CASE REPORT AND LITERATURE REVIEW

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A FAMILIAL MEDITERRANEAN FEVER PATIENT WITH MESANGIAL PROLIFERATIVE GLOMERULONEPHRITIS: A CASE REPORT AND LITERATURE REVIEW

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Abstract

Amyloidosis is the most important kidney complication determining the prognosis of familial Mediterranean fever (FMF) and presents with proteinuria at a nephrotic level. Other than amyloidosis, several other different renal involvements have been reported in FMF. The case is here presented of a patient determined with mesangial proliferative glomerulonephritis (MsPGN) in the kidney biopsy taken because of proteinuria and a good response with colchicine and azathioprine (AZA) treatment is presented. In this study, evaluations were made of cases with glomerulopathy other than amyloidosis in the literature. The data of 31 cases were analyzed, and it was seen that MsPGN was reported in almost half of these. Hematuria was also reported in some of these patients, most whom had nephrotic range proteinuria. Although colchicine treatment was sufficient in most cases, some patients were administered corticosteroid and AZA treatment. In conclusion, in FMF patients determined with proteinuria and/or hematuria, it should be kept in mind that there may be not only amyloidosis but also renal involvement other than amyloidosis, and the differential diagnosis should be made with kidney biopsy. Although colchicine treatment seems to be effective in renal involvements other than amyloidosis, immunosuppressive treatments may be necessary in some cases.

Keywords: Familial Mediterranean fever, amiloidosis, glomerulonephritis, colchicine

INTRODUCTION

Familial Mediterranean fever (FMF) is an autosomal recessive transmitted disease characterized by recurrent inflammatory attacks in serous and synovial membranes and fever (1). Secondary amyloidosis is frequently seen and is the most important complication determining disease prognosis in FMF (2). In biopsies taken from FMF patients because of proteinuria, different renal involvements other than amyloidosis have been reported (3-6). The aim of this paper was to review the literature related to this topic by presenting the case of an FMF patient diagnosed with mesangial proliferative glomerulonephritis (MsPGN).

CASE REPORT

A 44-year-old female patient first presented at our outpatient clinic in April 2007 with complaints of pain in the soles of the feet, swelling on the dorsal foot, and heel pain. It was learned

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that 7 years previously the patient had experienced swelling, redness and restricted movement in the left knee which lasted for 1 week and recovered spontaneously. Swelling developed in the ankle 3 years previously, and with a diagnosis of rheumatoid arthritis from the doctor consulted, treatment was started with methotrexate and steroids. The complaints regressed in a short time with this treatment, which the patient took for 6 months and then terminated. When the patient had complained of heel pain and swelling on the dorsum of the feet for the past year, it was learned that for the last 17 years, the patient had experienced pain spread across the whole abdomen lasting 2-3 days accompanied by fever, which then recovered spontaneously. The patient also stated that at the same time she experienced chest pain and joint complaints. The attacks occurred every 10-15 days and sometimes once a month. With high acute phase reactants and no pathology determined in the physical examination, the patient was diagnosed with FMF and treatment was started with colchicine 3x1. From the family anamnesis, it was learned that the patient's son had been recently diagnosed with FMF and Behçet's disease, and there was consanguinity of the patient's parents (first cousins). The laboratory test results were as follows: Erythrocyte sedimentation rate: 35 mm/h, urea: 28 mg/dL, creatinine: 0.7 mg/dL, aspartate aminotransferase: 18 IU/L, alanino aminotransferase: 13 IU/L, total protein: 7.1 gr/dL, and albumin: 3.8 gr/dL. Mild microcytic anemia (hematocrit: 33%) was determined on the hemogram and proteinuria in the full urine analysis. As approximately 1.5 g proteinuria was determined in the 24-hour urine test, rectal biopsy was planned with respect to amyloidosis, but the biopsy result was normal. On abdominal ultrasonography, other than increased liver dimensions (19 cm), there was no pathology. Complement levels, IgA, IgM, and IgG levels were normal, and the autoantibodies examined (anti-nuclear antibody, extractable nuclear antigens, anti dsDNA, and anti-neutrophilic cytoplasmic antibody) were determined to be negative. As M694V homozygote mutation was determined in the Mediterranean fever) gene, kidney biopsy was performed. Because of the biopsy, increased cells and mesangial expansion in some glomerules, thickening in basal membranes, periglomerular fibrosis in one glomerulus, and lymphocyte infiltration in the interstitium. No accumulation was detected in the glomeruli in the immunofluorescence examination (Figure 1). Amyloidosis was not determined by Congo red staining. With a diagnosis of MsPGN, treatment was started of mg/day azathioprine (AZA) and 50 mg/day losartan. After 6 months, protein of 542 mg/day was determined in the 24-hour urine test, and at the end of one year, 258 mg/day. The patient had no complaints under treatment.

LITERATURE REVIEW

To identify FMF cases with renal involvement other than amyloidosis, the Web of Science and PubMed databases were scanned using the headings of "FMF and MsPGN", "membranoproliferative (MP) GN" and "non-amyloid renal involvement". A total of 19 relevant cases/case series were identified, of which 3 (7-9) were excluded from the evaluation as they were mentioned by the same author in a 1992 publication (3). Together with the current case, 31 GN or nephropathy (NP) cases were identified in the literature, of which 54.8% were adult cases (3-6,10-21). The most reported GN type was MsPGN (15 cases) of which half were adults. In 3 adult and 2 pediatric cases of MsPGN, IgA NP was reported and in 1 pediatric case, IgM NP. In addition, IgA NP was reported in another 1 adult and 1 pediatric case, giving 7 (22.6%) cases of IgA NP. Other than MsPGN, cases were reported of MPGN (n=4), focal segmental glomerulosclerosis (n=5), rapidly progressive (RP) GN (n=2) and 1 case each of membranous GN, focal proliferative GN, and fibrillar GN (Table 1). Despite insufficient data in the publications, approximately half of the cases were seen to have proteinuria at a nephrotic level (3,6,11,12,20,21) and 14% had hematuria (12,13,18,21). Henoch-Schönlein purpura (HSP) was reported in only 4 cases, of which 1 also had polyarteritis nodosa (PAN) (4,10,18). Although IgA, IgM, IgG, and C3 accumulation was reported in the kidney biopsies of most patients, cases with no immune accumulation determined were also reported (19,21). Of the 10 cases, including the current case, with known mutations, M694V homozygote mutation was determined in 6 (6,11,14,17,18), of which 4 were reported as MsPGN. In addition, E148Q heterozygous positivity

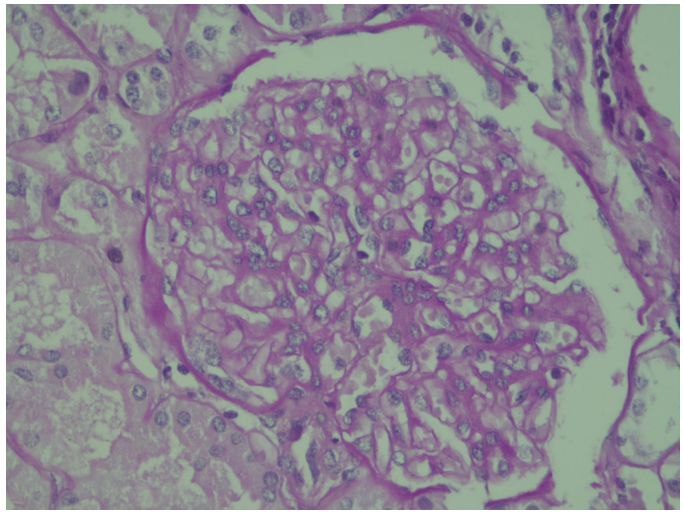

Figure 1. In the microscopic examination, there was mild swelling in the glomeruli, expansion in the mesangial matrix, and a slight increase in mesangial cells [Periodic acid Schiff (PAS)], X 200).

was determined in 2 cases with MsPGN. The publications were evaluated with respect to treatment; although treatment data for 4 cases could not be reached, it was observed that all of the cases used colchicine and 13 cases were in remission with only colchicine. A good response was reported to have been obtained with the other drugs corticosteroids (Cs) and AZA, as in the current case. The 2 cases of RPGN were given cyclophosphamide (CyP) in addition to Cs, and while one reached remission, the other was reported to have required chronic hemodialysis (3). In the case reported by Girisgen et al. (18), colchicine was administered for MsPGN (IgA), but it was emphasized that as the PAN clinical condition did not respond to Cs and CyP, intravenous immunoglobulin had to be administered.

DISCUSSION

Amyloidosis is the most important renal complication determining the prognosis of FMF and it presents with proteinuria. Long-term colchicine use can protect the patient

Table 1. Renal involvements other than amyloidosis in FMF patients

GN type (reference)		HSP/ PAN	n	Treatment	MEFV mutation	Outcome
Focal MsPGN (10)	Child (1)	HSP	2	Colchicine	ND	ND
Diffuse MsPGN[a] RPGN (3)	Child (3) Child	(-)	6 2	Colchicine Colchicine + CyP + Cs	ND	Improvement[b] 1 remission 1 hemodialysis
MPGN (5)	Child	ND	1	ND	ND	ND
MPGN FPGN (4)	Child	HSP (-)	1 1	ND	ND	ND
Fibrillary GN (12)	Adult	(-)	1	ND	M608I heterozygote	ND
MPGN (6)	Adult	(-)	1	Colchicine + Cs Azatioprin	M694V homozygote	Improvement[b]
MsPGN (11)	Child	(-)	1	Colchicine	M694V homozygote	Remission
MsPGN (IgA NP) (13)	Child	(-)	1	Colchicine	(-)	Remission
MsPGN (IgM NP) (14)	Child	(-)	1	Colchicine	M694V homozygote	Remission
IgA NPs (15)	Child	(-)	1	Colchicine	ND	Remission
Membranöz GN (16)	Adult	(-)	1	Colchicine	M680I/V726	Remission
IgA NP (17)	Adult	(-)	1	Colchicine	M694V homozygote	Remission
MsPGN (IgA NP) (18)	Child	HSP and PAN	1	Colchicine [c]Cs+CyP - IVIG	M694V homozygote	ND
MsPGN (19)	Adult	(-)	1	Colchicine	E148Q heterozygote	Remission
MPGN FSGS (20)	Adult	(-)	1 5	Colchicine + Cs Colchicine	ND	Non-nephrotic proteinuria
MsPGN (22)	Adult	(-)	1	Colchicine + Cs	E148Q heterozygote	Remission
MsPGN (current case)	Adult	(-)	1	Colchicine Azatioprin	M694V homozygote	Remission
Total	17 Adult 14 Child		31			

[a]Three adult patients had IgA NP, [b] Non-nephrotic proteinuria, [c]For PAN treatment
HSP: Henoch-Schonlein purpura, PAN: Polyarteritis nodosa, MsPGN: Mesangial proliferative glomerulonephritis, RPGN: Rapidly progressive glomerulonephritis, CyP: Cyclophosphamide, Cs: Corticosteroid, FPGN: Focal proliferative glomerulonephritis, MPGN: Membranoproliferative glomerulonephritis, FSGS: Focal segmental glomerulosclerosis

against the development of amyloidosis (2). Although there are no epidemiological studies of renal involvement other than amyloidosis, cases and case series have been reported. In a cohort of 106 FMF patients, Eliakim et al. (22) reported renal amyloidosis at a rate of approximately 12%, and renal problems other than amyloidosis in approximately 22% (temporary or permanent hematuria, recurrent acute pyelonephritis, typical acute post-streptcoccus GN, and other GN types). MsPGN has been reported in different systemic diseases such as systemic lupus erythematosus, HSP, rheumatoid arthritis, and vasculitis. The first publication related to glomerular diseases other than amyloidosis in FMF cases was by Flatau et al. (10) in 1982, in which focal MsPGN was determined in the biopsies of 2 cases with FMF and HSP. Subsequently, Said et al. (3) reported FMF cases with a diagnosis of IgA NP in whom a good response was obtained with colchicine (7,8). There have also been reports of MsPGN, MPGN, membranous GN, focal segmental glomerulosclerosis, and occasionally RPGN, IgM NP, focal proliferative GN, and fibrillar GN in FMF patients (13,23). The etiopathogenesis of GNs other than amyloidosis in FMF is not fully known. PAN has been reported in 1% of FMF cases and HSP in 5% (18). Kidney involvement in HSP is seen especially as IgA NP. In the review of literature performed in this study, HSP was determined in only 4 of 31 cases evaluated. Even if the other IgA NP cases were linked to HSP, the remaining cases couldnot be explained by this. The *MEFV* gene encodes pyrine, which is expressed in mature neutrophils and enables the suppression of inflammation. However, pyrite that has undergone mutation activates inflammasomes mediated by NF-kappa B and the activation of IL-1β and other inflammatory cytokines. Consequently, an abnormal immune response occurs. This increased inflammatory response is thought to facilitate immunological glomerular damage. Insufficient clearance of the immune complexes formed because of a hyper immune response can cause the development of glomerular disease (3,24-26). However, because immune complex accumulation was not seen in all cases, renal involvement other than amyloidosis cannon be explained by a single mechanism. Colchicine is effective in several non-amyloidosis renal involvements and has provided remission alone. The effect mechanism of colchicine in FMF is not exactly known, but it is thought to affect chemotaxis through its effect on microtubules. In addition, colchicine, which also has antioxidant properties, is thought to be effective in remission of proteinuria in FMF-related GN through these effects (11). However, in some cases, it is not sufficient alone, and remission can be achieved in these cases with immunosuppressive treatment and Cs use (6). In the case presented in this paper, because of GN developing under colchicine treatment, AZA was started and remission was obtained in the patient.

CONCLUSION

In FMF patients determined with proteinuria and/or hematuria, it should be kept in mind that there may be not only amyloidosis but also renal involvement other than amyloidosis, and the differential diagnosis should be made with kidney biopsy. Although colchicine treatment seems to be effective in renal involvements other than amyloidosis, immunosuppressive treatments may be necessary in some cases.

Ethics

Informed Consent: A written informed consent was obtained from the patient.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.Y., Ö.Ö.I., A.C., Concept: A.Y., D.K.Y., Design: A.Y., Data Collection or Processing: A.Y., Ö.Ö.I., A.C., Analysis or Interpretation: .A.Y., D.K.Y., Literature Search: A.Y., Ö.Ö.I., Writing: A.Y., Ö.Ö.I.

Conflict of Interest: The authors have no conflicts of interest to declare.

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