Systemic AL-k amyloidosis with lymph node, tracheobronchial, pulmonary and gastrointestinal involvement – a diagnostic and therapeutic challenge

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Abstract

Tracheobronchial and pulmonary involvement is uncommon in amyloidosis and it is not usually associated to its systemic forms. It is equally rare the presence of generalized lymphadenopathy as a form of presentation.

We present the case of a 75-years-old man with anorexia, weight loss and gastrointestinal complaints. At physical examination he had sparse rhonchi in pulmonary examination and an abdominal mass. Image exams showed abdominal adenopathies extending to the thorax and a micronodular pattern on both lung fields. Transbronchial biopsy showed hyaline material compatible with amyloidosis; similar findings were made in a peripheral adenopathy and in an abdominal fat pad biopsy. The bone marrow aspirate and biopsy were normal, and there were no monoclonal peaks in serum and urinary immune-electrophoresis. The immunohistochemistry revealed positivity for k light chains. Treatment was started with melphalan and prednisolone. The patient died six months later due to mesenteric ischemia. Pathological examination revealed interstitial and vascular amyloid deposits.

Key words: Amyloidosis, Trachea, Bronchi, Lymph nodes, Intestines, Diagnosis, Therapeutics.

INTRODUCTION

Light-chain amyloidosis (AL) is the most common form of systemic amyloidosis in industrialized countries, with an annual incidence of between five and twelve cases per million people.[1,2]

The amyloidogenic protein in AL amyloidosis is a light chain of an immunoglobulin or a fragment of an immunoglobulin produced by a monoclonal population of plasmacytes in the bone marrow.[3] It is typically a population with a low degree of proliferation and a cell load of around five to ten percent.[4,5] All classes of light chains can cause AL amyloidosis, but while the highest proportion of plasmacytes in normal bone marrow express k chains, λ light chains are involved in amyloid deposition two to three times more often than k chains.[3,6]

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The clinical spectrum of AL amyloidosis depends on the number and nature of organs affected. Clinical data suggests that factors related to their own proteins are probably involved in the creation of local conditions that may promote fibrillogenesis and mediate tissue damage.[4] Besides the physical effect on the tissue architecture caused by the mass of amyloid deposits, the formation of amyloid fibrils, by itself, has a direct cytotoxic effect, regardless of the amount of amyloid deposited.[6]

The most common clinical presentations of AL amyloidosis at diagnosis are nephrotic syndrome with and without renal failure (thirty percent of patients), restrictive cardiomyopathy (twenty percent of patients), and hepatomegaly (twenty-five percent of patients). Amyloid infiltration may also occur in other organs, particularly in the skin and soft tissue, vocal cords, glandular structures, lymph nodes, lungs, bone, articulations, and any other organ, with the exception of the brain.[1]

CASE REPORT

We describe the case of a male patient, Caucasian, seventy-five years of age, a retired carpenter, who was admitted to the Emergency Service with epigastric abdominal pain, nausea, vomiting, and watery diarrhea without blood, with about twelve hours of evolution.

TABLE I

Laboratory values at admission

Erythrocytes (x10^{12}/L)	4,92
Hemoglobin (g/dL)	12,7
Hematocrit (%)	39,3
MCV (fL)	79,9
MCHC (g/dL)	32,3
Leukocytes (x10^{9}/L)	12,7
Neutrophils (%)	87,8
Lymphocytes (%)	6,1
Eosinophils (%)	0,2
Basophils (%)	0,1
Monocytes (%)	5,6
Platelets (x10^{9}/L)	368
PT (sec.; normal 11.5)	13,6
APTT (sec.; normal 29.5)	24,9
Sodium (mmol/L)	137,0
Potassium (mmol/L)	2,8
Glucose (mg/dL)	161,0
Urea (mg/dL)	46,0
Creatinine (mg/dL)	1,1
Total bilirubin (mg/dL)	0,46
AST/GOT (U/L)	16,0
ALT/GPT (U/L)	14,0
Alkaline phosphatase (U/L)	48,0
Amylase (U/L)	34,0
Lipase (U/L)	15,0
LDH (U/L)	187,0
Proteins (g/dL)	6,9
Albumin (g/dL)	3,9
C-reactive protein (mg/L)	46,50
Urine type II	Normal

He described episodic fits of dyspnea, with wheezing, with onset five years earlier, which were alleviated with the use of bronchodilators. He reported anorexia and weight loss (10 kg) in the previous three months. For the investigation of these complaints, associated with rectorrhages, an outpatient colonoscopy was performed revealing level I hemorrhoids disorder and multiple congestive foci along the length of the rectum, with hematic "slime" in the passage of the colonoscope. An upper digestive tract endoscopy was also performed, with evidence of a hiatal hernia, reflux esophagitis, and moderate antral gastritis with marked mucosal friability and foci of erosion.

On admission the Emergency Services, the physical exam highlighted the presence of abnormal breathing sounds, with occasional ronchi, and the existence of an abdominal mass in the right para-umbilical region that was painful to the touch. The rest of the physical exam was normal. The analytical results are shown in *Table I*.

The lung x-ray showed elevation of the right dome of the diaphragm associated with homolateral paracardiac hypotransparency *(Fig. 1)*.

The electrocardiogram showed a sinus rhythm with a left anterior fascicular block and occasional isolated extrasystoles.

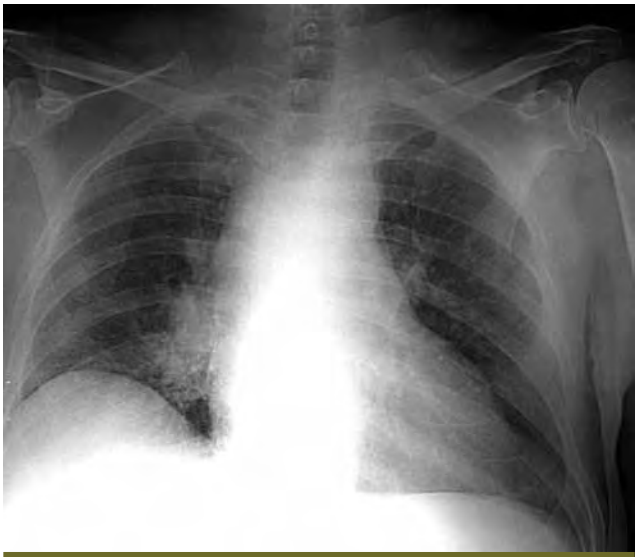
An abdominal ultrasound showed the presence of an echogenic mass in the supra-umbilical region, surrounding the blood vessels, with several more pronounced echohypogenic nodular areas.

The imaging study was complemented by an abdominopelvic CT scan in which the presence of multinodular mesenteric densification, following the route of the blood vessels, was confirmed, with similar images of both the lateroaortic area and the mesosigmoid, associated with calcifications suggesting adenopathies.

The patient was admitted to the Service of Internal Medicine for treatment of suspected acute gastroenteritis and continuing diagnostic investigation.

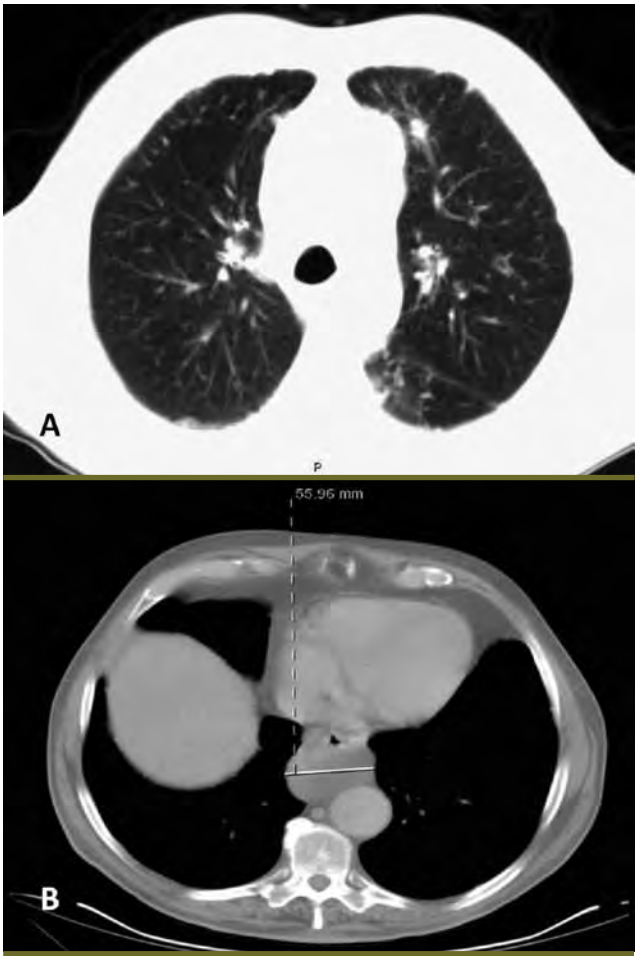
A thoracic CT scan showed calcified adenopathies along different groups of mediastinal and hilar region lymph nodes, some of them forming clusters. The pulmonary parenchyma presented a diffuse micronodular pattern, with some subpleural lymph nodes standing out in the upper third of both lung fields *(Fig. 2)*.

The analytical study was normal for serum β2-microglobulin, ACE, and immunoglobulins. Serum ADA was 31.9 U/L and the Mantoux test produced a skin reaction greater than 15mm in diameter. Both direct and cultural exams of the broncho-aveolar lavage performed later were negative for microbacteria. Bacteriological and parasitological stool exams were negative, as were the viral blood tests (CMV, Epstein Barr, VHB, VHC e HIV1 e 2).



Chest x-ray.

FIG. 1



Thoracic CT scan. A – Pulmonary parenchyma with micronodular pattern; B – Mediastinal adenopathy.

FIG. 2

The Doppler echocardiogram showed mild aortic insufficiency. The heart chambers were normal, as was the thickness of the ventricular walls. It showed hypokinesia of the lower wall, with preserved global systolic function.

A bronchofibroscopy of the bronchial aspirate was negative for neoplastic cells. A bronchial biopsy, showed perivascular, interstitial, and periglandular deposits of hyaline material, which when stained with Congo red, displayed birefringence compatible with a diagnosis of amyloidosis.

Biopsies of both abdominal fat and an inguinal lymph node were performed. In both samples, amorphous infiltrates with characteristics similar to those of the infiltrates present in the bronchial tissue were found.

Electrophoresis of serum proteins did not produce monoclonal peaks and there were no free light chains found in either serum or urine immunoelectrophoresis. Immunofixation did not reveal any monoclonal increase of light chains. The myelogram and bone marrow biopsy showed cell elements in balanced proportions, without any abnormal elements in the marrow.

Immuno-histochemistry performed on biopsy samples of subcutaneous tissue was positive for type κ immunoglobulin light chains.

A diagnosis of systemic AL-k amyloidosis with lymph node, tracheobronchial, and pulmonary involvement was established. A treatment regimen of melphalan and prednisolone was instituted and the patient was referred to Medical Oncology.

The patient died of mesenteric ischemia six months after starting therapy. The exploratory laparotomy to which the patient was submitted showed various segments of the small intestine with necrosis, and several segmental enterectomies and an appendectomy were performed. Death occurred as the result of the postoperative complications of nosocomial pneumonia. The anatomopathological examination of surgical specimens showed necrotic ischemic transparietal enteric lesions. Perivascular and interstitial deposits of amorphous material, birefringent with Congo red staining, as well as vascular thickening from material

with the same characteristics, were observed in the more preserved sections of the specimens.

DISCUSSION

The first goal in the investigation of a patient with suspected amyloidosis should be to confirm the diagnosis in a tissue biopsy. In the case presented, pathognomonic birefringence of the bronchial biopsy sample under polarized light was diagnostic.

Unlike multiple myeloma, in amyloidosis the concentration of monoclonal light chains is often too small to be detected by simple protein electrophoresis, making the use of electrophoresis with immunofixation necessary. In the case presented, and even using this method, the presence of monoclonal light chains could not be demonstrated, a situation that may occur in around 20% of patients.[1] The use of a nephelometric immunoassay (which enables the quantification of light chains with sensitivity ten times higher than electrophoresis with immunofixation[3]) might have been an alternative.

After documenting the presence of amyloidosis, AL must be confirmed. In order to adequately characterize the amyloidosis, and since antibodies exist against most amyloidogenic proteins, the authors opted for the use of immunohistochemical techniques, which leads to definitive diagnoses in about fifty percent of patients.[1,5] When a definitive characterization of the amyloid protein is not achieved using immunohistochemistry, specific genetic tests using PCR, direct sequencing of protein fibrils, or analysis using mass spectrometry may be able to determine the type of amyloid fibril, and are available in specialized centers.[1,7]

Even when a monoclonal light chain is identified in the serum or urine, and amyloid deposits are confirmed by immunohistochemistry, it is essential to perform a bone marrow biopsy to evaluate the plasmacytic load and eliminate the possibility of multiple myeloma or other less common diseases associated with AL amyloidsosis, such as Waldenström's macroglobulinemia. The coexistence of AL amyloidosis deposits is identified, at admission or at any other time during the course of the disease, in approximately ten to fifteen percent of patients with myeloma.[1,3]

After a diagnosis is obtained, evaluation of the extent of amyloid deposits is desirable and important for establishing the prognosis, outlining treatment strategies, and monitoring the response to them.[3]

In the case presented, a diagnosis was first established following a bronchial biopsy for the investigation of a profile of multiple adenopathies and diffuse pulmonary nodules. Caution must be used in diagnosing pulmonary AL amyloidosis, since pulmonary and tracheobronchial amyloidosis are both manifestations of localized amyloidosis. Additionally, systemic amyloidosis with pulmonary involvement usually presents as a diffuse interstitial pattern, with or without pleural effusion, which was not the situation in the case described.[8] As such, diagnosis requires a biopsy or evidence of amyloid deposit in another organ.[7] Given the ease of access and the need to perform a lymph node biopsy, the excision of an inguinal adenopathy and concomitant biopsy of subcutaneous tissue was performed, enabling a diagnosis of systemic amyloidosis.

Diagnosis of the disease in the gastrointestinal tract is often difficult to differentiate clinically from the autonomic symptoms that patients may be present, such as diarrhea, nausea, early satiety, and weight loss.[1] Documentation of intestinal involvement may be obtained via colonoscopy and biopsy, and in almost eighty percent of patients only vascular amyloid deposits are observed.[7] In the case presented, the diagnosis of vascular and interstitial intestinal involvement, demonstrated by alterations present in the endoscopic studies of the digestive tract and by the episode of intestinal ischemia, which may have been responsible for the symptoms of diarrhea and weight loss, was confirmed in a surgical specimen.

Aside from these organs, renal, cardiac, hepatic, and central nervous system (peripheral and autonomic neuropathy) involvement must always be assessed.

Following diagnosis and evaluation of the extent of amyloid deposit, it is important to establish a treatment plan. Currently, treatment of amyloidosis focuses on the reduction of the formation of amyloid via suppression of the production of the precursor fibril. Thus, in systemic AL amyloidosis, treatment includes, besides support therapy, the use of chemotherapy targeted at dyscrasia of the underlying B cells, with the objective of reducing the production of amyloidogenic light chains.

There are multiple therapeutic strategies, and the one chosen must be appropriate for the degree of proliferation and the general condition of the patient concerned. The use of high doses of melphalan in

combination with autologous stem cell transplant has demonstrated better survival, hematological response, and functional improvement of the affected organs than those reported with any other treatment regimen. The main obstacle to this strategy is the limited eligibility of patients, given the associated high rates of morbidity and mortality.[2,9]

One alternative that has received considerable attention lately is treatment with oral melphalan with high dose dexamethasone (*Mel-dex*). The initial results report rapid eradication of the production of monoclonal light chains.[9,10]

There are recommendations[1] that advocate the use of other therapies, specifically regimens of combinations like VAD (vincristine, Adriamycin, and dexamethasone) or intermediate doses of melphalan and dexamethasone. However, data collected since their publication favors the use of regimens of melphalan and dexamethasone.[9,10,11]

The use of oral melphalan in combination with prednisolone may be an option for patients who are unable to withstand more aggressive treatments.[1] This regimen has shown prolonged survival, from 8.5 to 18 months, when compared with patients treated only with colchicine.[12] Despite its good tolerability, it is effective in only twenty-five percent of patients and it may take months for a clinical and clonal response to occur, therefore, patients with rapidly progressive disease may not survive long enough to derive any benefits.[11]

The option of treatment with melphalan and prednisolone was selected, taking the age and functional state of the patient at time of diagnosis into account, and was based mainly on a principle which differentiates treatment prescribed for AL amyloidosis from that of multiple myeloma. While in myeloma emphasis is placed on the durability of the clonal response, which is associated with complete remission of the disease, in AL amyloidosis a partial clonal response may stop the deposition of amyloid and even lead to regression in certain patients. Attempts to achieve complete clonal response may cause serious toxicity and even death, especially in patients who are not in a fit state to undergo more aggressive treatments. The risk of using melphalan and prednisolone is that the progression of the disease may occur so rapidly that the patient dies as a result of progressive amyloid deposition before there is a response to the treatment. ■

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