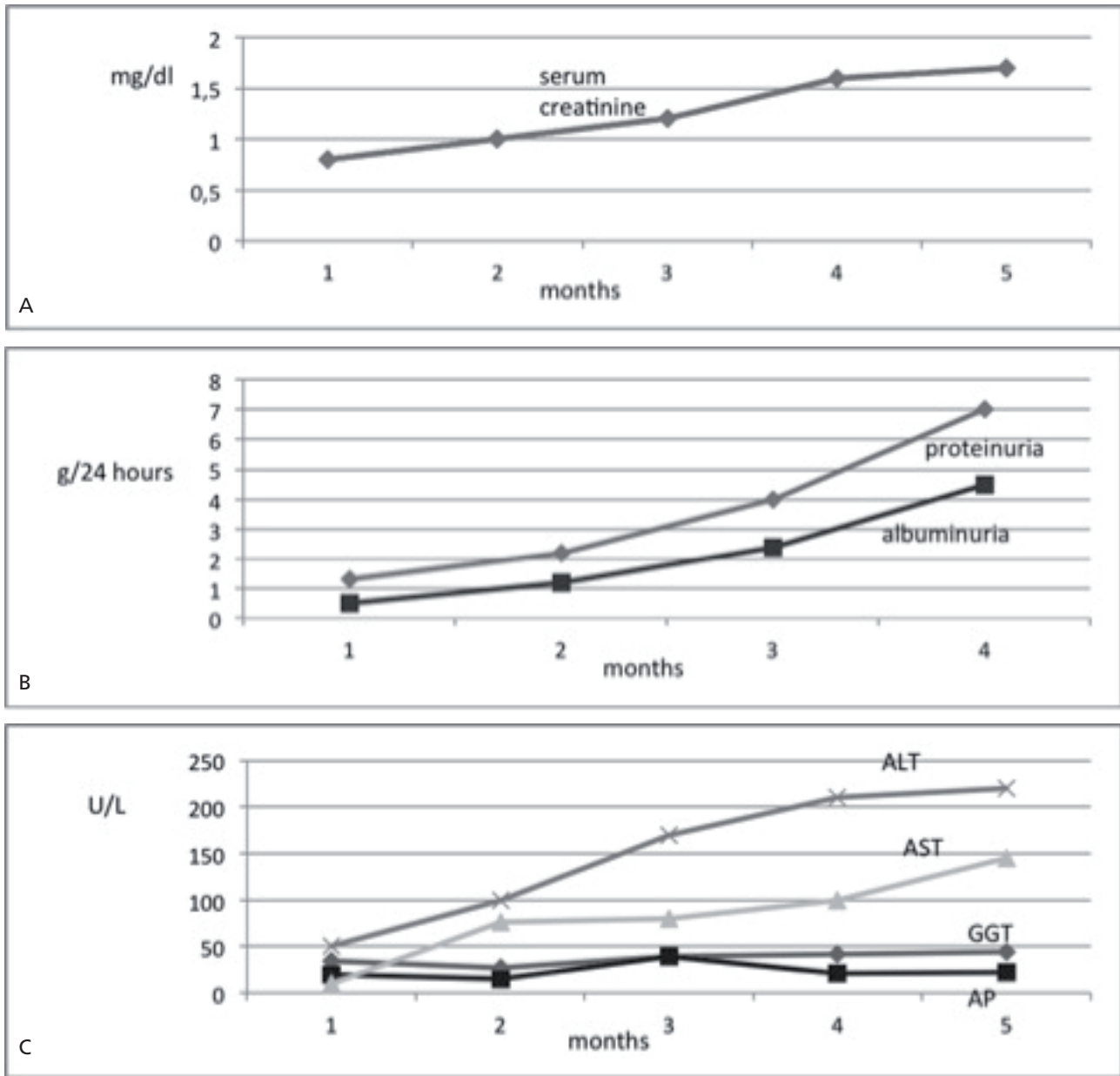


Figure 4 A-C, Progression of renal and liver impairment during 4-5 months: renal function was evaluated with serum creatinine (mg/dl), proteinuria and microalbuminuria (g/24 hours); hepatic function was evaluated with AST, ALT, GGT and AP (U/L). AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, Gamma-glutamyl transferase; AP, alkaline phosphatase.

with survival¹¹. Moreover B-type natriuretic peptide (BNP) and/or NT-proBNP can be useful to recognize cardiomyocyte stress earlier than cardiac ultrasonography. Patients with cardiac involvement have a mean survival of 1.1 years after diagnosis, and a survival less than 6 months if treatment is not provided once the first symptoms of heart failure are recognized¹²⁻¹⁴ especially if the signs of heart failure persist when the diagnosis is confirmed.

The occurrence of disease after pregnancy demonstrates its protective effect as reported in the literature¹⁵. In fact clinical and experimental evidence suggests that female sex hormones can modulate the inflammatory response. Progesterone has a strong anti-inflammatory effect that is mediated by several mechanisms, including inhibition of the transcription nuclear factor kappa-B, enhancement of corticosteroid production and induction of

kallikrein binding protein synthesis by the liver. Estrogens were also shown to exert anti-inflammatory effects by inhibition of T cell-induced inflammation suppression of polymorphonuclear leukocytes, suppression of serum amyloid component and induction of kallikrein binding protein synthesis by the liver.

The goal of treatment is the eradication of the monoclonal plasma cell population and suppression of the pathologic light chains that can result in organ improvement and extend patient survival. This clone of plasma cells is the source of the amyloidogenic light chains, histologically identical to those seen in the more common plasma cell dyscrasia, multiple myeloma. Given these similarities, treatments for AL-amyloidosis have been largely derived from those studied for the treatment of multiple myeloma^{16,17}. The efficacy of a treatment can be measured both in terms of reduction in the burden of clonal plasma cell disease (hematologic response) and by improvement in the organ function (organ response)¹⁸. The first effective treatment for AL-amyloidosis was HDM and prednisone. However, only a quarter of patients achieved a hematologic response to this treatment and the median survival was only 12-18 months¹⁹. High-dose melphalan followed by autologous stem cell transplantation (HDM/SCT) was explored in AL-amyloidosis based on its success in treating multiple myeloma. Two large studies from experienced centers confirmed the utility of HDM/SCT as a treatment for AL-amyloidosis. At Boston University, 312 patients with AL amyloidosis were treated with HDM/SCT at 200 mg/m² or 140 mg/m² based on age and cardiac status. Utilizing a multidisciplinary team for peri-transplant management, mortality related to treatment was reduced to 14% in these selected patients²⁰. In this series, the median survival for those who achieved complete response was more than 10 years compared to 50 months for those who did not achieve complete response²¹. A second large patient series from the Mayo Clinic reported 434 patients with AL-amyloidosis treated with HDM/SCT over 14 years. A hematologic response was seen in 76% of patients including 39% who achieved complete response. Treatment related mortality was 10%²².

Despite the reported efficacy, the use of HDM/SCT in AL-amyloidosis remains controversial. In fact only 20-25% of patients with AL-amyloidosis are eligible for such aggressive treatment²³. Strategies for those not eligible for transplantation include novel agents such as proteasome inhibitors.

Targeting the proteasome, the cellular machinery largely responsible for protein homeostasis was rational based on the misfolded nature of proteins in AL-amyloidosis. In our case the patient was treated with dexamethasone and bortezomib, a reversible inhibitor of the 26S proteasome, with a complete hematological response and good tolerance of the treatment²⁴. However, in terms of organ response our patient showed a sustained and rapid worsening of renal function despite therapy and a progressive GFR reduction until 20 ml/min.

CONCLUSIONS

Treatment with bortezomib and steroids can be an effective approach for AL-amyloidosis in order to reduce clonal plasma cell and give a complete hematological response. However, new approaches have to be developed in order to also improve organ response targeting amyloid deposit and harnessing the immune system.

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CONFLICT OF INTERESTS:

The Authors declare that they have no conflict of interests.

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