

Polyarteritis nodosa in case of familial Mediterranean fever

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Familial Mediterranean fever (FMF) is an autosomal recessive disease characterized by recurrent self-limited attacks of fever accompanied by peritonitis, pleuritis, and arthritis. Protracted febrile myalgia syndrome (PFMS) is a rare form of vasculitic disease which is an uncommon dramatic manifestation of FMF, characterized by severe crippling myalgia and high fever. Polyarteritis nodosa (PAN) is a systemic necrotizing vasculitis affecting medium or small arteries. It is rarely observed in children, but its incidence increases in the presence of FMF. In this article we described a 14-year-old child diagnosed with FMF associated with PAN. Physicians should be aware of this possible association.

Key words: familial Mediterranean fever, protracted febrile myalgia syndrome, polyarteritis nodosa.

Familial Mediterranean fever (FMF) is an autosomal recessive disease characterized by recurrent self-limited attacks of fever and inflammatory serositis. The clinical spectrum of FMF has recently been expanded and protracted febrile myalgia syndrome (PFMS) is now a frequently recognized component in these patients. Protracted febrile myalgia syndrome is characterized by severe paralyzing myalgia, high fever, abdominal pain, arthritis/arthralgia, and transient vasculitic rashes mimicking Henoch-Schönlein purpura (HSP). Sometimes, FMF can be diagnosed with PFMS as a first manifestation.^{1,2} Familial Mediterranean fever may be associated with several types of vasculitic diseases including polyarteritis nodosa (PAN), HSP and Behcet's disease. Polyarteritis nodosa is a necrotizing vasculitis of medium and/or small-sized arteries in childhood, characterized by a wide variety of clinical features including fever, constitutional symptoms, and systemic involvement. Malaise, fever, rash abdominal pain, and arthropathy as well as myalgia and hypertension are the main clinical features of PAN.^{3,4} A few case reports reveal the coexistence of FMF with PAN.⁵⁻⁷ Here we described a child diagnosed with FMF associated with PAN.

Case Report

A 14-year old male adolescent presented with fever, diffuse myalgia and abdominal pain lasting for about 4 weeks and purpura on his arms and legs for the last 5 days. His medical history revealed that he underwent an appendectomy when he was 6 years old and he had an episode of fever, myalgia and abdominal pain when he was 12 years old, but no recurrent episodes of abdominal pain. His parents have no consanguinity and there was no personal/family history of autoimmune or rheumatic diseases.

Physical examination showed normal anthropometric development, but high blood pressure (144/75 mmHg), fever (39°C), diffuse abdominal tenderness and severe muscular tenderness on all extremities. Along with tenderness, there was swelling and erythema on both shoulders, elbows and wrists. The liver was palpable about 2 cm below the right costal margin and the spleen was palpable about 3 cm below the left costal margin. Examination of the cardiovascular and respiratory system was normal.

Laboratory investigations revealed leukocytosis (15500/mm³), normal platelet (351000/mm³),

hemoglobin (13.3 g/dl) levels and normal serum urea, creatinine, creatine phosphokinase (CPK), electrolytes and transaminases. Erythrocyte sedimentation rate (ESR) (93 mm/h), C-reactive protein (CRP) (193 mg/L), and fibrinogen (6.68 mg/dL) were elevated. Immunoassays for hepatitis B, hepatitis C, hepatitis A, toxoplasmosis and cytomegalovirus were negative. Serum C3 and C4 levels were normal. Antinuclear antibody (ANA), anti-double stranded DNA (anti-ds DNA), perinuclear-antineutrophil cytoplasmic antibody (p-ANCA), and cytoplasmic-antineutrophil cytoplasmic antibody (c-ANCA) were negative. Blood, urine and throat cultures were negative for pathogenic bacteria. Chest X-ray and abdominal sonography did not reveal any pathologic finding. The urine analysis showed the presence of microscopic hematuria and mild proteinuria (19.5 mg/m²/h).

Based on the presence of persistent fever, paralyzing myalgia with normal CPK and elevated CRP, the diagnosis of PFMS was considered and prednisolon (1 mg/kg/day) was started. His symptoms resolved within two days and acute phase reactants declined rapidly, supporting the diagnosis of PFMS. Genetic analysis for FMF showed that the patient was homozygous for the M694V mutation. Colchicine was added to prednisone treatment.

A skin biopsy showed signs of vasculitis with leukocytoclasia. Skin biopsy revealed abundant neutrophil infiltrates around superficial dermal capillaries with fibrinoid necrosis, hemorrhage, and nuclear dusts, which was consistent with features of necrotizing vasculitis (Fig. 1). Study of skin biopsy by direct immunofluorescence showed negative findings. Concerning the findings of purpuric rash, skin biopsy findings, elevated blood pressure, hematuria and significant proteinuria, a vasculitic process, most probably PAN was suspected and a renal biopsy was performed. Pathologic examination of the biopsy specimen revealed pauci-immune focal and segmental necrotizing and crescentic glomerulonephritis confirming the clinically suspected diagnosis of PAN and direct immunofluorescence was negative for IgA and amyloid deposits (Fig. 2). His prednisolon dose was increased to 2 mg/kg/day and also azathioprine (2 mg/kg/day) was added to the treatment. So,

the patient who presented with PFMS was subsequently diagnosed as having FMF and PAN based on clinical features, genetic analysis and histopathological findings.

He responded well to prednisolone and azathioprine therapy in addition to colchicine. The patient has been symptom free during the 36 months of follow-up since he was discharged from hospital. On the following days, clinical symptoms subsided, blood pressure was controlled with the combination treatment of angiotensin-converting-enzyme inhibitor and calcium channel blocker, and acute-phase reactants returned to normal levels within 3 months. After 4 weeks, steroid treatment was tapered gradually and discontinued within 12 months. Azathioprine therapy was used for 2 years and then discontinued. He is currently on colchicine treatment and remains in remission.

Informed consent was received from the family.

Discussion

Familial Mediterranean fever, also known as paroxysmal polyserositis, is an autosomal recessive inflammatory disease characterized by a lifelong course and recurrent attacks of inflammation of serosal membranes and fever resulting in acute abdominal, chest, and/or joint pain. The identification of the MEFV gene on chromosome 16p and its protein called pyrin (or marenostrin) has led to significant progress in understanding the pathogenesis of FMF. The MEFV gene encodes the pyrin which is a part of the inflammasome complex. Inflammasomes are multimeric complex of innate immune receptors. Pyrin protein is expressed mostly in neutrophils and has an important role in the regulation of innate immunity, including possibly the downregulation of inflammation. The function of the normal pyrin protein is to interact with another protein, known as "apoptotic speck-like protein with a caspase recruitment domain" (ASC).^{8,9} The interaction between normal pyrin and ASC causes inhibition of ASC, thereby preventing the occurrence of inflammation downstream. However, in the presence of MEFV gene mutations, dysfunctional pyrin cannot inhibit ASC, resulting in the activation of caspase 1, also known as IL-1 β -converting enzyme (ICE), which converts pro-IL-1 β to mature IL-1 β . Uncontrolled production of IL-1 β drives the

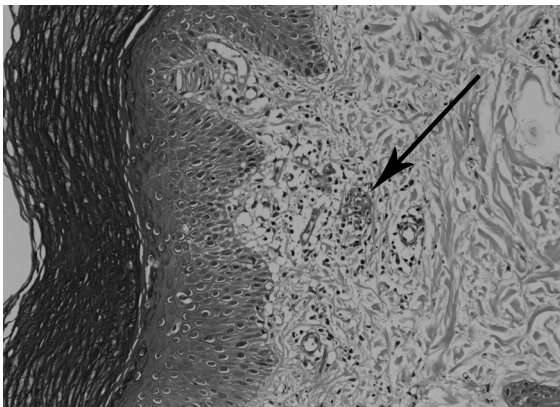


Fig. 1. Microscopic view of the skin biopsy showing fibrinoid necrosis with inflammatory cell infiltration of the superficial dermal capillaries (hematoxylin and eosin staining, x 200).

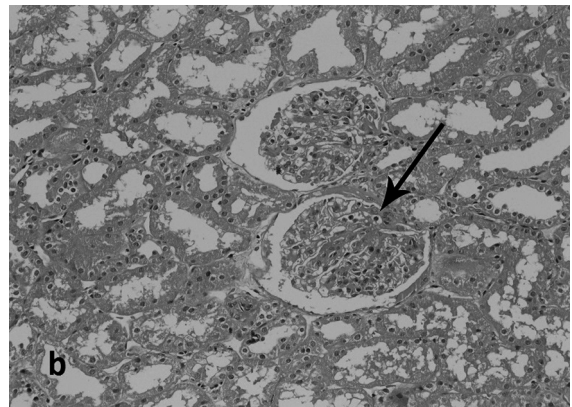


Fig. 2b. Polymorphonuclear leucocytes in the tuft necrosis (hematoxylin and eosin staining, x 200).

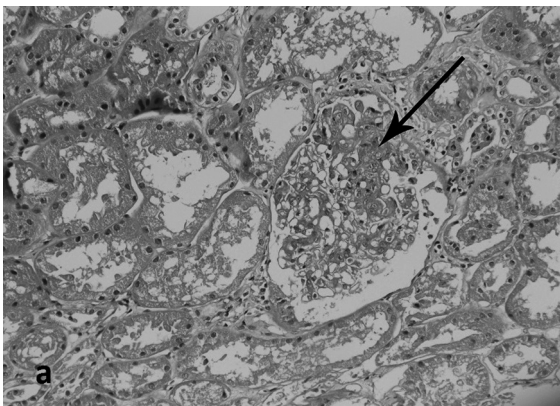


Fig. 2a. Microscopic view of the kidney biopsy showing the characteristic feature of PAN. Endocapillary proliferation with a segment of fibrinoid necrosis (hematoxylin and eosin staining, x 200).

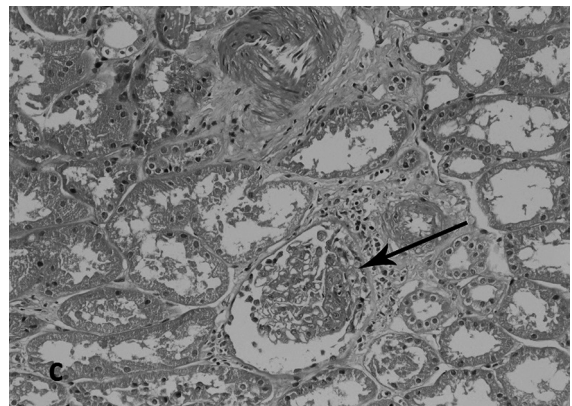


Fig. 2c. Extracapillary proliferation with fibrinoid necrosis (hematoxylin and eosin staining, x 200).

recurrent episodes of fever and inflammation in the peritoneum, pleura, and joints; persistent subclinical inflammation is also common.

Among rare symptoms of the disease, muscular manifestations may be seen as one of the main clinical manifestation or as its sole feature and should be recognized. Protracted febrile myalgia syndrome was first described in a group of FMF patients who had profound myalgia, fever, arthritis, and purpura lasting more than 1 month.¹⁰ It was also reported that PFMS may occur as a first attack before being diagnosed as having FMF.¹¹⁻¹³ Similarly, in our patient, the first attack of FMF was characterized by PFMS. Our patient who admitted with prolonged severe myalgia, fever and abdominal pain with no family history but previous history of clinical findings suspicious

for FMF was diagnosed as PFMS after excluding infectious and malignant conditions.

Studies evaluating the genotype-phenotype relationship showed that the homozygote M694V mutation was the most common in FMF-associated PFMS, as in our patient.^{1,14,15} Since patients having homozygous M694V mutation had higher disease severity scores, the association between the M694V allele and PFMS was not surprising. Indeed, this coincidence may be related to the fact that the homozygous M694V mutation is already very common in patients with FMF. Besides, different MEFV mutations other than M694V have been found in patients with PFMS.^{15,16}

Familial Mediterranean fever is associated with several types of vasculitis, including PAN, HSP and Behcet's disease.¹⁷ Polyarteritis nodosa is a systemic necrotizing vasculitis affecting medium or small arteries. It is rarely observed in children, but its incidence increases in

the presence of FMF. The European League against Rheumatism (EULAR), The Paediatric Rheumatology International Trials Organisation (PRINTO) and The Paediatric Rheumatology European Society (PRES) defined the final criteria for childhood PAN, which includes histopathologic or angiographic abnormalities (mandatory) plus one of the following: skin involvement, myalgia/muscle tenderness, hypertension, peripheral neuropathy, and renal involvement.⁴ Classical angiographic findings seen in PAN are aneurysmal dilation, vascular ectasia and occlusion. Doppler sonography or computed tomography (CT) may be used, but, if normal, CT angiography is recommended on suspicion of the diagnosis.⁵ Our patient had histopathologic abnormality which is necrotizing vasculitis on renal biopsy and four criteria (hypertension, myalgia, skin and renal involvement) sustaining the diagnosis of PAN according to final EULAR/PRINTO/PRES criteria. Although CT angiography was normal in our patient, because the diagnosis was established, conventional angiography was not applied.

Although the exact etiopathogenesis of FMF-associated vasculitis is not known, the underlying mechanisms possibly involve the effects of various environmental factors on the context of a genetic predisposition. FMF-related MEFV gene mutations favor TH1 polarization and cause a background of very high levels of proinflammatory cytokines including IL-1 β , IL-6, IL-18, IL-33, and INF- β .^{9,18} From vascular point of view, all these proinflammatory cytokines and other inflammatory mediators may play a role in vasculitis, and they may possibly serve as a link between FMF and associated vasculitides. Among those cytokines, IL-1 β is the most prominent one, and extremely high IL-1 β activity may favor vasculitis development in FMF patients. Initially, the proinflammatory cytokines may cause endothelial cell dysfunction (ECD), later followed by endothelial damage, leukocyte infiltration, and fibrinoid necrosis within the arterial wall.⁹ ECD in FMF favors vasculitis development. The contributing effects of environmental factors, especially the streptococcal infections, also seem to be important in the etiology of vasculitis.

In conclusion, since M694V is accepted to be associated with more severe inflammation as compared to other mutations, one can speculate that this enhanced inflammation may predispose to PFMS and PAN. Protracted febrile myalgia syndrome is a rare, dramatic situation in patients with undiagnosed FMF. Patients with clinical findings not typical for FMF should be considered for PFMS in the presence of long lasting myalgia, fever and increased acute phase reactants. MEFV mutation analysis should be performed earlier in such cases. MEFV mutations may act as a genetic susceptibility factor for vasculitis in FMF patients, and homozygous M694V mutation probably contribute to the risk to developing PAN. Familial Mediterranean fever patients with homozygote MEFV mutation and findings consistent with vasculitis syndromes should also be considered for PAN.

REFERENCES

1. Soylu A, Kasap B, Türkmen M, Saylam GS, Kavukçu S. Febrile myalgia syndrome in familial Mediterranean fever. *J Clin Rheumatol* 2006; 12: 93-96.
2. Bircan Z, Usluer H. Protracted febrile myalgia mimicking polyarteritis nodosa. *J Clin Rheumatol* 2008; 14: 222-225.
3. Yalçinkaya F, Özçakar ZB, Kasapçopur O, et al. Prevalence of the MEFV gene mutations in childhood polyarteritis nodosa. *J Pediatr* 2007; 151: 675-678.
4. Ozen S, Pistorio A, Iusan SM, et al. EULAR/PRINTO/PRES criteria for Henoch-Schönlein purpura, childhood polyarteritis nodosa, childhood Wegener granulomatosis and childhood Takayasu arteritis: Ankara 2008. Part II: Final classification criteria. *Ann Rheum Dis* 2010; 69: 798-806.
5. Bakkaloğlu SA, Muzaç S, Akpek S, Söylemezoğlu O, Buyan N, Hasanoğlu E. Polyarteritis nodosa in a case of familial Mediterranean fever. *Pediatr Nephrol* 2004; 19: 536-538.
6. Yılmaz A, Ağladioğlu S, Bakkaloğlu Ezgü S, Peru H ve ark. Ailevi Akdeniz ateşi ve poliarteritis nodoza birlikteliği olan pediatrik bir olgu sunumu. *Gazi Tıp Dergisi* 2008; 3: 144-146.
7. Ozen S, Ben-Chetrit E, Bakkaloğlu A, et al. Polyarteritis nodosa in patients with Familial Mediterranean Fever (FMF): a concomitant disease or a feature of FMF? *Semin Arthritis Rheum* 2001; 30: 281-287.
8. Samuels J, Ozen S. Familial Mediterranean fever and the other autoinflammatory syndromes: evaluation of the patient with recurrent fever. *Curr Opin Rheumatol* 2006; 18: 108-117.
9. Aksu K, Keser G. Coexistence of vasculitides with familial Mediterranean fever. *Rheumatol Int* 2011; 31: 1263-1274.

10. Langevitz P, Zemer D, Livneh A, Shemer J, Pras M. Protracted febrile myalgia in patients with familial Mediterranean fever. *J Rheumatol* 1994; 21: 1708-1709.
11. Majeed HA, Al-Qudah AK, Qubain H, Shahin HM. The clinical patterns of myalgia in children with familial Mediterranean fever. *Semin Arthritis Rheum* 2000; 30: 138-143.
12. Kaplan E, Mukamel M, Barash J, et al. Protracted febrile myalgia in children and young adults with familial Mediterranean fever: analysis of 15 patients and suggested criteria for working diagnosis. *Clin Exp Rheumatol* 2007; 25(4 Suppl 45): 114-117.
13. Gökçe İ, Demirkaya E, Gök F. Protracted Febrile Myalgia in a child as the presenting sign of familial Mediterranean fever: case report and review of the literature. *Balkan Med J* 2011; 28: 222-223.
14. Ozturk C, Halicioglu O, Coker I, et al. Association of clinical and genetical features in FMF with focus on MEFV strip assay sensitivity in 452 children from western Anatolia, Turkey. *Clin Rheumatol* 2012; 31: 493-501.
15. Majeed HA, El-Khateeb M, El-Shanti H, Rabaiha ZA, Tayeh M, Najib D. The spectrum of familial Mediterranean fever gene mutations in Arabs: report of a large series. *Semin Arthritis Rheum* 2005; 34: 813-818.
16. Soylu A, Kasap B, Türkmen M, Ulgenalp A, Uzuner N, Kavukçu S. Protracted febrile myalgia syndrome in a patient with familial Mediterranean fever homozygous for the E148Q mutation. *Semin Arthritis Rheum* 2008; 38: 161-162.
17. Tunca M, Akar S, Onen F, et al. Familial Mediterranean fever (FMF) in Turkey: results of a nationwide multicenter study. *Medicine (Baltimore)* 2005; 84: 1-11.
18. Aypar E, Ozen S, Okur H, Kutluk T, Besbas N, Bakkaloglu A. Th1 polarization in familial mediterranean fever. *J Rheumatol* 2003; 30: 2011-2013.