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BRIEF REPORT

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Polyarteritis nodosa in a case of familial Mediterranean fever

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Abstract We describe a 7-year-old boy with familial Mediterranean fever (FMF) complicated by polyarteritis nodosa (PAN) with distinct angiographic findings. On admission, he had abdominal pain, arthralgia, and severe fibromyalgia. During hospitalization, he displayed maculopapular eruptions, high blood pressure, gastrointestinal bleeding, and persistent constitutional symptoms mimicking a vasculitic process, most probably PAN. Renal angiography showed a perfusion defect compatible with a renal infarction secondary to a vasculitic process. He responded well to pulse methylprednisolone therapy with colchicine. We emphasize the rare association of FMF and PAN and the non-aneurysmal angiographic signs of PAN.

Keywords Familial Mediterranean fever · Polyarteritis nodosa · Renal angiography · Non-aneurysmal angiographic signs

Introduction

Familial Mediterranean fever (FMF) is an autosomal recessive disease, characterized by recurrent and self-limited attacks of fever, usually accompanied by polyserositis [1]. Several vasculitic diseases such as Henoch-Schönlein purpura and polyarterities nodosa (PAN) have been reported with increased frequency in patients with FMF [2]. Although the pathogenesis is not clearly defined, it has been hypothesized that immune complexes may play a role in the association of the vasculitides and FMF [3]. In this report we describe a patient with FMF associated with PAN.

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Case report

A 7-year-old boy who had been followed with a diagnosis of FMF for 3 years was referred to our hospital with fever, malaise, severe abdominal pain, arthralgia, myalgia, and swelling of the hands and feet. He was on colchicine treatment. Three years previously, he was admitted to a local hospital with abdominal pain and fever. Since the abdominal pain recurred periodically, FMF was suspected. Besides typical FMF attacks characterized by abdominal pain, fever, and an acute-phase response, a homozygous *MEFV* mutation (M694 V/M694 V) was also detected, confirming the diagnosis of FMF. The disease had been well controlled during the 3 years of colchicine treatment, with only an attack of arthritis in his left knee. There was no parental consanguinity. One of his two siblings (a 10-year-old girl) was suspected of having FMF due to her recurrent abdominal and joint pain.

The patient was admitted to our hospital with abdominal pain. On physical examination, he was well developed (body weight 31 kg, 90th percentile, height 132 cm, 75th–90th percentile). His blood pressure was 100/60 mmHg. He had diffuse abdominal tenderness, defense, and rebound. Both of his wrists were swollen. At the dorsum of his hands there was edema and hyperemia. He had an erysipelas-like rash around the lateral areas of the feet.

Labarotary investigations revealed a hemoglobin level of 14.9 g/dl, white blood cell count of 27,800/mm^3 with 64% neutrophils and 36% lymphocytes, and a platelet count of 530,000/mm^3. The erythrocyte sedimentation rate was 68 mm/h. The antistreptolysin O titer was 400 Todd units and C-reactive protein was 263 mg/dl (normal 0–6 mg/dl). The serum fibrinogen level was 683 mg/dl. Stools did not show gross or occult blood. Urinalysis was normal and remained normal throughout the course of the illness. Urine and throat cultures were negative. Blood urea nitrogen, creatinine, plasma protein levels, and liver and muscle enzymes were within the normal limits. C3 was 1.66 g/l and C4 was 0.26 g/l. Serological tests for rheumatoid factor, anti-nuclear antibody, anti-double-stranded DNA, hepatitis B surface antigen, hepatitis C virus antibody, cytomegalovirus, rubella and toxoplasma IgM were all negative. The IgD level was 15 IU/ml (2–99.3). p-anti-neutrophil cytoplasmic antibody (ANCA) and c-ANCA, *Salmonella* and *Brucella* agglutination tests were all negative.

Because of severe abdominal pain, arthralgia, severe fibromyalgia, and elevated acute-phase reactants, the dose of colchicine was increased (three times daily). On the 3rd day of hospitalization, gastrointestinal bleeding occurred. Nasogastric decompression was

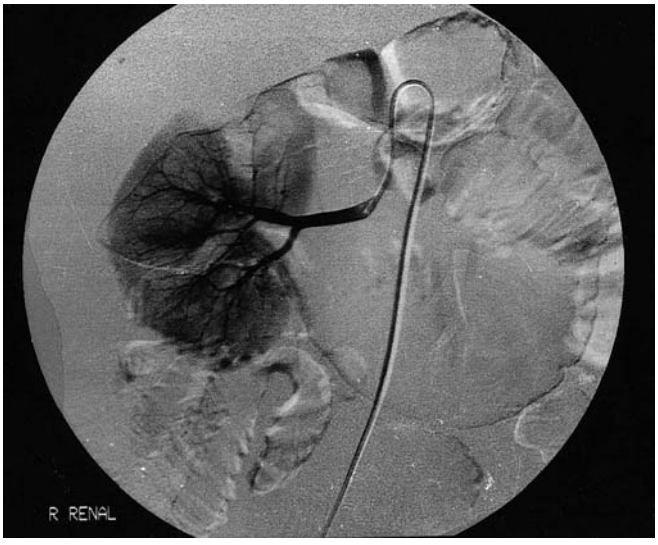

Fig. 1 Selective right renal angiography revealed an early cut-off appearance on the upper pole segmental artery and a perfusion defect at the parenchymal phase

performed. Abdominal ultrasonography revealed no pathological findings. Due to the increased likelihood for the development of a vasculitic process in patients with FMF, steroid therapy was given after re-evaluating all pathological, clinical, and laboratory parameters. Methylprednisolone pulses (30 mg/kg per day) were given for 3 consecutive days, followed by oral prednisolone at a dose of 2 mg/kg per day. Before and during this therapy, high blood pressure measurements were also noticed. On the 5th day of hospitalization his blood pressure was 140/90 mmHg. Although abdominal pain, arthralgia, and myalgia had partially improved and color renal Doppler ultrasonography revealed no pathological findings, angiography was performed because of a suspicion of PAN. The abdominal aorta, hepatic, celiac, and mesenteric vessels were normal. Bilateral selective renal angiography revealed a wedge-shaped perfusion defect on the upper pole of the right kidney whose apex was towards the hilus (Fig. 1). This finding was considered to be compatible with renal infarction secondary to vasculitis.

On the following days, maculopapular eruptions appeared on his lower extremities, gluteal region, and elbows. Clinical symptoms subsided, blood pressure was controlled without any antihypertensive medication, and acute-phase reactants returned to normal levels within 3 weeks. After 4 weeks, steroid treatment was tapered gradually and discontinued within 3 months. He is currently on colchicine treatment and remains in remission 6 months after cessation of steroids.

Discussion

PAN, first described by Kussmaul and Maier in 1866 [4], is a rare vasculitic disease in children. However, the incidence of PAN in patients with FMF is significantly higher than in the normal population. In the last few decades many cases of FMF associated with vasculitic syndromes have been reported [2, 3, 5, 6].

There is a considerable degree of overlap in the clinical features of FMF and PAN, as well as elevated acute-phase reactants in both conditions, which could cause confusion in the diagnosis of PAN in patients with FMF. Malaise, fever, rash, abdominal pain, and arthropathy, as well as myalgia and hypertension, are the main clinical features of PAN [7] and were all present in our patient. However, many of these clinical findings can also be seen during the course of FMF. Acute-phase reactants are expected to increase in both diseases and therefore are not informative for the differential diagnosis. Despite poorly defined diagnostic criteria, hypertension, gastrointestinal bleeding, persistent and severe abdominal pain, severe myalgia, rash, and thrombocytosis suggested a vasculitic process, most probably PAN. Despite normal Doppler sonographic findings, due to clinical clues, we performed an angiographic examination. Renal angiography showed a perfusion defect compatible with a renal infarction secondary to a vasculitic process. This supported the diagnosis. This discrepancy between two radiodiagnostic imaging techniques is considerable and indicates the superiority of renal angiography for detecting vascular lesions and related parenchymal findings. Furthermore, Doppler ultrasonography is an operator-dependent procedure and may be insufficient to detect such a perfusion defect.

In a recent retrospective study, Brogan et al. [8] described the angiographic findings in children with PAN. Although the classical angiographic finding in PAN is aneurysms affecting renal, celiac, and hepatic arteries [9, 10], less well-emphasized angiographic changes were described, including arterial cut-off, the presence of collateral arteries, nephrogram perfusion defects, a lack of peripheral renal arteries, etc. Among these, perfusion defects are reported to be one of the most reliable non-aneurysmal signs. However, the demonstration of such aneurysms is not pathognomonic [8]. Brogan et al. [8] demonstrated that there was a considerable increase in the sensitivity of renal angiography for the diagnosis of PAN when non-aneurysmal signs were included in definitions of angiogram positivity. In addition, non-aneurysmal changes were detected more commonly on renal angiography than aneurysms in PAN.

In conclusion, FMF and PAN are two separate entities that have a higher than expected association. Having similar features, the differential diagnosis of these conditions can pose problems. Despite this difficulty, the awareness of non-aneurysmal changes such as perfusion defects on renal angiography in patients in whom PAN is suspected is of particular importance and allows us to clarify the diagnosis. Since the overall prognosis of PAN is dependent on the definitive diagnosis and prompt and accurate treatment [11], renal angiography should be performed in selected individuals despite normal renal Doppler sonographic findings.

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