Case reports

PRIMARY AMYLOIDOSIS (AL) AS A CAUSE OF NEPHROTIC SYNDROME

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ABSTRACT

AL amyloidosis is a rare systemic disease resulting from tissue accumulation of amyloid fibrils derived from monoclonal immunoglobulin light chains. It can disrupt the tissue architecture and consequently cause organ dysfunction. The prognosis is poor with a median survival of 13 months in untreated patients.

By illustrating the case of a patient whose AL amyloidosis was detected after presenting a nephrotic syndrome, the characteristics of the disease are reviewed as well as diagnostic criteria and current available therapeutics.

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CLINICAL HISTORY

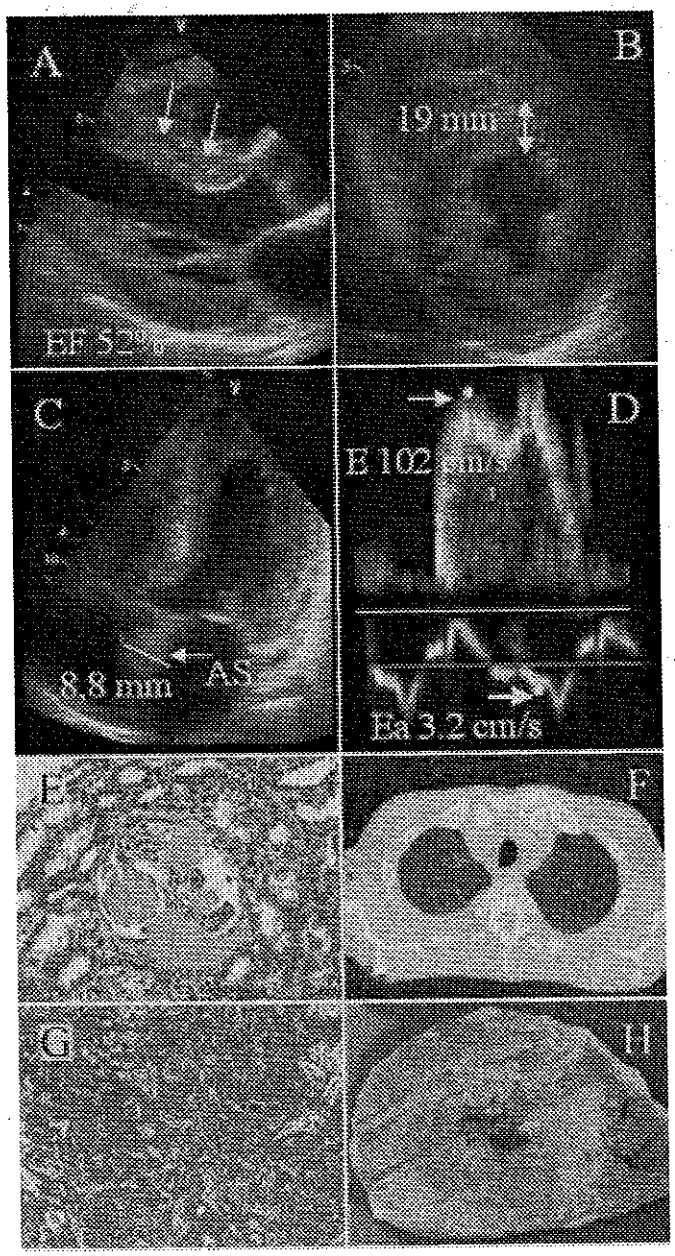
A 56-year-old man was referred for nephrotic syndrome. He complained of asthenia, weight loss, dysphagia, constipation, paresthesias and numbness of the legs. The past medical history included arterial hypertension and mild atheromatous disease of femoral arteries. Smoking was recently stopped. His usual medications were ASA, perindopril 2mg/day and recently furosemide 20mg/day. The clinical examination showed a normal weight patient (72.5 kg for 185 cm, B.M.I: 22.6 kg/m^2). The blood pressure was 140/74 mmHg without postural hypotension. The heart rate was 80 beats/min. Edema were noted in both lower limbs. Heart and lung auscultation were normal. No organomegaly or lymphnodes were noted. The neurological examination confirmed hypoesthesia and hyporeflexia of the lower limbs.

Blood analysis confirmed hypoproteinemia measured at 52 gr/l (N values: 65-85 g/l). The protein electrophoresis demonstrated decreased albumin and gammaglobulin and increased levels of alpha-2 globulins. Hypogammaglobulinemia was noted for all the immunoglobulin fractions. The c-ANCA, p- ANCA and antinuclear antibodies were negative. The complement fractions C3 and C4 were normal. Total cholesterol and triglycerides were increased at 2.96 gr/l and 2.48 g/L, respectively. Serum creatinine concentration was 9.6 mg/l (84 µmol/L) and creatinine clearance calculated by the Cockcroft and Gault formula was normal (88 ml/min/1.73 m^2).

Marked selective proteinuria of 8.5 gr was detected at the 24 hours urine collection. Bence-Jones proteinuria detection was negative. Renal biopsy was performed and showed amorphous, hyaline-like deposits,

mainly in the glomerulus (figure 1E), Congo red positive. No immuno-reaction for SAA protein was found but tissue specimen reacted with antisera to lambda light chains. Serum immunofixation was positive for low-level monoclonal IgM lambda and free light-chain lambda. A pattern of past antero-septal myocardial infarction was noted by electrocardiogram. Echocardiography revealed cardiac involvement (figure 1 A-D). Electroneuromyogram diagnosed axonal sensorimotor polyneuropathy compatible with amyloid neuropathy. Bone marrow biopsy contained mild plasmocytosis at 5.3% (N levels: 0-2 %). Skeletal X-ray didn't show bone lesions or general osteoporosis. Definitive diagnosis of primary amyloidosis (AL) was held. Treatment with autologous stem cell transplantation was decided. Few time after blood stem cell collection, the patient presented severe dyspnea and abnormal gas exchange. Chest C-T revealed an interstitial pattern (figure 1F). The lung biopsy confirmed interstitial amyloïd deposits. Finally, the patient developed a multiple organ failure and died 4 months after the diagnosis was held. Autopsy showed large amounts of amyloid in the chest alveolar septum (figure 1G), heart (figure 1H), kidneys, adrenals, gastrointestinal tract, liver, spleen and thyroid.

Figure 1:
A: Parasternal long-axis view showing typical "granular sparkling" of the myocardial wall, ejection fraction (EF) is quite normal.
B: Parasternal short-axis view showing concentric left ventricular hypertrophy.
C: Apical 4-chamber view demonstrating increased thickness of the atrial septum (AS).
D: Mitral inflow pattern and pulsed-wave tissue Doppler imaging obtained at the level of lateral mitral annulus: the ratio of early transmitral flow velocity (E) to early diastolic lateral mitral annulus velocity (Ea) is increased suggesting high filling pressure.
E: Microscopic view of the renal biopsy showing amorphous deposits mainly in the glomerulus.
F: Chest C-T showing interstitial pattern.
G: Microscopic view of the chest autopsy showing diffuse alveolar septal deposits.
H: Cut section of the heart showing a concentrically thickened left ventricle.



DISCUSSION

AL amyloidosis is the most frequent form of amyloidosis (70%) (1). Although it may complicate multiple myeloma, AL amyloidosis is often associated with a low burden of clonal plasma cells (2). Incidence of the disease is 8.9 cases per million person-year. Its occurrence is rare before the age of 40 years (2). Amyloidosis constitutes a group of diseases in which misfolding of extracellular protein has a prominent role. This dynamic process generates insoluble, toxic protein aggregates that are deposited in tissues in bundles of β-sheet fibrillar protein (3). In AL amyloidosis, substitutions of particular aminoacids at specific positions in the light-chain variable region destabilize light chains, increasing the likelihood of fibrillogenesis (1, 3). All amyloid deposits contain serum amyloïd P (SAP), a plasma glycoprotein that binds amyloid and protects deposits against proteolysis. Proteoglycans are also common in amyloid deposits facilitating fibril formation and having a role in the localisation in selective tissues (3). The clinical manifestations of the disease are extremely variable depending on the organs

predominantly involved and the extent of tissue deposition (2). Three quarters of the patients have involvement of multiple organs at presentation with, in order of frequency, kidneys (46%), heart (30%), liver (9%), gastrointestinal tract (7%), peripheral nervous system (5%) and soft tissues (3%) (3).

Renal amyloidosis usually manifests as proteinuria, often resulting in a nephrotic syndrome. Development of end-stage renal disease is common (1, 2). Hypertension is rare except in long-standing amyloidosis (2). Cardiac involvement may lead to cardiomegaly, congestive heart failure and different rhythm disturbances. The electrocardiographic findings include low voltage and, often, a pattern of myocardial infarction. Echocardiography usually reveals a concentric thickening of the left ventricule (1, 2). Increased myocardial echogenicity with "granular sparkling" appearance is very specific of the disease (2). In this patient, there were no cardiac symptoms in spite of echocardiographic findings. Among clinical gastrointestinal manifestations, disturbances in motility as dysphagia, constipation or diarrhea are not rare (2). In this case, the patient complained of constipation and dysphagia for a few months. To exclude another cause of dysphagia, a gastroscopy was performed and was negative. Hepatomegaly is common in patients with AL amyloidosis but frequently asymptomatic. In contrast, splenomegaly is a rare observation but the deposition of amyloid may lead to functional hyposplenism (2). Motor neuropathy is rare. Nevertheless, sensory neuropathy can be present, usually as a distal to proximal and symmetric pattern. Autonomic neuropathy is frequent and characterized by orthostatic hypotension, bladder dysfunction and impotence (2). In the course of the disease, severe orthostatic hypotension developed in our patient, leading to a dramatic reduction of diuretics. Vascular infiltration results in easy bruising, which is typified by the "raccoon-eyes" sign of spontaneous periorbital purpura (1). Macroglossia is a classic feature of amyloidosis and can produce a hoarse or weak voice (1), recently reported in this case by our patient. Pulmonary amyloidosis rarely causes symptoms, despite the fact that is a common autopsy finding. Dyspnea, though usually due to congestive heart failure, may infrequently be due to widespread pulmonary amyloidosis associated with a reticulonodular pattern on the chest x-ray film (1).

The diagnosis of amyloidosis is established by tissue biopsy of specific organ involved. Another procedure is to obtain a sample of subcutaneous abdominal fat (sensitivity 72%; specificity 99%) (4). The presence of amyloid is usually confirmed by a green apple birefringent aspect after Red Congo staining. Amyloid deposition must be distinguished between immunoglobulin-derived (AL), which is the most common form of amyloidosis, and reactive (secondary, AA) or familial, of whom transthyretin-associated (ATTR) amyloidosis is the most common type (1). Among AL diseases, the distinction between primary and myeloma-associated amyloidosis is based on criteria for the diagnosis of multiple myeloma. Primary amyloidosis is characterized by low concentrations of monoclonal immunoglobulins in the serum and/or urine (2). Monoclonal immunoglobulins or light chains are detected in 90 percent of patients with AL amyloidosis by means of immunofixation electrophoresis of serum or urine (1). A new marker, serum free light chains assay, is more sensitive than serum or urine immunofixation to detect free immunoglobulin light chain (5). The bone marrow biopsy usually shows an occult, often dispersed plasma cell proliferation in primary amyloidosis (2). A clonal dominance of plasma cells will be identified by immunohistochemical staining (1). Whole-body scintigraphy after the injection of ^{123}I-serum amyloid p component (SAP) can be used for diagnosing, locating and monitoring the extent of systemic amyloidosis (6).

The prognosis of amyloidosis is poor with a median survival of 13 months in untreated patients (7). Survival of patients with AL undergoing autologous stem-cell transplantation is prolonged to 54 months (8). This therapy presents many problems such as the optimal selection of eligible patients and very high transplantation-related mortality (7). Recently, a competitive inhibitor of SAP binding to amyloid fibrils has been developed. This compound leads to very rapid clearance of the SAP molecules by the liver and could provide a new therapeutic approach (9). In the future, the development of immunotherapy based on both active vaccination with fragments of light chains and passive immunization with amyloid-reactive antibody is expected (7).

This clinical history of primary amyloidosis is an interesting illustration of a multi-systemic disease. Because of the poor prognosis of this affection, a rapid evaluation of the extension of deposition and the etiology should be searched. Autologous stem-cell transplantation is the current optimal therapeutic approach. However, promising treatments are currently developed and evaluated.

RESUME

L'amyloïdose primaire (AL) est une maladie rare qui résulte de l'accumulation tissulaire de fibrilles amyloïdes dérivées de chaînes légères d'immunoglobulines monoclonales. Le dépôt de grandes quantités de matériel fibrillaire peut bouleverser l'architecture tissulaire et par conséquent causer une dysfonction organique. Le pronostic de la maladie chez les patients non traités est mauvais puisque la survie médiane est de 13 mois. A travers l'histoire d'un patient chez qui une amyloïdose AL a été détectée suite à une présentation clinique de syndrome néphrotique, nous revoyons les caractéristiques de la maladie, ses critères diagnostiques et les traitements disponibles.

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