

Carpal Tunnel Syndrome As a Predictor of Isolated Systemic Primary AL Amyloidosis

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The diagnosis of common carpal tunnel syndrome usually relies only on clinical grounds and electromyographic study. We present a 60-year-old woman who was diagnosed with systemic primary AL amyloidosis many years after the carpal tunnel syndrome had begun.

Key words: Carpal tunnel syndrome. Amyloidosis. Systemic primary AL amyloidosis.

Síndrome del canal carpiano como primera manifestación clínica de amiloidosis AL primaria sistémica aislada

El diagnóstico del síndrome del canal carpiano, frecuente, rara vez va más allá de un estudio clínico y electromiográfico. Presentamos el caso de una mujer de 60 años diagnosticada de amiloidosis AL primaria sistémica muchos años después de que se hubiera manifestado el síndrome del canal carpiano.

Palabras clave: Síndrome del canal carpiano. Amiloidosis. Amiloidosis AL primaria sistémica.

Introduction

Amyloidosis are a group of diseases characterized by the extracellular deposit of insoluble amyloid fibers joined to P protein. They are classified into a systemic and a localized form. Systemic forms can be primary, secondary or reactive and familiar, or hereditary. The modern classification is based on the nature of the deposited fibers (Table).

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Manuscript received January 26, 2006; accepted for publication March 19, 2006.

Systemic amyloidosis can affect all joints and therefore can be a source of confusion with other rheumatic diseases. Currently, amyloidosis is a mortal disease; it is common for the patient to die 1 year after diagnosis and no specific treatment is available.¹

We present a case of primary amyloidosis (AL), in a systemic form with a long natural history of the disease. A seemingly innocuous carpal tunnel syndrome and the severity of the disease, although slow to progress, justified early and systematic biopsies, a precocious treatment that is currently recommended.

Clinical Case

A 60-year-old female was attended for the first time in 1979 due to a clinical carpal tunnel syndrome which was predominantly right and had appeared 6 years earlier. She had started her menopause at 50. She had been diagnosed with osteoporosis (vertical trabeculae radiological reinforcement) and a calcification of the posterior annulus of the D12-L1 disk had been observed. She had ulcerous dyspepsia and no history of hepatitis, cholecystitis nor intestinal disorders.

She had an impaired glucose tolerance (controlled through diet) and dyslipidemia. Her arterial pressure was normal (130/70 mm Hg). Upon physical exploration she presented hypoesthesia, thenar eminence atrophy in the territory of the median nerve, with a positive Tinell sign, predominant on her right hand. Her erythrocyte sedimentation rate (ESR), the hemogram, renal function, liver tests, thyroid function, and urinary sediment were all normal. Proteinuria was negative.

She was treated with 3 infiltrations of corticosteroids in her right wrist with symptomatic improvement. Some months later, when paresthesias reappeared on the right wrist, a section of the transverse ligament of the right carpus was performed. Fifteen-five days after the intervention (May 1980) she presented inflammatory signs on the right wrist and arthritis of the metacarpophalangeal joints 2-3-4 on the right hand.

In 1981 she started presenting dyspnea after moderate efforts and reversible edema in her lower limbs. In 1982 she presented a stenosing de Quervain's tenosynovitis on her right wrist, which ceded after 2 local infiltrations with

TABLE. Classification of Amyloidosis. Some examples

Amyloid Protein	Precursor	Systemic (S), Localized (L)	Associated Disease
AA	Serum Amyloid A	S	Infection, chronic inflammation
AL	Light-chains κ/λ	S, L	Plasma cells
A β_2 M	Microglobulin β_2	S	Periodic hemodialysis
ATTR	Transtirenin (TTR)	S	Familial, mutations TTR
A β	A β	L	Alzheimer

Figure. The patient can barely stick her tongue out over her teeth/gums due to macroglossia.

steroids. Between 1988 and 1990 she started having small episodes of pain and inflammation of her left ankle and tenosynovitis of the flexor tendon of the third finger of the right hand. At the same time her left hands' acroparesthesias worsened and a severe median nerve entrapment was found requiring surgical liberation.

In 1990 she presented pain and permanent inflammation on her shoulders ("shoulder pad" sign), right hip syndrome with discreet paresthesia of the thigh in its internal part; a palpable mass with a hard (submaxillar) consistency as well as dysphagia to solids.

A sialography of the submaxillary glands was performed and demonstrated a basal glandular displacement. Because the glandular tree was normal a biopsy was not performed. Hand x-rays, after 13 years since disease onset, showed a triangular ligament calcification on the right wrist, erosions of the pyramidal bone, a radio-ulnar-carpal scaphoid entrapment on the left wrist, and erosions on metacarpophalangeal joints 2-3 on both hands.

Her shoulders had a caudal dislocation of the humeral head, with an increase in subacromial space bilaterally. She did not have any signs or symptoms of sicca syndrome.

A gammagram with gallium was negative. Cardiac Doppler echography showed hypertrophy of the ventricular walls with a reduction in the general mobility, discreet depression of systolic function (compatible with deposit myocardiopathy), and a slight pericardial effusion in the posterior sac. A left pleural effusion was also demonstrated. 100 mL of pleural fluid were obtained and proved to be a trasudate (proteins, <3 g; LDH <200 UI; normal ADA). She had difficulty talking and macroglossia could be observed. The patient barely could stick her tongue out beyond her teeth/gums (Figure).

She had an ESR of 30 mm/h that later ascended to 82 mm/h. Rheumatoid factor was negative. Protein electrophoresis showed a slight increase in gammaglobulins (21.2%), but no monoclonal bands were evident. No light chains were found either in the blood or 24-hour urine samples (immunofixation). She had 1 g/24 h of proteinuria, though her renal function was normal.

Joint fluid was obtained from the right shoulder and showed a yellow appearance and thick consistency, with 1600 erythrocytes/ μ L and 1900 leukocytes/ μ L (polymorphonuclear, 10%; mononuclear, 90%), without any crystals. After staining the centrifugate with Congo red, amyloid fibers were found.

The tongue biopsy and the Congo red stain confirmed the presence of amyloid through the characteristic green birefringence resistant to potassic permanganate, seen on the optical microscope under polarized light.

A sternal aspirate of bone marrow showed a diffuse and parched infiltration of 23% by plasmatic cells, with iron deposits that were increased and blocked. We practiced an aspiration biopsy of abdominal fat on her only daughter and it resulted negative for amyloid.

Due to all of the above we assumed it was a systemic primary amyloidosis (AL), in an isolated form. She was treated with support measures and colchicine (2 mg), with improvement of the ESR (it descended to 35 mm/h) and a reduction in proteinuria, but with clinical worsening (abdominal distention due to probable ascitis, pleural effusion, minimal effort dyspnea, pitting lower limb edema, a reduced consistency of her bowel movements, hypotension of 90/60 mm Hg, fatigue, and weight loss). A dental avulsion was performed to provide space for her tongue.

After a hematology consultation, treatment with cyclic melphalan and prednisone was suggested but not accepted by the patient's family due to its dubious response rate and the risk it carried. The patient died in 1993 after an episode of congestive heart failure.

Discussion

Systemic acquired amyloidosis, and some forms may have bone and joint affection, are constituted by the AL form (immunoglobulin light chain, primary), AA (reactive, secondary), and amyloid β 2 microglobulin (related to hemodialysis). In the general population, AL form is the most frequent. According to one study, it is of approximately 4.5 cases for every 100 000 inhabitants. It usually appears after 40. It is considered to have a rapid progression with a short survival, when presenting multisystem affection. These patients often die 1 year after the diagnosis.² Our case shows that the progression, from the start to the development of evident manifestations, can go on for 20 years. Amyloid deposits are extensive and can be found on extracellular spaces and on blood vessels in all organs.

AL amyloidosis is caused by a dyscrasia of plasmatic cells of monoclonal predominance. It may be isolated or concomitant to myeloma. Kappa or lambda light chains, or their fragments constitute amyloid fibers. In over 90% of AL forms a monoclonal protein or a light chain can be found by immunofixation in the serum as an expression of plasmatic cell dyscrasia.³

In our patient, in spite of an increase in plasma cells in the bone marrow, we found none.

The traditional diagnosis of amyloidosis is based on the demonstration of amyloid fibers (Congo red stain) with green birefringence through polarized light. Treating the sample with potassic permanganate making the AA protein (but not the AL) and amyloid β 2 microglobulin loose their affinity for Congo red. Immunohistochemistry, currently used in a common manner, has achieved more precision.⁴ In our case, back then we could not obtain, unfortunately, this last determination. Nonetheless, AL deposits can bind the antisera in a non-specific form. Immunoelectronic microscopy⁵ and more specifically, the mass spectrometry microsequence of small sequences of protein extracted from the fibrin deposits⁶ are the most trustable. Nonetheless, these techniques are frequently unavailable.

In order to obtain the sample, the least invasive test is abdominal fat aspirate, which is positive in 80%-90% of AL or ATTR amyloidosis and in 70% of AA forms.⁷ In the systemic forms, almost any tissue is valid for finding an AL form. Our patient, with a positive biopsy in a target organ (tongue) and joint effusion, did not present criteria for myeloma, had no active infections, polyarthritis, nor renal failure, and her daughter was a healthy person, with

a negative subcutaneous abdominal fat aspirate. Therefore, we assumed that the patient had an isolated systemic primary AL amyloidosis.

In this form, clinically, there is fatigue and weight loss. Proteinuria is frequent but progressive renal failure is rare. Cardiac failure is usually the rule (characteristic echocardiogram), with congestive heart failure with or without a pleural effusion. There is peripheral neuropathy, carpal tunnel syndrome, autonomic dysfunction with intestinal motility disorders, and hypotension. Macroglossia is pathognomonic, though it is found only in 10% of the patients.

Hepatic and splenic enlargement, as well as skin ecchymosis, and nail dystrophias can be found. Amyloid infiltration of the scapulohumeral joints offer the typical "shoulder pad" aspect that can be seen in football players. Between 10% and 30% of patients with AL amyloidosis present a carpal tunnel syndrome, have bilateral affection, and usually precede the other manifestations of disease. Our patient, faced with a very early diagnosis, would justify the systematic study for amyloid of all of the apparently "idiopathic" carpal tunnel syndromes, which are surgically treated. Other causes must be taken into account (pregnancy, arthritis, Colles fracture, hypothyroidism, diabetes mellitus, acromegaly, drugs, forced, and repetitive movements of the hand and wrist). Our patient had presented a unilateral wrist fracture and the clinical data was bilateral.

Radiology can show erosive arthropathy, an increase in the subacromial space, chondrocalcinosis, and disk calcifications,⁸ as was the case.

Patients with amyloidosis usually die a year after diagnosis, when vital organs are affected.

This case shows that a wide therapeutic window can exist that allows for early treatment.

We currently know that treatment with cyclic melphalan and oral prednisone modestly increases survival. Intravenous melphalan at high doses, followed by an autologous stem cell transplant, is more effective.⁹ CHCP, which favors the dissolution of amyloid fibers of the P protein is under study.¹⁰

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