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CASE REPORT

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Vasculitis in siblings with familial Mediterranean fever: a report of three cases and review of the literature

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Abstract Familial Mediterranean Fever (FMF) is characterized by recurrent attacks of self-limited polyserositis and fever. Several types of vasculitis are associated with FMF: polyarteritis nodosa, Henoch–Schonlein purpura (HSP), and protracted febrile myalgia (PFM). We describe three cases of vasculitis in four siblings of a Sephardic Jewish family with FMF and reviewed the literature. One brother and one sister developed severe HSP with intestinal involvement while another brother developed PFM. Genetic tests in three brothers confirmed the M694V mutation on both alleles. Vasculitides may be a clinical feature of FMF with a higher familiar prevalence. MEFV mutations may act as a genetic susceptibility factor for vasculitides in FMF patients.

Keywords Familial Mediterranean Fever · Henoch–Schonlein purpura · M694V mutation · Protracted febrile myalgia

Introduction

Familial Mediterranean Fever (FMF) is an autosomal recessive disease affecting people of Mediterranean ancestry (Sephardic Jews, Armenians, Arabs, and Turks) with recurrent self-limited attacks of fever and inflammatory serositis [1, 2]. Several types of vasculitis are associated with FMF: polyarteritis nodosa (PAN), Henoch–Schonlein purpura (HSP), and protracted febrile myalgia (PFM) [3, 4]. We describe three cases of vasculitis in four siblings with FMF and reviewed the literature.

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Case descriptions

Case 1

A 30-year-old man was admitted because of fever, abdominal pain, diarrhea, polyarthritis, and rash for 2 weeks. The patient was a Sephardic Jew. Both parents were healthy, but two brothers suffer from FMF. He was diagnosed with FMF at the age of 10 years and was treated with 1 mg colchicine daily. On admission, the patient appeared febrile (38.5°C) and was wheelchair-bound.

Lung and heart examination was unremarkable. The abdomen was diffusely tender but without signs of peritoneal irritation or organ enlargement. Rectal examination revealed waterlike, yellowish species with traces of blood. Synovitis of the right elbow and wrist, both knees, and right ankle was detected. Palpable purpura of different sizes was prominent on the lower limbs and buttocks. Laboratory tests showed an erythrocyte sedimentation rate (ESR) of 70 mm/h, C-reactive protein of 200 mg/l (normal: <20 mg/l), hemoglobin (Hb) 12.8 gram percent, white blood cells (WBC) 15×10^3/M (normal: $4–8\times10^3$/M) with normal differential count, platelets (PLT) 576×10^3/M (normal: $200–400\times10^3$/M), albumin 3.0 g/dl (normal: >3.5 g/dl), fibrinogen (Fb) 580 milligram percent (normal: <400 milligram percent), IgG 1,925 mg/dl (normal: <1,560 mg/dl), and IgA 454 mg/dl (normal: <350 mg/dl). Blood levels of glucose, electrolytes, and creatine kinase (CK), liver and kidney function, and levels of complement and protein electrophoresis (PEP) were within normal limits. Tests for rheumatoid factor (RF), antinuclear antibodies (ANA), antineutrophil cytoplasmic antibodies (ANCA), cryoglobulins, hepatitis B (HBV) and C (HCV) virus were negative. Several (10–15) red blood cells (RBC) were found upon urinalysis, but urine protein was negative. Cultures of stool were negative for common pathogens. Chest X-rays and electrocardiogram revealed no abnormalities. A skin biopsy showed signs of vasculitis with leukocytoclasis.

Despite treatment with oral prednisone 20 mg/day, his condition deteriorated due to profuse bloody diarrhea, exacerbation of rash, and appearance of several areas of

skin necrosis. The level of Hb dropped to 9.2 milligram percent without signs of hemodynamic compromise and laboratory signs of hemolysis. Colonoscopy showed severe ileocolitis with multiple superficial ulcers and massive bleeding. On biopsy, the mucous of both the ileum and colon were heavily infiltrated with lymphocytes, multiple ulcerations, and fibrin accumulation around necrotic areas, but neither granulomas nor signs of chronic inflammatory bowel disease were seen. After three daily intravenous pulses of methylprednisolone (1 g/day) with consequent prednisone (40 mg/day), the patient's condition improved. The diarrhea, skin lesions, and arthritis completely resolved. After 3 months, the prednisone was stopped, and the patient continued 1.5 mg colchicine daily. Over the next 3 years of follow-up, his condition remained stable.

Case 2

A 36-year-old man—brother of the patient in case 1—was admitted to hospital 23 years ago for severe muscular and joint pain. Previously, he had had recurrent attacks of abdominal pain and fever (above 38°C) for 2–3 days, which always resolved spontaneously. His general examination was unremarkable except for fever (38.0°C) and prominent tenderness above the proximal muscles of hands and lower limbs with normal muscle power. His laboratory tests revealed anemia (Hb, 11.7 gram percent), elevated ESR of 90 mm/h, and Fb of 640 milligram percent. Liver enzymes, kidney function tests, CK, PEP, complement, and urinalysis were normal. RF, ANA, ANCA, HBV, and HCV were negative. Electromyographic study was normal. Muscle biopsy did not reveal any pathology. The diagnosis of PFM related to FMF was suggested and treatment with naproxyn (1,000 mg/day) and colchicine (1.5 mg/day) was started. Over the next month, his muscle pain and fever resolved. He continues colchicine treatment (1.5 mg/daily) and has had neither FMF nor muscle pain attacks.

Case 3

A 23-year-old woman, sister of the two brothers described, was admitted to the hospital 10 years ago for arthralgia and pleurisy. She had suffered from periodic transient abdominal pain and fever in her past, but did not take any medication. On admission there were signs of left ankle arthritis, skin rash below the knees, and fever of 38.7°C. The rest of her physical examination was unremarkable. The laboratory data showed ESR 80 mm/h; Hb 9.9 gram percent; WBC 12.5×10^3/M with normal differential count; PLT 639×10^3/M; protein 6.0 g/dl; albumin 2.4 g/dl; alanine aminotransferase 111 U/dl (normal: <40 U/dl); aspartate aminotransferase 56 U/dl (normal: <40 U/dl), and alkaline phosphatase 204 U/dl (normal: <130 U/dl). Kidney function, glucose and electrolytes levels, PEP, immunoelectrophoresis, and complement were normal. Tests for ANA, RF, anticardiolipin antibodies, lupus anticoagulant, ANCA, cryoglobulins, extractable nuclear antigen, HBV, and HCV were negative. There was no growth on blood, urine, and stool cultures. There were 10–15 RBC in the urine. Daily urine protein was 550 mg/24 h. Lung X-ray and echocardiography were unremarkable. Skin biopsy confirmed vasculitis with prominent leukocytoclasis. Renal biopsy showed nonspecific minimal mesangial changes with negative staining for complement and immune complexes; the changes were not specified as lupus nephritis.

Despite treatment with oral prednisone (25 mg/day) and broad-spectrum antibiotics, her condition further deteriorated. The rash spread to the thighs, and uncontrolled diarrhea, vomiting, and severe cramping abdominal pain developed. Computed tomography of the abdomen showed intestinal volvulus. As conservative treatment had failed, the patient underwent laparotomy that revealed small intestinal volvulus and intestinal vasculitis. After surgical repair of volvulus, she was treated with parenteral nutrition, five intravenous pulses of methylprednisolone (1 g/day) followed by prednisone (60 mg/day). During massive steroid treatment, her abdominal symptoms resolved completely, as did her arthritis and rash. The levels of Hb, liver enzymes and blood proteins, and urinary protein gradually returned to normal range. She was slowly tapered off steroids over the next few months. Since discharge, she has refused follow-up and further treatment.

Case 4

A 26-year-old man from the described family was diagnosed with typical FMF attacks at an early age and has been treated with colchicine. His medical history is unremarkable. The three presented brothers agreed to undergo genetic tests for FMF and were found to carry the M694V mutation on both alleles. Their sister refused to undergo genetic analysis.

Discussion

The four patients described herein are siblings from a healthy Sephardic Jewish family. All have had recurrent episodes of febrile abdominal attacks of varying severity compatible with the clinical signs of FMF [5]. Two developed an aggressive course of vasculitis with skin, joint, and intestinal involvement compatible with HSP and one with PFM. In two brothers (#1, #4), the diagnosis of FMF was made in early childhood and confirmed later by genetic testing. In one of the siblings (#2), the possibility of underlying FMF was suggested only after the appearance of PFM, and the patient was later found to be a homozygote for the FMF mutation. In light of the FMF-associated vasculitis in two of the affected brothers, we reanalyzed retrospectively the vasculitis features in their sister (#3). Despite the absence of proper genetic analysis, it seems that this patient had systemic vasculitis related to FMF. The patients who developed systemic vasculitis with internal organ involvement responded well only to very high doses

of intravenous steroids but, interestingly, have succeeded in maintaining remission without steroids while being on ordinary colchicine doses (#1) or without any treatment (#3). The patient with PFM (#2) responded well to combined treatment (colchicine and naproxyn) and has been attack-free under a proper colchicine regimen.

Recurrent short attacks of painful febrile serositis, synovitis, and erysipelas-like skin reactions were extensively described in FMF patients [1–3]. Prolonged severe muscle pain accompanied by fever (PFM) has been recently recognized as a type of FMF vasculitis. In most patients, FMF attacks started before 20 years of age; mild disease might be overlooked and delay in diagnosis is not rare. Colchicine is the only drug that has been found to control disease attacks in most affected patients and has dramatically changed the fate of FMF by preventing renal amyloidosis [3]. The gene responsible for FMF (MEFV gene) was recently identified and mapped to the short arm of chromosome 16. Different mutations in the gene causing FMF suggest a variety in clinical features in the same ethnic groups [5, 6].

Classic vasculitides, such as PAN and HSP, have been reported in the FMF population [4, 7–11]. The overall incidence of vasculitis in FMF patients is 1% of PAN and 5% of HSP, and it is significantly higher in FMF than in the general population [4, 12]. The appearance of vasculitis can preclude or follow typical FMF attacks. Generally, patients with FMF developed vasculitis at younger ages; their disease course was often complicated by the development of perirenal hematomas [13]. Ozen et al. analyzed 17 cases of PAN in FMF patients and suggested that vasculitis may be a feature of FMF per se [13]. Ozdogan et al. [4] proposed considering intestinal vasculitis as an integral part of FMF because of the high incidence of occult blood in stool species during FMF attacks.

FMF and vasculitis have a remarkable similarity: fever, abdominal pain, arthritis, skin lesions, and blood in stool and urine. This makes a differential diagnosis extremely difficult. Confusion in recognition may have clinical consequences, as the treatment regimens of these conditions are different. The outcome of vasculitis in FMF patients is different; mild benign as well as severe or fatal courses of vasculitis have been described [7, 14, 15].

It is extremely rare to see the severe form of systemic vasculitis in siblings. The coexistence of systemic vasculitis with hereditary condition—Familial Mediterranean Fever—makes these cases especially interesting and raises the possibility of an inherited basis for the vasculitis syndrome. Data about a specific gene mutation in patients with vasculitis and FMF are conflicting. Akpolat et al. did not find a specific gene mutation in FMF patients and PAN [8]. In contrast to these data, Tekin et al. [12] found a high incidence of MEFV gene mutation in 23 children with FMF-associated vasculitis.

Two of our patients with vasculitis syndrome and FMF (#1, #2) carried the most common FMF gene mutation. Further genetic evaluation of FMF populations that suffer from vasculitis syndromes (PAN, HSP, and PFM) might throw light on this mysterious combination.

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References

1. 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
2. Livneh A, Langevitz P (2000) Diagnostic and treatment concerns in familial Mediterranean fever. Baillieres Best Pract Res Clin Rheumatol 14:477–498
3. Livneh A, Langevitz P, Zemer D, Padeh S, Mogdal A, Sohar E, Pras M (1996) The changing face of Familial Mediterranean fever. Semin Arthritis Rheum 26:612–627
4. Ozdogan H, Arisoy N, Kasapçapur O, Sever L, Çali_kan S, Tuzuner N, Mat C, Yazici H (1997) Vasculitis in Familial Mediterranean fever. J Rheumatol 24:323–327
5. Livneh A, Langevitz P, Zemer D, Zaks N, Kees S, Lidar T, Migdal A, Padeh S, Pras M (1997) Criteria for diagnosis of FMF. Arthritis Rheum 40:1879–1885
6. Touitou I, Ben-Chetrit E, Notarnicola C, Domingo C, Dewalle M, Dross C, Dupont M, Demaille J, Rosner I, Rozenbaum M (1998) Familial Mediterranean fever clinical and genetic feature in Druzes and Iraqi Jews: a preliminary study. J Rheumatol 25:916–919
7. Basaranoglu M, Mert A, Tabak F, Apaydin S, Aktuglu Y, Ozdogan H (1999) A case of Familial Mediterranean Fever and polyarteritis nodosa complicated by spontaneous perirenal and subcapsular splenic haemorrhage. Rheumatology (Oxford) 38:794–796
8. Akpolat T, Yilmaz E, Ozen S, Akpolat I, Danaci M, Kandemir B (1998) M6801/M694V mutations in a patient with FMF and polyarteritis nodosa. Nephrol Dial Transplant 13:2633–2635
9. Gershoni-Baruch R, Broza Y, Brik R (2003) Prevalence and significance of mutations in the familial Mediterranean fever gene in Henoch–Schonlein purpura J Pediatr 143:658–661
10. Glikson M, Galun E, Schlesinger M, Cohen D, Haskel L, Rubinov A, Eliakim M (1989) Polyarteritis nodosa and familial Mediterranean Fever: a report of 2 cases and review of the literature. J Rheumatol 16:536–539
11. Sachs D, Langevitz P, Morag B, Pras M (1987) Polyarteritis nodosa and familial Mediterranean fever. Br J Rheumatol 26:139–141
12. Tekin M, Yalcinkaya F, Tumer N, Akar N, Misirlioglu M, Cakar N (2000) Clinical, laboratory and molecular characteristics of children with of familial Mediterranean fever-associated vasculitis. Acta Paediatr 89:177–182
13. 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
14. 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
15. Braun E, Schapira D, Guralnik L, Azzam ZS (2003) Acute vasculitis with multiorgan involvement in a patient with familial Mediterranean fever. Am J Med Sci 325:363–364