Amyloid light-chain amyloidosis, myeloma and autonomic neuropathy

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Abstract

Systemic amyloidosis secondary to myeloma is an uncommon condition that often has an insidious onset and poses as a diagnostic challenge due to the lack of typical presenting symptoms and signs. Prompt diagnosis of amyloidosis and appropriate referral have the potential to improve outcome for these patients. Here, we report the unusual case of a man whose primary presenting complaint was of long-standing orthostatic hypotension.

Keywords

AL amyloidosis; multiple myeloma; autonomic neuropathy; rectal biopsy, serum amyloid P scan.

Clinical History

A 65-year-old Caucasian man presented with a 2-year history of dizziness on standing, paresthesia in the extremities of the limbs, impotence, nocturia and bilateral swelling in the lower limbs. He was an ex-smoker of 30 pack-years but otherwise had no past medical or family history of note. Physical examination revealed signs of autonomic and peripheral neuropathy, including orthostatic hypotension (systolic 138 mmHg lying, 82 mmHg standing), hair and sensory loss and peripheral oedema in the legs with normal reflexes and tooth indentation on the tongue; hepatosplenomegaly was also noted.

Laboratory investigations included haemoglobin 12.6 g/dL, urea 12.7 mmol/L, creatinine 193 μmol/L, γ-glutamyl transferase 152 IU/L, albumin 23 g/dL, a urine albumin/creatinine ratio of 18.1 mg/mmol. Short synacthen test was normal and adrenocorticotropic hormone level was within normal range. Autonomic function tests, including tilt-table test, demonstrated an orthostatic drop of 40 mmHg with non-compensatory tachycardia, confirming autonomic neuropathy. Electrocardiography demonstrated concentric left ventricular hypertrophy and echocardiography showed evidence of cardiac amyloidosis. Ultrasound and computer tomography of the chest/abdomen/pelvis revealed an enlarged liver segment VII, splenomegaly and bilateral kidney enlargement. The combination of peripheral oedema, anaemia, raised urine albumin/creatinine ratio and enlarged kidneys aroused suspicion of nephrotic syndrome. Urinary protein measured 9.94 g/24 h. Serum electrophoresis for paraproteinaemia confirmed a free lambda.
light-chain band in the gamma-region with a kappa/lambda ratio of 0.06; urine electrophoresis demonstrated Bence–Jones proteins.

**Diagnosis**

Systemic amyloid light-chain (AL) amyloidosis secondary to multiple myeloma (MM). There was significant widespread organ involvement including the autonomic and peripheral nerves, the liver, kidneys and heart. The patient was referred to the National Amyloidosis Centre, London. Rectal (Figs. 1 and 2) and bone marrow biopsies confirmed amyloidosis and the presence of a monotypic plasma cell population, respectively. A serum amyloid P scan demonstrated a large total body amyloid load in the liver, spleen and bone marrow (Fig. 3). His current treatment includes melphalan, an alkylating agent, and dexamethasone.
Discussion

Primary AL amyloidosis is a protein conformation disorder associated with clonal plasma cell dyscrasia. It is a rare multi-systemic disorder involving the renal, cardiovascular, respiratory, gastrointestinal and nervous systems, with a prevalence of 0.9 per 100,000 and median age of onset of 65 years\(^1\). It occurs in up to 30% of patients with MM. MM itself has an incidence of 5 in 100,000 with a peak age of 70 years. The prognosis in MM patients is poor with a median survival of <5 years; patients with MM with untreated AL amyloidosis have an even shorter survival of 2 years. As this case illustrates, these patients often present a diagnostic challenge, especially when the typical symptoms, including backache and bone pain, are lacking. Duston et al.\(^2\) found that the median duration of time from first symptom to diagnosis of AL amyloidosis was longer in patients whose first symptom was neuropathy (48 versus 12 months) which can precede amyloidotic infiltration of vital organs. It is therefore crucial that AL amyloidosis is considered early on as a differential diagnosis in patients presenting with unusual features, including autonomic neuropathy, to widen the therapeutic window\(^2\)–\(^4\).

Fig. 3. A serum amyloid P scan demonstrated a large total body amyloid load in the liver, spleen and bone marrow.
AL amyloidosis can be diagnosed by a rectal biopsy with a sensitivity of 73%[^4]. Amyloid proteins stained with Congo Red demonstrate apple-green birefringence under polarized light (Fig. 2). Abdominal fat pad aspiration biopsy stain has been described with a sensitivity of 73% and specificity of 90%[^4,5]. Serum amyloid P scan comprises scintigraphy with a radioisotope-labelled serum amyloid P component. Although it is not a diagnostic tool, it is used to identify the distribution of amyloid deposits, estimate total body burden and monitor response to treatment (Fig. 3)[^6].

The goal of treatment for AL amyloidosis in MM is to eradicate the plasma cell clone producing the amyloidogenic protein as rapidly as possible, thereby preventing ongoing amyloid deposition into tissues. Attainment of a complete haematological response is associated with improved patient survival and organ function[^7]. High-dose melphalan (140–200 mg/m²) and autologous peripheral blood stem-cell transplantation is considered the most effective treatment of AL amyloidosis. However, this regime is limited by its toxicity, with treatment-related mortality at 14–40%, and this was the reason our patient was not considered a suitable candidate. The alternative treatment, which our patient is receiving at the time of writing, consists of oral melphalan (0.22 mg/kg per day) together with dexamethasone administered at a high dosage (40 mg/day) in 4-day cycles each month. This regime leads to rapid eradication of monoclonal light-chain production and rapid reduction in N-terminal brain natriuretic peptide, a marker of amyloidosis-associated cardiac dysfunction[^8]. A detailed discussion of the treatment of AL amyloidosis is beyond the scope of this article but interested readers are directed to the excellent reviews by Sanchorawala and Dember[^9,10].

**Teaching points**

MM complicated by AL amyloidosis is a rare condition. It is crucial that AL amyloidosis is considered as a differential diagnosis in patients presenting with unusual features, including autonomic neuropathy, to ensure timely and appropriate management. Orthostatic hypotension is one of the most common symptoms of autonomic neuropathy in amyloidosis[^3]. Prompt diagnosis of amyloidosis and appropriate referral have the potential to improve outcome for these patients[^9].

**References**