

Amyloidoses as seen by the Rheumatologist

Le amiloidosi d'interesse reumatologico

J. Ch. Gerster

Professore di Reumatologia, Università di Losanna

Amyloidosis is due to extracellular deposition in various organs and tissues of amorphous materials made of protein fibrils, whose thickness is 10 nm. Seventeen different amyloid fibrils are known (1). Amyloidosis can be localised or systemic. There are 4 systemic amyloidoses (2):

Familial amyloidosis with mutated transthyretin.
Primary, paraprotein associated, amyloidosis AL.
Secondary AA amyloidosis in long-standing inflammation.

β_2 -microglobulin (β_2 -m) amyloidosis associated with chronic renal dialysis.

On Table 1, the main characteristics of the 3 systemic amyloidoses which can be seen by the rheumatologists are presented.

Correspondance to:

Proseur Jean-Charles-Gerster, médecin-chef. Service de Rhumatologie et Réhabilitation, CHUV, 1011 Losanna, Svizzera,
E-mail: Jean-Charles.Gerster@chuv.hospvd.ch.

AL AMYLOIDOSIS (PRIMARY)

It is the commonest type of systemic amyloidosis. Its incidence is 10 cases per million person-years. Amyloid fibrils in AL amyloidosis are fragments of immunoglobulin light chains produced by clonal plasma cells (2). It is myeloma associated in 20% of the cases and idiopathic (monoclonal gammopathy) in 80%. It is more common in men than in women; the average age at onset is 60 years. Affected organs are the kidney, the heart, subcutaneous tissues, the muscles (macroglossia), the nerves (polyneuropathy), the gut, the liver and the spleen. There can be vascular infiltration leading to haemorrhages and bruising. Bilateral carpal tunnel syndrome is observed in 20% of the cases (3). A polyarthritis resembling rheumatoid arthritis (RA) is reported in 5% (3, 4). In the hands, changes like scleroderma (when subcutaneous tissue and joints are involved) can be seen (5).

Table 1 - Main characteristics of the systemic amyloidoses.

Type of amyloidosis	Precursor protein	Clinical features	Main sites of deposition
AA (secondary)	Serum amyloid A protein	Chronic inflammation (RA, ankylosing spondylitis, Still's disease...)	Subcutaneous fat Rectum Kidney Heart
AL (primary)	Kappa or Lambda light chains	Myeloma (20 %) Idiopathic (80 %)	Subcutaneous fat Rectum Bone marrow Synovium Bone
$\text{A}\beta_2\text{-m}$ (chronic hemodialysis)	$\beta_2\text{-m}$ microglobulin	Carpal tunnel syndrome Bone cysts Joint and disc destruction	Synovium Peri-articular tissues Bone

In synovial fluid, which is paucicellular, synovial fragments containing amyloid deposits stained with Congo red have been described (6).

Osseous amyloid which is present in 8% of cases (3) can cause large bone geodes; pathologic fractures can result (7, 8). Severe upper cervical destruction has developed in one case (9). Laboratory studies for diagnosis are immunofixation electrophoresis of serum and urine. The final diagnosis is established by a tissue biopsy. A fat aspirate stained with Congo red will be positive in 85% of patients with AL amyloidosis (10), whereas biopsy of other involved organs will confirm the diagnosis in the remaining 15%. AL amyloidosis is as fatal as the worst cancers (1, 11). The gold standard treatment at present is melphalan-prednisolone. A derivate of doxorubicin (IDOX) combined with stem cell transplantation might improve survival of this deadly disorder (1, 11, 12).

AA AMYLOIDOSIS

The AA amyloid is composed of the N-terminal fragment of serum amyloid A. It is associated with long-standing infectious or non-infectious inflammatory diseases. AA amyloid deposition does not involve the locomotor system but organs such as the kidney, the heart, the subcutaneous fat and the rectum which are commonly affected. It was diagnosed in 5,8% of 1666 patients with RA (13); some cases have been observed in severe ankylosing spondylitis (14) and Still's disease. Proteinuria is the most common presenting symptoms (60% of cases) (13) followed by progressive renal failure (18%) (13), which can require chronic haemodialysis.

The diagnosis of AA amyloidosis is dependent on demonstration of amyloid in biopsies (e.g. of abdominal subcutaneous fat aspirates, rectum or kidney). A scintigram with iodine¹²³ labelled SAP component is useful in some cases to identify affected organs, quantify the deposits and monitor the disease over time (15). However availability of this investigation is limited at present. Decreasing acute phase reactants by giving medication such as alkylating agents (1) might be effective in slowing the development of AA amyloidosis. In a study of 34 RA patients with amyloidosis, the time with a satisfactory renal function was longer in the 12 patients on cyclophosphamide or chlorambucil than in the 22 patients who received neither agent (16).

AMYLOIDOSIS β_2 -M

High serum levels of β_2 -m are due to failure of dialysis membranes to metabolise this product. As a result, as many as 50% of the chronic haemodialysis patients suffer from β_2 -m amyloidosis after 10 years (17). The most common expression of β_2 -m amyloidosis is tendinous (carpal tunnel syndrome) articular and skeletal (7). Serum protein electrophoresis is normal. On X-rays, large cystic lucencies can be observed (19). On magnetic resonance images, amyloid deposits appear as masses with a low T₁ and T₂ signal intensity (7, 18). A destructive arthropathy of the wrist, hip joints (19), cervico-occipital hinge (20) or spine (21) can be seen. Amyloid deposits are detected on histological examination, including Congo red stain, in synovium, tendons, ligaments or bones. On the other hand, subcutaneous fat and rectum wall are not involved. Surgical therapy (decompression of carpal tunnel, joint arthroplasty) may be needed. As dialysis membrane has been suggested as a contributor to β_2 -m amyloidosis, highly biocompatible membranes should be used. However renal transplantation remains the most effective treatment of dialysis arthropathy. A functional allograft results in a rapid lowering of serum β_2 -m and improves the disease (22).

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