IgA Nephritis in a Patient with Familial Mediterranean Fever: 5 Years-Follow-up

Ailevi Akdeniz Ateşi ile İzlenen bir Hastada IgA Nefriti: 5 Yıllık Takip

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ABSTRACT

Familial Mediterranean Fever (FMF) is an inflammatory autosomal recessive disease characterized by serosal and synovial involvement. Although secondary amyloidosis is the most common of the renal diseases observed with FMF, other glomerular involvements have also been demonstrated. Unfortunately only a few cases about IgA nephritis in patients with FMF have been reported in literature. Here we present a 56-year-old male patient who was diagnosed with chronic IgA nephritis by renal biopsy after detection of intermittent hematuria and proteinuria while he was being monitored for FMF disease. The patient was followed up for 5 years and treated with regular colchicine. Our case shows that amyloidosis is not only the type of renal involvement in patients with FMF. Kidney biopsy should be performed in patients with FMF displaying micro- or macroscopic hematuria with or without proteinuria.

KEY WORDS: Familial Mediterranean Fever, Renal involvement, IgA nephritis, Colchicine

ÖZ

Ailevi Akdeniz Ateşi (AAA) serozal ve synovial tutulumla karakterize inflamatuvar otozomal resesif bir hastalıktır. AAA ile birlikte en sık görülen böbrek tutulumu sekonder amiloidoz olmasına rağmen nadiren diğer glomerüler hastalıklarla da birliktelik tanımlanmıştır. Maalesef literatürde AAA ile IgA Nefriti nadiren bir arada tanımlanmıştır. Biz burada AAA tanısı ile izlenirken tekrarlayan hematüri ve proteinüri tespit edildikten sonra renal biyopsi yoluyla Kronik IgA Nefriti tanısı konulan 56 yaşındaki erkek hastayı sunduk. Hasta beş yıldır polikliniğimizde takip ediliyor ve düzenli kolşisin tablet kullanıyordu. Olgumuz AAA'lı hastalarda böbrek tutulumunun tek tipinin amiloidoz olmadığını göstermektedir. Proteinüri olsun ya da olmasın mikroskopik veya makroskopik hematüri tespit edilen tüm AAA'lı hastalarda böbrek biyopsisi yapılmalıdır.

ANAHTAR SÖZCÜKLER: Ailevi Akdeniz Ateşi, Böbrek tutulumu, IgA Nefriti, Kolşisin

INTRODUCTION

Familial Mediterranean Fever (FMF) is an autosomal recessive disease with unknown etiology. The MEditerranean FeVer gene (MEFV) which codes the pyrin or marenostrin genes has been shown on the short arm of the 16th chromosome (1-3). This gene is involved in the suppression of the inflammatory cascade mutations of the MEFV gene and has been shown to be responsible for the disease (4). The disease is characterized by recurrent episodes of fever, pleuritis, peritonitis, synovitis and pericarditis. The major complication of FMF is the development of renal amyloidosis leading to end stage renal failure and it remains the leading cause of FMF-related mortality (5-8). Colchicine was found to be an effective drug in the treatment of FMF (9).

Although amyloidosis is the most common of the renal diseases observed with FMF, other renal involvements have also been demonstrated. Mesangioproliferative glomerulonephritis (MPGN), mesangiocapillary GN, diffuse endocapillary GN, focal glomerulosclerosis (FGS), membranous GN, polyartheritis nodosa are the other glomerulary involvements (4).

IgA nephropathy is one of the primary glomerulonephritis showing no other systemic evidence, developing with asymptomatic hematuria and mild proteinuria (10-11). It is more frequent in males than females,

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occurring mostly in the third decade (12). Autoimmune reasons and past viral infections are usually blamed in the etiology (13). It may be accompanied by hypertension Definitive diagnosis is made by renal biopsy and demonstrating IgA precipitation in immunofluorescent stains of glomerular mesangium (14).

Here we describe a patient diagnosed with FMF presenting with intermittent hematuria and proteinuria during attacks, in whom kidney biopsy documented the presence of mesangial IgA deposits and the absence of amyloidosis.

CASE

A 56-year-old male patient presented with complaints of darkened urine in 2005. The patient had suffered from long-term arthritis, recurring abdominal pain and fever. He was diagnosed with FMF at the age of 33 and treatment was with a colchicine tablet 1.5 mg/day but the compliance was poor. Genetic examination of the patient revealed the homozygous M 694V / M694 V MEFV gene mutation.

On physical examination his blood pressure was 150/90 mmHg, without edema. Other physical examination results were unrevealing. The laboratory assessments revealed the following results; urea: 94 (10-50) mg/dL, creatinine: 2.0 (0.5-1.5) mg/dL, uric acid: 5.4 (3.4-7) mg/dL. Urinalysis showed Ph: 6, density: 1020, protein 1.125 g/day. There were many dysmorphic erythrocytes and many leucocytes in the urine sediment microscopically. The glomerular filtration rate (GFR) was 46.2 ml/min. Hemogram and erythrocyte sedimentation rate were normal. Serum antistreptolysin O titer, serum glutamate pyruvate transaminase, serum glutamate oxalacetate transaminase, lactate dehydrogenase, complement (C) 3, C4 were in normal range. Antinuclear antibody, anti-double-stranded DNA antibody, antiphospholipid antibody were negative. Serum immunoglobulin (Ig) levels (Ig G, M, E) were normal, while the IgA level was elevated at 477 mg/dl (70-400). Urinary system graphs were normal. Renal ultrasonography demonstrated increased renal parenchymal echogenicity. No abnormal sign existed in cystoscopy and intravenous pyelogram except for the small bleedings in the vesical wall mucosa. Amyloid was negative at rectal biopsy.

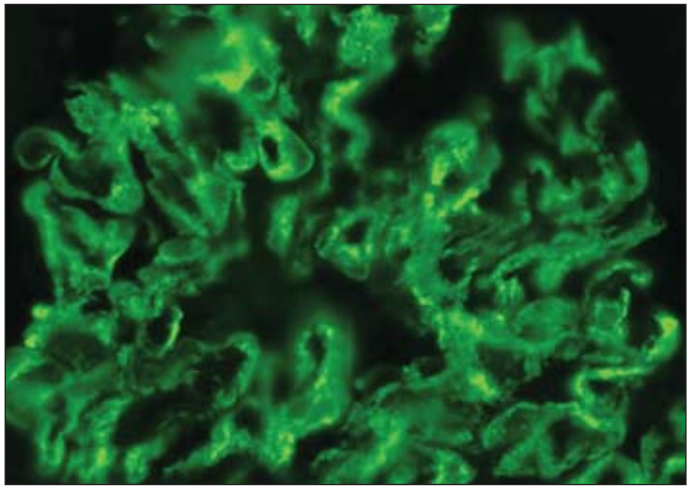

Figure 1: *Renal biopsy demonstrating mesangial IgA deposits.*

Renal biopsy was reperformed due to the haematuria, proteinuria and renal function disorders. Most of the glomeruli showed global or segmental (6/12 and 4/12 respectively) sclerosis on microscopic examination. Increased mesangial cells and matrix were seen in non-sclerotic segments. In addition, tubular atrophy, interstitial fibrosis, inflammation and hyaline arteriosclerosis were present. No amyloid accumulation was detected by the congo red stain. Immunofluorescent microscopy revealed strong IgA and C3 positivity both on basement membranes and in the mesangium (Figure 1). These findings were interpreted as Chronic IgA Glomerulonephritis.

The patient was monitored for 5 years and treated with regular colchicine. Hypertension was detected and an ACE inhibitor was started. Fish oil and antilipidemic treatment were added to the treatment. His recent urea and creatinine levels were 100 mg/dl and 2.3 mg/dL respectively. GFR was 40 ml/min. Urinalysis result were Ph: 6, density: 1018, protein 0.7 g/day. There were few dysmorphic erythrocytes and many leucocytes in the urine sediment microscopically. By this time he did not need dialysis. He had incomplete clinical recovery without recurrent FMF symptoms during his follow-up.

DISCUSSION

FMF is an autosomal recessive disease characterized by recurrent and self limited attacks of fever usually accompanied by polyserositis. FMF may represent a potentially fatal disease related to a high incidence of renal amyloidosis that worsens its prognosis. Due to increased inflammatory response observed in FMF, immunological glomerular injury, a common cause of glomerulonephritis, may occur more frequently in patients with FMF (3-9, 15).

The frequency of renal involvement varies among the different populations with FMF (16). Since a large proportion of all the FMF patients in the world live in Turkey, the Turkish FMF Study Group (FMF-TR) was founded to develop a patient registry database. The cohort in that study was composed of 2838 patients and followed for 7 years. Amyloidosis was still remarkably frequent in that group of patients (12.9 %) and twenty-two patients (0.8 %) had nonamyloid glomerular diseases (17). The studies from Israel and Arab countries show quite variable incidence of amyloidosis ranging from 0 to 26.5 % in patients with FMF (18-19).

Unfortunately, nonamyloidotic glomerulonephritis associated with FMF is poorly documented. There are no satisfactory epidemiological and treatment outcome reports.

Eliakim et al. described renal manifestations of 106 patients with FMF showing 12.3 % had renal amyloidosis and 21.7 % renal damage other than amyloidosis (20). Similar to

the Turkish FMF Study Group, this report showed various types of glomerulonephritis such as mesangioproliferative, mesangiocappillary, IgM nephropathy, and vasculitis including both polyarteritis nodosa (PAN) and Henoch Schonlein purpura to occur in the FMF population as well with variable prevalence (17,20). Both Flatau et al. and Cagdas et al. described patients with FMF who developed MPGN in the absence of renal amyloidosis (21-22). Tekin et al. described four patients with FMF presenting symptoms of vasculitis. Renal biopsy revealed focal proliferative glomerulonephritis and MPGN in this group of patients (23).

IgA nephropathy is the most common primary glomerulopathy and a significant proportion of affected patients progress to end stage renal disease (24). A few cases of IgA nephritis in patients with FMF have been reported in the literature. Rigante et al. reported a patient with FMF where the kidney biopsy documented the presence of mesangial IgA deposits and absence of amyloidosis (25). Said et al. reported two patients diagnosed with FMF and IgA nephritis treated with colchicine who were not taking drugs regularly before the GN diagnosis. They had significant improvement at 3-6 months after regular treatment (26). In a recent study, Gok et al. described a patient with FMF who presented with gross hematuria and protracted febrile myalgia. The kidney biopsy of this patient revealed the presence of mesangial IgA deposits and absence of amyloidosis and continuous colchicine treatment induced remission (24).

Colchicine is the most used agent in the management but there is not much evidence that it alone would be sufficient to treat FMF-related glomerulonephritis (24). Only one case was reported cured with colchicine alone (22). However, regular colchicine treatment may have a protective role for GN to prevent FMF attacks and amyloidosis (24).

To our knowledge, the patient presented by this report is the longest followed case in the literature. He was treated with regularly colchicine and had stable renal functions. Does regular colchicine treatment have a protective role in a patient with FMF complicated by GN? This question remains open for further studies.

In conclusion, amyloidosis is not only the type of renal involvement in patients with FMF. Kidney biopsy should be performed in all patients with FMF displaying micro- or macroscopic hematuria with and without proteinuria.

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