CASE REPORT

Familial Mediterranean fever without fever as a cause of monoarthritis

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SUMMARY

Familial Mediterranean fever (FMF) is an autosomal recessive hereditary disease. FMF-related arthritis affects large joints, especially in the lower extremities. It starts with acute pain and swelling and affects one joint at a time. Fever is the most common symptom in FMF. Monoarthritis as the sole symptom is relatively rare and thus delayed diagnosis of the disease in a patient who had been suffering from monoarthritis for several years. Genetic analysis showing typical mutations in the patient eventually resulted in correct diagnosis, although classical clinical diagnostic criteria were not met. The patient received appropriate therapy with colchicine, which led to remission of the symptoms.

BACKGROUND

Familial Mediterranean fever (FMF) is an autosomal recessive hereditary disease, which primarily affects Sephardic Jews, Turks, Armenians and Arabs. FMF affects both sexes equally,¹ although some studies have reported a male predominance.² The disorder is characterised by recurrent attacks of fever, peritonitis that can resemble acute abdomen, pleuritis and arthritis. The most common musculoskeletal manifestation is acute recurrent monoarthritis.

Missense mutations in the MEFV gene in the short arm of chromosome 16 were discovered in 1997.^{3–4} The MEFV gene encodes pyrin/marennin. This protein is mainly expressed in myeloid/monocytic cells and regulates processing of interleukin-1 β , inflammation and apoptosis. Mutated pyrin/marennin probably results in uncontrolled inflammation. About 30 mutations associated with FMF have been identified. During attacks there is a massive influx of granulocytes due to increased chemotactic activity in serosal tissues. The fact that FMF has clinical manifestations resembling autoimmune syndromes, such as systemic lupus erythematosus (fever, arthritis and serositis) raises the possibility of an autoimmune pathogenicity but FMF does not respond to corticosteroids or other immunosuppressive medications. There are no autoantibodies for specific laboratory tests. Diagnostic criteria have been described by Livneh *et al.*⁵ Thus the diagnosis of FMF is based on clinical criteria. Diagnosing FMF at an early stage is essential in preventing the patient from developing amyloidosis, the most significant complication of FMF usually affecting the kidney, liver, spleen and the gastrointestinal tract. The frequency of amyloidosis differs among ethnic groups and is related to colchicine therapy.

CASE PRESENTATION

We present an atypical case of an immigrant in his mid-20s from a southeast European country who was admitted to our hospital suffering from monoarthritis of the left knee and anaemia without any other signs of FMF, such as fever or abdominal pain. Physical examination revealed a swollen and tender left knee with atrophic muscles of the left lower limb, painful right shoulder and pain in the lumbar region. Laboratory tests showed haemoglobin 10.4 mg/dL and leucocytes were 3270/ μ L. Rheumatoid factor, anti-cyclic citrullinated peptide antibodies and human leucocyte antigen B27 (HLA-B27) were negative. Erythrocyte sedimentation rate was 81 mm/h (normal range 1–10 mm/h) and C reactive protein 17.7 mg/dL (normal range 0–0.5 mg/dL). The patient had no fever, no abdominal or pleuritic pain and was bedridden. MRI of the left knee revealed effusion as well as degeneration of the cartilage and the bony structures (figure 1)—Whole-Organ Magnetic Resonance Imaging Score (WORMS) of the knee was assessed by a radiologist experienced in musculoskeletal imaging and was about 130.⁶ In native radiological examination of the knee it was graded after Kellgren-Lawrence grade III.⁷ Examination of the effusion excluded gout and chondrocalcinosis by histological analysis. No signs of bacterial infection were found. MRI of the abdomen revealed a splenomegaly. Rectal biopsy showed no amyloidosis. Scintigraphy showed massive inflammation of the left knee and degeneration of the right shoulder. MRI of the sacroiliac joint showed no signs of sclerosis. The patient did not show any other typical symptoms of FMF. Although Livneh *et al.*⁵ diagnostic criteria were not met; the patient reported a history of abdominal pain and joint effusion of the right shoulder and the left knee in childhood, which had not been interpreted as a symptom of FMF in his native country. At the time of consultation in our centre, the patient had lived as an immigrant in our country for 3 years and had not experienced any oligoarthritic symptoms apart from knee inflammation. Pain in the right shoulder was considered as an ‘irrelevant fact’ by the patient and was only mentioned on closer enquiry. Radiological imaging as well as genetic testing excluded HLA-B27-negative spondyloarthropathy. Because of his ethnic origin, we performed a gene analysis for mutations in the MEFV gene that revealed a homozygosity of M694V mutation, which could be attributed to FMF in a case of ‘atypical FMF’. The patient received daily colchicine therapy, which resulted in remission of the

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Figure 1 MRI showing degeneration of the left knee with destruction of cartilage (T1-weighted).

symptoms although there was some residual difficulty in walking.

OUTCOME AND FOLLOW-UP

The patient received daily colchicine therapy, which resulted in remission of the symptoms although there was some residual difficulty in walking. Initial Knee Injury and Osteoarthritis Score (KOOS) improved from 350 to 300 within 6 months.⁸ A knee arthroplasty was performed due to massive degenerative changes in the knee joint and reduced mobility. Pain measured by visual analogue scale improved slightly from 7 to 5, but regular medication of non-steroidal anti-inflammatory drugs was needed.

DISCUSSION

Recurrent monoarthritis is a feature of a number of diseases such as reactive arthritis, seronegative spondyloarthropathies, gout and FMF. Diagnosing recurrent monoarthritis may prove to be difficult if other manifestations of the primary disease are subtle or absent. According to Lidar *et al*,⁹ several variables such as ethnicity, earlier onset of disease, family history of FMF, favourable response to colchicine, fever during attack and a predominance of MEFV mutated alleles are more characteristic of FMF than the presence of other forms of episodic monoarthritis.

There are three common forms of arthritis in FMF: asymmetrical, non-destructive arthritis (75%) which usually completely resolves, migratory polyarthritis resembling acute rheumatic fever and chronic destructive arthritis sometimes including HLA-B27-negative spondyloarthropathy manifested by sacroileitis, enthesitis and inflammatory back pain (2–5%). FMF arthritis affects large joints, especially those in the lower extremities. It starts with acute pain and swelling and affects one joint at a time. Shoulders, temporomandibular or sternoclavicular joints can also be affected. Acute monoarthritis usually appears spontaneously but can sometimes be precipitated by trauma or prolonged muscular activity. Protracted destructive arthritis as seen

in our case develops mostly in the hips and knees. Although complete recovery is the rule, disabling joint damage can occur and may in some cases require joint replacement. In our case, recurrent inflammation of the knee as well as shoulder monoarthritis had led to joint degeneration. It should be noted that at the time of consultation in our centre, our patient had not experienced oligoarthritic symptoms. It can, however, be assumed that the patient had suffered from coincidental inflammation of the shoulder and knee joints together with abdominal pain, which had obviously not been interpreted as FMF.

Cloning MEFV is a non-invasive, sensitive, readily available and reliable molecular genetic diagnostic test for FMF. About 30 mutations associated with FMF have been defined. The five most common mutations are M694V, M680I, M694I, E148Q and V726A. The M694V mutation as it was the case in our patient accounts for about 25% of all mutations in patients with FMF.¹⁰ Genetic test provides a reliable diagnosis of FMF in the absence of the classical clinical syndrome. Early diagnosis allows early colchicine therapy, thus preventing amyloidosis and significantly reducing morbidity and disability.

Homozygosity for M694V is more common in Jewish patients and less prevalent in Arabs and is associated with a severe course of FMF.¹¹ This mutation is often seen in patients with musculoskeletal symptoms but the presence of a typical FMF-genotype is not necessarily associated with the development of FMF.

Colchicine therapy is of major importance in preventing FMF amyloidosis. It may also help to arrest the progression of amyloidosis. The adult dose is 1 mg daily and in non-responders it can be increased to 2 mg daily. Daily colchicine therapy is the basic therapy for the disease, resulting in complete remission or marked reduction in the frequency and duration of attacks in most patients.

Owing to increased immigration to western countries from the Middle East and Africa, differential diagnosis has modified. We therefore recommend performing genetic testing in patients of ethnic origin with a high prevalence of FMF who present with unexplained symptoms of FMF. Cloning of the MEFV gene has increased our diagnostic ability, particularly in atypical presentations.

Although genetic testing for double MEFV mutation is not specific for FMF, in our case it was shown to be a vital component in reaching proper diagnosis and in enabling the patient to receive appropriate and early treatment thus avoiding serious complications.

Learning points

- ▶ Ethnic origin should be taken into consideration in the differential diagnosis of monoarthritis to ensure that a less common disorder is not overlooked.
- ▶ Genetic testing for MEFV mutations can be a vital component in reaching proper diagnosis in the absence of the classical clinical syndrome.
- ▶ Early initiation of adequate therapy in patients with arthritis can prevent further complications.

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Competing interests None.

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