Arq Neuropsiquiatr 2004;62(3-A):725-729

AXONAL NEUROPATHY AS INITIAL MANIFESTATION OF PRIMARY AMYLOIDOSIS

Report of a case submitted to bone marrow transplantation

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ABSTRACT - Amyloidosis is a syndrome characterized by deposition of a highly insoluble protein material in the extracellular space that may affect several organs. It may be generalized and idiopathic (primary amyloidosis). We describe the case of a 48 years-old woman with axonal neuropathy associated with proteinuria, whose final investigation resulted in diagnosis of primary amyloidosis (AL). She was submitted to autologous bone marrow transplantation. We discuss some aspects related to diagnosis of neuropathy and current treatment of AL.

KEY WORDS: amyloid neuropathies, amyloidosis, autologous bone marrow transplantation, autologous transplantation.

Neuropatia axonal como manifestação inicial de amiloidose primária: relato de caso submetido a transplante de medula óssea

RESUMO - A amiloidose é uma síndrome caracterizada pela deposição no meio extracelular de material protéico altamente insolúvel e que pode afetar vários órgãos. Pode ocorrer como doença generalizada e pode ser idiopática (amiloidose primária). Descrevemos o caso de mulher de 48 anos com neuropatia axonal associada a proteinúria na qual a investigação final resultou no diagnóstico de amiloidose primária (AL). Foi submetida a transplante autólogo de medula óssea sem complicações. Discutiremos aspectos relacionados ao diagnóstico da neuropatia e do tratamento atual da AL.

PALAVRA-CHAVE: neuropatias amilóide, amiloidose, transplante autólogo de medula óssea, transplante autólogo.

Amyloidosis results from deposition of insoluble and amyloid protein in the extracellular space of organs and tissues. In clinical practice, primary or idiopathic amyloidosis (AL) is most often observed; it is a plasma cell dyscrasia characterized by autonomous proliferation of plasma cells and overproduction of monoclonal immunoglobulins[1]. It may be associated with chronic inflammatory diseases or monoclonal gammopathy (secondary amyloidosis - AA). The monoclonal components are mostly light-chain immunoglobulins. At least 20% of the AL patients suffer from multiple myeloma, and the remaining suffer from other monoclonal gammopathies, light-chain diseases or even agammaglobulinemia[1-2]. Approximately 15-20% of the patients with multiple myeloma suffer from amyloidosis. The monoclonal antibodies produced by the bone marrow are lambda and kappa light chains, and lambda prevails over kappa (2:1).

The amyloid deposits may occur in any organ. The organs most often affected are kidneys, heart, gastrointestinal tract, liver, and peripheral nerves. The initial symptoms depend on the organs involved. Cardiac involvement is the most severe manifestation of systemic amyloidosis and the main cause of death in these patients. Several organs are simultaneously affected in most patients. Current studies demonstrate an incidence of 1-5 cases/100,000 persons/year[1-2]. Less than 20% of the cases show some response to chemotherapeutic agents for a

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Received 9 October 2003, received in final form 12 February 2004. Accepted 22 March 2004.

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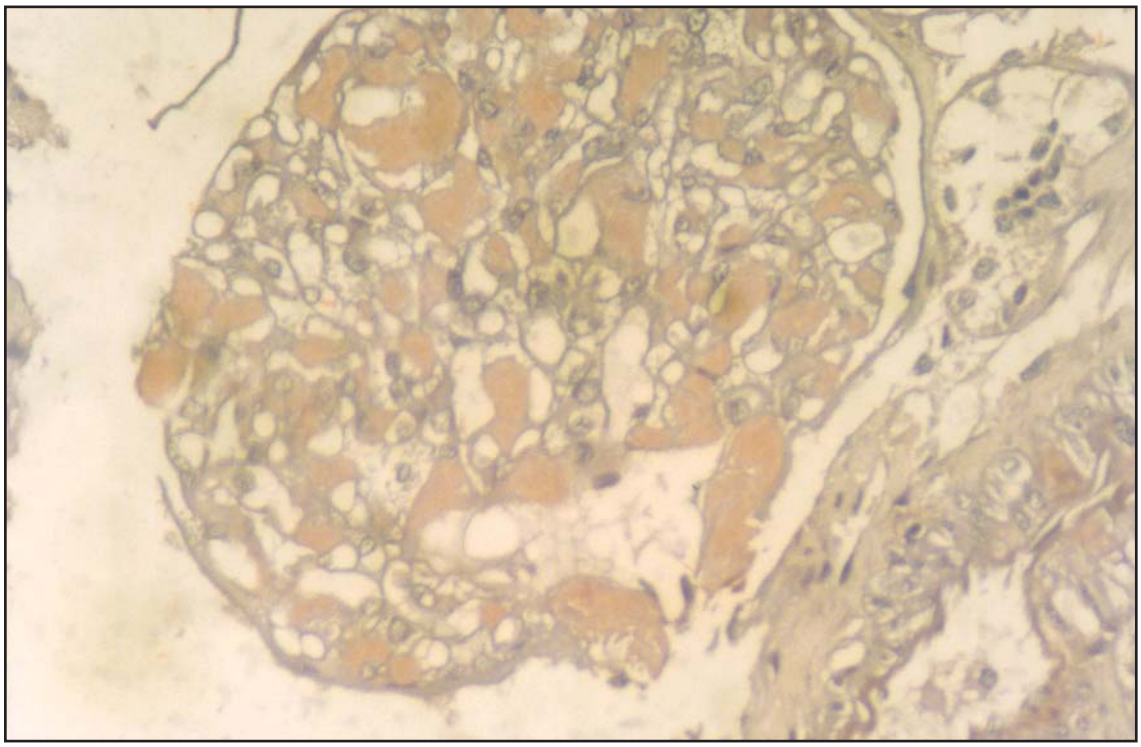

Fig 1A. Mesangial deposits stained orange-red by Congo red (400x).

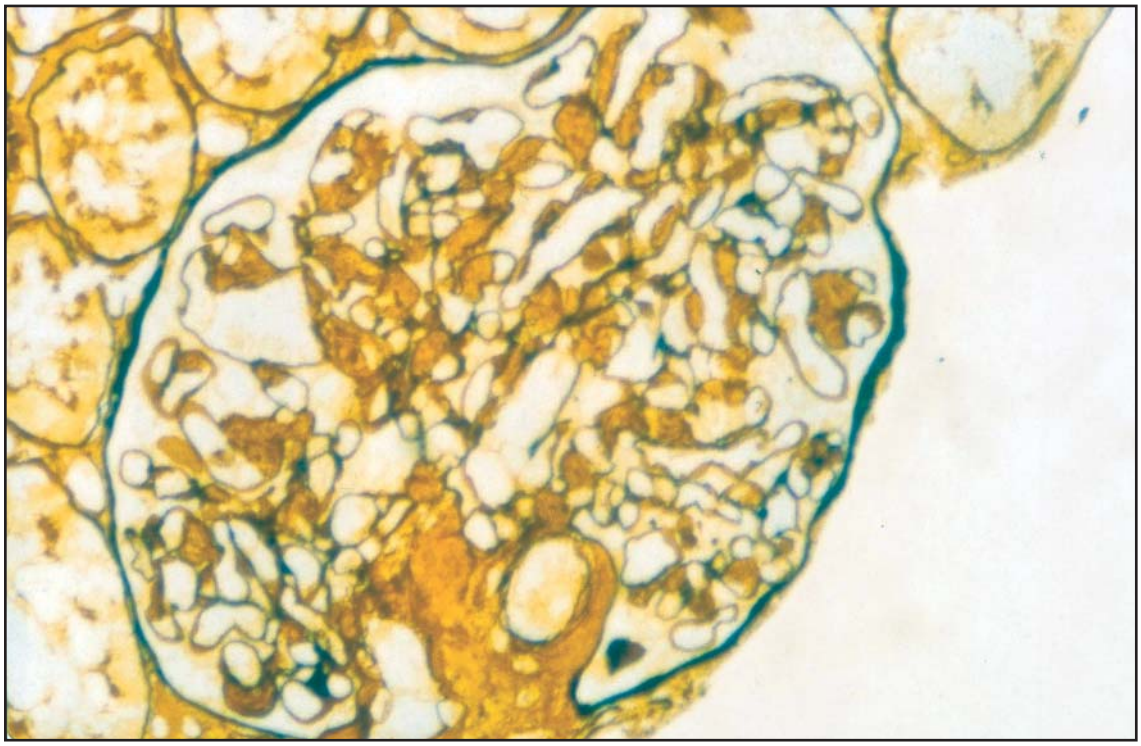

Fig 1B. Mesangial deposits negative by silver impregnation (Jones' Silver, 400x).

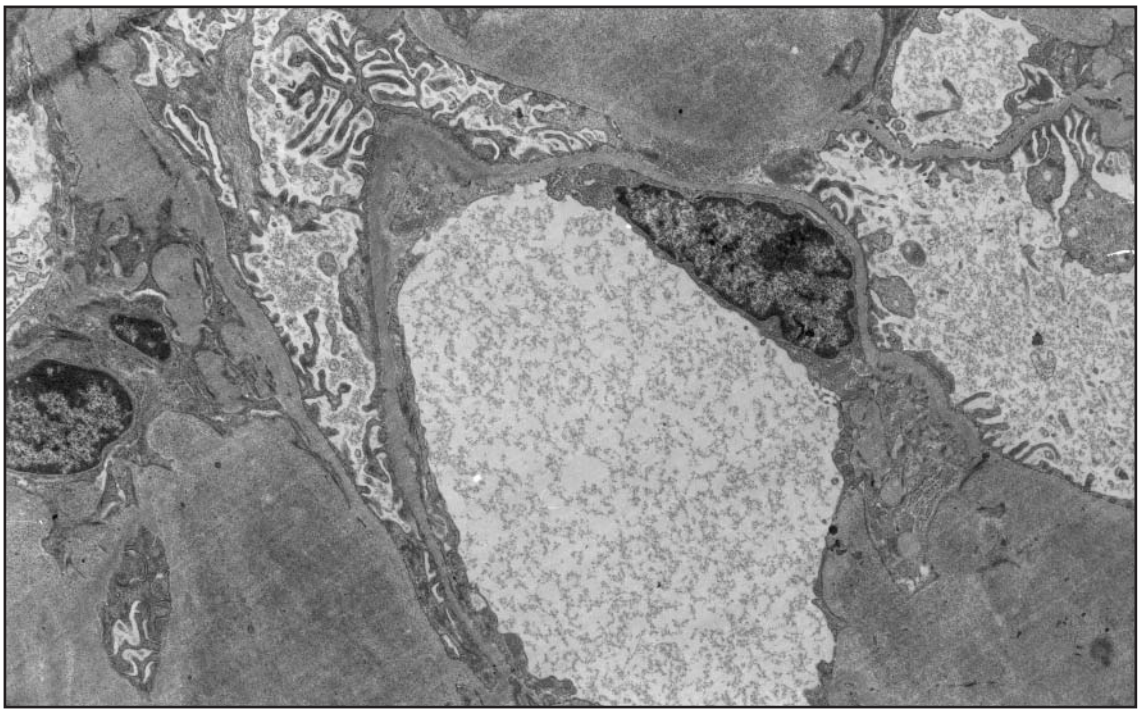

Fig 2A. Capillary loop with typical endothelial cells. Notice massive fibrillary deposits in the mesangial area (Transmission electron microscopy - 5000x).

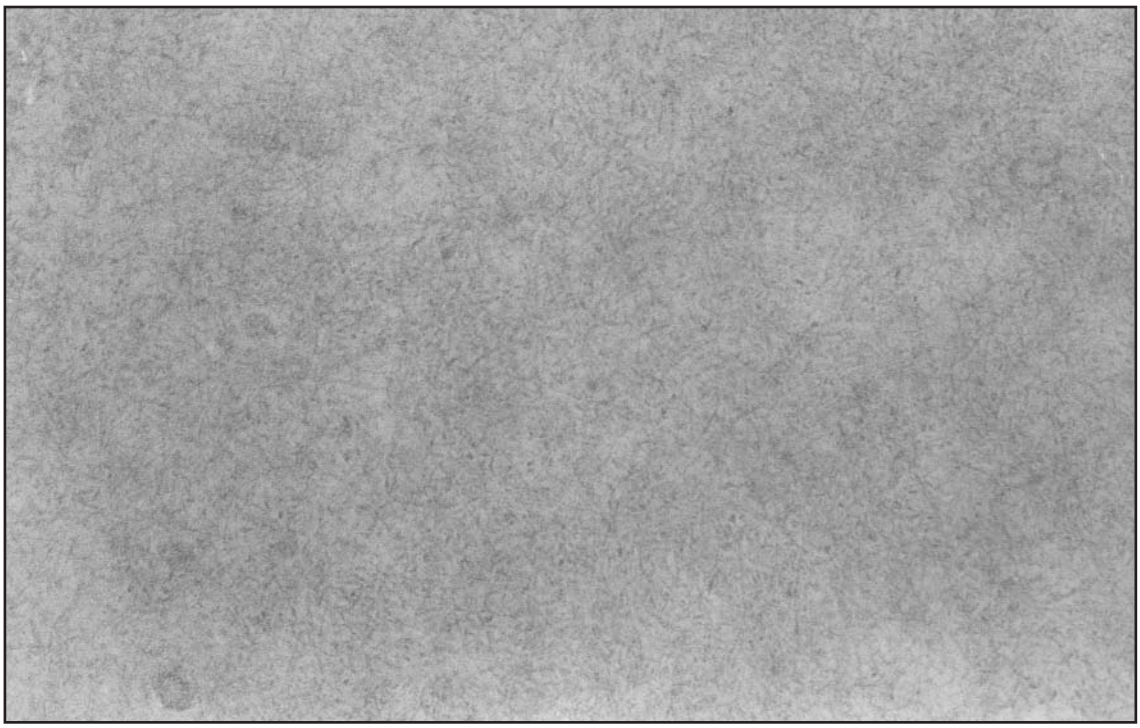

Fig 2B. Thin fibrillary deposits randomized distributed in mesangium (Transmission electron microscopy, 50000x).

short period, such as melphalan, at conventional doses. At present, high doses of melphalan may be used to effectively destroy bone marrow cells. In order to restore hematopoiesis, stem cells are collected from peripheral blood before chemotherapy and returned after treatment to reestablish bone marrow functions[3]. Stem cells are defined as cells having clonogenic and regenerative capacity that differentiate into multiple lineage cells. Recent studies have suggested some similarity between stem cells in adult tissues and bone marrow stem cells due to their marked plasticity and pluripotentiality. Bone marrow stem cells are able to generate blood and endothelial cells, cartilage, bone, adipocytes, cardiac and skeletal muscle, neuronal, gastrointestinal and lung epithelial cells, as well as thymus cells. Neuropathy associated to multiple myeloma and other plasma cell malignancies, such as Waldenstrom's macroglobulinemia, may attain a satisfactory response with bone marrow transplantation[4].

This report describes a patient presenting polyaxonal neuropathy as the initial manifestation of AL, and submitted to bone marrow transplantation with good results.

CASE

A 48-years old woman, residing in Uberlândia - MG reported insidious onset of burning and dysesthesia in the lower limbs approximately 18 months ago. Three months later, the same symptoms manifested in the upper limbs, but were less intense. The symptoms progressed continuously. At admission to hospital, presented impaired gait, decreased muscle strength distally in the limbs and presence of sensory ataxia, which led to some falls. Apart from these symptoms, she complained of dry mouth, and permanent ocular irritation. She brought urine test results showing proteinuria (5g/24hs) in one urine sample. She also reported weight loss of about 8 kg within six months. At clinical examination, she presented good general appearance, anicteric, and eupneic. Neurological examination showed generalized hyporeflexia, with bilateral areflexia in Achilles tendon, painful and tactile glove and stocking-type hypoesthesia, signs of distal atrophy in the limbs, and impaired deep sensibility in lower limbs. Possible polyneuropathy and proteinuria guided the exams. Cerebrospinal fluid (CSF) examination showed high protein levels (160mg/dl) and did not show oligoclonal bands. ESR=95mm, rheumatoid factor < 9.6 UI/ml, positive ANF 1/640, no anti-Ro and anti-La antibodies reacting, non-reacting ANCA, angiotensin converting enzyme at normal levels, negative viral serology including HIV and hepatites. Abdomen CT showed homogeneous hepatoesplenomegaly. Proteinuria in 24-hour urine (3.13g/24h). Electroneuromyography demonstrated sensory-motor polyneuropathy with axonal pattern. Echocardiogram revealed restrictive myocardiopathy with infiltrative pattern. The patient was submitted to renal biopsy that demonstrated AL renal amyloidosis, with predominant glomerular deposition (Figs 1a,1b, 2a, 2b).

The hematopoietic stem cells of the patient were mobilized with GCSF 10ug/kg/day for 4 days, and after processing 12 liters of blood using Cobe equipment for aphaeresis were processed, with a yield of $4.34x10^8$ mononuclear lymphocytes/kg and $4.16x10^6$ CD34 cells/kg. The cells were frozen in a mechanical freezer at -80°C, with DMSO and HES. Transplant recipient was conditioned with melphalan 200 mg/m^2, the total dose divided into two consecutive days, and the cells collected were reinfused after thawing. Bone marrow recovery occurred on day 11 and was characterized by over 1000 granulocytes/mm^3 in peripheral blood for two consecutive days. On the same day the patient became platelet transfusion independent with platelet count > 20000/mm^3. There were no significant clinical or infectious events during the procedure. As to progression of neuropathy after transplantation, so far the clinical picture has remained stable, with no evidence of progressive course of neurological disorder.

DISCUSSION

Primary amyloidosis is a multisystemic disease, involving renal, cardiovascular, gastrointestinal, articular, and nervous systems. It may affect any racial groups with no preference. It is more prevalent in males, in a proportion of 2:1. Deposition of amyloid fibrils in peripheral nerves occurs in up to 20% of AL cases, and most patients have more prominent sensory symptoms; however, some individuals might have greater involvement of the autonomous nervous system and carpal tunnel[5-6]. Autonomic neuropathy may cause orthostatic hypotension, diarrhea or impotence. Involvement of cranial nerves and association with motor neuron disease has been occasionally observed[7]. In a study by Kyle et al., at Mayo Clinic, neuropathy was the first manifestation of systemic amyloidosis in 17% of 229 patients[8].

The onset of sensorial alterations, such as paresthesia and very unpleasant dysesthetic sensations in both feet and hands, may precede systemic involvement. Distal muscle weakness appears later as the disease progresses and there is no relation between severity of systemic involvement and severity of peripheral neuropathy. Symptoms of distal sensorial involvement are common, and pain and temperature sensations are more significant than deep sensibility. The course of neuropathy is gradually

progressive, involving the sensory, motor and autonomic portions, making most patients unable to walk during the advanced stages of the disease[5]. In most cases CSF examination in AL patients shows increased protein levels, and protein electrophoresis may reveal elevated IgG fractions[6,9]. The electrophysiological studies evidence axonal neuropathy with reduced or absent amplitude of sensorial or motor potentials and slowed motor conduction time. There might be evidence of acute or chronic denervation of more distally positioned muscles in electromyography. Biopsy of the sural nerve may reveal presence of amyloid deposits when Congo red technique is applied[2-3].

The response of primary amyloidosis patients to the standard therapy with melphalan and prednisone is very poor. It occurs in approximately 20% of the patients, with mean survival of 12-18 months. High-dose chemotherapy with autologous bone marrow rescue and conditioning with melphalan modified prognosis. Patients now have a mean survival rate of 42 months. The indices regarding hematologic and organ response significantly improved to 62% and 44%, respectively. These facts contrast with the results obtained in conventional chemotherapy. Nevertheless, the mortality rate related to this procedure ranges from 15 to 43%, and poor prognosis depends on the clinical conditions of patients, especially those in the advanced stage of the disease and presenting involvement of more organs[10-13]. This case report may draw attention to early diagnosis and treatment in order to have better hematologic and organ response in AL patients.

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