Unusual Fibrillary Glomerulonephritis in a 19-Month-Old Male Patient: A Case Report and Review of the Literature

Ondokuz Aylık Erkek Bir Hastada Olağandışı Fibriler Glomerülonefrit: Olgu Sunumu ve Literatürün Gözden Geçirilmesi

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ABSTRACT

Fibrillary glomerulonephritis (FG) is an immune-mediated type of glomerulonephritis characterized by Congo red-negative fibrillary electron-dense deposits. The incidence of FG is less than 1% in adults and it is very rare in children. We herein present a case of FG in a child with steroid-resistant nephrotic syndrome (SRNS). Nephrotic syndrome was diagnosed in a 19-month-old male patient based on the presence of periorbital edema and nephrotic-range proteinuria. Renal biopsy was performed because of the lack of response to eight weeks of prednisolone treatment and FG was diagnosed by electron microscopy. Unusual IgM deposits were present on immunofluorescence microscopy, contrary to previous reports in the literature. Because steroids and cytotoxic drugs were ineffective for the treatment of FG, an angiotensin-converting enzyme inhibitor (ACEi) was started. Monotherapy with the ACEi, caused the proteinuria to fall from the nephrotic-range to the subnephrotic-range. This case illustrates that although very rare in childhood, FG should be considered as a differential diagnosis of SRNS. Additionally, the prognosis of FG childhood is much better than that of FG in adulthood. ACEi therapy alone may be considered in the treatment of FG in childhood.

KEY WORDS: Fibrillary glomerulonephritis, Childhood steroid resistant nephrotic syndrome, Angiotensin converting enzyme inhibitors

ÖZ

Fibriler glomerülonefrit (FG), Kongo-kırmızısı boyası negatif boyanan, fibriler elektron-yoğun birikimlerle karakterize immün-aracılı glomerülonefrit tipidir. FG insidansı erişkinlerde %1'in altındadır ve çocuklarda da çok nadirdir. Biz burada steroid-rezistan nefrotik sendrom (SRNS) ayırıcı tanısında FG saptadığımız bir çocuk olguyu sunduk. Ondokuz aylık erkek hastada periorbital ödem ve nefrotik düzeyde proteinüri varlığı nedeniyle nefrotik sendrom tanısı konuldu. Sekiz haftalık prednizolon tedavisiyle remisyon sağlanamayınca renal biyopsi uygulandı ve elektron mikroskopi bulgularıyla FG tanısı konuldu. İmmünfloresan mikroskopide, daha önce literatürde bildirilenin aksine yoğun IgM birikimi mevcuttu. Steroid ve sitotoksik ilaçlar FG tedavisinde etkisiz oldukları için hastaya anjiotensin-dönüştürücü enzim inhibitörü (ADEi) tedavisi başlandı. ADEi ile yapılan monoterapi, nefrotik düzeyde proteinürinin subnefrotik düzeylere düşmesine neden oldu. Bu olgu bize, her ne kadar çocukluk çağında çok nadir olsa da SRNS ayırıcı tanısında FG'i de düşünmemizi gösterir. Ayrıca, çocukluk çağı FG'inin prognozu erişkin çağı FG'inden daha iyidir. Tek başına ADEi tedavisi, çocukluk çağı FG tedavisinde düşünülebilir.

ANAHTAR SÖZCÜKLER: Fibriler glomerülonefrit, Çocukluk çağı steroid-rezistan nefrotik sendrom, Anjiotensin-dönüştürücü enzim inhibitörleri

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INTRODUCTION

Fibrillary glomerulonephritis (FG) is an immune-mediated glomerulonephritis characterized by Congo-red-stain-negative, fibrillary electron-dense deposits that are stored in the glomerular mesangium and capillary walls (1,2). The deposits are predominantly composed of randomly arranged fibrils 12 to 30 nm in diameter, of

which the larger were immunotactoid glomerulopathy (ITG) fibrils, and the smaller were amyloid fibrils. Another difference between FG and ITG is that the deposits of FG comprise polyclonal immunoglobulin G4 (IgG4). However, both types of glomerulonephritis have been categorized as fibrillary-immunotactoid glomerulonephritis (3-6). The incidence of FG is less than 1% in adults, and it is very rare in children and only seven cases have been reported to date in childhood (1, 7-11). FG is most commonly seen in the fifth and sixth decades of life and with an equal incidence in men and women (2). The disease usually presents with proteinuria (often in the nephrotic-range), hematuria, renal failure and hypertension. Pediatric patients usually present with asymptomatic proteinuria and/or microscopic hematuria (1,7,9,11). Excluding occasional cases of systemic disease, serum complement levels are usually normal (12-16). The fibrillary electron-dense deposits mainly comprise IgG and C3, deposition of IgM is very rare (17). The prognosis is poor in adults, even with steroid and cytotoxic treatment, and chronic renal failure develops in 2 to 4 years in about half of affected patients (1-6). However, the prognosis is better in children (2,7,9,11,18). We herein present a case of FG with unusual IgM accumulation in a child. This case is extremely rare in terms of both the type of glomerulonephritis in children and the IgM deposition.

CASE REPORT

Nephrotic syndrome was diagnosed in a 19-month-old male patient based on the presence of periorbital edema and proteinuria in the nephrotic-range. At the time of diagnosis, the blood pressure was 80/50 mm Hg, hemoglobin 11.7 g/dl, hematocrit 36.1%, white blood cell count 11,700 mm^3, platelet count 464,000 mm^3, urea 8 mg/dl, creatinine 0.25 mg/dl, sodium 140 mmol/l, potassium 3.5 mmol/l, albumin 2.8 g/dl, total cholesterol 95 mg/dl, triglyceride 81 mg/dl, and 24-hour urine protein 335 $mg/m^2/h$. Hbs Ag, anti-HCV, anti-HIV, and antinuclear antibody studies were negative, and C3 and C4 serum levels were normal. Urinalysis revealed 4+ proteinuria and microscopic hematuria. Parvovirus B19, Epstein-Barr virus, and cytomegalovirus studies showed negative results. The urine protein electrophoresis value was 83% by the weight of albumin. Prednisolone treatment was begun at 2 mg/kg/day. Despite 8 weeks of treatment with prednisolone, the proteinuria remained in the nephrotic-range, and the serum albumin level remained normal. A podocin gene study and renal biopsy were then performed. The patient was negative for podocin gene mutation. Serial kidney sections revealed up to 48 glomeruli. Moderate to significant lobulation and enlargement of glomeruli as well as a mild increase in the number of mesangial cells and matrix volume were observed (Figure 1). Irregular thickening of the glomerular basal membrane and duplication (double contour appearance) in some places were also identified (Figure 2). The tubulointerstitial area, arterioles, and interlobular arteries were normal. Immunofluorescence microscopy revealed diffuse, mainly segmental, peripheral (capillary) dominant, coarse granular, and in some places band-style 3 (+) IgM deposition (Figure 3). There was no deposition of IgG, IgA, C3, C1q and lambda antibodies in the glomeruli. Mild granular kappa light chain antibody depositions in the glomeruli (focal, segmental, peripheral and mesangial) were present. Congo-red-dye-staining was negative. Electron microscopic examination revealed extensive accumulation of fibrillary and annular depositions in the mesangium, glomerular basal membrane, and subendothelial

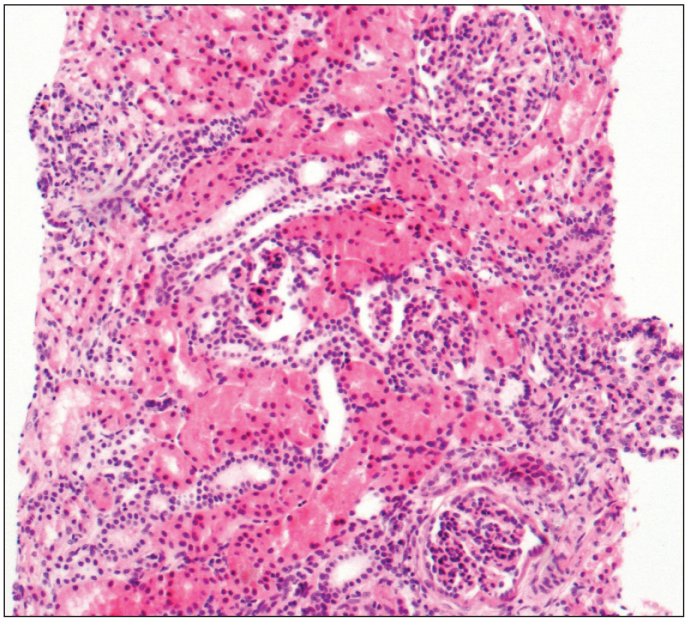

Figure 1: *Significant increases in lobulation of glomeruli associated with diffuse, moderate to significant mesangial cell proliferation are seen. Tubulointerstitial areas are generally protected (H&E, x 100).*

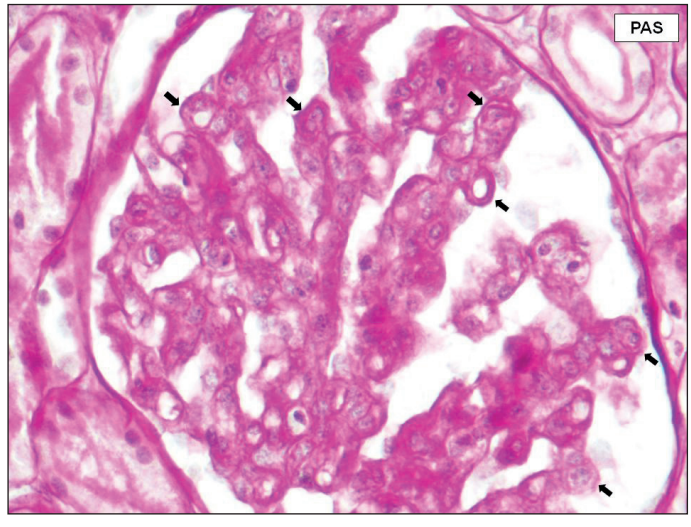

Figure 2: *An increase in glomerular lobulation, obliteration of some endocapillary lumens because of increased mesangial cells and duplication of the glomerular basement membrane (arrows) are seen (PAS, x400).*

areas in addition to extensive podocyte foot process effacement (Figure 4). The fibril thickness varied from 6.82 to 17.06 nM (mean, 11.90 nM) (Figure 5). Electron-dense deposits suggestive of immune complex deposition were not observed. The diagnosis of FG was made based on these findings. C3 nephritic factor and cryoglobulinemia test results were negative. Because the nephrotic-range proteinuria continued despite repeated steroid treatments, the patient was followed without treatment for a while. Monotherapy with the angiotensin-converting enzyme inhibitor (ACEi) (enalapril) was then started and the proteinuria fell to the subnephrotic level (Figure 6). The patient had normal renal function test results and subnormal serum albumin levels (3.0-3.5 g/dl) but subnephrotic-range proteinuria for five months under this treatment.

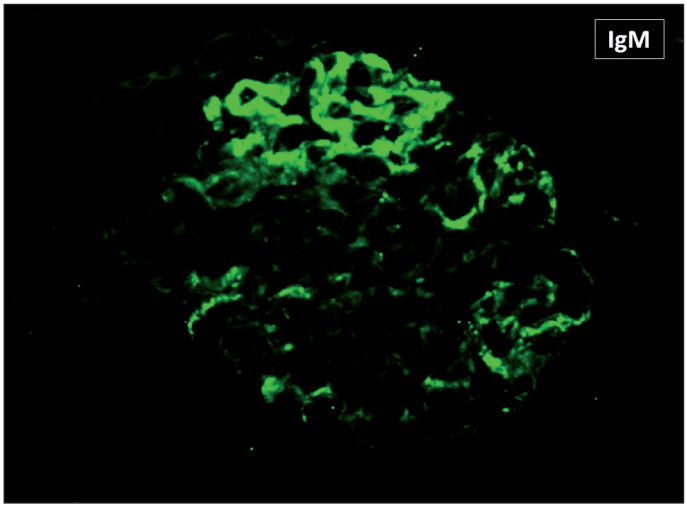

Figure 3: *Significant IgM deposition in the capillary walls, especially in areas of duplication and glomerular basal membrane thickening, is seen (DIF, Ig M, x400).*

DISCUSSION

Fibrillary Glomerulonephritis is extremely rare in children. Based on our literature review, only one previous case of FG associated with IgM deposition in childhood has been reported (10). We have herein reported the second pediatric case of FG associated with IgM deposition.

As discussed below, FG is histologically diverse like membranoproliferative glomerulonephritis (MPGN), mesengial proliferative/sclerosing glomerulonephritis, endocapillary proliferative glomerulonephritis by light microscopy and requires the necessary fibrillar infiltrate only visible by electron microscopy and a negative Congo red stain for diagnosis (4). The renal depositions in patients with FG usually consist of IgG and C3.

Fibrillary Glomerulonephritis has been found to be idiopathic in some studies but other studies have found it to be associated with malignancy (mainly carcinoma), autoimmune diseases (mainly Crohn's disease, systemic lupus erythematosus, Graves' disease, and idiopathic thrombocytopenic purpura) and hepatitis-C virus infection (2,4,6,19-25). The clinical

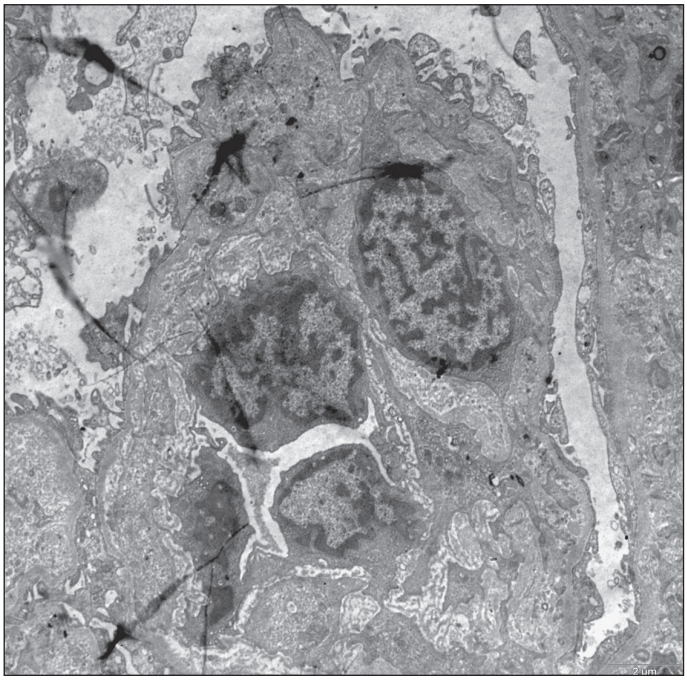

Figure 4: *Radiolucent expansion in glomerular basal membrane, duplication and mesangial interposition, vacuolization and foot process effacement of podocytes are seen (electron micrograph, bar:2µm)*

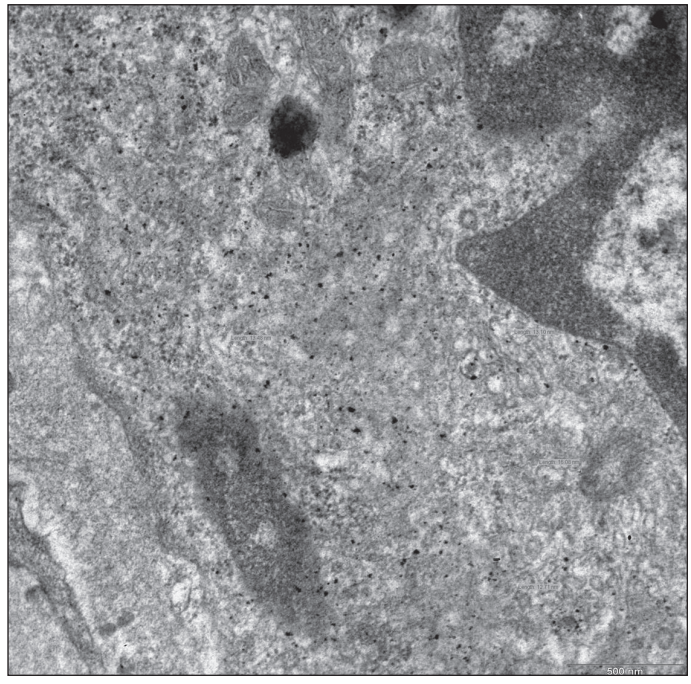

Figure 5: *Fibrillary and annular depositions in mesangium among the cytoplasmic extensions of mesangial cells are present (electron micrograph, bar: 500 µm).*

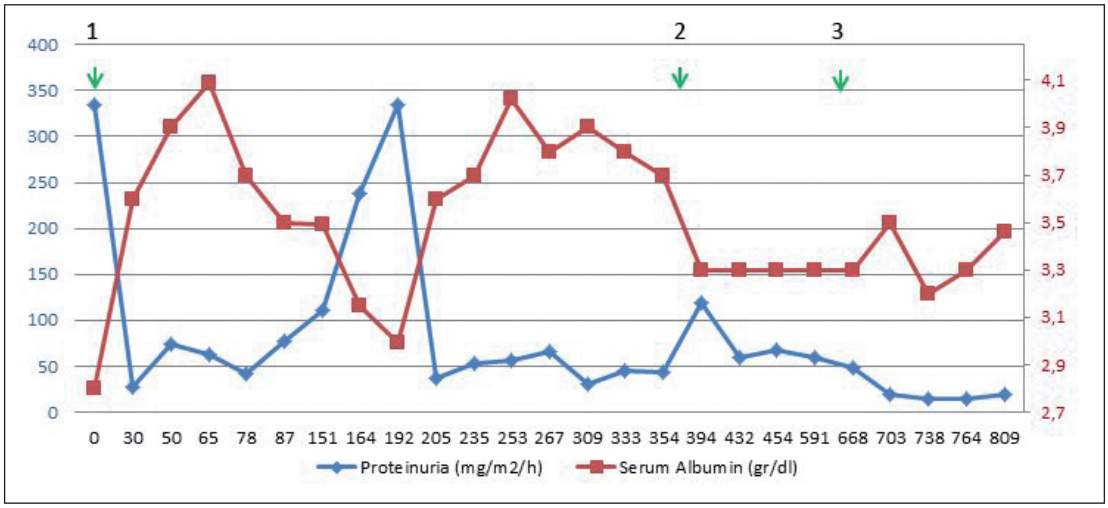

Figure 6: *Course of proteinuria and serum albumin levels in days following the diagnosis of FG. The arrows indicate treatments. 1st Arrow; the beginning of steroid (2 mg/kg/day), 2nd Arrow; follow-up without treatment, 3th Arrow; beginning of ACEi treatment alone (h: hour)*

presentation of FG in childhood usually involves asymptomatic proteinuria and/or microscopic hematuria but pediatric clinical presentations of MPGN, acute poststreptococcal glomerulonephritis and systemic lupus erythematosus at the beginning of the disease have also been reported (1,7-11, 20). The patient described herein presented with periorbital edema and nephrotic-range proteinuria, but he had no clinical or laboratory findings suggestive of systemic disease.

The pathogenesis of fibril formation in FG is unclear. Fibrillary deposition is usually limited to the kidney. There is sufficient evidence that fibrils are composed of immunoglobulins (25,26). Immunoglobulin subtype analysis in patients with FG has mainly revealed polyclonal IgG4 deposits (2,25-27). Normally, IgG4 comprises less than 5% of all immunoglobulins in the circulation. These observations have led to the hypothesis that FG mainly results from a long-term immune response resulting in Ig G4 formation (28).

Hypocomplementemia is very rare in patients with FG. In a study of 61 patients with FG and six patients with ITG, only one patient with FG and two with ITG had hypocomplementemia. Notably, all three of these patients had systemic diseases such as SLE and autoimmune vasculitis (4). As expected, the complement levels were normal in the present case. The renal depositions in patients with FG usually consist of IgG and C3, and to a lesser extent IgM, IgA and C1q. Based on our literature research, only one child and one adult with FG had unusual IgM deposition. In one case, a 69-year-old female patient presented with nephritic syndrome, and microscopic examination revealed IgM fibrillary deposits and multifeatured "barbed wire" appearance (29). In other case, 12-year-old patient had hypocomplementemia associated with moderately intense IgM deposition (10). In that case, the hypocomplementemia was interpreted as a hereditary partial complement deficiency rather than complement consumption. Likewise, the present case exhibited extensive deposition of IgM , but had normocomplementemia.

The reported prognosis of the diffuse sclerosing, diffuse proliferative and MPGN subtypes of FG is poor; that of the mesangial proliferative subtype is good; and that of the membranous subtype is fair (1-4,21). The present case was the MPGN subtype. However, the prognosis of different histological subtypes in six previously described pediatric patients including the MPGN subtype was relatively good (2,7,9,11,18).

There is no known effective treatment for FG/ITG. Nearly half of adult cases slowly progress to end-stage renal failure in 2 to 4 years (3-6). Steroids and cytotoxic drugs do not stabilize or improve renal function (13,21,27). Based on the observations that polyclonal IgG, which usually IgG4 subclass dominant, accumulates in the FG has led some to postulate that FG is an autoimmune condition that may be treated with rituximab (RTX), a monoclonal anti-CD20 antibody (3). RTX has been beneficial for the glomerular deposition of IgG in some adult patients (30-32). In a recently published study, long-term follow-up of 12 adult patients showed that RTX treatment applied in the early stages protected renal function (33). Another case report indicated that an adult patient benefited from plasmapheresis (34). The clinical course and prognosis of FG in childhood is good and renal function is preserved during an average 1- to 8-year follow-up period (1,7-11). Remission with only ACEi has been reported in adults (21,30). However, steroid and cytotoxic treatments are often needed in adults. A one-year follow-up of ACEi treatment alone in a 12-year-old male patient with concurrent sickle cell anemia and ITG revealed continued nephrotic-range proteinuria, but the absence of edema and normal renal function test results (18). Two years have passed since the initial diagnosis in the present case, and the patient currently has normal renal function, no edema, and subnormal serum albumin levels. With ACEi treatment alone, his nephrotic-range proteinuria levels fell to subnephrotic levels for five months.

Fibrillary deposits in renal transplantation in FG affects more than 50% of patients, but recurrent disease exhibits a relatively benign course (28).

CONCLUSION

Although very rare in childhood, FG should be considered as a differential diagnosis of steroid-resistant nephrotic syndrome. Additionally, practitioners should know that the prognosis is good, in contrast to the poor prognosis in adults. Monotherapy with ACEi treatment may be considered in the treatment of pediatric FG.

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