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.

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/m²). 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 gr/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 m²).

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,

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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 plasmacytosis 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 amyloid 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.

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 fibrillogensis (1, 3). All amyloid deposits contain serum amyloid 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.

Figure 1:
A: Parastrernal long-axis view showing typical "granular sparkling" of the myocardial wall. Ejection fraction (EF) is quite normal.
B: Parastrernal 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 transmirtal 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 anoporous 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.

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predominantly involved and the extent of tissue deposit-

ion (2). Three quarters of the patients have involve-

ment 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). Hyperten-
sion is rare except in long-standing amyloidosis (2).

Cardiac involvement may lead to cardiomegaly, con-
gestive heart failure and different rhythm disturbances.

The electrocardiographic findings include low voltage

and, often, a pattern of myocardial infarction. Echocar-
diography usually reveals a concentric thickening of

the left ventricle (1, 2). Increased myocardial echo-
genicity with "granular sparkling" appearance is very

specific of the disease (2). In this patient, there were no

cardiac symptoms in spite of echocardiographic find-
ings. 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 gas-
troscopy was performed and was negative. Hepatome-
galy 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 hypoplasmenism (2). Motor neuropat-

hy is rare. Nevertheless, sensory neuropathy can be

present, usually as a distal to proximal and symmetric

pattern. Autonomic neuropathy is frequent and charac-
terized by orthostatic hypotension, bladder dysfunction

and impotence (2). In the course of the disease, severe

orthostatic hypotension developed in our patient, lead-
ing to a dramatic reduction of diuretics. Vascular infil-

tration results in easy bruising, which is typified by the

"raccoon-eyes" sign of spontaneous petechial 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 amy-

loidosis 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 tis-

tue biopsy of specific organ involved. Another proce-
dure 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 bire-
fringent aspect after Red Congo staining. Amyloid de-
position must be distinguished between immunoglobu-
lin-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 charac-
terized by low concentrations of monoclonal immu-

noglobulins 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 immu-

nohistochemical staining (1). Whole-body scintigraphy

after the injection of 123I-serum amyloid p component

(SAP) can be used for diagnosing, locating and moni-
toring the extent of systemic amyloidosis (6).

The prognosis of amyloidosis is poor with a me-

dian 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 com-
petitive 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.

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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.

REFERENCES