Rheumatol Int (2012) 32:529–533
DOI 10.1007/s00296-010-1766-x

SHORT COMMUNICATION

Polyarteritis nodosa and Henoch–Schönlein purpura nephritis in a child with familial Mediterranean fever: a case report

Ilknur Girisgen · Ferah Sonmez · Kutsi Koseoglu · Seda Erisen · Dilek Yılmaz

Received: 27 August 2010 / Accepted: 30 December 2010 / Published online: 23 January 2011

Abstract Familial Mediterranean fever is an autosomal recessive disease characterized by recurrent self-limited attacks of fever accompanied by peritonitis, pleuritis, and arthritis. Approximately 5% of individuals with familial Mediterranean fever have been reported to have Henoch–Schonlein purpura and about 1% to have polyarteritis nodosa. A 7-year-old girl presenting with complaints of purpuric rash, abdominal pain, arthritis, hematuria, and proteinuria and having IgA depositions on renal biopsy was diagnosed as Henoch–Schönlein nephritis. She had a history of recurrent fever, abdominal and joint pain and M694 V compound homozygote mutation. Colchicine treatment was started for the diagnosis of FMF. When constitutional symptoms such as myalgia, weight loss, fatigue, fever, and hypertension were added to the clinical picture, the diagnosis of polyarteritis nodosa HSP was thought and confirmed by the demonstration of microaneurisms on renal arteries. There was no response to corticosteroid and cyclophosphamide treatments; however, the symptoms were rapidly and dramatically reduced after the administration of intravenous immunoglobulin. In conclusion, polyarteritis nodosa and Henoch–Schonlein purpura can be seen together with familial Mediterranean fever. It is also suggested that IVIG might be an important adjunct therapy in selected patients with polyarteritis nodosa, especially in the lack of response to steroids and immunsuppressive drugs.

Keywords Familial Mediterranean fever · Vasculitis · Genetic susceptibility · Intravenous immunoglobulin

I. Girisgen (✉) · F. Sonmez · D. Yılmaz
Department of Pediatrics, Pediatric Nephrology, Adnan Menderes University, Aydin, Turkey
e-mail: igirisgen78@hotmail.com

F. Sonmez
e-mail: ferahsonmez@yahoo.com

D. Yılmaz
e-mail: drdlkylmz@yahoo.com

K. Koseoglu
Department of Radiology, Adnan Menderes University, Aydin, Turkey
e-mail: kutsikoseoglu@yahoo.com

S. Erisen
Department of Pediatrics, Adnan Menderes University, Aydin, Turkey
e-mail: sedaerisen@hotmail.com

Introduction

Familial Mediterranean fever (FMF) is an autosomal recessive disease characterized by recurrent self-limited attacks of fever accompanied by peritonitis, pleuritis, arthritis, and erythema resembling erysipelas [1–4]. It affects certain ethnic groups, mainly Jews, Turks, Arabs, and Armenians. The estimated prevalence of FMF in Turkey is 1/1,000, and the carrier rate is 1:5 [4]. The disease is caused by mutations in the MEFV gene. The most serious complication is the development of amyloidosis, causing chronic renal failure.

Henoch–Schonlein purpura (HSP) is a systemic small-vessel vasculitis involving the skin, kidney, joints, and gastrointestinal tract. The incidence of HSP is 22 per 100,000. The pathogenesis of HSP remains unknown; however, HSP is generally believed to be immune complex–mediated disease characterized by the presence of polymeric IgA1-containing immune complexes predominantly in dermal, gastrointestinal, and glomerular capillaries [5–7].

Polyarteritis nodosa (PAN) is 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 [8, 9]. Malaise, fever, rash abdominal pain, and arthropathy as well as myalgia and hypertension are the main clinical features of PAN [10]. Corticosteroids and cyclophosphamide are the first-line treatment of PAN [9]. In recent years, the benefits of high-dose intravenous immunoglobulin (IVIG) have been described for a variety of autoimmune disease including PAN [11–13]. Vasculitis such as PAN, HSP, Behçet syndrome, and protracted febrile myalgia (PFM) have been increasingly reported in FMF [1–4, 14, 15]. The overall incidence of vasculitis in FMF patients is 1% for PAN and 5% for HSP, and it is significantly higher in FMF patients than in normal population [1–3, 14, 16, 17]. However, as much as we searched the literature, we could not find any case having HSP, PAN, and FMF together.

In this report, a 7-year-old girl together with HSP, PAN, and FMF was presented.

Case report

A 7-year-old girl whose parents were first-degree consanguineous admitted to our hospital with fever, myalgia, abdominal pain, vomiting, weakness, loss of weight accompanied by painful swelling of the left knee. In her history, we learned that she had developed abdominal pain, had purpuric rash over the ankles and had hematuria, was diagnosed as HSP, and was treated with prednisolone (2 mg/kg/day) 1 month ago. The patient and her brother had a history of recurrent fever and abdominal and joint pain.

Physical examination revealed growth retardation. Abdominal palpation was painful with defense and rebound, and her left knee was swollen with tenderness and high fever. Her blood pressure was normal.

Initial laboratory studies revealed hemoglobin as 9.6 gr/dl, white blood cell count as 22,800/mm^3, platelet count as 1.212.000/mm^3, erythrocyte-sedimentation rate as 106 mm/h, C-reactive protein as 202 mg/L, serum fibrinogen level as 566 mg/dl. Serum urea, creatinine, and liver enzymes were within normal levels. The urine analysis showed the presence of microscopic hematuria and mild proteinuria (11 mg/m^2/h). Stool was positive for occult blood. Abdominal ultrasonography showed mesenteric lymphadenopathy and thickening of the colon. Based on these clinical and laboratory findings, the patient was diagnosed as having HSP with renal, skin, joint, and gastrointestinal system involvements. The dose of prednisolone treatment was increased to 2 mg/kg/day. Renal biopsy was performed and mesangial cell proliferations with IgA deposits were found in the mesangial regions. No crescent formation or necrotic lesions were seen. Skin biopsy showed mononuclear infiltration in the dermis.

As her brother and she had a recurrent fever and abdominal and joint pain, FMF mutation analysis was performed. Detection of homozygous MEFV (M694 V) mutation confirmed the diagnosis of FMF, and colchicines treatment was also started.

Although he had prednisolone therapy, colicky abdominal pain and tenderness, arthralgia, high fever, and elevated acute-phase reactants continued. On the seventh day of hospitalization, her blood pressure was 140/90 mmHg and hypertension was confirmed by ambulatory blood pressure monitoring. Calcium canal blocker was added to the treatment. Response to abdominal pain, arthralgia, fever, and myalgia was not observed in spite of colchicine and prednisolone treatments. With the suspicion of PAN, Doppler ultrasonography and magnetic resonance angiography were performed and found normal. However, bilateral selective renal angiography demonstrated microaneurisms on the branches of left renal arteries (Fig. 1). Tests for ANA, Anti DNA, p-ANCA, C3, C4, rheumatoid factor, HBV and HCV antibodies were negative. Intravenous pulse methyl prednisolone (30 mg/kg/dose) for three consecutive days and then cyclophosphamide (2 mg/kg/day) were administered for the treatment of PAN. For all of these, treatments were unsuccessful, intravenous immunoglobulin was given at a dose of 0.4 g/kg/dose day for five consecutive days. Abdominal pain, fever, and myalgia were resolved 2 days after the first dose of IVIG and acute-phase reactants dramatically decreased 1 week after the treatment.

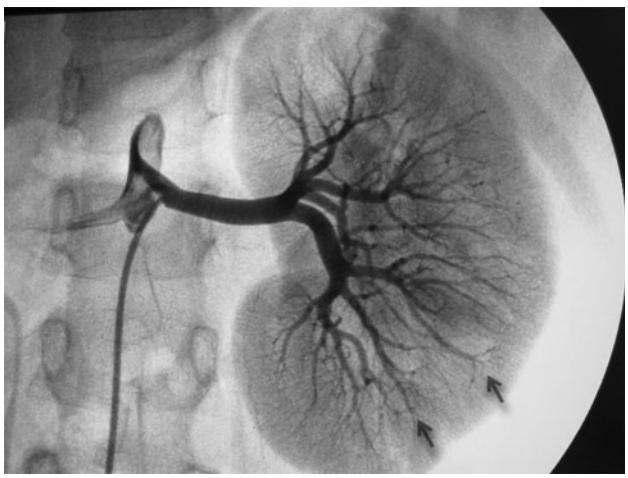

Fig. 1 Bilateral selective renal angiography demonstrated microaneurisms on the branches of left renal arteries

Following up for a year, she had no complaints and only colchicine treatment was continued.

Discussion

HSP is most common necrotizing vasculitis affecting children. The American College of Rheumatology has defined the diagnostic criteria for HSP as the presence of two or more of the following: palpable purpura, an age of 20 years or less at onset, bowel symptoms suggestive of ischemia, and histologic documentation of leukocytoclastic vasculitis. Final Eular/Printo/Pres criteria for HSP was defined as the presence of purpura (mandatory criterion) and at least one of the four following criteria: abdominal pain, histopathology, arthritis or artralgia, and renal involvement [18]. Based on these clinical and laboratory findings, the patient was diagnosed as having HSP with renal, skin, joint, and gastrointestinal system involvement according to the ACR and Eular/Printo/Pres-defined criteria [18, 19]. Mesangial cell proliferation with IgA deposits in the mesangial regions in her renal histology confirmed the diagnosis of Henoch–Schonlein nephritis.

Familial Mediterranean fever (FMF) is an autosomal recessive disease characterized by recurrent inflammatory febrile attacks of serosal and synovial membranes [4]. The disease is caused by mutations in the MEFV gene. The protein encoded by MEFV consists of 781 amino acids and is called pyrin/marenostrin. Pyrin is expressed in neutrophil and is thought to have suppressive effects on inflammation. The FMF-associated mutations and resultant structural changes in the protein prevent the normal pyrin/marenostrin-mediated negative feedback mechanism and trigger inflammation [1–3]. Our patient with the history of recurrent fever and abdominal and joint pain as her brother caused the suspicion of FMF. Detection of homozygous MEFV (M694 V) mutation confirmed the diagnosis of FMF.

PAN is a systemic necrotizing vasculitis affecting medium or small arteries. The ACR criteria for PAN require at least three of the following ten criteria: granulocyte or mixed leukocyte infiltrate in arterial wall on biopsy, arteriographic abnormalities, livedo reticularis, myalgia, diastolic blood pressure >90 mmHg, neuropathy, elevated renal function tests, testicular pain, hepatitis B reactants, and weight loss >4 kg [18, 19]. Jennette et al. [2, 9] divided PAN into classic and microscopic polyangiitis: they have defined classic PAN as a necrotizing inflammation of small- or medium-sized arteries without glomerulonephritis or vasculitis in arterioles, capillaries, or venules. Pediatric patients are often not limited to this description, and the disease has certain characteristic features in children. Thus, an attempt has been made to classify childhood PAN patient with the recently developed Eular/Printo/Pres criteria for the classification of childhood PAN. Final Eular/Printo/Pres criteria for PAN histopathology or angiographic abnormalities (mandatory) plus one of the five following criteria: skin involvement, myalgia, hypertension, peripheral neuropathy, and renal involvement. Our patient had four of the ten criteria for the diagnosis of PAN according to ACR criteria and angiographic abnormality with two criteria for Final Eular/Printo/Pres criteria (weight loss, fever, hypertension, myalgia, and angiographic abnormalities).

MEFV mutations may act as a genetic susceptibility factor for vasculitis in FMF patients [1, 2, 4]. The overall incidence of vasculitis in FMF patients is 1% of PAN and 5% of HSP, and it is significantly higher in FMF patients than in normal population [1–3, 14, 16, 17]. In a large series of 425 FMF patients, 10 developed HSP (2.3%), 9 patients had PAN (2.1%) [2]. In a review of 207 Turkish patients with FMF, 15 FMF patients (7%) had HSP and 3 patients had PAN (1%) [20]. Turkish FMF study group having the largest series of FMF patients reported the prevalence of HSP as 2.7/100 and PAN as 9/1,000 among FMF patients [4]. Factors that trigger the development of vasculitis in FMF patients remain to be determined, and it has been hypothesized that immune complexes may play a role in the association of vasculitis with FMF [1]. Environmental and/or genetic factors are possibly involved in the pathogenesis of vasculitis in FMF [1, 14]. The carrier rate of MEFV mutations was found to be 20% in healthy Turkish people. Yalcınkaya et al. [8, 21] reported that 38% of Turkish children with PAN carried at least one mutant MEFV allele, which is nearly two times higher than the carrier rate in the Turkish population. Their study showed that alterations in the MEFV gene are important susceptibility factors for the development of PAN. As a trigger of vasculitis in FMF, some infectious agents such as streptococcus have been proposed [1]. Indeed, both PAN and HSP may occur after streptococcal infections. High ASO levels of our patient also might support this idea.

Because both FMF and PAN are characterized by fever and abdominal pain, diagnosis of PAN in patients with FMF may be difficult. A classical FMF attack lasts 1–3 days and resolves spontaneously [1]. Although purpuric rash, arthritis, abdominal pain, fever, increased ESR, CRP, fibrinogen levels can be seen during FMF attacks, HSP, hypertension, thrombocytosis and myalgia are not typical [1, 16]. Fever, rash, abdominal pain, and arthropathy as well as myalgia and hypertension are the main clinical features of PAN and were present in our patient. It develops at a younger age compared with classical PAN, and an overall good prognosis has been reported in patients with PAN and FMF [1, 2, 16]. Perirenal hematoma and central nervous system involvement are well-known complications and are most

common findings with FMF and PAN association than isolated PAN [1, 2, 16, 17, 22]. This vasculitis is not associated with positive ANCA or HbsAg. Early initiation of treatment with steroids and immunosuppressives is important. HSP lasts longer and causes more corticosteroid use when it is associated with FMF. HSP is 5–7 times more common among FMF patients when compared with the normal population [3, 17, 18].

Since the overall prognosis of PAN is dependent on the definitive diagnosis and prompt and accurate treatment, renal angiography should be performed in selected individuals despite renal Doppler sonographic findings [10]. Despite normal magnetic resonance angiography and Doppler ultrasonography, angiography was performed for our patient for the suspicion of PAN. Together with clinical findings such as abdominal pain, fever, myalgia, hypertension, and laboratory results such as elevated acute-phase reactant, thrombocytosis, and radiological findings (microaneurisms on the branches of left renal arteries), the diagnosis of PAN was established according to the Eular/Printo/Pres-defined criteria [18].

M694 V was the most common mutation in patients with FMF and PAN mutation, and this is also the most common mutation in Turkish patients [1, 2]. Tekin et al. [1] found high incidence of MEFV gene mutation with FMF-associated vasculitis, but Akpolat et al. did not find a specific gene mutation in FMF patients and PAN [14, 23]. Our patient also had M694 V mutation.

The vasculitic symptoms in FMF patients usually respond dramatically to corticosteroids with or without immunosuppressive agents. Treatment is aimed at decreasing systemic vascular inflammation with high-dose steroids, and oral cyclophosphamide has been effective in most cases [9, 20]. In life-threatening cerebral vasculitis or rapidly deteriorating renal function, pulse administration of cyclophosphamide and corticosteroids should be favored. Cangüneri et al. [24] presented a patient having colchicines, pulse methylprednisolone and cyclophosphamide, and redeveloped symptoms. They suggested that interferon may be a useful adjuvant for the treatment of resistant attacks in FMF patients with vasculitis. Machet et al. [25] reported as a first study that some cases of necrotizing vasculitis have been treated with intravenous immunoglobulin (IVIG). When there is a lack of response to standard treatment, IVIG had been successfully used [11, 26, 27]. Our patient failed to respond to high-dose methylprednisolone and cyclophosphamide; however, she was successfully treated with IVIG.

In conclusion, MEFV mutations may act as a genetic susceptibility factor for vasculitis in FMF patients, and FMF may predispose to HSP and PAN in children. We suggest that IVIG might be an important adjunct therapy in selected patients with PAN, especially in the lack of response to steroids and immunosuppressive drugs.

References

1. Tekin M, Yalçinkaya F, Tümer N, Akar N, Misirlioğlu M, Cakar N (2000) Clinical, laboratory and molecular characteristics of children with familial Mediterranean fever-associated vasculitis. Acta Paediatr 89:177–182
2. Ozen S, Ben-Chetrit E, Bakkaloglu A, Gur H, Tinaztepe K, Calguneri M, Turgan C, Turkmen A, Akpolat I, Danaci M, Besbas N, Akpolat T (2001) Polyarteritis nodosa in patients with familial Mediterranean fever (FMF): a concomitant disease or a feature of FMF. Semin Arthritis Rheum 30:281–287
3. Tekin M, Yalçinkaya F, Tümer N, Cakar N, Koçak H, Ozkaya N, Gençgönül H (1999) Familial Mediterranean fever renal involvement by diseases other than amyloid. Nephrol Dial Transplant 14:475–479
4. Tunca M, Akar S, Onen F, Ozdogan H, Kasapcopur O, Yalcinkaya F, Tutar E, Ozen S, Topaloglu R, Yilmaz E, Arici M, Bakkaloglu A, Besbas N, Akpolat T, Dinc A, Erken E (2005) Turkish FMF study group familial Mediterranean fever (FMF) in Turkey: results of a nationwide multicenter study. Med (Baltim) 84:1–11
5. Sozeri B, Mir S, Ertan P, Kara OD, Sen S (2009) Rapidly progressive glomerulonephritis in a child with Henoch-Schönlein Vasculitis and familial Mediterranean fever. Pediatr Rheumatol Online J 7:7–8
6. Sohar E, Gafni J, Pras M, Heller H (1967) Familial Mediterranean fever. A survey of 470 cases and review of the literature. Am J Med 43:227–253
7. Livneh A, Langevitz P (2000) Diagnostic and treatment concerns in familial Mediterranean fever. Baillieres Best Pract Res Clin Rheumatol 14:477–498
8. Yalçinkaya F, Ozçakar ZB, Kasapçopur O, Oztürk A, Akar N, Bakkaloğlu A, Arisoy N, Ekim M, Ozen S (2007) Prevalence of the MEFV gene mutations in childhood polyarteritis nodosa. J Pediatr 151:675–678
9. Geary DF, Schafer F, Bakkaloglu A, Ozen S (1998) Wegener's Granulomatosis, Microscopic polianjiitis, and childhood polyarteritis nodosa. Compherensive Pediatr Nephrol 28:352–358
10. Bakkaloğlu SA, Muzaç S, Akpek S, Söylemezoğlu O, Buyan N, Hasanoğlu E (2004) Polyarteritis nodosa in a case of familial Mediterranean fever. Pediatr Nephrol 19:536–538
11. Asano Y, Ihn H, Maekawa T, Kadono T, Tamaki K (2006) High-dose intravenous immunoglobulin infusion in polyarteritis nodosa: report on one case and review of the literature. Clin Rheumatol 25:396–398
12. Uziel Y, Silverman ED (1998) Intravenous immunoglobulin therapy in a child with cutaneous polyarteritis nodosa. Clin Exp Rheumatol 16:187–189
13. Kroiss M, Hohenleutner U, Gruss C, Glaessl A, Landthaler M, Stolz W (2001) Transient and partial effect of high-dose intravenous immunoglobulin in polyarteritis nodosa. Dermatology 203:188–189
14. Gurman A, Nahir A, Moscovici Y (2007) Vasculitis in siblings with familial Mediterranean fever: a report of three cases and review of the literature. Clin Rheumatol 26:1183–1185
15. Soylu A, Oztürk Y, Kasap B, Akman N, Türkmen M, Kavukçu S (2005) Clinical quiz: a pediatric case presenting with fever and diffuse myalgia. Rheumatol Int 25:314–316

16. Akar S, Goktay Y, Akinci B, Tekis D, Biberoglu K, Birlik M, Onen F, Tunca M, Akkoc N (2005) A case of familial Mediterranean fever and polyarteritis nodosa complicated by spontaneous perirenal and subcapsular hepatic hemorrhage requiring multiple arterial embolizations. Rheumatol Int 25:60–64
17. Ozkaya O, Bek K, Alaca N, Ceyhan M, Acıkgöz Y, Tasdemir H (2007) Cerebral vasculitis in a child with Henoch-Schölein purpura and familial Mediterranean fever. Clin Rheumatol 26:1729–1732
18. Ozen S, Pistorio A, Iusan SM, Bakkaloglu A, Herlin T, Brik R, Buoncompagni A, Lazar C, Bilge I, Uziel Y, Rigante D, Cantarini L, Hilario MO, Silva CA, Alegria M, Norambuena X, Belot A, Berkun Y, Estrella AI, Olivieri AN, Alpigiani MG, Rumba I, Sztajnbok F, Tambic-Bukovac L, Breda L, Al-Mayouf S, Mihaylova D, Chasnyk V, Sengler C, Klein-Gitelman M, Djeddi D, Nuno L, Pruunsild C, Brunner J, Kondi A, Pagava K, Pederzoli S, Martini A, Ruperto N (2010) 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 69:798–806
19. Lightfoot RW Jr, Michel BA, Bloch DA, Hunder GG, Zvaifler NJ, McShane DJ, Arend WP, Calabrese LH, Leavitt RY, Lie JT et al (1990) The American college of rheumatology criteria for the classification of polyarteritis nodosa. Arthritis Rheum 33:1088–1093
20. Ozdogan H, Arisoy N, Kasapçapur O, Sever L, Calişkan S, Tuzuner N, Mat C, Yazici H (1997) Vasculitis in familial Mediterranean fever. J Rheumatol 24:323–327
21. Yilmaz E, Ozen S, Balci B, Duzova A, Topaloglu R, Besbas N, Saatci U, Bakkaloglu A, Ozguc M (2001) Mutation frequency of familial Mediterranean fever and evidence for a high carrier rate in the Turkish population. Eur J Hum Genet 9:553–555
22. Bakkaloğlu SA, Muzaç S, Akpek S, Söylemezoğlu O, Buyan N, Hasanoğlu E (2004) Polyarteritis nodosa in a case of familial Mediterranean fever. Pediatr Nephrol 19:536–538
23. Akpolat T, Yılmaz E, Ozen S, Akpolat I, Danacı M, Kandemir B (1998) M6801/M694 V mutations in patients in patient with FMF and polyarteritis nodosa. Nephrol Dial Transplant 13:2633–2635
24. Calguneri M, Apras S, Ozbalkan Z, Ozturk MA (2004) The efficacy of interferon-alpha in a patient with resistant familial Mediterranean fever complicated by polyarteritis nodosa. Intern Med 43:612–614
25. Machet L, Vincent O, Machet MC, Barruet K, Vaillant L, Lorette G (1995) Cutaneous periarteritis nodosa resistant to combined corticosteroids and immunosuppressive agents. Efficacy of treatment with intravenous immunoglobulins. Ann Dermatol 122:769–772
26. Balbir-Gurman A, Nahir AM, Braun-Moscovici Y (2007) Intravenous immunoglobulins in polyarteritis nodosa restricted to the limbs: case reports and review of the literature. Clin Exp Rheumatol 25:28–30
27. González-Fernández MA, García-Consuegra J (2007) Polyarteritis nodosa resistant to conventional treatment in a pediatric patient. Ann Pharmacother 41:885–890