

Case report

Is amyloid A (AA) amyloidosis always secondary?

C P J MAURY, T TÖRNROTH, AND O WEGELIUS

From the Fourth Department of Medicine, University of Helsinki, Helsinki, Finland

SUMMARY The case is reported of a patient with systemic AA amyloidosis associated with non-specific mesenteric lymphadenitis and chronic sideropenia. Renal, small bowel, and rectal biopsies showed amyloid deposits containing AA protein, as defined by potassium permanganate sensitivity and by reactivity with AA antiserum. Reversal of the nephrotic syndrome occurred during steroid–azathioprine therapy.

Key-words: reactive amyloidosis, idiopathic amyloid A amyloidosis, nephrotic syndrome.

The underlying disease in reactive (secondary) amyloidosis is usually a rheumatic, chronic infectious, or neoplastic disorder,¹ all characterised by systemic inflammatory responses, including raised levels of the circulating putative amyloid A protein (AA) precursor, serum amyloid A protein (SAA). We report here a patient who developed systemic AA amyloidosis, which was not associated with any definable underlying chronic inflammatory disease. The clinical picture closely resembles that described by Pras *et al.*² as 'primary' or 'idiopathic' AA amyloidosis.

Case report

In 1981 a 40-year-old man was admitted to the University Central Hospital in Helsinki for evaluation of a nephrotic syndrome. The patient, a farmer with no family history of amyloidosis, had been healthy until 1970, when he was referred for hospital examination because of fatigue, mild microcytic, hypochromic anaemia (Hb 10.5 g/dl) and high erythrocyte sedimentation rate (63 mm/h). Initial examinations showed low serum iron concentration, subnormal total iron-binding capacity, slightly raised plasma cell count, and subnormal iron stores in the bone marrow but no paraproteinaemia or

Bence Jones proteinuria. Iron absorption was normal. In 1971 exploratory laparotomy was carried out because of a suspected pancreatic neoplasm. The

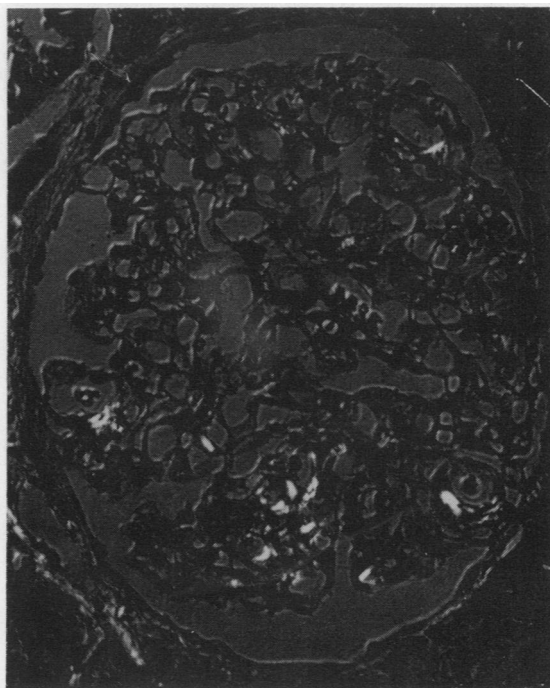


Fig. 1 Renal biopsy specimen showing small glomerular amyloid deposits (light areas). (Congo red, polarised light, $\times 300$).

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Correspondence to Dr C P J Maury, Assistant Professor of Medicine, Fourth Department of Medicine, Helsinki University Central Hospital, Unioninkatu 38, SF-00170 Helsinki 17, Finland.

only abnormalities found were a slightly enlarged liver and multiple lymph nodes, 1–3 cm in diameter, in the small bowel mesentery. Microscopic examination of the mesenteric modules showed non-specific lymphadenitis with no signs of amyloid deposits or malignancy. Following discharge from hospital the patient continued his work at the farm. Repeated examinations over the years revealed mild anaemia, hypoferraemia, raised sedimentation rate (40–100 mm/h), and slightly increased alkaline phosphatase, predominantly of hepatocellular origin. Laboratory examinations for autoimmune and infectious disorders were repeatedly negative. Chest radiography and intravenous pyelography showed no abnormality. The patient received both oral and parenteral iron therapy. In 1980 proteinuria developed and the condition rapidly progressed to the nephrotic syndrome.

On admission in 1981 the patient had pretibial oedema and vesicular dermatitis on the elbows and knees. Immunohistological examination of skin biopsies showed deposition of IgA, complement, and fibrinogen in the lesions and in the perilesional skin; a diagnosis of dermatitis herpetiformis was made. The biopsies were negative to Congo red. A

slight polyclonal increase in immunoglobulin M was noted; no monoclonal serum component or Bence Jones proteinuria was recorded. Bone marrow examination showed no abnormality. Cultures for *Mycobacterium tuberculosis* from the bone marrow aspirate were negative. Chest radiography, x-rays of the skeleton, and bone scanning showed no abnormality. Amyloid was found in renal, small bowel, and rectal biopsies. Partial villous atrophy was seen in jejunal biopsy. The patient's HLA type was: A2; A11; B12, B15, Bw4, Bw6; Cw4; DR3, DR7. Treatment consisted of azathioprine (150 mg/day) combined with prednisone (40 mg/day–10 mg/day), in addition to diuretic therapy and a gluten-free diet.

Material and methods

HISTOCHEMISTRY AND IMMUNOHISTOCHEMISTRY

Biopsy specimens were fixed and processed routinely into paraffin. Sections were stained with haematoxylin and eosin and in selected cases with alcian-blue–periodic acid–Schiff reagent (AB–PAS)

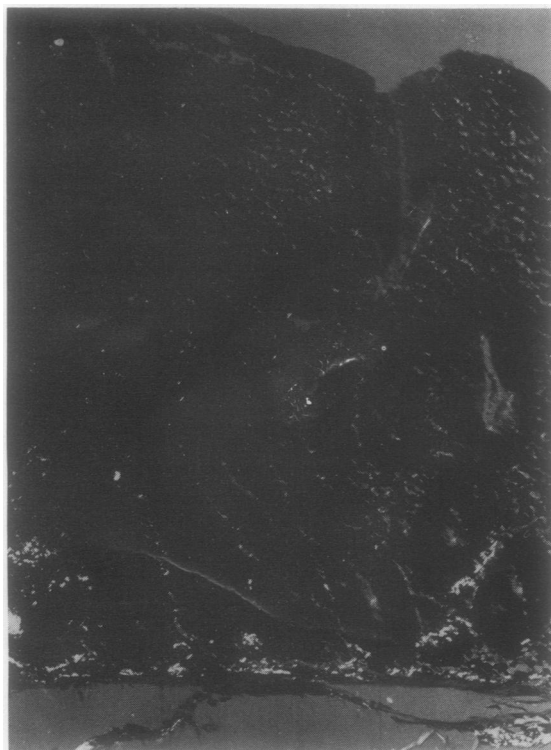


Fig. 2 Amyloid deposits (light areas) in the jejunal biopsy. Congo red, polarised light, $\times 140$.



Fig. 3 Section adjacent to that shown in Fig. 2 stained with anti-AA antiserum, showing dark reaction product over amyloid deposits ($\times 140$).

(jejunal biopsy) or with PAS, Masson's trichrome and periodic acid-silver methenamine (kidney biopsy). To show the amyloid deposits a series of consecutive sections were cut and stained as follows: (1) with alkaline Congo red;³ (2) with Congo red after treatment with potassium permanganate;⁴ and (3) with goat antihuman AA, by the unlabelled antibody peroxidase (PAP) method.⁵ Controls in the PAP method included omission of the primary antiserum and its replacement with normal goat serum. In addition known positive and negative control sections (AA and AL amyloid) were included.

AMYLOID-RELATED SERUM COMPONENT, SAA

SAA was measured from serum samples by radial immunodiffusion as described elsewhere.⁶

Results

Mesangial accumulations of amyloid were seen in most of the glomeruli in the renal biopsy (Fig. 1).

Amyloid was also present in arteriolar walls but not in larger vessels. The tubules were slightly atrophic and the interstitium focally fibrotic. The jejunal biopsy specimen showed partial villous atrophy and a moderate amount of amyloid located patchily in the muscularis mucosae and lamina propria (Fig. 2). In the follow-up biopsy specimen obtained after eight months of gluten-free diet considerable improvement in the villous architecture was seen; the amount of amyloid remained similar. In the rectal biopsy specimen moderate amounts of amyloid occurred in the walls of the submucosal blood vessels, in the muscularis mucosae, and segmentally beneath the surface epithelium. In the renal and gut biopsy specimens the amyloid lost its ability to be stained with Congo red after treatment with potassium permanganate and reacted specifically with anti-AA antiserum (Fig. 3).

Clinical reversal of the nephrotic syndrome occurred during steroid-azathioprine therapy: proteinuria decreased, serum proteins and cholesterol returned to normal, and oedema was resolved. These

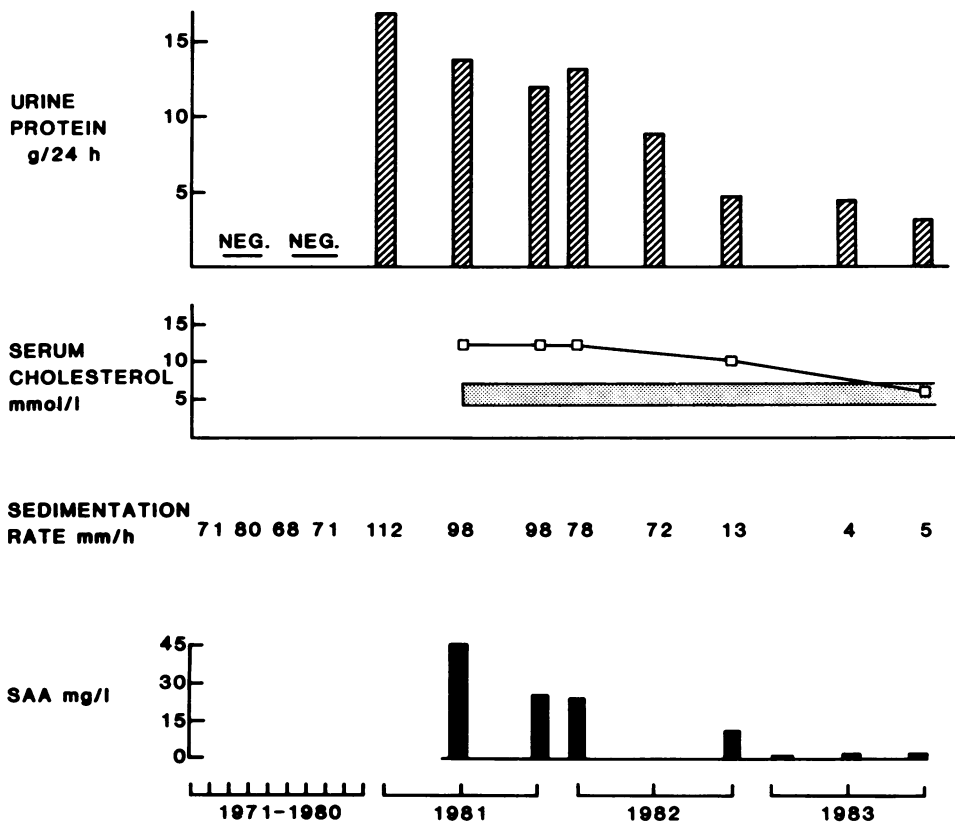


Fig. 4 Decrease in proteinuria and normalisation of serum cholesterol, SAA, and sedimentation rate during steroid-azathioprine therapy.

changes were accompanied by a return to normal of serum iron concentration and the SAA level (Fig. 4).

Discussion

The tissue distribution, histochemistry, and immunohistochemistry of the amyloid deposits in the present case justify the classification of the amyloid disease as AA amyloidosis. This type of amyloidosis occurs as a complication of inflammatory, infectious, and neoplastic disorders. Repeated examinations for such diseases were negative. Explorative laparotomy revealed multiple mesenteric nodes and enlarged liver but no other abnormalities. The lymph node morphology did not contribute to the diagnosis. In these respects the clinical picture of our patient resembles that described by Pras *et al.*² for a case of 'primary' or 'idiopathic' AA amyloidosis. Their patient had no definable underlying disease but like our patient had a markedly raised erythrocyte sedimentation rate, lymphadenopathy, and mild hepatomegaly and an elevated alkaline phosphatase level. Although clinically different from our patient's disease, it is of interest that AA protein was also reported in a Japanese patient with primary type amyloidosis.⁷

The resemblance of the clinical picture of our case with that of giant lymph node hyperplasia and amyloidosis^{8,9} is intriguing. However, lymph node morphology in our case lacked the characteristics of giant lymph node hyperplasia.

At the time of the development of the nephrotic syndrome dermatitis herpetiformis appeared. With respect to the formation of amyloid we believe that the dermatitis was unimportant, since it occurred late in the disease history; moreover in a preliminary study of 11 patients with dermatitis herpetiformis we found no amyloid in the jejunal biopsy specimens, and the concentration of SAA was not raised (unpublished). The amount of amyloid in the jejunal biopsy specimens was similar before and after gluten withdrawal, suggesting that the changes in villous architecture were not secondary to amyloid. The villous changes obviously relate to the dermatitis herpetiformis.¹⁰ Since no defect in iron absorption could be shown, the chronic hypoferraemia of our patient was probably not related to the villous changes.

The nephrotic syndrome responded to azathioprine-steroid treatment. Since renal biopsy

before therapy showed predominantly glomerular amyloid, and no other changes, the cause of the nephrotic syndrome was interpreted as being due to amyloid. Thus the present results suggest that immunosuppressive therapy may be beneficial in the treatment of renal manifestations of AA amyloidosis. However, the results should be interpreted with some caution, since spontaneous remission of nephrotic syndrome in renal amyloidosis has been reported.¹¹

In conclusion the present case could be classified as 'idiopathic' AA amyloidosis, but the justification for the use of such terminology seems questionable, since in spite of our failure to define an underlying chronic inflammatory disease in our patient several laboratory parameters could be interpreted as evidence for the existence of chronic inflammation.

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