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AMYLOIDOTIC MUSCLE PSEUDOHYPERTROPHY

Case report

Rosana Herminia Scola[3], Lineu Cesar Werneck[1], Cássio Slompo Ramos[4], Ricardo Pasquini[1], Hans Graf[3], Walter Olesko Arruda[2]

ABSTRACT – The authors report one case of amyloidosis associated with muscular pseudohypertrophy in a 46-year-old woman, who developed weakness, macroglossia and muscle hypertrophy associated with primary systemic amyloidosis. Electromyography showed a myopathic pattern and bilateral carpal tunnel syndrome. The muscle biopsy presented with a type I and II fiber hypertrophy and infiltration of amyloid material in the interstitious space and artery walls. She underwent bone marrow transplantation with stabilization and subjective improvement of the clinical picture.

KEY WORDS: muscular hypertrophy, muscle biopsy, amyloidosis.

Pseudo-hipertrofia muscular associada com amiloidose: relato de caso

RESUMO - Descreve-se um caso de pseudo-hipertrofia muscular associada a amiloidose primária em uma paciente do sexo feminino, com 46 anos, que apresentava astenia e macroglossia. O estudo eletromiográfico mostrou padrão miopático e síndrome do túnel do carpo, bilateral. A biópsia muscular revelou hipertrofia de fibras tipo I e II, com infiltração de material amilóide no interstício e parede dos vasos, principalmente arteriais. A paciente foi submetida a transplante autólogo de medula óssea, evoluindo com estabilização do quadro e um sentimento subjetivo de melhora.

PALAVRAS-CHAVE: hipertrofia muscular, biópsia muscular, amiloidose.

Amyloidosis is a rare and fatal disease caused by deposition of sulfated mucopolissacarides in many organs and tissues and can be classified as primary, which includes the familial and atypical forms as well as the form associated with multiple myeloma, and secondary, which is associated with chronic diseases[1-3]. Neuromuscular involvement in amyloidosis can be primary or secondary, and usually takes the form of carpal tunnel syndrome[4,5]. It is very rare for amyloidosis to be characterized by muscle pseudohypertrophy and/or generalized weakness of skeletal muscle[4].

We hereby report a case of muscle pseudohypertrophy associated with primary amyloidosis in which the diagnostic methods and treatment are emphasized.

CASE

A 46 years of age, woman, reported swelling of lower limbs for the past 2 years ago, that worsened at the end of the day. At that time, she was diagnosed as having iron deficiency anemia and hypothyroidism, and treated with L-thyroxine 150 mg/day and iron reposition. Approximately 1 year later, the patient showed a progressive muscle enlargement associated with weakness, bradikynesia and muscle pain. The patient presented dysarthria, difficulty in swallowing, paresthesia from the second to the fourth fingers, and numbness in her arms at night. The muscle hyperthrophy gave her an athletic appearance, like that of a person who was attending muscle building sessions. In fact, the patient was asked many times about the place and the program she was having her workouts.

Physical examination showed arterial blood pressure 110/70 mmHg, pulse and heart rate 60 beats per minute. Brittle hair, dry, cold and yellow skin were observed on the patient's face as well as infiltration of the tongue and jaw with a hard rubbery consistency, which caused difficulty in speech articulation. Thorax examination revealed normophonetic, rhythmic sounds in her heart, and her lungs presented bilateral vesicular murmurs. Her abdo-

Serviço de Doenças Neuromusculares da Disciplina de Neurologia e de Propedêutica Médica do Departamento de Clínica Médica do Hospital de Clínicas da Universidade Federal do Paraná (UFPR) Curitiba PR, Brasil: [1]Professor Titular; [2]Professor Assistente; [3]Professor Adjunto; [4]Médico Residente em Clínica Médica.

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Dra. Rosana Herminia Scola – Serviço de Doenças Neuromusculares, Hospital de Clínicas da UFPR - Rua General Carneiro 181 / 3° andar - 80060-900 Curitiba PR - Brasil. FAX: 041- 264 3606 – E-mail: scola@hc.ufpr.br

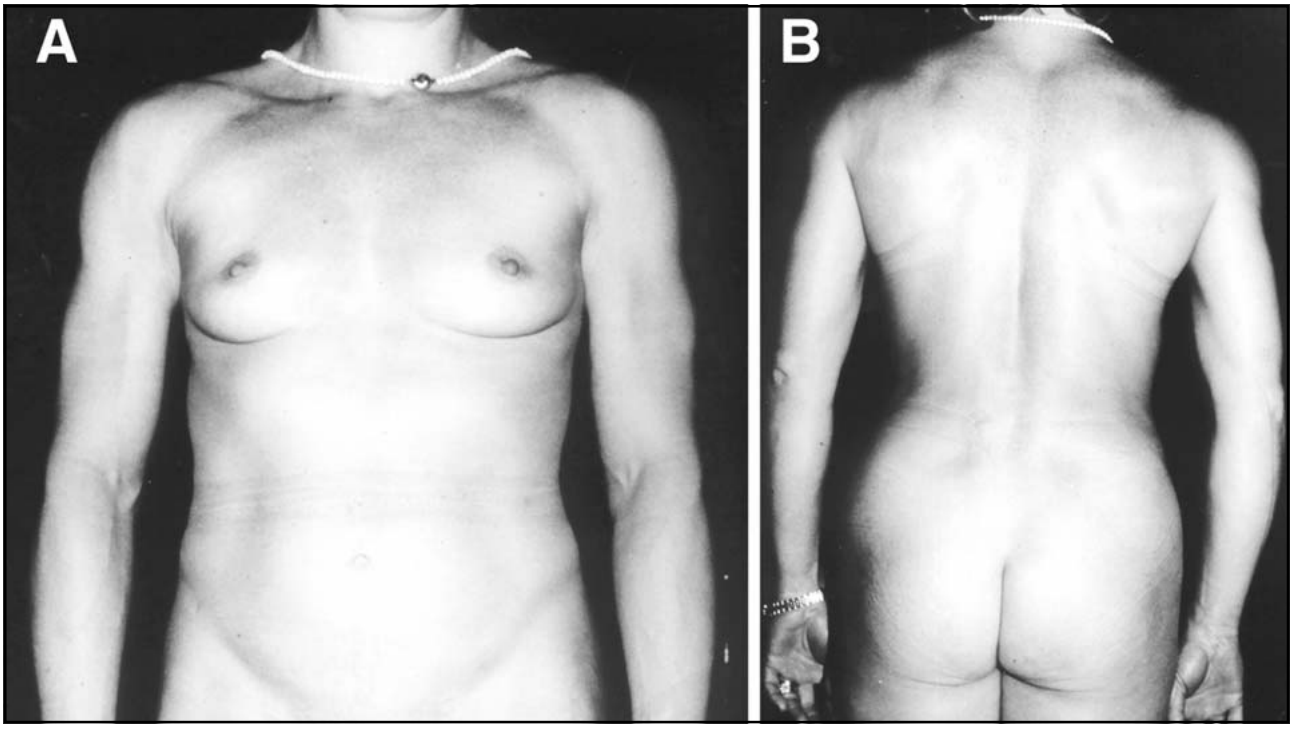

Fig 1. Photograph of the case. A. Anterior view. B. Posterior view.

men was flat, flaccid and no pain occurred on superficial and deep palpation, and there was no visceromegally. There was muscle hypertrophy. (Fig 1 A and B) Upon neurological examination, the cranial nerves were normal. Proximal muscle strength in the lower and upper limbs was grade IV, and distal muscles were grade V (MCRM). Tonus, gait, coordination, superficial and deep sensitivity were normal. There was absence of deep tendon reflexes.

Hemogram, ESR, sodium, potassium, calcium, magnesium, phosphorus, blood sugar, creatinine, serum aldolase, lactic dehydrogenase, oxalacetic glutamic transaminase, total cholesterol, HDL – cholesterol, anti-nuclear factor, triglycerides, C reactive protein, prolactin, estradiol, insulin, pro-thrombin time, thrombin time, X factor activity, somatomedin, T3, anti-thyroglobulin antibody and antimicrosomal antibody were normal. T4 3.8 (Normal (N): 4,5-12,5), TSH 0.04 (N: 0,43-3,8), serum creatine kinase 201 IU (N:up to 70 UI), serum immunoglobulins IgA 664 mg/dl (N: 60-400), IgM 18,8 mg/dl (N: 60-300), IgG 322 mg/dl (N: 700-1500), total proteins 6,21 g/dl (N: 6,3-7,9) [albumin 51,04%, alpha-1 globulin 5,15%, alpha-2 globulin 14,65%, beta globulin 24,95%, gamma globulin 4,18%], urinary protein/osmolarity 0,27 (N: < 0,12), and total protein in 24 hour urine 101 mg/24 hs (N: 27-93). The thyroid scintillography showed a two hour test below normal. Thorax X-ray, abdominal echography and sella tursica magnetic resonance imaging were normal. The echocardiogram showed an ejection fraction of 68% and normal diastolic function . Serum immunofixation showed a monoclonal protein IgA kappa. Urine immunoelectrophoresis and immunofixation revealed a monoclonal protein IgA kappa. Bone marrow biopsy and aspiration showed 35% of plasmatic cells. Stain to amyloid (red Congo) in the bone marrow was negative, but positive in the adipose tissue.

The electromyography showed a myopathic pattern in the left biceps, in left and right anterior tibial, and borderline myopathy in the right biceps and the left deltoid. The nervous conduction study showed elevated distal motor and sensory latencies in the median nerve, without decrement, compatible with bilateral carpal tunnel syndrome. The potential amplitude was reduced in the lower limbs (edema).

The muscle biopsy revealed a deposit of homogeneous, hyaline material in the interstitious, which stained pink in Haematoxylin-Eosin and slightly green in Gomori, without the typical aspect of fibrosis. There was no fatty infiltration. There was presence of dense wall vessels only in the capillaries, which suggested a deposit of hyaline material. Hypertrophy of type 1 and 2 fiber was found. Cresil violet and crystal violet demonstrated a metachromatic material, red, with an amyloid aspect, which also involved the vessel walls (Fig 2A). Red Congo showed stained deposits in conjunctive tissue, related to the perimysium and endomysium of some vessels and, also, stained deposits around the muscle fiber (Fig 2B).

The electronic microscopy revealed interstitious and muscle fiber with sarcoplasmatic accumulation of a filamentarous material with amyloid characteristics (Fig 3).

The patient underwent autologous bone marrow transplantation without progression of the disease in the follow-up.

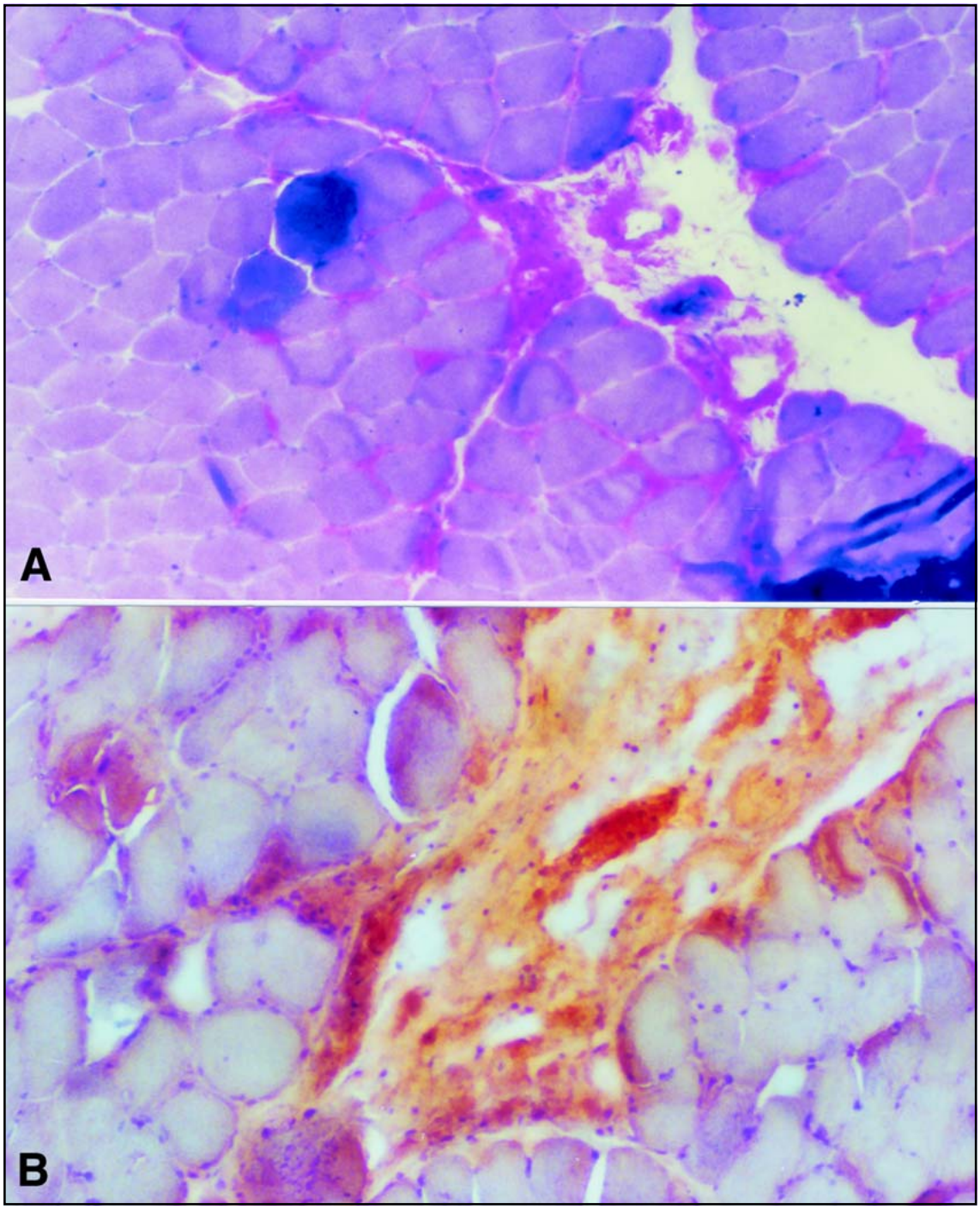

Fig 2. Muscle Biopsy. A. Amyloid material involving the vessel walls. (Magnification x174, Crystal Violet). B. Amyloid material in the perimysium and endomysium of some vessels, and, also, around the muscle fiber. (Magnification x 174, Red Congo).

DISCUSSION

Amyloidosis occurs in 6 to 15 percent of patients with myeloma, mainly in the form of light chain myeloma[2,6]. The amyloid tissue, which infiltrates and weakens the muscular tissue is rare[7]. Lubarsh made the first description of the presence of macroglossia and firm muscles with a wooden consistency in 1929. Macroglossia, difficulty in swallowing, difficulty in speech, pseudohypertrophy of skeletal muscles, hypertrophy of small joints and gastrointestinal symptoms are common findings in most patients with pseudohypertrophy associated with amyloidosis[5].

The etiology of primary amyloidosis is unknown. The protein deposits are fibrils, which are similar to

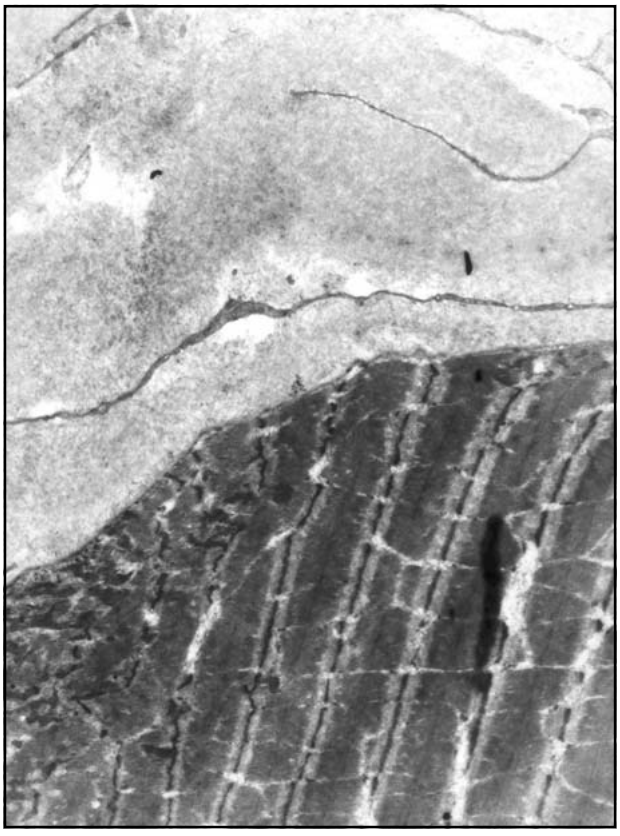

Fig 3. Electronic microscopy. Interstitious and muscle fiber with sarcoplasmatic accumulation of amyloid material (Magnification x 4000).

the immunoglobulins variable portion, which represent an excessive deposit or a deficient removal[5,8]. The extracelular fibril deposits are insoluble, generally resistant to proteolyses, and cause a disorganization of the tissular architecture. This material is recognized immunohistochemically by green birefringence when stained with red Congo and examined under polarized light[9,10].

The pathogenesis of myopathy is also unknown. The muscular contraction could be mechanically impaired by the inefficient muscular elasticity caused by an amyloid deposit. Perimisial infiltration could cause muscular atrophy. The perivascular and perimisial connective tissue with amyloid deposits could interfere with normal muscular nutrition as well as with the exchange of waste products, and the perivascular infiltration most likely causes muscular ischemia[7,8]. The amyloid infiltration can also interfere in the propagation of action potentials along the sarcolemmal membrane[8]. Although accurate mechanisms of the motor deficit are not known; the accumulation of amyloid tissue in the muscle is the most probable cause of muscular weakness[4,6].

Despite the fact of its being a very rare disease, with only 10 related cases (Lubarsh 1929; Osserman et al 1964; Martin et al 1970; Ikeda et al 1973; Miyazaki et al 1973, Whitaker et al 1977; Terashima et al 1978; Miyasaki et al 1979; Komiyama et al 1996), the clinical features are uniform, with macroglossia, difficulty in swallowing and in speech, weakness, pseudohypertrophy of skeletal muscles with an athletic appearance. Other disorders are also common such as the carpal tunnel syndrome, gastrointestinal symptoms and cardiomyopathy[9]. The reported case showed the clinical features commonly observed, the exception being cardiomyopathy. One clinical finding was absence of tendon reflexes, which is not common in such cases.

The electrophysiological studies usually reveal a myopathic pattern with normal nerve conduction. In this patient, the motor and sensory distal latencies in the median nerve were elevated and the nerve conduction velocity was decreased in the left motor; there was no conduction in the right sensory compatible with bilateral carpal tunnel syndrome. The association between muscular pseudohypertrophy with carpal tunnel syndrome is frequent[11]. The finding of a myopathic pattern is not specific, because it can be found in several types of myopathies.

The muscular biopsies described are usually a variable degree of muscular atrophy, mainly type II fibers, and amyloid deposits in the muscle are primarily in the vessels[8]. In our case, we found amyloid deposits in the vessel walls, mainly in the arteries, although there was hypertrophy of type I and II fibers, which was possibly associated with muscle overwork.

Currently, the treatment of primary amyloidosis with high doses of bussulphan and melphalan, or only melphalan associated with autologous marrow infusion and peripheric blood stem cell has been of paramount importance. Treatment with dimetilsulfoxide (DMSO), which, in vitro, promotes the solubilization of amyloid tissue, did not show effective results in primary amyloidosis. However, when DMSO is associated with plasmapheresis, there is improvement in motor, respiratory and renal functions, yet the results are moderate and of limited duration[4]. Therapies which involved prednisone, melphalan and colchicine did not show any significant inprovement, however the association of these drugs is better than the use of colchicine alone[12,13] . The impossibility of quantifying the total amount of amyloid tissue in the organism makes the therapy results difficult to evaluate[14,15].

Since the majority of amyloid associated pseudohypertrophies were diagnosed by autopsy, there are no current data in an ideal treatment for this type of amyloidosis. Our patient was the first case of amyloid associated pseudohypertrophy treated with melphalan associated with autologous bone marrow transplantation. After the procedure, the patient reported a subjective sense of well being, but a longer follow up period is needed to verify the rate of success in this type of treatment.

The case described shows that, despite its being a rare disease, the clinical features are characteristic, nevertheless there must be confirmation by muscle biopsy. Current treatments are ineffective as far as cure is concerned, but they can contribute to a higher rate of survival of these patients, whose prognostic is limited. These reasons explain the relevance of an early diagnosis, as the damage caused by the illness is still reversible in its early stages[16,17].

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