AJNT

Case Report

Rheumatic Heart Disease Associated with Secondary Renal Amyloidosis

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Abstract

Introduction: Amyloidosis is a disorder of protein folding in which normally soluble proteins undergo conformational changes and are deposited in the extracellular space in an abnormal fibrillar form. Accumulation of these fibrils causes progressive disruption of the structure and function of tissues and organs, and the systemic forms of amyloidosis are frequently fatal. The conditions that underlie amyloid deposition may be either acquired or hereditary. Amyloid-A (AA) amyloidosis is the most common form of systemic amyloidosis worldwide, AA amyloidosis occurs in the course of chronic inflammatory diseases, hereditary periodic fevers, and with certain neoplasms such as Hodgkin disease and renal cell carcinoma. Amyloidosis due to rheumatic heart disease (RHD) is not common but can be seen. We report here a patient with RHD and AA renal amyloidosis.

Case Report: we present a 30 year-old Egyptian male with a history of RHD, accidently discovered to have nephrotic range proteinuria and rising serum creatinine. Serology studies were negative or normal, including antinuclear antibody (ANA) and antineutrophil cytoplasmic antibody (ANCA). C3 and C4 complement levels were normal. Kidney biopsy revealed AA renal amyloidosis. CT chest and abdomen revealed bilateral hilar and mediastinal lymphadenopathy and para-aortic lymph nodes. Endobronchial biopsy and bronchoalveolar lavage revealed non-specific chronic inflammatory changes. The patient's secondary amyloidosis was presumed to be related to the long standing RHD after exclusion of other causes of secondary amyloidosis. The patient finally died due to heart failure and acute pulmonary edema.

Conclusion: Long standing RHD can lead to secondary AA amyloidosis.

The authors declared no conflict of interest

Introduction

Amyloidosis is a disorder of protein folding in which normally soluble proteins undergo conformational changes and are deposited in the extracellular space in an abnormal fibrillar form. Accumulation of these fibrils causes progressive disruption of the structure and function of tissues and organs, and the systemic (generalized) forms of amyloidosis are frequently fatal. The conditions that underlie amyloid deposition may be either acquired or hereditary, and at least 20 different proteins can form amyloid fibrils in vivo [1].

Renal dysfunction is one of the most common presenting features of patients with systemic amyloidosis, and amyloid accumulation is the major pathological finding in approximately 2.5% of all native renal biopsies. Most such patients have either reactive systemic (AA) amyloidosis or monoclonal immunoglobulin light-chain (AL) amyloidosis, but in few cases, the disease is hereditary [2].

The spectrum of renal symptoms and signs in amyloidosis is variable such as isolated proteinuria, nephrotic syndrome, hypertension, hypotension and renal insufficiency. The kidneys are affected in almost all patients with AA amyloidosis but less frequently in AL amyloidosis [3].

Here we report a patient with long standing mitral and tricuspid valve disease due to rheumatic heart disease (RHD) and renal AA amyloidosis.

Case report

A thirty year- old Egyptian male with a history of mitral and tricuspid valve disease due to long standing RHD

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Figure-1: AA (amyloid A) amyloidosis. A: positive Congo red staining of the amyloid deposits in the mesangium and arterial walls. B: Pretreatment with potassium permanganate eliminates Congo red staining proving the AA nature of the amyloid.
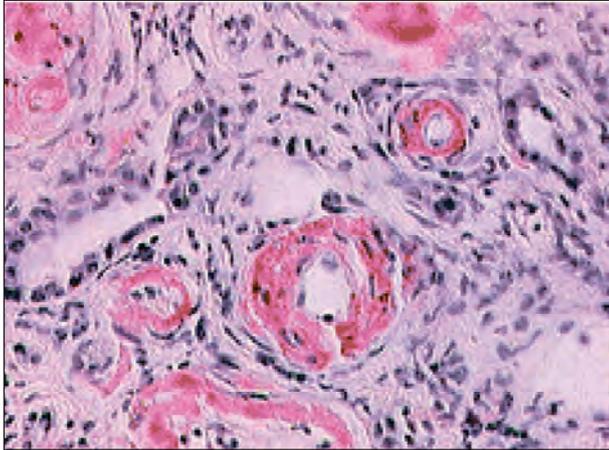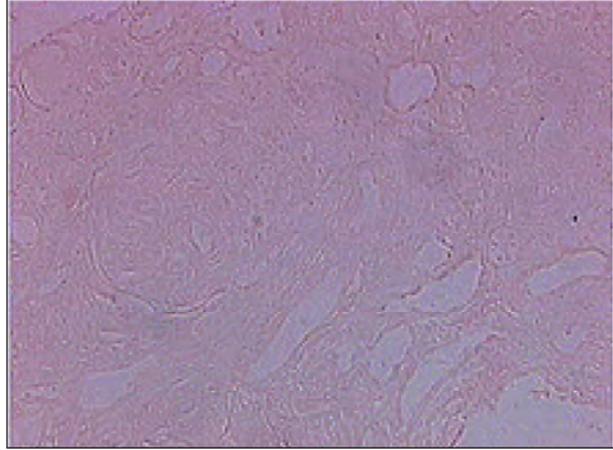
Fig.1A

Fig.1B

was discovered accidentally to have proteinuria and rising serum creatinine, while he was being prepared for mitral valve replacement. He had no history of diabetes mellitus, hypertension or tuberculosis. Physical examination revealed a well-developed male, with a blood pressure of 115/70 mm Hg, heart rate of 85 bpm and no raised jugular venous pressure. He had no palpable lymphadenopathy, apart from a small left inguinal lymph node. Examination of the lungs revealed normal vesicular breathing. Heart examination revealed a pansystolic murmur over the apex propagated to the axilla. There was no rub and no gallop. In the abdomen, the liver, spleen and kidneys were not palpable. There was no lower limb edema.

His laboratory data were as follows: hemoglobin 11 g/dL, WBCs 4.6x10⁹/uL, hematocrit 36%, platelet count 285x10⁹/uL, serum creatinine 1.2 mg/dL, blood urea 80.6 mg/dL, 24 hour urine protein 18 g/day, creatinine clearance 68 ml/min/1.7m². His serum aspartate aminotransferase (AST) was 18 U/L (normal range, 10–40 U/L); alanine aminotransferase (ALT) 16 U/L (normal range, 10–45 U/L), serum albumin 35 g/L, total calcium 8.8 mg/dL, ESR 54 mm/hr. Urinalysis revealed 4+ proteinuria and a bland sediment. Purified protein derivative (PPD) test was negative. Hepatitis C antibody and hepatitis B surface antigen were negative. All other relevant serological studies were negative or normal, including antinuclear antibody (ANA), antineutrophil cytoplasmic antibody (ANCA), and C3 and C4 complement levels. Serum and urinary protein electrophoresis were normal; there was no evidence of monoclonal antibodies in the serum or urine.

A chest radiograph showed clear lung fields with cardiac enlargement; electrocardiogram (ECG) revealed normal

rhythm and voltage, an echocardiography revealed mitral stenosis, mitral regurgitation, severe pulmonary hypertension, left ventricular ejection fraction (LVEF) 56% and no evidence of infiltrative disease. Abdominal ultrasound showed normal kidneys size, and maintained cortico- medullary differentiation. CT chest and abdomen revealed bilateral hilar and mediastinal lymphadenopathy and para-aortic lymph nodes. Endobronchial biopsy and bronchoalveolar lavage revealed non-specific chronic inflammatory changes and no evidence of acid fast bacilli. Fine needle aspiration of mediastinal lymph nodes revealed no malignancy or metastatic lesions, Congo red stain not done because the amyloid protein is deposited extracellularly and fine needle aspiration revealed cellular elements only. Transbronchial biopsy of mediastinal lymph nodes revealed no malignancy or metastatic lesions, but revealed amyloid deposits with the Congo red stain, as well as chronic inflammation. Bone marrow examination was normal.

Kidney biopsy recovered two cores of tissue, showing 16 glomeruli. The glomeruli showed diffuse mesangial and nodular deposits of amorphous hyaline material with focal near complete glomerular obliteration. The tubules showed vacuolization and there was mild interstitial inflammation. There was 30% tubular atrophy and interstitial fibrosis. Renal vessels showed deposit of amorphous hyaline material, the deposits showed apple green birefringence on Congo red stain and lost the birefringence on pretreatment with potassium permanganate (Kmno4) [Fig-1; A and B]. Immunohistochemical stains for IgA, IgG, IgM, C3, C4, Kappa and Lambda light chains were negative. The pathological diagnosis was secondary AA amyloidosis.

Mitral valve replacement was considered to have an inappropriately high risk because of severe pulmonary hypertension. The patient received conservative treatment in the form of lisinopril 20 mg/day, alphacalcidol 0.25 mcg/day, caltrate 600 mg twice daily, furosemide 40 mg daily and colchicine 1.5 mg twice daily. Colchicine was stopped after two months due to deteriorating kidney function and diarrhea. As there was no clinical evidence of rheumatoid arthritis or inflammatory bowel disease and after the exclusion of tuberculosis and malignancy, the patient's secondary amyloidosis was presumed to be related to the long standing rheumatic heart disease.

The patient presented nine months later with acute pulmonary edema, hypotension, potassium level of 7.0 mmol/L and serum creatinine concentration of 6 mg/dL. Urgent hemodialysis was initiated, but unfortunately the patient expired due to heart failure and acute pulmonary edema.

Discussion

Amyloid-A (AA) amyloidosis is the most common form of systemic amyloidosis worldwide. It is characterized by extracellular tissue deposition of fibrils that are composed of fragments of serum amyloid A (SAA) protein, a major acute-phase reactant protein, produced predominantly by hepatocytes. AA amyloidosis occurs in the course of a chronic inflammatory disease of either infectious or noninfectious etiology, hereditary periodic fevers, and with certain neoplasms such as Hodgkin disease and renal cell carcinoma [4].

In developing countries, the most common trigger of AA amyloidosis is chronic infection; in industrialized societies, rheumatic diseases, such as rheumatoid arthritis (RA), are the usual stimulus. The United States is a major exception to this in that immunoglobulin-related amyloid light chain type (AL) of amyloidosis is more frequent than AA as the cause of systemic amyloid deposition [5].

In AA amyloidosis, the kidney, liver, and spleen are the major sites of involvement. The tissue fibril consists of a 7500-dalton cleavage product of the SAA protein, an acute-phase protein produced in numerous tissues. The major source of the circulating protein is the hepatocyte. Under the influence of the inflammatory cytokine interleukin (IL-6), hepatic transcription of the messenger ribonucleic acid (mRNA) for SAA may increase 1000-fold when exposed to an inflammatory stimulus [5]. Intact circulating SAA (molecular weight 12,500 dalton) is complexed with high-density lipoproteins (HDL). During the course of inflammation, the apolipoprotein SAA (apoSAA) apparently displaces apolipoprotein A1 (apoA1) from the HDL particles and facilitates HDL-cholesterol uptake by macrophages [5].

Several lines of evidence have indicated that the conversion of SAA into amyloid fibrils occurs through its specific interaction with heparan sulphate, a ubiquitously expressed glycosaminoglycan component of the extracellular matrix [6].

In general, secondary amyloidosis shortened the median life span 7.7 years, and survival strongly depended on controlling the underlying inflammatory process. Amyloid deposits regressed in 60% of patients who had a median SAA concentration of less than 10 mg/L, and survival among these patients was superior to survival among those in whom amyloid deposits did not regress. Sustained increased concentration of SAA is the most significant risk factor in AA amyloidosis, whereas reduction of SAA concentration improves survival and is associated with arrest or even regression of amyloid deposits [7-9].

The degree of renal involvement is important, with patients who have elevated creatinine levels doing worse compared with patients with a normal creatinine levels. The pattern of renal involvement is also important. Specifically, glomerular involvement with amyloid and fibrosis appear to have clinical course characterized by deteriorating renal function compared to patients with other types of renal involvement. Generally, however the median survival is over 5 years [10, 11].

The CT findings of diffuse low-density nodal enlargement should prompt the possible diagnosis of associated amyloidosis, Lymph node involvement occurs in up to 37% of patients with systemic amyloidosis .The hilar, mediastinal, and para-aortic lymph nodes are most commonly involved [12]. Hodgkin lymphoma as a cause of secondary amyloidosis was excluded in this case by doing fine lymph node aspiration and biopsy.

Although amyloidosis secondary to collagen disease, in particular to Behcet's disease, is frequently reported, rheumatic heart disease (RHD) with amyloidosis is rare [13]. Paydas reported 59 patients with renal amyloidosis, one of whom had rheumatic heart disease who had been operated for mitral stenosis 14 years before [14].

In our case there was no clinical evidence of rheumatoid arthritis, inflammatory bowel disease, tuberculosis or malignancy. The patient's secondary amyloidosis and lymphdenopathy was presumed to be related to the long standing rheumatic heart disease.

Conclusion

A long standing inflammatory process such as RHD can lead to secondary AA amyloidosis.

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