

## Case Reports

### Secondary Amyloidosis Following Juvenile Chronic Arthritis

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Amyloidosis is a syndrome characterized by the deposition of amyloid, an insoluble proteinaceous material in the extracellular matrix of one or several organs, thus disrupting the structure and function of the organ. Secondary amyloidosis occurs as a potentially fatal complication of long standing poorly controlled inflammation(1). We report 2 cases of secondary amyloidosis in children with Juvenile Chronic Arthritis (JCA). One child presented as nephrotic syndrome and malabsorption and the other as refractory anemia.

#### Case Reports

*Case 1:* A 10-year-old girl, a known case of JCA for the last 8 years, presented in July, 1987 with generalized swelling of the body and loose stools for the last 3 months. On examination, she had polyarticular JCA, anasarca, angular stomatitis and anemia. Investigations revealed: Hb-10g/dl; TLC-13,000/cu mm; ESR-48 mm/1st h, 24 hours urinary protein -720 mg and normal renal functions. Schilling's test (97% with a maximum rise of 30 mg%), D-xylose test (0.3 g /5 g/ 5 hours) and fecal fat excretion

test (4.72 g/day) were abnormal. A kidney biopsy established the diagnosis of amyloidosis. Parents of the child opted out of therapy and she died shortly after diagnosis.

*Case 2:* An 8-year-old boy, presented in November, 1992 with polyarticular JCA. He had been symptomatic for 3 years and had been on irregular therapy. On examination, he had multiple small and large joint deformities, severe pallor and hepatomegaly. Investigations revealed: Hb-6 g/dl; reticulocyte count-0.1%; microcytic hypochromic type of anemia on the peripheral blood smear; TLC-14,000/ cu mm; DLC-N<sub>60</sub>L<sub>36</sub>M<sub>2</sub>E<sub>2</sub>; ESR-40 mm/ 1st h; total serum proteins 4.5 g/dl; albumin 2.0 g/dl; and normal total serum bilirubin, liver enzymes and alkaline phosphatase levels. Renal functions were normal initially but gradually worsened with progression of disease; 24 hours urinary protein was 4.6 g. Coagulation profile was normal at admission, but both prothrombin time and partial thromboplastin time were prolonged towards the terminal stage of the disease. Bone marrow examination showed depleted iron stores. Hence tests for malabsorption were performed. D-xylose test (0.4 g/ 5 g/ 5 hours) was grossly abnormal and an endoscopic duodenal biopsy revealed amyloidosis. He was initially treated for JCA with aspirin and started on chlorambucil after the diagnosis of amyloidosis was confirmed. The child needed multiple blood transfusions to treat anemia, which failed to respond to hematinics (oral as well as parenteral). Despite therapy, renal functions deteriorated, he developed bleeding diathesis, septicemia and died.

#### Discussion

Juvenile Chronic Arthritis (JCA) complicated by secondary amyloidosis indicates a grave prognosis for the patient, with renal failure often being the cause of death(1). The incidence varies from 0.1% in North America to 11% reported from Poland(2). Ansell *et al.* have reported an

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incidence of 7.4% in the United Kingdom (3). The incidence of secondary amyloidosis in India is not known.

Secondary amyloidosis is known to occur after 2-7 years of a chronic inflammatory process; however, an onset as early as 9 months of life is known(4). Amyloidosis in JCA is seen in the systemic and polyarticular types(5).

The pathogenesis of secondary amyloidosis is unclear. The protein subunit of reactive amyloid is termed amyloid A (AA). An increased production of the protein precursor SAA, appears to be a prerequisite in secondary amyloidosis. On the other hand, high serum concentrations of SAA reflects disease activity in chronic inflammatory states like JCA(6). However, neither the concentrations nor the pattern of raised SAA, predicts which of these patients would finally develop amyloidosis(7). The interactive factors seem to be genetically determined. Woo *et al.* reported a significant association between patients of JCA with amyloidosis and a DNA polymorphic site 5.6 kb upstream of the SAP gene, which may be in linkage disequilibrium with DNA sequence variations in either the promoter or coding regions of the SAP gene(8).

Secondary amyloidosis in JCA should be suspected if the patient develops nephrotic syndrome, proteinuria, hepatomegaly, malabsorption, severe anemia or bleeding diathesis(1). The refractory anemia in Case 2 was attributed to multiple factors like malabsorption, occult gastrointestinal bleed and renal failure.

Confirmation of diagnosis of reactive amyloidosis was till now by histopathological examination of renal, rectal or fat biopsies(1). Kidney biopsy may be hazardous because of the decreased contractility and elasticity of blood vessels due to deposition of amyloid and prolonged partial thromboplastin time and prothrombin time. Fine needle biopsy of subcutaneous abdominal fat and rectal

biopsy (which should include the submucosa) appear to be simple and well tolerated, but may have false negative rates of 20% and 15-25%, respectively(9-12). The light microscopic appearance of amyloid is an amorphous eosinophilic material which stains with Congo red and has a characteristic apple green birefringence under polarized light(1). In 1988, Hawkins *et al.* described a non-invasive method of evaluation of systemic amyloidosis by scintigraphy with I<sup>123</sup> labelled serum amyloid B (SAB) component(13). This may also prove useful in monitoring the course of the disease.

Till late sixties there was no effective treatment for amyloidosis. Dimethyl sulfoxide resulted in some improvement but the long term results were disappointing(14). Chlorambucil is now an accepted mode of therapy for amyloidosis(9). Chlorambucil cross-links DNA and proteins, thereby preventing cell replication. Ansell *et al.* compared the efficacy of chlorambucil with that of other cytotoxic drugs. The patients treated with chlorambucil (dose = 0.1 mg/kg/day) had 85% ten-years survival as compared to only 23.5% ten-years survival in patients on other drugs like azathioprine, cyclo-phosphamide or only therapy for JCA (NSAIDs, steroids, chloroquine, penicillamine, sulphasalazine). The higher percentage of survival is also attributed to better management of renal failure and infections(9). Chlorambucil though promising predisposes the patient to potential risks of malignancy and infertility, thus necessitating the search for a better drug. Colchicine has been used in amyloidosis secondary to Familial Mediterranean Fever. However, it is ineffective in amyloidosis due to JCA(15).

There are no clinical predictors as yet for the early diagnosis of amyloidosis in JCA. The emphasis is thus on close monitoring of patients of JCA for development of proteinuria by a simple 6-monthly dipstick test, in the hope that early intervention will lead to better therapeutic outcome.

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