Pleural AA amyloidosis preceding the diagnosis of inflammatory bowel disease

Amioloidosis AA pleural que precede el diagnóstico de una enfermedad inflamatoria intestinal

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ABSTRACT

Pleural amyloidosis constitutes a rare presentation of a rare disease. We report a case of amyloidotic pleural effusion that preceded the diagnosis of inflammatory bowel disease by six months. The patient had a paucisymptomatic gastrointestinal disease but an exuberant AA amyloidosis that progressed to involve multiple organs, including lung, kidney and heart. Despite immunomodulatory treatment with corticosteroids and infliximab with good gastrointestinal response, the patient eventually passed away 2 years after diagnosis.

Keywords: AA amyloidosis, pleural amyloidosis, inflammatory bowel disease.

INTRODUCTION

Amyloidosis is characterized by the extracellular deposition of insoluble proteins in the form of amyloid fibrils. These insoluble proteins are the result of the misfolding of several different precursor proteins. The origin of the precursor protein defines the type of amyloidosis. AA amyloidosis (AAA) results from the misfolding of serum amyloid A (SAA), an acute phase protein produced mainly by hepatocytes.

CASE REPORT

A 62-year-old woman with a remote history of breast cancer presented to our Emergency Department with 5 days of dyspnea. She also reported 5 months of anorexia and intermittent diarrhea for several years, with up to 4 bowel movements per day, without mucus or blood and without abdominal pain. She had undergone a colonoscopy the previous year which had been normal. Physical exam was remarkable for absent breath sounds on the left hemithorax, low extremity edema and macroglossia.

Initial workup showed acute kidney injury with an elevated creatinine (1.2 mg/dL from baseline 0.8 mg/dL), elevated erythrocyte sedimentation rate (107 mm/1h) and C-reactive protein (147 mg/L), decreased levels of hemoglobin (7.9 g/dl, normocytic, normochromic) and serum albumin (2.8 g/dl). Urinalysis revealed non-nephrotic proteinuria. A computed tomography scan of the chest, abdomen and pelvis showed bilateral pleural effusions (Figure 1). A thoracentesis was performed, and pleural fluid studies demonstrated a non-purulent exudative effusion (per Light's Criteria), lymphocyte predominance (80%) and normal pH. There were no structural or functional heart changes on transthoracic echocardiogram. Pleural biopsy was performed, identifying AA type amyloid infiltration. The same type of amyloid was identified in a rectal biopsy taken during a sigmoidoscopy which did not identify any macroscopic abnormalities. *Mycobacterium tuberculosis* was not identified in either pleural or colon biopsies. Serum amyloid A protein level was 12.0 mg/dL (normal <6.0). A diagnosis of systemic inflammatory amyloidosis was established, with pleural and intestinal deposition and presumed renal involvement. The patient was treated with furosemide and was discharged with resolution of the pleural effusions and no dyspnea.

In the three months following her discharge, the patient underwent extensive investigation of the cause of her amyloidosis. Work-up included normal immunoglobulin and light chain levels, normal serum and urine electrophoresis and immunoelectrophoresis, and normal bone marrow biopsy. Whole-body scans did now show any evidence of malignancy, including focused breast studies (mammography, breast echography and magnetic resonance), which were not suggestive of cancer recurrence. HIV serology, tuberculin skin test and IGRA studies were negative. An upper endoscopy was done and the duodenal biopsy did not show signs of infection by *Tropheryma whipplei*. Cytomegalovirus DNA was not isolated from a colon biopsy. Auto-immunity work-up revealed a positive IgA anti-ASCA. A repeat colonoscopy 6 months later showed multiple new deep ulcers between the transverse colon and rectum with areas of uninvolved mucosa (Fig. 2). Histological analysis suggested inflammatory bowel disease, with glandular architecture distortion and inflammatory infiltrate extending to the *muscularis mucosa*e.

Figure 1. CT scan of Thorax showing left pleural effusion (arrow).

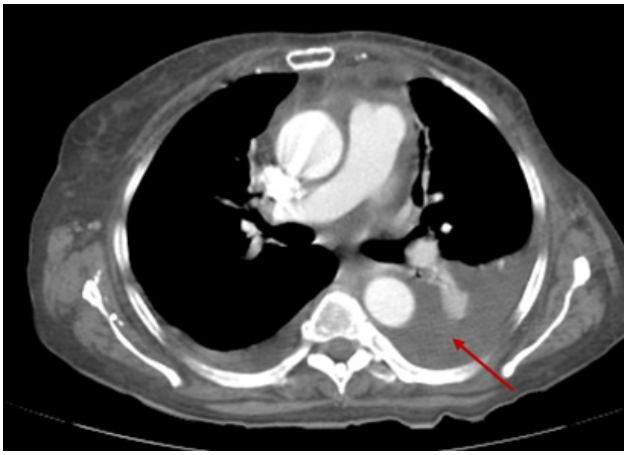

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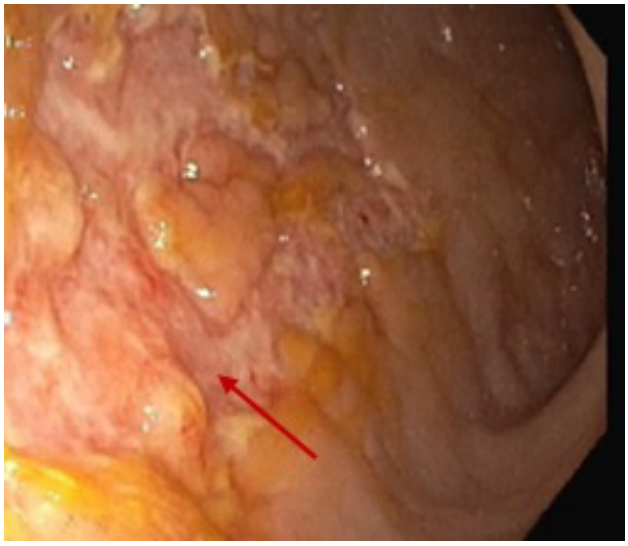
Figure 2. Colonoscopy showing colonic ulcers (arrow).



Immunomodulatory therapy was started with prednisolone 40 mg/day and mesalamine 3 g/day. Following treatment, calprotectin remained elevated and colonoscopy showed persistent colonic ulcers, prompting initiation of infliximab (5 mg/kg at weeks 0, 2 and 6, followed by 5 mg/kg every 8 weeks).

Early into immunomodulatory therapy, the patient experienced clinical deterioration with anasarca secondary to hypoalbuminemia and fulminant heart failure requiring diuretics. Following immunomodulators, albumin levels and fluid distribution stabilized, erythrocyte sedimentation rate normalized, and there was resolution of the colonic ulcerative lesions on repeat endoscopy.

Two years after the diagnosis the patient was admitted to our Emergency Department with acute heart failure. Transthoracic echocardiogram now showed signs of cardiac involvement by amyloidosis, with left ventricular hypertrophy with diastolic dysfunction and normal systolic function. A week into hospitalization she went into cardiac arrest. A do not resuscitate request was followed.

DISCUSSION

Chronic inflammation is associated with elevated levels of SAA. Different diseases can lead to chronic inflammation and subsequent AAA, notably chronic inflammatory arthritides, periodic fevers, vasculitides, chronic infections, neoplasia and inflammatory bowel disease[1]. Despite the long list of possible causes of AAA, this is a rare entity, and the majority of patients with these inflammatory syndromes do not develop AAA. It is not known why some patients develop AAA while others do not. One theory is that patients with poorly controlled inflammation are more likely to develop AAA[2]. Usually a diagnosis of AAA is made years after the primary disorder is diagnosed[2], and the symptoms result from dysfunction of the organs affected by amyloid deposition[1]. Virtually any organ can be affected by amyloidosis, but in AAA the kidney is most frequently involved, with nephrotic syndrome being the most common presentation. Diagnosis of AAA requires biopsy of the affected organ and relies on the appearance of an apple-green birefringence with polarized light and positive Congo red staining of the amyloid fibrils[1]. The management of AAA relies on the treatment of the primary inflammatory disorder. In the case of inflammatory bowel disease, anti-TNF drugs have shown positive results[1].

Our case is remarkable because the diagnosis of AAA preceded that of the paucisymptomatic inflammatory bowel disease by several months, and the initial presentation was characterized primarily by respiratory symptoms secondary to pleural involvement. Pleural amyloidosis is rarely reported. When present it is normally a sign of AL amyloidosis, another type of amyloidosis associated with plasma cell dyscrasia[3]. AAA with pleural involvement has been reported before[4], but there are no previous descriptions of inflammatory bowel disease associated with pleural amyloidosis. AAA diagnosis before of the causing disease is well described and, recently, investigation protocols were proposed[5]. The clinical significance of pleural amyloidosis is debatable. It is often difficult to discern whether it is the sole cause of pleural effusion, as the same patient can have concomitant heart failure and nephrotic syndrome secondary to amyloid deposition in the heart and kidneys[3]. In our case, the pleural effusion can be attributed to at least two factors: hypoalbuminemia with resulting lower plasma oncotic pressure and pleural deposition of amyloid with subsequent impairment of pleural fluid reabsorption.

CONFLICT OF INTEREST

No potential conflict of interest was reported by the authors

SOURCE OF FUNDING

This research had no funding sources.

ETHICAL ASPECTS

All participants submitted a consent form to be included in this study.

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