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Case Report

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A Challenging Presentation of Familial Mediterranean Fever- Associated Glomerulonephritis: A Case Report

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Abstract

Familial Mediterranean Fever (FMF) is a hereditary autoinflammatory disorder characterized by recurrent episodes of fever and abdominal pain. We report a case of a 13-year-old boy who developed kidney manifestations with a history of FMF from two years of age. The patient was diagnosed with FMF, but he did not comply with colchicine therapy. He presented with acute glomerulonephritis with gross hematuria, hypertension, nephrotic-range proteinuria, and impaired kidney function. Previous evaluations at several hospitals resulted in varying diagnoses because FMF-associated glomerulonephritis (GN) is rare. He was initially diagnosed with post-infectious glomerulonephritis and lupus nephritis, but there was no improvement despite various management strategies. After a comprehensive review, the patient was referred to our center and was diagnosed with FMF-associated membranoproliferative glomerulonephritis (MPGN). However, we could not exclude concurrent FMF-associated amyloidosis because of the absence of an Electron microscopy study of the kidney biopsy. Treatment with pulse Methylprednisolone, Colchicine, Enalapril, and interleukin-1 receptor antagonist (Anakinra) resulted in the resolution of proteinuria and hematuria and normalization of the kidney function. This case highlights the difficulties in diagnosis, timing of early intervention, and comprehensive treatment, including unconventional modalities in FMF-associated glomerular diseases. Further research is needed to optimize the management of FMF-associated kidney complications in pediatric patients.

Keywords: Familial mediterranean fever; FMF, Amyloidosis; Hematuria; Proteinuria; Glomerulonephritis; Membranoproliferative glomerulonephritis; MPGN; Case report

Introduction

Familial Mediterranean fever is an uncommon autosomal recessive, inherited autoinflammatory disorder that primarily affects individuals of Mediterranean origin. The commonly observed symptoms in these patients include recurring fever and abdominal pain, sometimes associated with skin lesions, synovitis, and serositis. Gene defects associated with FMF mainly involve MEFV mutations, which lead to an aberrant innate immune system and excessive release of pro-inflammatory cytokines [1]. FMF usually starts in childhood, with around 65% of patients having their first attack before age ten and 90% before age twenty years [2].

Among the major but uncommon complications of FMF, is kidney involvement. Amyloidosis of AA type, due to the deposition of the serum

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amyloid A protein in kidneys, has been described in up to 8.6% of FMF patients. However, a more uncommon development in FMF patients is MPGN, as documented by a retrospective study conducted at Cumhuriyet University where 3 out of 64 (4.7%) patients carrying FMF-gene mutations developed MPGN [3], in adults some reported up to 30% of patients with MEFV mutation develop MPGN [4,5].

The pathogenesis of FMF-associated MPGN is poorly understood, but it is thought to be related to the dysregulated immune response of FMF characterized by immune complex deposition and activation of the complement system within glomeruli, leading to proliferative changes. Managing the coexistence of FMF and MPGN poses diagnostic challenges, as distinguishing the underlying cause of glomerulonephritis is crucial for appropriate management [6].

This is a case report of a 13-year-old male child with FMF who has complicated kidney manifestations. The present case explains the diagnostic challenge, early institution of treatment, and possibilities of unconventional therapies. This case highlights the need for a dedicated diagnostic approach to rule out the various differential diagnoses of glomerulonephritis and amyloidosis in FMF patients.

This case report has been reported in accordance with the CARE criteria [7].

Case Report

Our patient is a 13-year-old male child, who has been diagnosed with FMF since he was two years old. Genetic testing revealed a homozygous mutation in M694V of MEFV gene. He has had poor adherence to colchicine treatment and was admitted to our hospital for evaluation after a three-month history of gross hematuria, hypertension, nephrotic range proteinuria, and elevated kidney function test. He was evaluated at three different hospitals, each providing varying diagnoses and management strategies, but there was no significant clinical improvement.

Over the course of 11 years since his diagnosis of FMF, the patient occasionally took colchicine, he did not adhere to the treatment consistently. During this time, he experienced recurrent episodes of fever, severe abdominal pain, and, at times, chest pain. These episodes typically lasted for two to three days and occurred approximately every three to four weeks. No regular investigations were conducted during these episodes as his parents usually managed him at home with the administration of a few days course of ibuprofen and ensured he was taking colchicine. Despite these measures, he continued to neglect the regular use of colchicine. Throughout this period, the parents denied any history of gross hematuria or edema.

The patient was in the previously mentioned health condition until the most recent illness, which occurred three months before the admission to our hospital. Initially, he presented to the first medical center after one week of tonsillitis, exhibiting symptoms such as generalized edema, gross hematuria, myalgia, arthralgia, abdominal pain, and occasional fever.

Urine analysis revealed abundant dysmorphic red blood cells (RBCs) and sub-nephrotic range proteinuria, serum albumin was slightly decreased at (3.4 g/dl), while serum creatinine was elevated at (1.46 mg/dl), which gradually improved and reached a normal level after few days of receiving Intravenous (IV) steroid therapy. The patient's inflammatory markers (ESR, and CRP) were also elevated and improved with the IV steroid treatment.

The patient was diagnosed with post-infectious glomerulonephritis (PIGN) despite a low C4 level in addition to low C3 which is unusual in PIGN, along with a negative Antistreptolysin O test (ASOT). At this stage, lupus nephritis was ruled out as both antinuclear antibodies (ANA) and double-stranded DNA (DsDNA) were negative, and there were no clinical criteria met for Systemic lupus erythematosus (SLE). Other lab findings are summarized in Table 1.

The patient received diuretics for the fluid overload, which resulted in slight improvement of the edema, and he was administered three doses of steroid (2 days of Intravenous (IV) Dexamethasone 4 mg, and one day of oral prednisolone 20 mg), which is unusually given in PIGN but the serum creatinine and the inflammatory markers improved, however they didn't fully normalize.

Unfortunately, the patient continued to experience various symptoms, like abdominal pain, myalgia, arthralgia, occasional fever, in addition to the persistence of gross hematuria and edema leading to the admission to the second medical center.

In the second center, the patient was edematous and hypertensive, he was administered unknown medications to control his blood pressure, investigations (details provided in Table 1) revealed elevated kidney function test, increased inflammatory markers (ESR, and CRP), sub-nephrotic range proteinuria (Urine protein-to-Creatinine ratio: 1.1 g/g), and low serum albumin (3 g/dl).

A kidney biopsy was performed and revealed diffuse proliferative glomerulonephritis on a light microscope with no chronic changes, negative Immunofluorescence (IF) including Congo-red stain. An electron microscope examination was not conducted due to unavailability in our country.

An Echocardiogram indicated signs of myocarditis, and the troponin enzyme levels were elevated, while virology studies were negative.

The patient was diagnosed with Lupus Nephritis (LN) and

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myocarditis, as C3 and C4 were low in one test, while the dsDNA test result was equivocal. He received another course of pulse steroid treatment (IV Methylprednisolone 500 mg for three days) and was subsequently maintained on a daily dose of oral prednisolone 20 mg.

It is important to note that repeated tests for C3 and C4 returned to normal levels on multiple occasions, and both ANA and dsDNA tests were negative in subsequent evaluations. After a few days of steroid treatment, the kidney function normalized, though inflammatory markers remained elevated.

The patient was referred to a third medical center for further evaluation due to the persistence of the same symptoms including fluid overload, gross hematuria, and high blood pressure. Investigations revealed normal kidney function tests, mild hypoalbuminemia, improved inflammatory markers, normal complement C3 and C4 levels, and negative results for ANA, dsDNA, RF, and ASOT.

Urine protein excretion showed nephrotic range proteinuria along with abundant red blood cells (RBC) in the urine. A repeat echocardiogram indicated improved contractility, with a slightly depressed ejection fraction, but otherwise normal findings.

The patient was again diagnosed with PIGN and was started on oral prednisolone, Additionally, the dose of colchicine was increased, and Enalapril was added to the treatment regimen.

The patient was eventually discharged home after three months of hospitalization across different facilities. At the time of discharge, he was hypertensive and still experiencing gross hematuria, myalgia, and abdominal pain. A week later, the patient was readmitted to our hospital due to a generalized convulsion. A brain MRI revealed Posterior Reversible Encephalopathy Syndrome (PRES). During this hospitalization, his blood pressure was elevated, exceeding the cutoff for second-stage hypertension based on his gender, age, and height. The hypertension was effectively managed with intravenous labetalol drip. Although he did not experience any further convulsions, he continued to complain of diffuse myalgia and arthralgia, persistent abdominal pain, gross hematuria, and mild edema.

Investigations at our center revealed normal kidney function tests but high inflammatory markers (ESR and CRP) and mild hypoalbuminemia (3.3g/dl). Complement levels (C3 and C4) were normal, and the infectious and immunology workup was negative. A urine protein-to-creatinine ratio revealed nephrotic range proteinuria. The echocardiogram was normal.

We excluded the previous medical center's diagnoses of PIGN and lupus nephritis, as both the ANA and dsDNA were negative on multiple occasions, complement levels (C3 and C4) were normal, ASOT was negative, and the kidney biopsy findings were inconsistent with these diagnoses. We also ruled out polyarteritis nodosa, as the abdominal CT angiography appeared normal.

Table 1: Investigations and Imaging.

Medical Center	Investigations and Imaging
First center	Serum Creatinine: 1.46 mg/dl → 0.66 mg/dl
	BUN: 47 mg/dl
	Serum Albumin: 3.4 g/dl
	Serum Electrolytes: Na: 142 mEg/L, Cl:110 mEg/L, K:4.6 mEq/L
	ALT:4 U/L
	AST:9 U/L
	CBC: WBC:11.3 cell/µL, Hb:10.7 g/dl, platelet:239 X10^9/L
	ESR:45 mm/hr
	CRP: 153 → 79 → 39
	C3: 25 (low)
	C4: 9.9 (low)
	ANA: negative
	dsDNA: not done
	ANCA: negative
	ASOT: Negative
	Urine Analysis: protein+2, RBC: many, dysmorphic RBCs: many
	Urine protein/creatinine ratio: 0.3 g/g
	Abdominal/ Kidney Ultrasound: The liver measures 15.7 cm with a normal echo pattern, spleen measures 14 with normal echo pattern. Both kidneys normal in size, with normal cortical thickness.
	Echocardiography: Normal

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Second center	Serum Creatinine: 1.19mg/dl → 0.4 mg/dl
	BUN:74 mg/dl → 49
	Serum Albumin: 3 g/dl
	Serum Electrolytes: Na:136 mEq/L, Cl:102 mEq/L, K: 5.2 mEq/L
	ALT: 15 U/L
	AST: 21 U/L
	CBC: WBC: 15 cell/µL , Hb:10.2 g/dl, platelet: 331 X10^9/L
	ESR: 62 mm/hr → 80 mm/hr → 50 mm/hr
	CRP: 58 mg/L →154 mg/L →73 mg/L
	C3: low → Normal → Normal
	C4: low → Normal → Normal
	ANA: borderline
	dsDNA IgM: 22.6 IU/ml (equivocal) → Negative
	Lupus anti-coagulant: negative
	Rheumatoid factor: negative
	ANCA: negative
	PCR of COVID-19 antigen, Influenzas A+B, CMV IgM and EBV IgM were negative.
	Urine Analysis: Protein +3, RBC: many, dysmorphic RBCs: many
	Urine protein-to-creatinine ratio:1.1 g/g
	Abdominal/ Kidney Ultrasound: Right kidney measures 11 cm. Left kidney measures 10.9 cm, both kidneys show slightly increased echogenicity, otherwise normal kidneys. The spleen measures 15.5 cm
	Echocardiography: Picture of myocarditis with decreased function (Ejection Fraction: 51%), rising troponin 56, minimal left ventricular dilatation, trace Tricuspid and Mitral Regurgitation with signs of moderate pulmonary hypertension.
Third center	Serum Creatinine: 0.48 mg/dl → 0.4 mg/dl
	BUN: 31.8 mg/dl → 26 mg/dl
	Serum Albumin: 3.1 g/dl
	Serum Electrolytes: Na:124 mEq/L, Cl:103 mEq/L, K: 3.5 mEq/L
	ALT: 26.3 U/L
	AST: 26.6 U/L
	CBC: WBC: 14.1 cell/µL, Hb:8.86 g/dl, platelet:147 X10^9/L
	ESR: 18 mm/hr
	CRP: 23 mg/L
	C3: 107 mg/dl (normal)
	C4: 15 mg/dl (normal)
	ANA: negative
	dsDNA: negative
	Lupus anti-coagulant:
	Rheumatoid factor: negative
	ANCA: negative
	ASOT: negative
	Urine Analysis: protein+3, RBC:200 cell/hpf, dysmorphic RBCs: 50%.
	Urine protein excretion in 24-hour urine collection: 53 mg/kg/hour (nephrotic range)
	Abdominal/ Kidney Ultrasound: The liver measures 14 cm with a normal echo pattern, spleen measures 15.7 with normal echo pattern. Both kidneys normal in size, slight increased cortical echo pattern.
	Echocardiography: Trace Mitral Regurgitation, good global function, Ejection Function:63% (Normal).

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At our Medical hospital	Serum Creatinine: 0.46 mg/dl
	BUN:19 mg/dl
	Serum Albumin:3.3 g/dl
	Serum Electrolytes: Na:141 mEq/L, Cl:107 Meq/L, K:3.8 mEq/L
	ALT:8 U/L
	AST:19 U/L
	CBC= WBC:18.6 cell/µL, Hb:10.2 g/dl, platelet: 229 X10^9/L
	ESR:55 mm/hr
	CRP:201 mg/L
	C3: 133 mg/dl (normal)
	C4: 28.9 mg/dl (normal)
	ANA: Negative
	dsDNA IgM titter: Negative
	Lupus anti-coagulant: negative
	Rheumatoid factor: Negative
	ANCA: negative
	ASMA: negative
	Cryoglobulin: negative
	ASOT: Negative
	Hepatitis B s Antigen: negative
	Hepatitis C serology: negative
	Serum Amyloid A (SAA): 98.4 mg/L (high)
	Urine Analysis: Protein+2, RBC: >100
	Urine protein-to-creatinine ratio: 5.6 g/g
	Abdominal/ Kidney Ultrasound: Liver is enlarged measuring about 17.5cm with normal texture Spleen is enlarged measuring about 15cm in bipolar length (upper limit of normal size according to age is 11.7cm). Both kidneys show increased echogenicity suggesting parenchymal renal disease and appending slightly enlarged, measuring about 11.3cm on the right and 11.8cm on the left in bipolar length.
	Echocardiography: Normal

We believe that the patient's underlying chronic medical condition, familial Mediterranean fever (FMF), has significantly contributed to the development of glomerulonephritis (GN). Upon analyzing the clinical and laboratory findings, including the kidney biopsy-which revealed endocapillary proliferation, mesangial hypercellularity, lobular accentuation, and neutrophilic infiltration; we diagnosed the patient with FMF-associated MPGN. However, we could not entirely rule out FMF-associated amyloidosis. Although the Congo red stain and immunofluorescence results were negative, a definitive diagnosis through electron microscopy is necessary to exclude this possibility [8].

Unfortunately, this examination is not available in our resource-limited country. Thus, we are working with two potential diagnoses, but we believe that FMF-associated amyloidosis is unlikely, considering the duration of the illness and the negative Congo red stain results.

During the hospitalization at our center, serum amyloid A (SAA) was tested and found to be elevated. It is well known that SAA levels increase during attacks of FMF. In some cases, SAA may remain elevated due to subclinical inflammation. Prolonged high level of SAA is associated with the development of amyloidosis. Unfortunately, we were unable to repeat the test during the follow-up because it must be sent abroad and is costly [9].

It is important to note that immunofluorescent (IF) in MPGN typically shows the deposition of immunoglobulin, mainly IgG, and/or complement deposition, primarily C3. However, in our case, the IF was negative. This does not rule out the diagnosis of MPGN, as it is possible to present with negative IF staining [10].

Managing glomerulonephritis (GN) related to FMF is challenging due to its rarity and the lack of established treatment guidelines. Treatment should focus on the suspected underlying condition, which is FMF.

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Initially, Colchicine was reintroduced, with a gradual dosage increase of 1.5 mg per day for one week, followed by an increase to 2 mg per day. Additionally, the patient received intravenous methylprednisolone (60 mg daily) for seven days, followed by 60 mg of oral prednisolone daily, with a slow tapering schedule. The patient was also prescribed Enalapril (10 mg daily) and Amlodipine (10 mg daily) to manage hypertension.

After one month of treatment, the patient's blood pressure was well-controlled; however, he continued to experience symptoms including gross hematuria, nephrotic range proteinuria, severe abdominal pain, diffuse myalgia, and arthralgia; Consequently, a second-line treatment for FMF was initiated with Anakinra (IL-1 receptor antagonist) administered subcutaneously at a dose of 50 mg subcutaneously daily. After one week of daily in-hospital Anakinra injections, the patient was asymptomatic and able to move without arthralgia or myalgia, and his gross hematuria had resolved. His blood pressure remained within the normal range, and Amlodipine and Enalapril were discontinued after two months. Investigations showed normal kidney function and normalization of the inflammatory markers. He returned for follow-up visits to the pediatric nephrology and rheumatology clinics at two weeks, one month, two months, four months, and six months (as outlined in Table 2). During this time, the dose of steroids was gradually tapered by 5 mg each week after the initial two weeks until the medication was discontinued.

Discussion

In this paper, we report on a child with a history of Familial Mediterranean Fever (FMF) and non-adherence to colchicine, who presented with glomerulonephritis (GN). We believe this condition is related to FMF and is classified as membranoproliferative glomerulonephritis (MPGN).

The patient's diagnosis was missing at various hospitals as FMF-associated glomerulonephritis. This case illustrates the diagnostic challenges associated with FMF, a relatively uncommon disorder that can manifest in various ways. The study aims to emphasize the importance of early diagnosis and the timely initiation of appropriate management to prevent further progression and complications of this disease.

Lupus nephritis and other autoimmune diseases can be ruled out in this case due to the absence of clinical criteria and negative results from the autoantibody tests, including negative ANA, dsDNA, C-ANCA, and P-ANCA [11]. Additionally, the low level of complement C3 and C4 makes other potential diagnoses, such as post-infectious glomerulonephritis, which typically presents with suppressed C3 and a normal C4 level [12]. Furthermore, the kidney biopsy and the clinical scenario of the patient help eliminate other possible differential diagnoses, including IgA nephropathy, polyarteritis nodosa, and Henoch-Schonlëin purpura. As a result, secondary MPGN emerge as the main potential diagnosis.

Table 2: Progression of patient's condition after discharge.

Presentation	Admission	Two weeks	One Month	Two months	Four Months	Six Months
Abdominal Pain	Severe	No	No	No	No	No
Arthralgia	Severe	No	No	No	No	No
Myalgia	Severe	No	No	No	No	No
Gross Hematuria	Yes	No	No	No	No	No
RBC in urine analysis	> 100 cells/HPF	45 cells/HPF	40 cells/HPF	35 cells/HPF	8-10 cells/HPF	3-5 cells/HPF
Protein in urine analysis	3	1	Trace	Negative	No protein	No protein
Urine Protein-to-creatinine ratio (g/g)	6.5	2.12	0.3	0.3	0.27	0.33
ESR (mm/hr)	75	60	32	30	32	33
CRP (mg/L)	201	27	Negative	Negative	Negative	Negative
Medications	-Colchicine 1. 5 mg TID	-Colchicine 2 mg BID	-Colchicine 2 mg BID	-Colchicine 2mg BID	-Colchicine 2 mg BID	-Colchicine 2 mg BID
	-Prednisolone 30 mg BID	-Prednisolone 60 mg OD	-Prednisolone 50 mg OD	-Prednisolone 40 mg OD	-Prednisolone 15 mg OD	-Anakinra 50 mg SC OD
	-Enalapril 5 mg BID	-Anakinra 50 mg SC OD	-Anakinra 50 mg SC OD	-Anakinra 50 mg SC OD	-Anakinra 50 mg SC OD	
		-Enalapril 10 mg OD	-Enalapril 10 mg OD	-Enalapril 10 mg OD		
		-Amlodipine 10 mg OD	-Amlodipine 10 mg OD	-Amlodipine 10 mg OD		

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This case study highlights the limitations of performing a kidney biopsy without access to electron microscopy. Electron microscopy is essential for diagnosing FMF-associated amyloidosis and differentiating it from other conditions [8]. In this case, without electron microscopy, a definitive diagnosis could not be established, and the possibility of amyloidosis could not be excluded.

Electron microscopy provides critical information about ultrastructural changes, deposits, and the patterns of immune complexes, which aid in identifying and classifying kidney disorders [13]. Unfortunately, it is also an expensive procedure that many developing, low-income countries cannot afford [14].

The management of FMF aims to achieve several goals: prevention of acute attacks, reduction of subclinical inflammation between attacks, and prevention of the development of end-stage kidney disease and its progression. Treatment strategies for kidney diseases related to FMF vary depending on the underlying cause. For FMF-associated Amyloidosis or GN, colchicine is the recommended initial therapy for all patients, regardless of the frequency or severity of their attacks [15].

Corticosteroid therapy has been found to benefit some patients with FMF who also have glomerular disease, particularly in cases where colchicine therapy has not been effective. This treatment can help prevent the disease from progressing to a more severe stage, such as FMF-associated GN [15]. However, there are instances where both colchicine and corticosteroid therapies may not work. In such cases, alternative treatments, such as early intervention with biological medication like interleukin-1 receptor antagonists offer more promising and a safe option [16].

One example of an IL-1 inhibitor is Anakinra, which has shown promising results in the treatment of FMF. According to a systematic review, 77% of the 64 patients treated with Anakinra experienced a complete response, leading to a reduction in the frequency of inflammation and attacks. Additionally, 19% had a partial response, while three patients did not show any clinical improvement [17,18].

Clinical data on Anakinra about kidney involvement related to familial Mediterranean fever (FMF) are scarce, as most of them report amyloidosis cases. These reports suggest that Anakinra may help improve treatment outcomes, leading to partial or complete resolution of proteinuria. However, we did not find any specific studies addressing the use of Anakinra in FMF-associated membranoproliferative glomerulonephritis (MPGN) [19-21].

The adverse effects of Anakinra are generally mild, with the most common being a local reaction at the injection site [15]. However, in our case, no local reaction or any other adverse effects were observed. The patient responded well to Anakinra after showing significant resistance to colchicine and steroid. Additionally, there was an improvement in kidney function, along with the resolution of hematuria, proteinuria, and abdominal pain. This highlights the importance of considering alternative therapies for patients who experience significant organ involvement or have a poor response to traditional treatments of FMF.

This case report emphasizes several important aspects of FMF and its impact on kidney health. FMF is an autosomal recessive autoinflammatory disorder primarily affecting individuals of Mediterranean descent. A significant complication of FMF is kidney involvement, which often manifests as amyloidosis. Although glomerulonephritis, including MPGN, is a rare complication of FMF, diagnosing FMF-associated GN can be challenging. It requires a comprehensive evaluation, including additional diagnostic tests in some cases. More research into the underlying mechanisms of FMF-associated GN is essential for the development of targeted treatment strategies.

Conclusion

This case report highlights the importance of recognizing kidney diseases associated with FMF, such as amyloidosis and glomerulonephritis, including MPGN, in patients with FMF who present with heavy proteinuria, nephrotic syndrome, gross hematuria, hypertension, or kidney impairment. Accurate diagnosis and effective management are essential for improving patient outcomes. Additionally, considering biological therapies like Anakinra for cases of colchicine-resistant FMF-associated kidney disease may preserve kidney function. Further research is needed to enhance our understanding of the progression of these conditions and to optimize treatment strategies for FMF-associated glomerulonephritis.

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