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Case Report

AA amyloidosis presenting with acute kidney injury, curable or not?

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ABSTRACT

Background. Amyloidosis is a group of disorders with extracellular accumulation of autologous fibrillary insoluble proteins in various tissues and organs such as the kidneys, liver, spleen, heart and gastrointestinal tract leading to impairment of normal organ function. Childhood amyloidosis is an exceedingly rare entity mainly caused by familial Mediterranean fever (FMF) and the other autoinflammatory diseases such as mevalonate kinase deficiency (MKD).

Case. A 16-year-old male was referred to pediatric nephrology for coincidentally discovered proteinuria. He had no significant findings on physical examination except for urochromic color. He had nephrotic range proteinuria with 109 mg/m2/h and serum creatinine was 1.35 mg/dl. Kidney biopsy was performed because of nephrotic range proteinuria with acute kidney injury. In hematoxylin-eosin-stained tissue sections, amyloid was suggested as extracellular amorphous material that is lightly eosinophilic in the glomeruli. Diagnosis was confirmed by Congo red positivity, with apple-green birefringence under polarized light. MEFV gene mutation was negative and a compound heterozygote mutation found in mevalonate kinase gene. A 6-month-trial of colchicine, enalapril, and losartan combination was not successful; Canakinumab was started thereafter. Proteinuria and creatinine decreased to 7 mg/m2/h and 0.6 mg/dl respectively 4 years after treatment.

Conclusions. Amyloidosis should be considered especially in children presenting with proteinuria and with a history of recurrent fever. This report also emphasizes the efficacy of canakinumab to prevent or decelerate chronic renal failure in these patients although it does not reduce tissue deposition in long-term use.

Key words: amyloidosis, kidney injury, mevolonate kinase deficiency, canakinumab.

Nephrotic range proteinuria in the setting of acute kidney injury is a serious and alarming clinical problem. It can be secondary to acute glomerulonephritis, focal segmental glomerulosclerosis, infections, acute tubular necrosis, interstitial nephritis, nephrotoxic medications and renal vein thrombosis. One of these, renal amyloidosis is an exceedingly rare progressive disease in children caused by the deposition of insoluble amyloid fibrils. The diagnosis is confirmed by microscopic examination of faintly red amyloid fibrils on Congo red staining also showing typical apple-green birefringence under polarized light. Childhood amyloidosis is mostly in AA form, mainly caused by familial Mediterranean fever (FMF) and the other autoinflammatory diseases such as mevalonate kinase deficiency (MKD).[1]

MKD is an autoinflammatory disease characterized by recurrent episodes with fever, abdominal pain, mucoid and cutaneous lesions, conjunctivitis, and arthralgia. Episodes occur more frequently in children than adults and people with MKD may develop long-term complications including AA amyloidosis although it is rare in childhood period.[2]

In this report, a case with incidental nephrotic proteinuria diagnosed as amyloidosis after renal biopsy and diagnosed as MKD with a favorable response to canakinumab was presented.

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Case Report

A 16-year-old male presented with dry skin was referred to pediatric nephrology for coincidentally proteinuria. He denied any complaints including fever, fatigue, diarrhea, vomiting, cough and abdominal or joint pain with no notable past medical history. There was no consanguinity between parents and no known family history of kidney or inflammatory disease. On examination, he had urochrome color. The temperature was 36.9°C, the pulse was 85 beats/min, the blood pressure measured as 120/70 mmHg and the respiratory rate was 20 breaths/min. His body weight was measured as 57.1 kg (10-25 percentile), height as 164 cm (3-10 percentile). Other system examination was normal.

Laboratory tests revealed: serum urea 40 mg/dl (normal: 5-20 mg/dl), serum creatinine 1.35 mg/dl, uric acid 8.9 mg/dl (normal: 0-7.0 mg/dl), albumin 2.8 g/dl (normal: 3.8-5.4 g/dl), cholesterol 315 mg/dl (normal: 0-170 mg/dl). Other biochemical findings were normal as well as C-reactive protein (CRP), sedimentation rate (ESR), C3, C4, anti-nuclear antibody (ANA) and anti-double-stranded-DNA (anti-dsDNA) titers. Urinalysis showed 3+ proteinuria with no leukocytes, erythrocytes, and glycosuria. Nephrotic range proteinuria was confirmed by a 24-hour urine test (109 mg/m^2/h). Abdominal ultrasonography revealed increased renal echogenicity as grade 1.

Nephrotic range proteinuria with acute kidney injury indicated a kidney biopsy. In hematoxylin-eosin-stained tissue sections, amyloid was suggested as extracellular amorphous material that is lightly eosinophilic in the glomeruli, resulting in expansion of mesangial areas and thickening of capillary basement membranes. Tubular epithelium showed bubbly appearance due to protein resorption droplets (Fig. 1). No interstitial fibrosis or tubular atrophy was seen in biopsy specimens. The Congo red stain, special for the diagnosis of amyloidosis, showed reddish or intense orange deposits (Fig. 2). Diagnosis was confirmed by Congo red positivity, with apple-green birefringence under polarized light. Histologic identification of AA Amyloidosis was also performed using immunohistochemistry (Fig. 3).

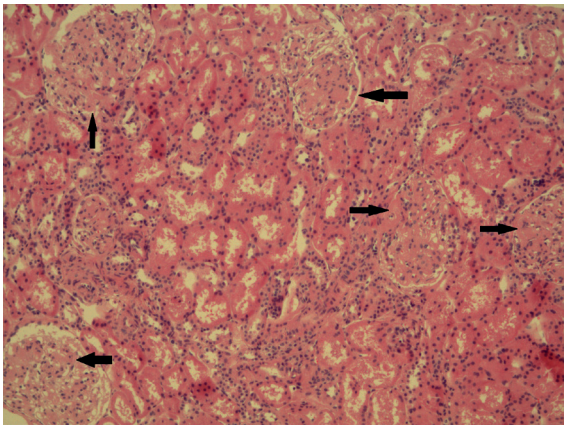

Fig. 1. H&E-stained tissue sections from first biopsy with amyloid, amorphous, acellular eosinophilic material in the glomeruli (hematoxylin and eosin, x100).

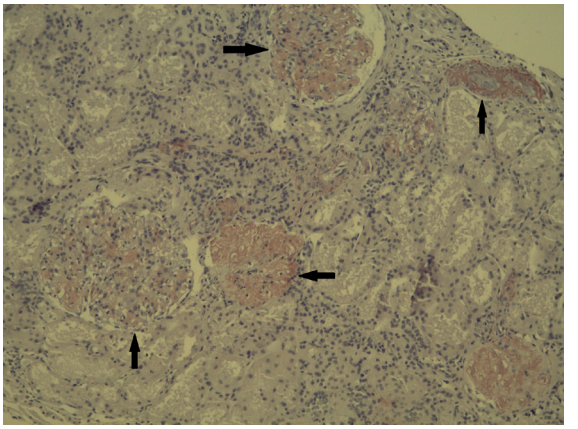

Fig. 2. Positivity with Congo red staining (Congo red, x100).

After the diagnosis of AA amyloidosis, M-mode echocardiography and tissue Doppler echocardiography was performed and showed no signs of systolic and diastolic dysfunction as well as hypertrophy. The additional laboratory workup revealed unexpectedly normal level of fibrinogen measured as 274 mg/dl and above normal level of serum amyloid-A (SAA) as 10.7 mg/L (normal <6.4 mg/L). Chronic infections including tuberculosis, brucella, salmonella, hepatitis A, hepatitis B, hepatitis C and human

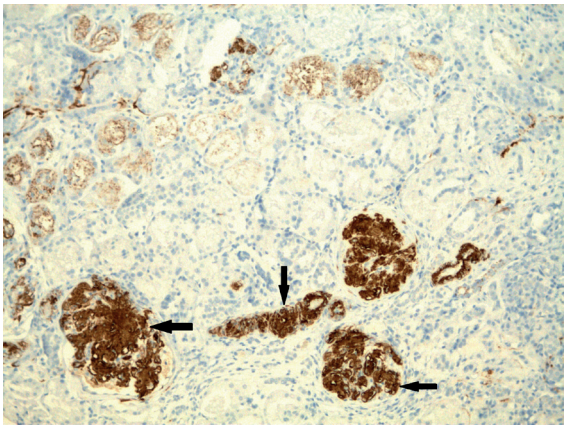

Fig. 3. Positivity with anti-AA immunohistochemistry (x100).

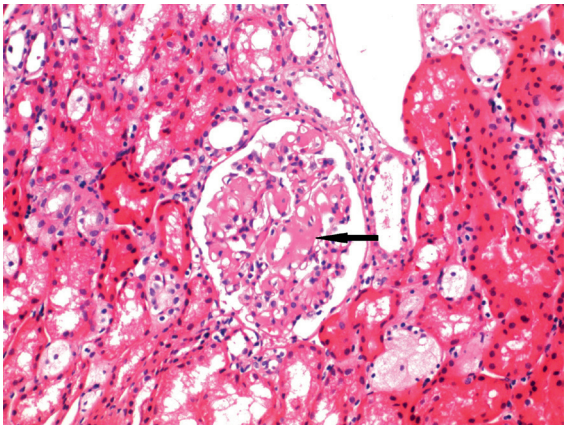

Fig. 4. Second biopsy after 4 years of canakinumab treatment with persisting amyloid accumulation (hematoxylin and eosin).

immunodeficiency virus (HIV) were ruled out by negative serology tests, negative PPD and normal chest X-ray. He had no relevant history of arthritis or arthralgia associated with rheumatoid arthritis or spondyloarthropathy with negative test results of rheumatoid factor (RF). Symptoms of FMF, the most frequent of all hereditary autoinflammatory syndromes, were reevaluated. Although there were no mentioned symptoms of an autoinflammatory disease or family history, insistent questioning revealed recurrent fever attacks every two weeks through infancy and chronic kidney disease in three relatives of the father. Genetic analysis of FMF revealed no *MEFV* gene mutation. A compound heterozygote mutation with p. Val377Ile (c.1129G>A) and p. Arg388*(c.1162C>T) variants in *mevalonate kinase gene* (MVK -NM_000431) was found.

Colchicine (2 mg/day), enalapril (10 mg/day) and losartan (25 mg/day) were given. There was no decrease in nephrotic range proteinuria after six months; and canakinumab treatment was started at monthly intervals as 150 mg subcutaneously. Nephrotic range proteinuria decreased to 48, 23.4, 15 and 7 mg/m^2/h through 7th, 9th, 36th and 48th months of the treatment, respectively. A control renal biopsy showed persistent tubular protein depositions, thick capillary basement membranes and expansion of mesangial areas (Fig. 4).

A written informed consent was received from the parents for the publication.

Discussion

Acute kidney injury (AKI), presenting with nephrotic range proteinuria , is a major and severe clinical problem especially in children older than 10 years old and kidney biopsy should be considered in these conditions. Since our patient was 16-year-old at presentation and he had massive proteinuria and acute kidney injury, kidney biopsy was performed immediately. Amyloid fibril deposits were identified with Congo red positivity and apple-green birefringence under polarized light in biopsy material and AA type was confirmed with immunohistochemistry.

Amyloidosis is a group of disorders with extracellular accumulation of autologous fibrillary insoluble proteins in various tissues and organs leading to impairment of normal organ function. AA type amyloidosis, probably the most common type in pediatrics, is associated with chronic inflammatory diseases such as FMF, juvenile rheumatoid arthritis, ankylosing spondylitis, inflammatory bowel disease, chronic infections such as tuberculosis, and chronic granulomatous disease.[3,4] Proteinuria may be the earliest clinical manifestation of AA amyloidosis in chronic inflammatory conditions

and may precede to nephrotic syndrome and renal insufficiency.[5] Although FMF was the most common cause of secondary amyloidosis in childhood, its incidence had decreased dramatically with colchicine therapy. However other autoinflammatory diseases like MKD and cryopyrin-associated periodic syndrome (CAPS) are becoming more frequent in the etiology of seconder amyloidosis. Common causes of AA amyloidosis such as tuberculosis, inflammatory bowel disease, juvenile rheumatoid arthritis, brucella, salmonella, hepatitis A, hepatitis B, hepatitis C, HIV and malignancies were excluded with appropriate diagnostic tests in our patient.

MKD is defined as a periodic fever syndrome (PFS) presented by periodic, recurrent fever caused by recurrent inflammatory episodes with autosomal recessive inheritance. Hyperimmunoglobulinemia D and periodic fever syndrome (HIDS) and mevalonic aciduria (MA) both result from mutations in the gene encoding mevalonate kinase (MK) and both are part of the MKD spectrum. They result from mutations in the gene encoding mevalonate kinase (MK).[2,6-9] Rare but the most devastating complication of the MKD is type AA amyloidosis.[6,10] Secondary amyloidosis due to MKD had been reported in 3% of patients, which is more rare than reported for the other monogenic autoinflammatory syndromes.[11,12] A review declared amyloidosis prevalence at about 6%[13], which is compatible with the 5% of MKD patients with amyloidosis in a recently published article in which the genotypes of 15 of the 17 patients included at least one p.(Val377Ile) variant similar with our patient.[14] p.(Val377Ile), which is the most frequent variant likely and mainly reported in MKD-HIDS, is also one of the heterozygote mutations described in our patient. Although the genotypes including p.(Val377Ile) (homozygous or compound heterozygous) are more frequent in mild systemic forms they are also sometimes related with severe disease leading to amyloidosis. Our patient had no systemic inflammation due to MKD at the diagnosis but infantile periodic fever history supports the systemic inflammation occurring through infancy which resulted as amyloidosis.

Colchicine treatment is the backbone therapy for the protection against amyloidosis in FMF whereas in other autoinflammatory syndromes such as MKD, this protection is often achieved with biologic treatment like anti-TNF, anti-IL-1 therapy.[1] In our case; although creatinine decreased immediately after treatment, proteinuria persisted within the nephrotic range for 6 months. Therefore, canakinumab was started at monthly intervals as 150 mg subcutaneously. After four years of canakinumab treatment, a major regression in proteinuria occurred whereas amyloid depositions persisted in control renal biopsy. Although there are previous reports claiming regression of proteinuria by biologic treatments, there is no evidence of ceased progression of amyloidosis at the tissue level.[1,5,15-17] The decrease in proteinuria may evoke regression of amyloid deposition. However, both Topaloglu et al.[16] and Yıldırım et al.[18] could not demonstrate a significant change in extent of amyloid accumulation in control renal biopsy even though there was complete remission of proteinuria, just like in our patient. They concluded that the incompatibility between clinical improvement and lack of change in amyloid deposition may be explained with the suppressed inflammation resulting in a decrease in glomerular permeability despite persistence of amyloid deposition.[16,18]

In this report it was emphasized that there was ongoing amyloid burden at tissue level in control biopsy performed four years after anti-IL1 therapy. Therefore, although canakinumab treatment has been shown to reduce proteinuria in these patients, it is unknown whether this treatment initiated after amyloid accumulation prevents chronic renal failure.

Ethical approval

A written informed consent was obtained from the parents for the publication.

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: BU; data collection: BU, BAV; analysis and interpretation of results: BU, BAV; draft manuscript preparation: BU, BAV. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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