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Massive Proteinuria and Acute Glomerulonephritis Picture in a Patient With Familial Mediterranean Fever and *E148Q* Mutation

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Familial Mediterranean fever (FMF) is an inherited auto-inflammatory disorder. Secondary AA amyloidosis is the most devastating complication of FMF. Nonamyloid renal involvements have also been reported in association with FMF, including vasculitis, focal and diffuse glomerulonephritis, and IgA nephropathy. We describe a patient with FMF and *E148Q* mutation who presented with massive proteinuria, elevated serum creatinine level, and acute glomerulonephritis picture. Disease remission was achieved after treatment with corticosteroids and colchicine.

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Case Report

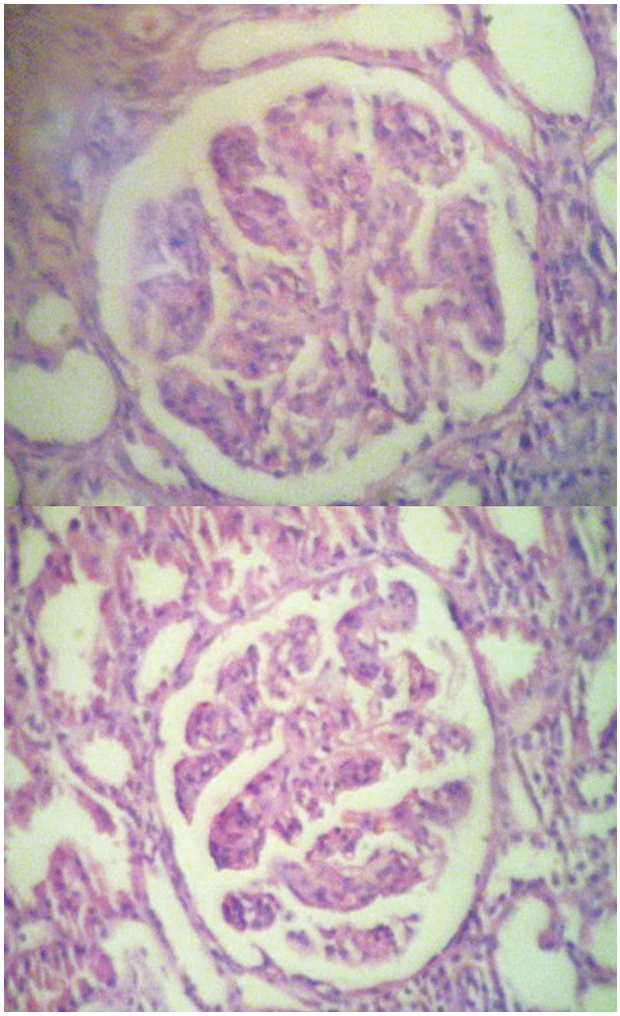
INTRODUCTION

Familial Mediterranean fever (FMF) is an autosomal recessive auto-inflammatory disorder. Secondary AA amyloidosis is the most devastating complication of FMF. Nonamyloid renal lesions have also been reported in association with FMF including vasculitis (polyarteritis nodosa and Henoch-Schonlein purpura nephropathy), glomerulonephritis, rapidly progressive glomerulonephritis, immunoglobulin A (IgA) nephropathy, IgM nephropathy, and membranoproliferative glomerulonephritis.[1,2] Although *M694V* is the most common mutation worldwide, *E148Q* mutation is also a common finding in some populations with FMF.[3-5] Herein, we describe a patient with FMF and *E148Q* mutation who presented with massive proteinuria, elevated serum creatinine, and acute glomerulonephritis presentation.

CASE REPORT

A 63-year-old woman was admitted because of lower extremities edema. Physical examination revealed blood pressure of 130/80 mm Hg and normal cardiovascular examination. She had a positive history for self-limited episodes of abdominal pain, lasting 1 or 2 days during the last 10 years. Her serum creatinine level was 1.7 mg/dL and protein excretion was 8.4 g/d. Hematuria (3+) and leukocyturia were also detected, and urine microscopic examination confirmed the prescience of dysmorphic erythrocytes and glomerular hematuria. Serum albumin level was 2.5 g/dL. Erythrocyte sedimentation rate was 76 mm/h, and C-reactive protein level was 24 mg/L without any detectable infectious disease. Blood smear for malaria was negative. Serum antistreptolysin O titer and complement C3, C4, and CH50 levels were within normal ranges. Serum serology for antinuclear antibody, anti-double-stranded DNA antibody, antineutrophil cytoplasmic antibodies, antiglomerular basement membrane antibody, anticyclic citrollinated peptide, and cryoglobulin were negative. Urine and serum protein immunoelectrophoresis showed no evidence of monoclonal gammopathy. Renal ultrasonography showed normal-sized kidneys.

Kidney biopsy revealed mesangial and endocapillary proliferation with glomerular tuft segmentation without extracapillary proliferation (crescent). There was endocapilary polumorphonuclear infiltration (Figure).



Glomerular capillary tuft segmentation and capillary loop closure with meningeal cell proliferation and leukocytes infiltration without extra capillary proliferation (crescent) formation.

Immunofluorescent staining was negative for IgA, IgM, IgG, C3, and C4 deposit. Congo red staining was negative. Analysis of the *MEFV* gene for FMF showed heterozygous mutation for *E148Q* mutation. The patient was of northwest Iranian origin from Azerbaijan.

She received 2 days of methylprednisolone pulse, 500 mg/d, followed by a tapering dose of prednisolone, 1 mg/kg, for 1 month and continuing dose of colchicine, 0.5 mg/d. After 6 months, proteinuria decreased to 1100 mg/d and kidney function returned to normal (serum creatinine level, 1.0 mg/dL), while she was on colchicine and angiotensin-converting enzyme inhibitor and angiotensin receptor antagonist therapies. Two years after treatment, her 24-hour protein excretion was 200 mg/dL, serum creatinine level was 1.2 mg/dL, and she did not have any abdominal pain episode during this period.

DISCUSSION

Late onset attacks of abdominal pain that disappeared after colchicine initiation, heterozygous mutation of *E148Q*, massive proteinuria, and acute glomerulonephritis-like picture in biopsy without any evidence of infectious etiology, all were an unusual combination in our patient. Nonamyloid kidney disease should be considered in the differential diagnosis of renal involvements in patients with FMF.[6] In a study of 15 patients with a long-standing history of FMF and renal involvement, 7 patients had amyloidosis and 6 patients had mesangial proliferative glomerulonephritis. Immunofluorescent studies disclosed mesangial IgA deposits in 3 of them and IgM mesangial deposits in another 3 patients with mesangeal proliferation. Two patients out of these 15 patients presented with rapidly progressive glomerulonephritis.[7]

Infectious-related glomerulonephritis was our first consideration, but we did not find any clinical sign of infection, since serum complement levels were normal and there was no C3 deposit on immunoflurescent microscopy.[8] Because of increased inflammatory response immunologic glomerular injury may occur more frequently in patients with FMF.[6] Mutated pyrin associates with uncontrolled inflammation through interleukin-1b and nuclear factor kappa-light-chain-enhancer of activated B cells activation.[9,10] Whether or not *E148Q* mutation directs these inflammatory conditions toward the kidney or not needs future investigation. In a report from Iranian Azeri Turkish patients, the most common mutation in FMF patients were p.*M694V* (42.4%), followed by p.*V726A* (17%), p.*E148Q* (16.2%), and p.*M680I* (c.2040G>C; 15.2%).[4]

In a study of 44 patients with *E148Q* mutation, 1 patient had rapidly progressive glomerulonephritis course.[11] In another report, *E148Q* mutation presented with proteinuria and mesangial proliferative glomerulonephritis.[11] It seems that *E148Q* mutation have heterogeneous clinical presentations. Other genetic modifiers may link to *E148Q*-associated clinical symptoms. In our patient, there was a discrepancy between clinical and pathologic findings.[13,14] Increased inflammatory response may facilitate immunologic glomerular injury. Whether FMF should be considered in

the differential diagnosis of idiopathic meningeal proliferative glomerulonephritis in FMF endemic region needs future investigation.[14]

CONFLICT OF INTEREST

None declared.

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