

Biopsy Proven Non-Amyloid Glomerular Diseases in Patients With Familial Mediterranean Fever

Can Hüzmeli, Ayşe Şeker Koçkara, Ferhan Candan, Mansur Kayataş

Can Hüzmeli, Ayşe Şeker Koçkara, Ferhan Candan, Mansur Kayataş, Department of Nephrology, Cumhuriyet University Hospital, Sivas, Turkey

Correspondence to: Ayşe Şeker Koçkara, Department of Nephrology, Cumhuriyet University Hospital, Sivas, Turkey.

Email: drayse14@hotmail.com

Telephone: +5325680187

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ABSTRACT

AIM: Kidney involvement is the most serious organ involvement of Familial Mediterranean Fever (FMF), while the most common cause is AA type amyloidosis with serum amyloid AA deposition. However, vasculitis and other types of glomerulonephritis (GN) also have been reported. With this study we evaluated biopsy proven non-amyloid glomerular diseases in patients with FMF.

METHODS: At our Nephrology clinic, total 950 patients followed by diagnosis of FMF have been evaluated. Nine patients who had positive proteinuria (>500 mg/day) but had negative amyloidosis in the tissue biopsy were made renal biopsy.

RESULTS: Nine patients underwent a renal biopsy, two patients were found to have IgA nephropathy (IGAN), three mesangioproliferative glomerulonephritis (MsPGN), three membranous glomerulonephritis (MGN) and one had immune complex glomerulonephritis. Two patients with IGAN and one patient with MGN with non-nephrotic proteinuria exhibited significant improvement with colchicine and angiotensin receptor blocker (ARB) therapy. Other patients were treated with colchicine, an ARB and immunosuppressive drugs. Upon evaluation for the FMF gene mutation, different mutations have been found for the same glomerulonephritis type.

CONCLUSIONS: Other glomerular causes also must be investigated alongside amyloidosis in the case of kidney involvement in FMF patients. While patients with IGAN and other glomerulonephritides with non-nephrotic proteinuria can respond well to colchicine

treatment, patients with more aggressive kidney involvement may require immunosuppressive therapy. Further studies are needed for revealing the relationship between FMF gene mutation and non-amyloid glomerular diseases.

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Key words: Familial Mediterranean fever; Nonamyloidotic proteinuria; Glomerulonephritis

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INTRODUCTION

Familial Mediterranean Fever (FMF) is an inflammatory disease with an autosomal recessive inheritance pattern characterized by fever, pain associated with episodes of serositis and synovitis and skin lesions. It is common among Sephardic Jews, Turks, Arabs and Armenians from the Mediterranean Sea region^[1]. A field study of Özen et al. recently revealed its prevalence in Turkey as 1:1075^[2]. Mutations of the MEFV gene, on the short arm of chromosome 16, codes for pyrin or marenostrin proteins is responsible for the disease. The MEFV mutation is found in less than 70% of patients diagnosed with FMF. Four mutations have been defined in 85% of patients from the mentioned 4 ethnic groups (M694V, M680I, M694I V726A)^[3-5].

AA type amyloidosis is the result of serum amyloid A protein deposition in tissues. It is the best understood and the most serious reason for kidney failure in patients with FMF. In a report from Turkey, amyloidosis rates among FMF patients were found to be 7%^[6]. There is no publication proving an increase of glomerulonephritis among FMF patients. Kidney involvement of FMF may occur due to vasculitis. But, other cases of glomerulonephritis (crescentic, rapidly progressing

glomerulonephritis, mesangial IgA nephropathy, IgM nephropathy, diffuse proliferative glomerulonephritis) have also been reported in patients with FMF^[7-9]. We hereby present nine FMF patients with biopsy proven glomerulonephritis, who have been followed by the Nephrology Department of Cumhuriyet University.

MATERIALS AND METHODS

Patient selection

950 FMF patients who had been followed by the Nephrology Department of our university between 2004 to 2013 were evaluated. The diagnosis of FMF was made according to the Tel Hashomer criteria^[10].

Major Criteria: 1. Recurrent febrile episodes accompanied by peritonitis, pleuritis, or synovitis; 2. Amyloidosis of AA-type without predisposing disease; 3. Favorable response to continuous colchicine treatment

Minor Criteria: 1. Recurrent febrile episodes; 2. Erysipelas-like erythema; 3. Positive history of FMF in a first-degree relative

Definite Diagnosis: 2 major criteria or 1 major and 2 minor criteria

Probable Diagnosis: 1 major and 1 minor criterion

During follow-up encounters, proteinuria was assessed by a 24 hour urine collection in patients with FMF. Patients with proteinuria levels exceeding 500 mg/day were further assessed for amyloidosis by rectal or gum biopsies. The Congo red method was used to detect amyloid in tissue sections. Amyloid was identified as the AA type on immunohistochemical testing with the use of monoclonal antibodies specific to SAA. ANA, anti-ds DNA, ANCA, anti GBM, complements, anti-HIV and anti-hepatitis B and C antibodies also have been measured in patients with proteinuria more than 500 mg/day. Kidney biopsies were performed in nine patients with more than 500 mg/day proteinuria and tissue biopsies negative for amyloidosis. Exclusion criteria were: malignancy, SLE and systemic vasculitis, use of immunosuppressive drugs, chronic renal failure and liver cirrhosis.

Genetic Analysis

DNA was isolated from peripheral blood leukocytes by standard procedures and amplified with sequence-specific primers using the polymerase chain reaction (PCR) technique. Depending on the laboratory, denaturing gradient gel electrophoresis, PCR/RFLP, amplification of refractory mutation system, and DNA sequencing methods were used to screen for MEFV gene mutations.

RESULTS

950 patients were followed by our nephrology team and tissue biopsies were performed for patients with proteinuria greater than

500 mg/day with 24 hour urine collection to investigate amyloidosis. Nine patients with a negative tissue biopsy for amyloidosis underwent a kidney biopsy and were subsequently diagnosed with glomerulonephritis. The diagnosis of two patients with IGAN, three patients with MsPGN, three patients with MGN and one patient with immune complex GN was made. Four of nine patients were diagnosed with FMF and had been receiving colchicine therapy before biopsy. The other five patients were diagnosed FMF and glomerulonephritis on the same date and thus had not yet received any therapy. One patient with a high initial creatinine level (creatinine clearance of 30 ml/minute) and kidney biopsy of MsPGN, did not respond to colchicine, ARB and azathioprine treatment and later progressed to being dialysis dependent. Another patient with a high creatinine level (creatinine clearance of 40 mL/minute) was diagnosed with immune complex GN and kidney function was restored with colchicine, ARB, prednisolone and azathioprine treatment.

Clinical data of the patients, results of the genetic analysis for FMF, biopsy findings, and therapy for both glomerulopathy and FMF are summarized in Table 1

CASE 1

A 22 year-old female patient complained of episodes of knee and hip joint pain for a year. Family history includes cousins with FMF. Results of physical examination were within normal limits. Blood analysis revealed a creatinine level of 0.7 mg/dL and urinalysis revealed hematuria and proteinuria (++) . A 24-hour urinary protein collection revealed 2.3 g/day. Serological tests of hepatitis markers, ANA, Anti-dsDNA, p-ANCA, c-ANCA, anti-GBM antibodies were all negative and C3 and C4 were within normal limits. FMF gene analysis revealed a heterozygote M694V mutation. Renal biopsy found an increase in mesangial cells and matrix, IGAN with IgA (+++) and C3(+++) and poor IgG staining. Congo red was negative (Figure 1). Colchicine tablet 3×0.5 mg/day and valsartan 160 mg/day were administered. The patient reported improvement with her joint pain. Follow-up after two months revealed a 24-hour urinary protein level of 620 mg/day.

CASE 2

A 30 year-old female patient with recurrent episodes of abdominal, chest and joint pain for 10 years was evaluated during an outpatient clinic visit. Family history reveals that the patient's father has FMF and chronic renal failure. Physical examination was within normal limits. Blood analysis revealed a creatinine level of 0.81 mg/dL, urinalysis revealed proteinuria (+), hematuria, and a 24 hour urinary protein collection of 960 mg/day. Serological tests for

Table 1 Clinical data, results of the genetic analysis for FMF, biopsy findings, and treatment of the patients.

ID	Age (years)	Sex	24-h proteinuria (g)	Creatinine (mg/dL)	FMF Genetic Analysis	Glomerulopathy	Treatment*
1	22	K	2.3	0.7	Heterozygous M694V	IGAN	ARB, colchicine
2	30	K	0.96	0.8	Heterozygous E148Q	IGAN	ARB, colchicine
3	65	E	6.8	5.1	Heterozygous E148Q	MzPGN	ARB, colchicine, Aza 2×50 mg
4	29	K	1.2	0.6	Heterozygous M680I	MzPGN	ARB, colchicine, pred 30 mg/day, Aza 2×50 mg
5	55	E	1.4	0.8	Heterozygous M694V ve M680I	MzPGN	ARB, colchicine, pred 30 mg/day, Aza 2×50 mg
6	32	K	0.95	0.9	Heterozygous E148Q	MGN	ARB, colchicine
7	37	K	8	0.7	Heterozygous M694V ve P369S	MGN	ARB, colchicine, pred 1 mg/kg/day, Cyc 1g monthly (6 month), siklosporin 200 mg/gün
8	46	K	13	0.2	Heterozygous V726A	MGN	ARB, colchicine, ASA, pred 1mg/kg/day, Cyc 1g monthly
9	35	E	3.4	2.3	Heterozygous A744S	Immune complex GN	ARB, colchicine, pred 30 mg/gün, Aza 2×50 mg

* ARB: Angiotensin receptor blocker, Aza: Azathioprine, Cyc: Cyclophosphamide, pred: prednisolone, ASA: acetylsalicylic acid.

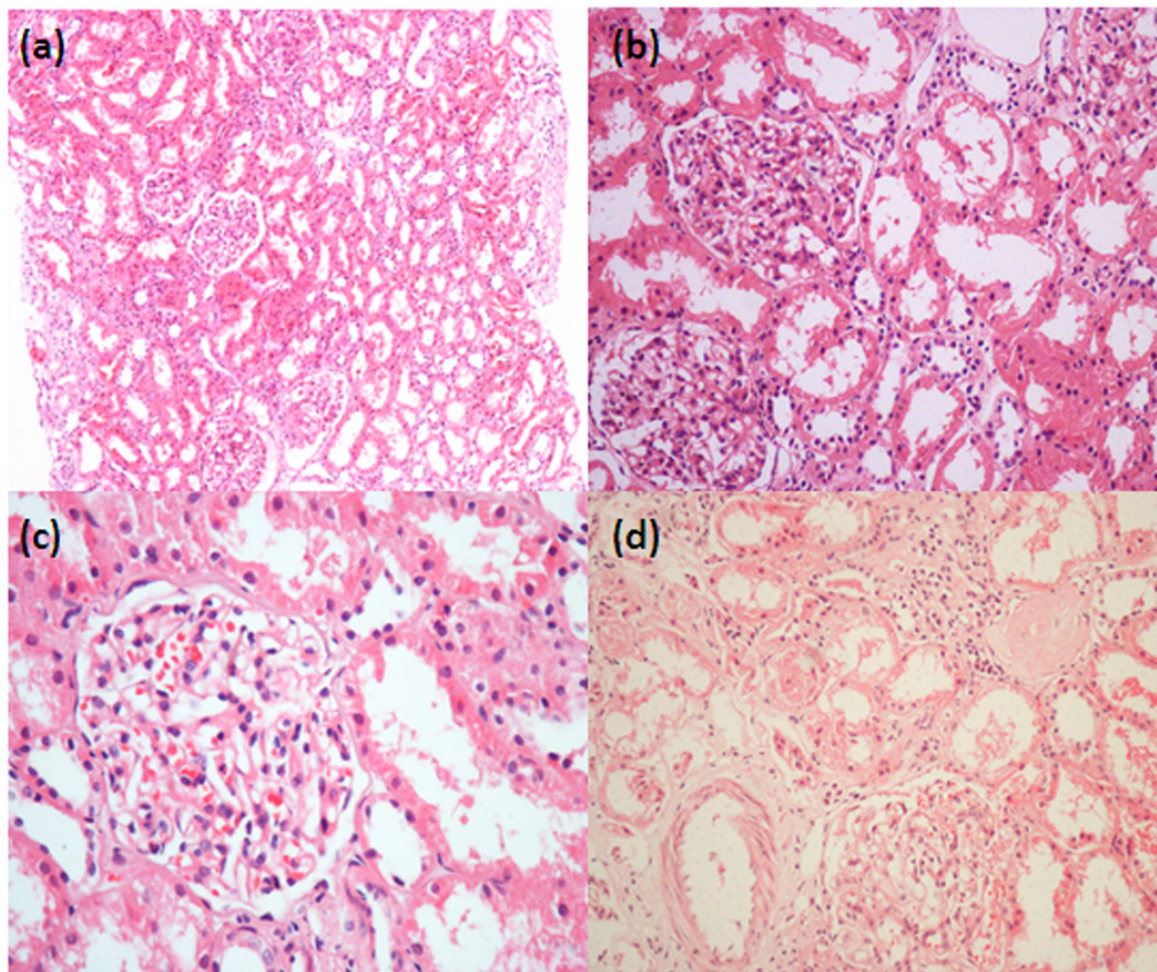


Figure 1 Light microscopy findings in patients who developed glomerulopathy associated with FMF. (a) Case 1. HE: Increased mesangial cell and matrix of glomeruli, also segmental sclerosis of 2 glomeruli, HE,x50 (b) Case 4. HE: Increase in number of mesangial cells. (HE,x100) (c) Case 6. Thickening of glomerulus basal membrane, HE,x200 (d) Case 9. Increase of mesangial cells of the glomerulus on the bottom, global sclerosis, interstitial fibrosis and chronic inflammation and tubular atrophy of the glomerulus on the upper-right corner (HE, x50).

hepatitis markers, ANA, Anti-ds DNA, p-ANCA, c-ANCA, Anti-GBM antibodies were all negative and C3 and C4 were within normal limits. Renal biopsy reported IGAN with a mild mesangial increase and proliferation, (+) mesangial staining of glomeruli with IgG and IgM by immunofluorescence, (+++) mesangial staining with IgA. Congo red was negative. Gene analysis for FMF revealed heterozygote E148Q mutation. A colchicine tablet 3×0.5 mg/day and valsartan 160 mg were administered. The patient had no episodes following colchicine treatment. The follow-up 24 hour urinary protein was 420 mg/day after three months.

CASE 3

A 65 year-old male patient presented with complaints of swelling on his feet and shortness of breath. Past medical history includes diabetes and hypertension for last 20 years and coronary artery disease for a year. Upon further investigation, we learned the patient has episodes of abdominal pain, fever and joint pain for 40 years, which significantly have increased over the last 20 years. He has children who have been diagnosed with FMF. Blood pressure was 160/90 mm Hg, heart rate was 63 bpm, body temperature was 36.5 C. Rales were auscultated upon pulmonary and the patient had pretibial edema bilaterally. Blood analysis revealed BUN level 46 mg/dL (9-23), creatinine 5.1 mg/dL (0.9-1.3). Urinalysis revealed proteinuria

(++++), hematuria, a 24 hour urine total protein of 6.8 g/day and a creatinine clearance of 30 mL/minute. Ophthalmologic examination for investigating diabetic retinopathy was negative for retinopathy. A heterozygote E148Q mutation was discovered with FMF gene analysis. Serological tests of hepatitis markers, ANA, Anti-ds DNA, p-ANCA, c-ANCA, AntiGBM antibodies were all negative and C3 was low and C4 was within normal limits. Renal biopsy showed an increase of mesangial matrix and cells, consistent with MsPGN and negative for Congo red. Colchicine tablet 2×0.5 mg/day, azathioprine 2×50 mg/day and valsartan 160 mg/day were administered. The patient presented to the ER with uremic symptoms two months later and underwent hemodialysis. During the follow-up period, the patient was started on a hemodialysis program.

CASE 4

A 29 year-old female patient was diagnosed with FMF based on fever and joint pain 7 years ago. She was on colchicine tablet 3×0.5 mg/day. FMF gene analysis revealed a heterozygote M680I mutation. Upon physical and laboratory examination, her blood pressure was 120/80 mmHg, creatinine was 0.68 mg/dL, urinalysis revealed protein (+) and 24 hour urinary protein was 1.2 gr/day. Serological tests for hepatitis markers, ANA, Anti-ds DNA, p-ANCA, c-ANCA, Anti-GBM antibodies were all negative and C4 was within normal

limits and C3 was low. Renal biopsy showed a mild increase in the mesangial matrix and mesangial cellularity, C3 (++) , focal mesangial deposition of IgG and IgM on immunofluorescence. Congo red was negative and the diagnosis was reported to be MsPGN. Azathioprine tablet 2x50 mg/day, prednisolone tablet 30 mg/day and valsartan 160 mg/day were administered. The 24 hour urinary protein level was 179 mg/day at follow-up 3 months later.

CASE 5

A 55 year-old male patient who had been diagnosed with FMF ten years previously presented to our clinic. Gene analysis for FMF revealed heterozygote M694V and heterozygote M680I mutation. The patient was started on colchicine tablet 3x0.5 mg/day and had no episodes since treatment began. Blood analysis of creatinine was 0.8 mg/dL, urinalysis of protein (+) and the 24 hour urinary protein was 1.4 g/day. Serological tests of hepatitis markers were, ANA, Anti-ds DNA, p-ANCA, c-ANCA, anti-GBM antibodies were all negative and C3 and C4 were within normal limits. Renal biopsy found intermediate proliferation of mesangial cells, increase of mesangial matrix and mesangial deposition of C3 (++) , mesangial granular deposition of IgM (+) at immunofluorescence staining and negative for congo red staining, the diagnosis given was MsPGN. Azathioprine tablet 2x50 mg/day, prednisolone tablet 30 mg/day and Valsartan 160 mg/day were added to the treatment plan. Urine protein level was 330 mg/day after 2 months of treatment.

CASE 6

A 32 year-old female patient who was diagnosed with FMF 4 years ago presented to our clinic. FMF gene analysis revealed heterozygote E148Q. She responded well to colchicine tablet 3x0.5 mg/day treatment. Physical examination findings were within normal limits. Upon laboratory blood analysis, creatinine was 0.9 mg/dL and urinalysis revealed protein (+), 24 hour urinary protein was 950 mg/day. Serological tests of hepatitis markers were, ANA, Anti-ds DNA, p-ANCA, c-ANCA, anti-GBM antibodies were all negative and C3 and C4 were within normal limits. Renal biopsy revealed thickening of the glomerular basal membrane, moderate staining of basal membrane with C3 and IgM, Congo red staining was negative and the diagnosis was reported as MGN. Valsartan 160 mg/day was included in the treatment plan. The 24 hour urinary protein level was 400 mg/day, measured two months after treatment had been initiated.

CASE 7

A 37 year-old female patient presented to our clinic with complaints of swelling of feet, joint pain and proteinuria. Past medical history includes pulmonary embolism and deep vein thrombosis, subsequently the patient was being treated with Warfarin. Physical examination findings were, blood pressure of 150/85 mmHg and pretibial edema. Upon laboratory investigation, creatinine level was 0.7 mg/dL, urinalysis revealed proteinuria (+++), 24 hour urinary protein was 8 g/day and creatinine clearance was 70 mL/minute. Serological tests of hepatitis markers were negative, ANA, Anti-dsDNA, p-ANCA, c-ANCA, anti-GBM antibodies were negative and C3 and C4 were within normal limits. Mutations of heterozygote P369S and heterozygote M694V were found during FMF gene analysis. Further, the patient has a known familial history of FMF. The patient was diagnosed with FMF and prescribed colchicine 3x0.5 mg/day. The patient was subsequently followed up with a renal biopsy which revealed thickening of the glomerular basal membrane, granular deposition of C3 and IgG on glomerular basal membrane and negative for congo red staining; the diagnosis was reported as

MGN. Valsartan 160 mg/day, atorvastatin 20 mg/day, prednisolone 1 mg/kg and 1 g cyclophosphamide monthly treatment administered. The patient received 6 sessions of cyclophosphamide, but did not respond well to the treatment (24 hour urinary protein was 12 g/day). When the patient did not respond to cyclophosphamide treatment, cyclosporine was administered as 200 mg/day. At follow-up visit after three months, 24 hour urinary protein was 197 mg/day.

CASE 8

A 46 year-old patient with a diagnosis of FMF since she was 13 and has been treated with colchicine 3x0.5 mg/day, presented to our clinic for routine outpatient follow-up. Several children of this patient have been diagnosed with FMF. Gene analysis of the patient resulted V726A mutation. Physical examination revealed a blood pressure of 160/100 mmHg and pretibial edema. Blood analysis revealed creatinine of 0.25 mg/dL, urinalysis revealed proteinuria (++) and 24 hour urinary protein was 13 g/day. Serological tests of hepatitis markers, ANA, Anti-dsDNA, p-ANCA, c-ANCA, anti-GBM antibodies were all negative and C3 and C4 were within normal limits. Renal biopsy revealed thickening of the glomerular basal membrane, granular deposition of C3 and IgG on glomerular basal membrane and negative for congo red staining, the diagnosis was reported to be MGN. Valsartan 160 mg/day, acetylsalicylate, atorvastatin 20 mg/day, 1 mg/kg/day prednisolone and 9 sessions of cyclophosphamide treatment administered. 24 hour urinary protein at follow-up was 288 mg/day. Azathioprine was included in the treatment plan.

CASE 9

A 35 year-old male patient was referred to our outpatient clinic with complaints of swollen feet, fever and joint pain episodes. Gene analysis for FMF revealed an A744S mutation. Blood pressure was measured as 130/80 mmHg, other physical examination findings were normal. Blood analysis revealed creatinine to be 2.3 mg/dL and urinalysis revealed proteinuria (++) , 24 hour urinary protein was 3.4 g/day and creatinine clearance was 40 ml/minute. Serological tests of hepatitis markers, ANA, Anti-ds DNA, p-ANCA, c-ANCA, anti-GBM antibodies were all negative and C3 and C4 were within normal limits. Renal biopsy revealed increase of mesangial cells, global sclerosis, interstitial fibrosis, tubular atrophy, and mesangial focal staining with C3 and IgM the diagnosis was reported as immune complex glomerulonephritis, chronic tubulointerstitial glomerulonephritis and negative for congo red staining. Valsartan 160 mg/day, prednisolone 30 mg/day, azathioprine 2x50 mg/day and colchicine tablet 2x0.5 mg/day were administered. At follow-up two months later, the 24 hour urinary protein was 900 mg/day, creatinine was 1.2 mg/day and creatinine clearance was 60 mL/minute.

DISCUSSION

Proteinuria of FMF patients must make the clinician also consider non-amyloid glomerular diseases (IgA nephropathy, IGAN, focal and diffuse glomerulonephritis, MsPGN and rapidly progressing glomerulonephritis). In a study conducted by a Turkish FMF working group, 2,436 FMF patients have been evaluated for renal involvement^[11]. From these patients, 12.9% had amyloid deposition, 0.9% had PAN, 2.7% had HSP and 22 patients (0.8%) had non amyloid glomerular disease. Six of these 22 patients had mesangiocapillary GN, six of them had MsPGN, five of them had diffuse endocapillary proliferative GN, one of them had focal glomerular sclerosis, one of them had MGN, one of

them had IGAN, two of them had PAN, four of these patients also had renal amyloidosis^[11]. Eliakim *et al* investigated 106 FMF patients and found 22% of them had non-amyloid kidney disorders (transient or permanent hematuria, recurrent acute pyelonephritis, acute post streptococcal glomerulonephritis and other types of glomerulonephritis)^[12]. Kukuy *et al* describes findings in a retrospective study that included all patients with FMF undergoing kidney biopsy for proteinuria > 0.5 g/24 h. They found that among 25 FMF patients, 10 (40%) had nonamyloid kidney disease^[13]. Said *et al* conducted a study which evaluated renal biopsies of 15 FMF patients with proteinuria and found amyloidosis in seven of them, MsPGN in six of them, RPGN in two of them^[8].

Studies have found that vasculites such as polyarteritis nodosa (PAN) and Henoch-Schönlein purpura (HSP) are more common in patients with FMF compared with the normal population. Other than reports of HSP and PAN, there are no large epidemiological studies suggesting that non-amyloid glomerular disease is more frequent in FMF patients than in the general population^[14].

We found MsPGN in three of nine patients, for which we had kidney biopsies. Two of these patients had been diagnosed with FMF previously and were receiving colchicine treatment, in addition to that treatment, azathioprine and prednisolone were also administered, their proteinuria improved. For the other patient with nephrotic range proteinuria and impaired renal function, we administered colchicine and azathioprine. The patient did not responded well to this treatment, upon follow-up visit three months later, he presented with uremic symptoms and oliguria; thus he was started on hemodialysis and enrolled in a routine hemodialysis program. Çağdaş *et al.* showed that colchicine treatment for an FMF case with a MsPGN diagnosis made upon renal biopsy provided a complete cure for this patient [9]. Eroğlu E *et al* diagnosed a patient with FMF and MsPGN and the patient responded well to colchicine treatment^[15].

Two of our cases had FMF with IGAN. Two cases had hematuria and non-nephrotic proteinuria, they had no amyloid deposition. The patients were administered colchicine and valsartan and but did not received immunosuppressive treatment. During the follow-up period, we observed a significant decrease in the rate of episodes and a decrease in proteinuria. Said *et al.* reported IgA nephropathy in two patients with FMF in 1988, and noticed significant improvements at kidney functions with colchicine treatment^[16]. Rigante D *et al*, Gok F *et al*, Ceri M *et al* and Güllü *et al* found IgA nephropathy with FMF, and these patients responded well response to colchicine treatment^[17-20]. Koukoui L *et al.* reported a patient with IgA nephropathy and a carrier of a mutation in the FMF gene (MEFV), in whom continuous colchicine treatment induced remission^[21].

We observed MGN with three of our FMF patients. Two of these patients were already having colchicine treatment with FMF diagnosis. One of these patients had non-nephrotic proteinuria, a decrease at proteinuria only established by ARB and colchicine. Two other cases with MGN had hypertension and nephrotic proteinuria, these patients received immunosuppressive treatment. One patient did not respond to cyclophosphamide treatment, so cyclosporine was administered and proteinuria improved three months later. Proteinuria of another case improved with cyclophosphamide. Ceri *et al.* reported that a patient who was diagnosed with FMF and MGN initially presented with 2.5 gr/day proteinuria and with colchicine treatment proteinuria decreased 50% after six months and the patient was completely cured after 12 months^[22].

Immunologic mechanisms have an important role on FMF pathogenesis. The MEFV gene is expressed in mature neutrophils and codes pyrin which suppresses inflammation. Mutated pyrin

activates inflammatory cytokines. Increased inflammatory response of patients with FMF usually facilitates immunogenic glomerular damage. Colchicine is the most frequently used drug for FMF associated glomerulonephritis. It is thought to affect chemotaxis by its influence on microtubules, thus it limits migration of leucocytes to the inflammatory area. In addition to that, with its antioxidant effect, it is effective in causing the remission of proteinuria for patients with MsPGN, IGAN and IgM nephropathy^[8,23]. However, this treatment is not effective for patients with FMF and diffuse proliferative glomerulonephritis. In this case, prednisolone, cyclophosphamide or azathioprine might be included in the treatment plan^[8]. In a recently published study, a kidney biopsy was performed in 12 patients with FMF and nephrotic-range proteinuria. It was found amyloidosis in 50% (6/12), focal segmental glomerulosclerosis (FSGS) in 41.7% (5/12), and MPGN in 8.3% (1/12). With colchicine and angiotensin converting enzyme inhibitors, a marked improvement was seen in patients with amyloidosis, but no improvement was seen in patients with FSGS^[24].

Akpolat T *et al* have suggested that colchicine prevents glomerular disease, and that the irregular use of this drug triggers GN attacks^[25]. In our study, four of nine patients were diagnosed as FMF and were receiving regular colchicine before biopsy. Four patients using regular colchicine, two were found to have MsPGN and two were found to have MGN. These findings are inconsistent with other publications that suggest a protective role of regular colchicine for GN^[25].

Homozygosity for the M694V mutation is a major risk factor for renal amyloidosis in FMF patients^[14]. The role of mutations other than M694V for non-amyloid glomerular disease is unknown. Our study revealed different mutations in the same type of glomerulonephritis (Table 1). Further studies are needed to evaluate an association between mutations and glomerulonephritis types in FMF.

CONCLUSION

In patients with FMF, glomerulonephritis must be considered as a cause of non-amyloid renal involvement and kidney biopsies must be obtained. Good responses may be achieved with colchicine for patients with mild kidney involvement GN such as IGAN or MsPGN. But in cases of patients with nephrotic range proteinuria and more severe kidney involvement, immunosuppressive therapy must be included in the treatment plan. Further studies are needed for assessment of the relationship between type of glomerulonephritis and FMF gene mutation.

CONFLICT OF INTERESTS

The authors declare no conflict of interest.

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- Peer reviewers:** Gabriela E. Garcia, Associate Professor, Department of Medicine, University of Colorado Denver, 12700 East 19th Avenue, MS C281, Aurora, CO 80045, USA; Velibor Tasic, MD, PhD, Professor, Department of Pediatric Nephrology, University Children's Hospital, 17 Vodnjanska, 1000 Skopje, Macedonia.