

AA Amyloidosis and Systemic Lupus Erythematosus: an uncommon association

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■ ABSTRACT

Amyloidosis is one of the major causes of nephrotic syndrome in adults, mainly in older patients. It is caused by the accumulation of amyloid fibrils in the extracellular tissue and while there are several types of amyloid fibrils, serum amyloid A protein has been associated with chronic inflammatory diseases. The AA type of amyloidosis usually presents with proteinuria followed by renal failure.

Although systemic lupus erythematosus (SLE) is a well-known chronic inflammatory disease, there are only a few published papers that describe an association between SLE and amyloidosis. Little more than 25 cases expressing an association between AA amyloidosis and SLE have been described in English language medical literature over the last 40 years. It is not known why this association is so rare.

The authors describe a case of a 39 year old female patient who presented to the emergency room with complaints secondary to a nephrotic syndrome. During the diagnostic work up she presented more than 4 criteria of lupus (ACR Criteria), such as arthritis, serositis, renal disorder, haematologic disorder, antinuclear antibody and immunologic disorder, which led to the diagnosis of SLE. When a kidney biopsy was performed to obtain a histological confirmation of SLE, the diagnosis was AA amyloidosis. Investigation for a secondary cause of amyloidosis was negative, leading to a final diagnosis of AA amyloidosis secondary to SLE.

The authors gather together the scant information available and review the above issue.

Key-Words:

AA amyloidosis; chronic renal failure; proteinuria; systemic lupus erythematosus.

■ INTRODUCTION

Amyloidosis is a generic term which refers to a group of diseases secondary to deposition of fibrils made up of low molecular weight proteins derived from multiple types of serum proteins. AA amyloidosis is a subtype of amyloidosis derived from serum amyloid A protein and which has been associated with multiple chronic inflammatory diseases. Although several reports are available of cases of AA amyloidosis associated with rheumatoid arthritis, juvenile chronic arthritis, cancer and hereditary forms, SLE has not been classically described in association with AA amyloidosis, and the authors of this article are aware of only slightly over 25 cases described in English language medical journals over the last 40 years¹.

■ CASE REPORT

A 39-year old woman, with a four-year history of polyarthralgia under no follow-up or medication, was admitted to the local hospital complaining of chest

pain, fatigue after mild exertion and polyarthralgia of the hands. On physical examination she had eye and lower limb oedema and an atypical malleolar rash. There was no evidence of erosive changes in X-rays of the hands. Chest X-ray showed bilateral small pleural effusions. Before her admission she had no other complaints, and no previous hospital stays or physician consultations.

Laboratory investigation showed normochromic normocytic anaemia (8.9 g/dl), with positive Coombs test, thrombocytopenia (17000/mm³), without leucopenia, severe renal failure (creatinine 5.6 mg/dl and BUN 112 mg/dl), hypoalbuminaemia (2.1 mg/dl) and hypertriglyceridemia (1053 mg/dl). The 24h urine test revealed nephrotic-range proteinuria (9.3 gr/24h) and an active urinary sediment. Laboratory tests showed positive antinuclear antibodies (ANA) (1:360), positive Anti-dsDNA (151 U/ml) and normal complement levels. The abdominal ultrasound showed homogeneous hepatomegaly. Tests for HIV, HBV, HCV, VDRL, cryoglobulins, rheumatoid factor, anti-phospholipid antibodies, c-ANCA and p-ANCA were negative. Serum and urinary immunoelectrophoresis were normal. The blood cultures were negative.

The ECG was normal, but the echocardiogram showed a thickening of the anterior leaflet (vegetation?) of the mitral valve and it also suggested possible concentric left ventricular hypertrophy secondary to the deposit of material. Renal ultrasound showed normal sized kidneys, with increased ecogenicity and maintained differentiation, without hydronephrosis.

These clinical (presence of more than 4 American College of Rheumatology criteria) and laboratory results led to a diagnosis of SLE. This diagnosis, in tandem with the echocardiography findings with negative blood cultures, led the authors to consider a second diagnosis of Libman-Sachs Endocarditis.

A renal biopsy was performed to obtain a histological diagnosis of SLE and to classify the SLE in line with the World Health Organization (WHO) classification.

The renal specimen showed glomerular infiltrate with Congo red and green birefringence under polarised light. Immunohistochemical staining using an antibody against the AA protein showed positive

staining for amyloid AA, but not for amyloid fibrils (anti-AL and anti-TTR). The specimen did not show any changes (light microscopy or immunofluorescence) specific to SLE. The light microscopy also showed a high percentage (approximately 70%) of glomerular sclerosis. The measurement of SAA levels was not available.

During her hospital stay the patient experienced a prolonged period of vomiting and diarrhoea with deterioration of her nutritional condition, necessitating intravenous feeding. A colonoscopy and colonic biopsy was performed. Methylprednisolone pulses (1gr intravenous for 3 days followed by oral prednisone), double rennin-angiotensin system blockade with enalapril (20mg/day oral) and losartan (50mg/day oral), statins (simvastatin 20mg/day oral) and supportive therapy was started, but the patient began renal replacement therapy due to worsening of renal function, and never recovered renal function. The patient refused any cytotoxic therapy.

Non-specific malar alterations led to a skin biopsy being performed, despite a negative lupus band test (LBT) (no immune deposits were detected under immunofluorescence at the dermal-epidermal junction in the skin). The bowel biopsy showed amyloidosis, but failed to identify the sub-type.

The patient was released with a final diagnosis of AA amyloidosis, Libman-Sachs endocarditis and systemic lupus erythematosus. Her present clinical status is good and she is on dialysis three times a week.

■ DISCUSSION

Amyloidosis is a generic term that refers to a group of diseases secondary to the extracellular tissue deposit of fibrils. Nowadays at least 23 different protein precursors of amyloid fibrils have been identified. There are several types of hereditary forms, but amyloidosis is also secondary to other diseases. Amyloid fibrils are insoluble polymers composed of low molecular weight subunit proteins. These subunits are derived in turn from soluble precursors which undergo conformational changes that lead to the adoption of a predominantly antiparallel beta-pleated sheet configuration. Fibril formation is also associated with the co-deposit of other substances,

notably glycosaminoglycans, serum amyloid P-component and specific apolipoproteins. Cofactors may influence the deposit phase of amyloid in tissue, as well as resorption.

AA amyloidosis is associated with high SAA titration. The protein resulting from the delamination of SAA deposits on the glomerular mesangium and can be seen as a quite distinctive apple-green colour under refractory light after staining with Congo red. Nephrotic-range proteinuria is often the first sign of disease.

AA amyloidosis is known to be secondary to the presence of a chronic inflammatory disease. However, doubt remains as to why reporting of combined cases of SLE (a widely known chronic inflammatory disease) and AA amyloidosis is so rare.

While there are reports of associations between cutaneous lupus² or lupus localised in a given organ³ and systemic amyloidosis, the simultaneous presence of systemic lupus and amyloidosis has hardly been reported^{1,4}.

Serum amyloid component P (SAP) is a normal component of a number of basement membranes and belongs to pentraxin protein family (SAP and C reactive protein (CRP)). SAP interacts with nuclear ligands, including chromatin exposed by cell death, and has a role in the clearance of nuclear ligands from apoptotic and necrotic cells⁵. In humans, SAP is predominantly a physiological protein, although in the rat it acts as an acute phase reactant protein.

But why is SLE so seldom associated with amyloidosis?

A low level of amyloid P protein in SLE is one possible explanation for such a rare association. This assumption has already been discarded in previous studies⁶, however, and it is known that this protein does not act as an acute phase protein in SLE and that SAP levels do not fluctuate with disease activity.

Could it be that serum anti-protein P antibodies⁷ prevent the elevation of amyloid P protein and consequent formation of the amyloid tissue, thus preventing the pathogenic mechanism of amyloidosis from being triggered? It is known that SAP-DNA complexes are lower in patients with SLE than in healthy controls, and Zandman-Goddard *et al* proved that

anti-SAP antibodies titres are raised in patients with active SLE compared to those with inactive SLE, and they influence disease activity.

The fact that this association is extremely rare is also consistent with the fact that acute phase proteins such as “amyloid-A” and “C-reactive protein” do not increase during re-exacerbations. However, there are descriptions of elevated levels of secondary amyloid A protein in SLE⁸. Doubt prevails. While it can be taken for granted that this association exists, it is uncommon and we are still without an explanation for it.

The case presented by the authors is one of those rare reports. Despite a four-year history of polyarthralgias, the patient did not consult her doctor and was not under any treatment. During this period there were no complaints compatible with any other inflammatory disease.

During her stay in the hospital, the presence of six different criteria established by the American College of Rheumatology (arthritis, renal alterations, alterations of the erythrocyte series, alterations of platelets, immune alterations and presence of anti-nuclear antibodies) made lupus a more than likely diagnosis. In addition, the presence and high specificity of anti-dsDNA antibodies led us to make the diagnosis of Systemic Lupus Erythematosus.

The kidney biopsy showed no data compatible with SLE (no changes in optic microscopy or immune or complement deposits), but revealed the presence of amyloid AA.

Although the kidney biopsy was compatible only with amyloidosis, it also showed a high percentage (70%) of sclerosis, an indicator of a chronic condition. In this context the authors considered the presence of an advanced stage of SLE (probably grade VI of the WHO classification), without clear SLE renal histology. This situation is not new in literature; other cases have also been published in which kidney biopsy did not show any abnormalities that might support a pathological diagnosis of renal lupus³.

The presence of a negative LBT does not exclude the diagnosis of SLE, as this test has a low negative predictive value⁹, and a low sensitivity for SLE.

The authors report this clinical case to add to knowledge of this rare condition which associates AA Amyloidosis and System Lupus Erythematosus.

Conflict of interest statement. None declared.

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