

Complete remission of nephrotic syndrome in secondary amyloidosis of familial Mediterranean fever following colchicine treatment

Ailevi Akdeniz ateşi ve sekonder amiloidozise bağlı nefrotik sendromun kolşisin tedavisi altında remisyonu

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A 25-year-old woman of Turkish origin with an 18 year long history of familial Mediterranean fever (FMF) attacks characterized with fever, arthritis and abdominal pain developed symptoms of the nephrotic syndrome in 1999. The renal biopsy revealed small amounts of amyloid deposits. Intestinal mucosa (rectum) also showed amyloid infiltration. The patient was homozygous for M694V mutation. She has responded to colchicine with a resolution of clinical signs and nephrotic range proteinuria. Similar cases have been rarely described. In this case, an 18-year delayed diagnosis and treatment of FMF, reversible nephrotic stage of amyloidotic renal disease by colchicine and a favorable course were discussed.

Key words: AA amyloidosis, familial Mediterranean fever, nephrotic syndrome, colchicine

Ateş, artrit ve karın ağrısı atakları ile 18 yıldır ailevi Akdeniz ateşi hikayesi olan 25 yaşında Türk kadın hasta, 1999 yılında nefrotik sendrom kliniği ile hastanemize başvurdu. Renal ve intestinal mukozadan (rektum) yapılan biyopsilerde amiloid depolanması saptandı. Hastada homozigot M694V mutasyonu mevcut idi. Kolşisin tedavisi altında klinik belirtiler ve nefrotik düzeydeki proteinüri kayboldu. Literatürde benzer vakalar nadir olarak tarif edilmiştir. Bu hastada ailevi Akdeniz ateşin tanı ve tedavisinde 18 yıllık bir gecikme ve kolşisin tedavisi altında sekonder amiloidozise bağlı nefrotik sendromun kaybolarak iyi bir seyir göstermesi tartışıldı.

Anahtar kelimeler: AA amiloidozise, ailevi Akdeniz ateşi, nefrotik sendrom, kolşisin

Familial Mediterranean Fever (FMF) is an autosomal recessive disorder characterized by episodic, self-limited attacks of fever accompanied by unexplained arthritis, sterile peritonitis, pleurisy and/or skin rash. Renal amyloidosis is one of the most severe complications of the disease that causes chronic renal failure and death in patients with FMF (1,2). It is well known that colchicine therapy is effective in the decreasing of the attack frequency and in the prevention of amyloid deposition in patients with FMF, but reversal of the nephrotic syndrome secondary to amyloidosis in FMF after prolonged treatment with colchicine and a favorable course are infrequently reported (3-8).

Here we report a case of FMF complicated by renal amyloidosis in nephrotic stage, with normal kidney function, and the remission of the nephrotic syndrome completely on colchicine treatment.

Case report

A 25-year-old female patient described an 18-year history of acute febrile attacks accompanied by arthritis or abdominal pain. Repeated abdominal pain and fever lasted 2 to 3 days. The joints were normal between acute arthritic attacks, involving the knees and the ankles and lasting 1 to 2 weeks. Probably because of her fever and arthritic attacks she was suspected to have rheumatic fever and she received aspirin and prophylactic penicillin therapy. She was referred to

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our department in March 1999 with edema of the lower extremities and massive proteinuria

On physical examination, she was pale, had splenomegaly (3 cm below the left costal margin), pitting edema and erysipelas like erythema on the lower extremities. She had weakness. She developed an attack of abdominal pain and fever (37.9 °C) lasting 2 days during her stay in the hospital. During the attack, her leukocyte count was 23000 mm³ and fibrinogen concentration was 925 mg /dl. The diagnosis of FMF was made according to the accepted criteria (2). Both the renal and rectal biopsies demonstrated the presence of amyloid deposition. The small deposits of homogeneous poorly staining material was restricted to the mesangium and hardly perceptible deposits also lied within the wall of an interlobular artery. The kidney biopsy was insufficient for immunohistochemical analysis as well as for an immunofluorescence study. Intestinal mucosa (rectum) revealed the deposition of Amyloid A by immunohistochemical analysis. An abdominal fat pad biopsy was negative for amyloidosis.

The laboratory tests revealed hemoglobin 10 g/dl, hematocrit 30.8%, serum iron 26 m/dl (40-130 m/dl), ferritin 245 ng/ml (9-120ng/ml) and transferrin 29% (20-55%), a raised erythrocyte sedimentation rate (ESR; 135 mm/h), an increased CRP concentration (13 mg/dl, normal:0-5 mg/dl), and negative results for rheumatoid factor and antinuclear antibodies. The urinary protein excretion was 5.07g/day. The serum biochemical analysis showed hypoalbuminemia, hyper-cholesterolemia, hypertriglyceridemia (albumin 1.7g/dl, total protein; 4.3g/dl, total cholesterol; 207mg/dl and triglyceride; 396 mg/dl) with normal renal function. Serum protein electrophoresis showed an increased alpha-2 fraction (23.3%). The serum levels of C3 and C4 were within normal limits. Mutation analysis revealed homozygosity for M694V. Urinary protein excretion gradually decreased and completely disappeared between 1999 and 2001 on colchicine treatment (1.5mg /day), and urine has remained free of protein in 2003. Also no symptoms of FMF have been observed after the treatment.

Discussion

Amyloid is defined as an amorphous, eosinophilic proteinaceous deposit. The precursors of amyloid fibril proteins differ from each other with respect to primary structure and function. They are able to form aggregates under specific circumstances, which lead to the deposition of amyloid. FMF-related amyloidosis is the most form of hereditary systemic amyloidosis. The amyloid protein in FMF is of the AA type. The mean age of the onset of FMF in Turkish FMF patients having amyloidosis is 6.5 years (9), as in our patient. The diagnosis of FMF is based main on clinical symptoms. A delay in the diagnosis of FMF is seen in most cases with a mean period of 8.3 years in Turk-

ish patients with FMF accompanied by amyloidosis. The delay is longer (23.9 years) in patients without amyloidosis (9). In another study from Turkey, the duration of the disease before the diagnosis of amyloidosis was between 2 to 14 years (10). In our case, there was an 18-year delay.

Yalçinkaya et al. compared the MEFV mutations, including that of M694V in FMF patients with and without amyloidosis in the absence of therapy. The authors strongly suggest that the development of amyloidosis is not due only to the presence of homozygosity in the M694V mutation (9). Gershori et al. reported that M694V homozygotes have a severe form of the disease and often endure renal amyloidosis (11). Livneh et al. reported that the absence of the M694V/694V mutation is consistent with the presence of a milder disease and with the absence of amyloidosis (12). Despite unfavorable conditions such as, an 18-year delay in diagnosis and treatment, being in the nephrotic stage of amyloidotic renal disease and the homozygosity of the M694V mutation, the patient showed a favorable course on colchicine therapy during the follow-up of 4 years.

Colchicine treatment has been a well-established treatment for FMF during the last 25-30 years, although total remission of the nephrotic syndrome is rarely seen. The successful treatment of FMF and renal amyloidosis is reported in the literature as case report(s) (5-8,13). Zemer et al. reported the reversal of nephrotic syndrome in three patients with FMF-renal amyloidosis and their experience indicates that colchicine treatment may reverse the nephrotic syndrome (5). Livneh et al. reported that 7 of the 14 patients presenting with nephrotic syndrome with amyloidosis of FMF improved in most of the patients proteinuria resolved, while, the other 7 patients deteriorated (6). Hojberg et al. described two siblings (aged 6 and 10 years) with FMF and renal amyloidosis, one having nephrotic syndrome and the other severe proteinuria, in whom the proteinuria was reduced by continuous colchicine therapy (7). The resolution of the amyloid deposits is possible in vivo and the morphologic regression of AA amyloid was demonstrated by histological examinations in two patients after the treatment of the underlying infection (14). We could not have control biopsies proving regression of amyloid deposits after colchicine treatment. However, Keven et al. reported that the regression of amyloid deposits by renal biopsy was not revealed in a case of mixed type of localized Castleman's disease complicated with AA amyloidosis, despite complete remission of nephrotic syndrome (15).

Finally, we observed the complete remission of nephrotic syndrome following colchicine treatment in a patient with FMF-related amyloidosis, although little is known about the effect of colchicine to amyloidogenesis.

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