

Vasculitis, left bundle branch block, and Raynaud's phenomenon as a manifestation of familial Mediterranean fever

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Submitted: 27 November 2008

Accepted: 3 January 2009

Arch Med Sci 2008; 4, 4: 460–464

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Abstract

Familial Mediterranean fever (FMF) is inherited as an autosomal recessive trait. Usually FMF affects persons of Mediterranean origin. Because of human migration, FMF is spread all over the world. Cardiovascular complications, especially life threatening arrhythmias, are rare in FMF. The current paper deals with presentation of a patient with FMF who developed vasculitis, left bundle branch block, and Raynaud's syndrome. The combination of fever, rash, arthralgias, serositis, vasculitis, Raynaud's phenomenon and cardiac conduction defect in this patient caused diagnostic problems. Interestingly, the mentioned cardiovascular manifestations responded well to colchicine therapy.

Key words: familial Mediterranean fever, heart, vasculitis, diagnosis.

Introduction

Familial Mediterranean fever (FMF) is inherited as an autosomal recessive autoinflammatory disorder. The causative gene (Mediterranean FeVer – MEFV) is located on the short arm of chromosome 16 [1, 2]. Usually, but not exclusively, FMF affects subjects of Mediterranean origin (e.g. Sephardic Jews, Armenians, Arabs) [3, 4]. The disease has also been referred to in the literature as periodic disease, benign paroxysmal peritonitis, familial paroxysmal polyserositis, periodic amyloid syndrome, periodic peritonitis syndrome, recurrent polyserositis, etc. Due to massive human migration, FMF is spread all over the world, and, nowadays, is frequently diagnosed in countries where it was not an endemic disease decades ago [4, 5]. Obviously, awareness among clinicians of this mysterious disease and its multiple systemic manifestations has substantially increased over the last decades, which has resulted in improved diagnosis of FMF. A staggering amount of diverse case reports of FMF has been published so far. Clinical presentation of classic periodic inflammatory attacks of the disease and its transformation into amyloidosis have been thoroughly analyzed [2, 6]. Several environmental and genetic factors, particularly M694V missense mutation of the MEFV gene, have been shown to be associated with amyloidosis due to FMF [3]. Nevertheless, genotype-phenotype correlations of FMF and its diverse manifestations are not fully understood, and diagnosis of the disease is still based on thorough clinical evaluation, and sometimes expert opinion is crucial.

The aim of this report is to present a rare case of combination of vasculitis, Raynaud's syndrome and left bundle branch block (LBBB) in FMF. An informed consent form was obtained from the patient.

Case report

Medical history

A 53-year-old male patient was admitted to the hospital with high grade fever and shortness of breath. He was originally from Spain, but moved to Switzerland at the age of 23. In summer 2006, physical examination revealed an abdominal pale, reddish rash, with elements slightly elevated above the surrounding skin, and upper respiratory tract infection. 'Viral infection with atypical dermatitis' was diagnosed with administration of corresponding treatment. The symptoms disappeared within days. Two months later the abdominal rash erupted again, and this time was accompanied with recurrent pruritic spots on both calves and a burning sensation on the feet with sock-like distribution. Elements of the rash changed in size and intensity, but did not disappear. A few days later, the patient developed diffuse intensive abdominal pain, which had occurred periodically before, occasionally accompanied with watery diarrhoea. Later on, intensive migrating myalgia and arthralgia with stiffness, mostly in the right shoulder and knees, also appeared.

In winter, severe bilateral Raynaud's syndrome, involving the 2nd, 3rd, 4th and 5th fingers, was diagnosed. Signs of Raynaud's syndrome regularly appeared, linked to exposure to cold. Of note, the patient was a smoker (up to 30 cigarettes per day), but he had never had Raynaud's phenomenon in the past. A few days later, the patient developed high grade fever (up to 40°C) with paroxysmal diffuse night sweating. These symptoms recurred twice a month without significant weight loss.

Three days before admission to the hospital, the patient was complaining of pleuritic pain and shortness of breath.

Clinical presentation

At his first admission the body temperature was 36.2°C, pulse rate 76/min, blood pressure 108/68 mm Hg. A diffuse, pale reddish rash was visible on the abdomen and the back, and rash elements were palpable. Conjunctivae were pale and soft. Oral cavity was of normal appearance. Peripheral lymph nodes were not palpable. Thoracic outlet compression could not be detected. Breath rate was 20/min, oxygen saturation was 96% while he was breathing ambient air. Lungs were clear. Cardiac apex was bulging, 1st heart sound was permanently spitted and diffuse 2/6 systolic

murmur was auscultated. Liver and spleen were palpable. Mild synovitis of both knee joints was detected. Petechial spots and purpura were detectable on both calves. Peripheral arterial pulses were normal. The rest of the examination was normal.

Diagnostic work-up

Medical history and clinical presentation was discussed with consultants in rheumatology and infectious diseases. The differential diagnostic work-up considered the probability of infectious disease, vasculitis and FMF.

Laboratory

During a high grade febrile episode (39.8°C), erythrocyte sedimentation rate and C-reactive protein levels were significantly elevated: 68 mm/h and 74.8 mg/l, correspondingly. White blood cell count (10; normal range 4.0-10) and neutrophil granulocytes were in the upper range (74%, 4-74).

Blood cultures failed to detect any pathogen. Tests for viral hepatitis B and C, HIV, Whipple's disease, *Entamoeba histolytica*, brucellosis, *Clostridium difficile*, salmonellas, tuberculosis and syphilis were negative. Increased levels of IgG antibodies against cytomegalovirus, toxoplasmosis, Epstein-Barr, herpes virus, and hepatitis A virus were detected, but these results were suggestive of inactive infections and could not explain the origin of periodic high grade fever and related symptoms.

Liver function tests, serum electrolytes, creatinine, and procalcitonin (0.25 µg/l) were within the physiological range. Cryoglobulins were not detectable. IgD values were normal and there was no evidence for a monoclonal gammopathy. Antibodies against c-/p-ANCA, ds/DNA, SS-A/B-B, cardiolipin and SIL-2 receptor were also within normal limits.

Importantly, a high concentration of anti-neutrophil antibodies was detected (183 U/ml), and there was a perinuclear staining pattern specific for myeloperoxidase. The latter was suggestive of microscopic polyangiitis.

Urinalysis did not detect abnormalities. Total urinary protein/creatinine ratio was normal.

Skin biopsies of the petechial spots of the calves. Microscopic examination revealed subdermal inflammation close to the surface and extensive necrosis in the deeper layers. Infiltration was mostly neutrophilic, with a few small lymphocytes surrounding small blood vessels. Besides, fragmentation of the internal elastic lamina, as well as intimal hyperplasia with patchy lymphocytic infiltrates in the adventitia, was detected in two small arterioles. The histological changes were typical for microscopic vasculitis.

Imaging studies

Computed tomography scanning combined with contrast injection failed to detect any pathological changes in the thorax, abdomen and pelvis suggestive of the origin of recurrent fever in this patient. At the same time, minor pleural and pericardial effusion, and mild spleno- and hepatomegaly without focal lesions were detected. There were no signs of necrosis or calcification. Ultrasound examination of peripheral joints confirmed mild symmetric synovitis of shoulder and knee joints.

Cardiological check-up

Levels of Pro-BNP, troponin and D-dimer were within the normal range. Computed tomography scanning did not detect enlargement of heart chambers. ECG detected complete LBBB (Figure 1). Echocardiography detected grade C1 pericardial effusion (by Horowitz classification) [7]. Dimensions of the atria and ventricles, and left ventricle's mass were normal. Because of LBBB there was atypical contraction of the left ventricle: posterior and inferior segments contracted first, followed by contraction of lateral, interventricular and septal regions. There were no signs of endocarditis or valvular disease.

Final diagnostic work-up

Infectious pathology was excluded. Palpable purpura due to microscopic blood vessels involvement, the results of skin biopsy and presence of anti-neutrophil antibodies were suggestive of microscopic polyangiitis. However, pathological changes were atypical for Kawasaki disease or Cogan's syndrome [8]. Goodpasture's syndrome is more common among heavy smokers [9]. The presented patient was also a heavy smoker. However, in this case there was no haemoptysis or signs of glomerulonephritis, and consequently Goodpasture's syndrome was also ruled out.

The patient presented with numerous clinical criteria suggestive of the diagnosis of FMF. Of note, his father had also suffered from periodic fever of unknown origin and died at the age of 54 of end-stage renal disease. Additionally, *mutation-genetic analysis of the MEFV gene* allowed M694V/E148Q compound heterozygous genotype to be detected in our patient. Interestingly, these mutations were shown to be quite common in Spanish descendants of Sephardic Jews [10]. The same analysis detected E148Q/0 heterozygous genotype in the 18-years-old son of the patient, who was apparently healthy. To sum up, the presented patient fulfilled 3 major, 1 minor and 3 supportive criteria of the Lidar and Livneh classification of FMF [6].

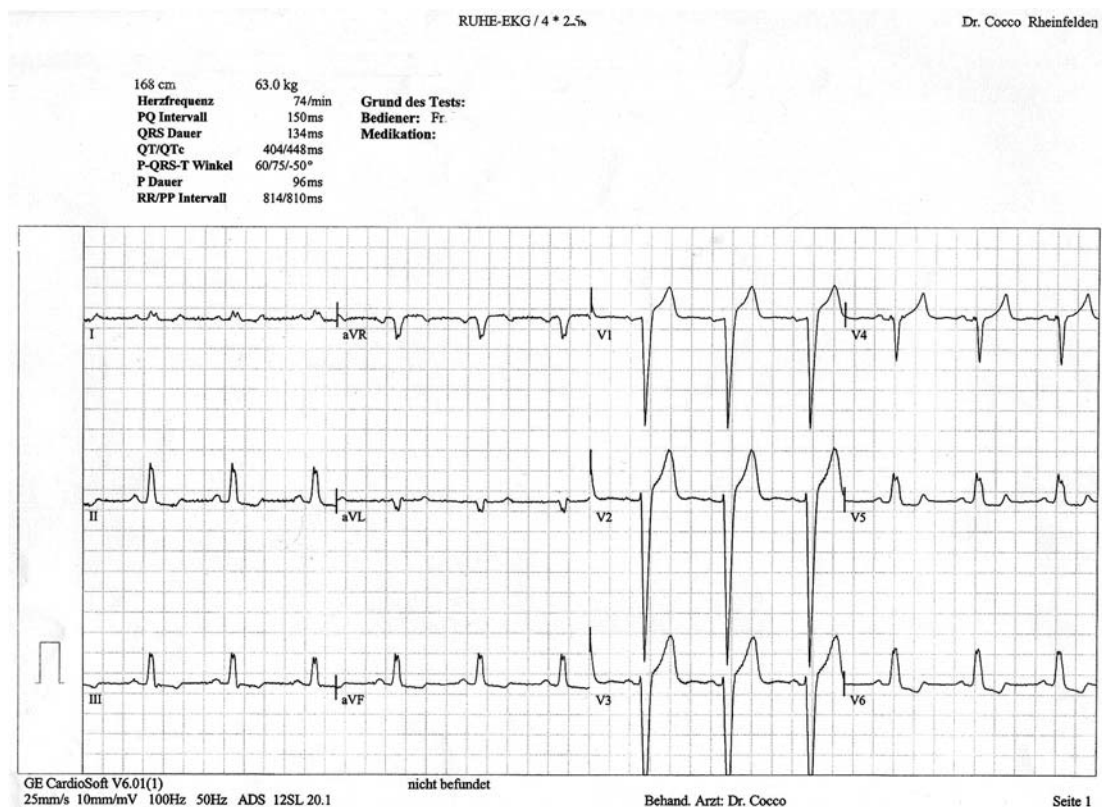


Figure 1. LBBB in the presence of FMF

Treatment and follow-up

The patient was treated with 0.5 mg/day colchicine with further titration up to 1 mg/day. Malaise, periodic fever episodes, rash, vasculitic lesions of calves and the abdomen completely disappeared after three months of colchicine therapy. Erythrocyte sedimentation rate and C-reactive protein levels normalized: 12 mm/h and 3 mg/l, correspondingly. On ECG there was no LBBB (Figure 2). Echocardiography was normal. There were no febrile attacks of FMF, rash, signs of vasculitis, Raynaud's syndrome or LBBB over 12 months of colchicine therapy. Only myalgia and arthralgia were present after long-term therapy, suggestive of unresponsiveness of these symptoms to colchicine.

Discussion

The presented case meets established diagnostic criteria of FMF [6]. In this case FMF was accompanied with small vessel vasculitis, which is uncommon in FMF [2, 5, 6]. Severe Raynaud's phenomenon was also diagnosed, which, at first sight, contradicts FMF. However, it is possible that the heavy smoking habit of the patient could contribute to the occurrence of both vasculitis and Raynaud's phenomenon. Importantly, in this case colchicine was used without concomitant administration of steroids or immunosuppressive agents, and a good response was achieved,

indicating inflammatory and immune disturbances due to FMF as a culprit of the observed vasculopathy.

To the best of our knowledge, there has not been any reported case of LBBB in FMF. The association between LBBB and FMF is not well understood. The patient had systemic vasculitis and it is logical to link coronaritis with LBBB. Coronaritis could also cause myocardial infarction (MI). However, in our patient troponin was negative and diagnosis of infarction was unlikely. More likely, neutrophils, as target cells of systemic inflammation induced by FMF, and where the product of the *MEFV* gene, pyrin protein, is highly expressed, could infiltrate coronary vessels and cause damage with subsequent development of LBBB. The basis of pathophysiology of FMF is thought to be abnormal function of pyrin [3]. Pyrin dysfunction may induce oxidative stress [11], which primarily affects medial smooth muscle cells. The latter can induce LBBB in a predisposed patient. Colchicine, as an agent coping with oxidative stress, might be viewed as a means against LBBB in the presented patient with FMF.

Acknowledgments

The author is grateful to Dr. Armen Yuri Gasparyan, MD, PhD, for editorial assistance and professional comments.

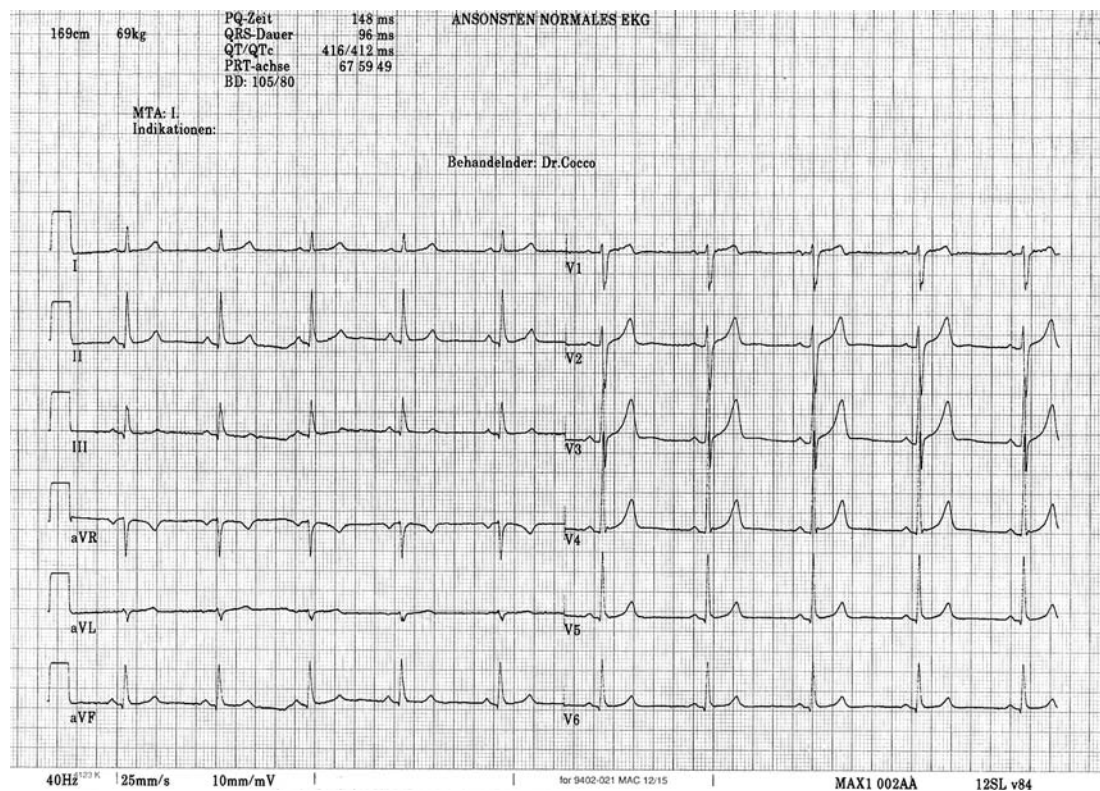


Figure 2. Disappearance of the LBBB under therapy with colchicine

References

1. Bhat A, Naguwa SM, Gershwin ME. Genetics and new treatment modalities for familial Mediterranean fever. *Ann N Y Acad Sci* 2007; 1110: 201-8.
2. Onen F. Familial Mediterranean fever. *Rheumatol Int* 2006; 26: 489-96.
3. Touitou I. The spectrum of Familial Mediterranean Fever (FMF) mutations. *Eur J Hum Genet* 2001; 9: 473-83.
4. La Regina M, Nucera G, Diaco M, et al. Familial Mediterranean fever is no longer a rare disease in Italy. *Eur J Hum Genet* 2003; 11: 50-6.
5. Aringer M. Periodic fever syndromes – a clinical overview. *Acta Med Austriaca* 2004; 31: 8-12.
6. Lidar M, Livneh A. Familial Mediterranean fever: clinical, molecular and management advancements. *Neth J Med* 2007; 65: 318-24.
7. Horowitz MS, Schultz CS, Stinson EB, Harrison DC, Popp RL. Sensitivity and specificity of echocardiographic diagnosis of pericardial effusion. *Circulation* 1974; 50: 239-47.
8. Goldberger ZD, Weinberger SE, Nicosia RF, Saint S, Young BA. Clinical problem-solving. Variations on a theme. *N Engl J Med* 2008; 359: 1502-7.
9. Kathiresan S, Kelsey PB, Steere AC, Foster CS, Curvelo MS, Stone JR. Case records of the Massachusetts General Hospital. Case 14-2005. A 38-year-old man with fever and blurred vision. *N Engl J Med* 2005; 352: 2003-12.
10. Domingo C, Touitou I, Bayou A, et al. Familial Mediterranean fever in the 'Chuetas' of Mallorca: a question of Jewish origin or genetic heterogeneity. *Eur J Hum Genet* 2000; 8: 242-6.
11. Papin S, Cazeneuve C, Duquesnoy P, Jeru I, Sahali D, Amselem S. The tumor necrosis factor alpha-dependent activation of the human Mediterranean fever (MEFV) promoter is mediated by a synergistic interaction between C/EBP beta and NF kappaB p65. *J Biol Chem* 2003; 278: 48839-47.11.