Rheumatol Int (2003) 23: 41–43
DOI 10.1007/s00296-002-0239-2

CASE REPORT

Nurgül Arinci Incel · Meryem Saraçoğlu
H. Rana Erdem

Seronegative spondyloarthropathy of familial Mediterranean fever

Received: 14 March 2002 / Accepted: 31 July 2002 / Published online: 11 September 2002

Abstract Familial Mediterranean fever (FMF) is characterized by an autosomal inheritance pattern, Mediterranean ancestry, and history of recurrent fever. We present a 30-year-old Turkish man with FMF and accompanying seronegative spondyloarthropathy. His diagnose depended on the clinical course of his disease: recurrent fever accompanied by abdominal pain attacks together with a positive family history and his ethnic origin and sacroiliitis. We review the common manifestations of FMF and remind physicians that sacroiliac joint involvement must be kept in mind in presence of articular symptoms in a FMF patient.

Keywords Familial Mediterranean fever · Seronegative spondyloarthropathy · Sacroiliitis

Introduction

Familial Mediterranean fever (FMF) is a genetically inherited polysystemic disease of unknown origin characterized by recurrent self-limited attacks of fever and accompanying abdominal, chest, and articular pain [1]. These manifestations are due to inflammation of serous membranes and synovium [2]. A striking feature of the disease is that it occurs predominantly in individuals of Mediterranean origin, particularly in non-Askhenazi Jewish, Armenian, Turkish, and eastern Arab populations [2, 3]. Case reports of patients with symptoms of FMF first appeared in the literature at the beginning of the twentieth century. Not until 1945, however, did anyone document the constellation of symptoms and laboratory findings as a clinical entity, when Siegal [4] compiled ten cases of benign paroxysmal peritonitis [5]. In the years since then the literature has referred to the disease as "recurrent polyserositis," "periodic peritonitis," "recurrent hereditary polyserositis," "periodic disease," and "familial Mediterranean fever." The term "familial Mediterranean fever" refers to three of the classic aspects of the disease: an autosomal inheritance pattern, Mediterranean ancestry, and history of recurrent fever [6].

The most severe complication of FMF is the development of amyloidosis, ultimately leading to renal failure which can be fatal [2, 3]. Colchicine is the drug of choice for FMF as it prevents the attacks and inhibits the development of amyloidosis in the majority of those treated properly [6]. The diversity and the nonspecificity of the various clinical manifestations of FMF can often obscure the diagnosis. To date the identification of the FMF gene and its various mutations enable the application of a noninvasive, sensitive molecular genetic testing for an accurate diagnosis of this disease [7]. Nevertheless, however, the diagnosis of FMF still remains mostly clinical [8].

Here we present a case of FMF with accompanying seronegative spondyloarthropathy and review the literature for sacroiliac joint involvement in FMF patients.

Case report

A 30-year-old Turkish man was referred to our clinic in summer 2001 for low back pain, exacerbating with rest. His pain had resisted for years, and he had consulted numerous physicians without a satisfactory explanation and had received therapy only with nonspecific medications. The patient had a history of FMF. His attacks began when he was 17 years old, with typical abdominal pain episodes lasting for 3 days with accompanying fever rising to 39°C. These attacks recurred every 7–10 days, with no known triggering factors. After 5 years in which he suffered from these attacks without a certain diagnosis, he was diagnosed as having FMF and received colchicine therapy. Regular colchicine treatment dramatically reduced the frequency of his attacks to once in 2–3 months. After him, his brother, his sister, and his sister's daughter also had a diagnosis of FMF with similar attacks. Neither

N. Arinci Incel (✉)
Mucize sokak 5/1, O6510 Beştepe, Ankara, Turkey
E-mail: nincel@hotmail.com
Fax: +90-312-4477209

N. Arinci Incel · M. Saraçoğlu · H.R. Erdem
Ankara Education and Research Hospital,
2nd Department of Physical Medicine and Rehabilitation,
Ankara, Turkey

he nor his family members have any evidence of psoriasis or inflammatory bowel disease. He was on colchicine therapy for 8 years at 0.5 g daily, having milder attacks recurring every 3–4 months. His articular complaints started at the age of 18 years with hip and buttock pain. No evidence of acute arthritis or any complaints at other joints was present. Probably because of his fever attacks he was suspected to have rheumatic fever, and therapy was started, with no healing in his pain. Two years before presentation he consulted a physician for his low back pain, and computed tomography (CT) of the lumbar vertebrae revealed a lumbar disc herniation.

The patient was admitted to our clinic for ongoing low back pain. He was a healthy-looking young man with no apparent spinal deformations. Physical examination revealed minimally restricted lumbar movements, especially flexion with finger to floor distance of 25 cm. Straight leg raising and femoral stretch tests were negative. Sacral compression, Gaenslen, Yeoman, Mennel and Patrick-Fabere tests were all positive, with pain radiating from the sacroiliac joint. Other joint examinations including hip were normal. Neurological examination revealed normal findings. His chest expansion was 2.5 cm at the nipple line. His occiput to wall, tragus to wall, chin to chest distances were within normal limits.

Complete blood cell count, urinalysis, electrolyte, and immunoglobulin levels were all normal. Antinuclear antibodies (by enzyme-linked immunosorbent assay) and rheumatoid factors (Latex) were negative. C-reactive protein and erythrocyte sedimentation rate were slightly elevated. Urine and throat cultures for bacterial growth were negative. The patient was found to be HLA-B27$^{(-)}$. Computed tomography of the lumbar region revealed a diffuse disc bulging resulting in a neural foraminal stenosis without impingement on dural sac at the level of L 4–5. Radiography and computed tomography of the sacroiliac joint showed apparent narrowing and erosive changes especially on the iliac side, marked sclerosis, and bilateral sacroiliitis (Fig. 1). Despite his smoking 10 cigarettes/day for 10 years, his pulmonary function tests were within normal levels and high-resolution computed tomography was nonspecific. Abdominal ultrasonography was normal. Bone mineral density values with dual-energy X-ray absorptiometry were osteopenic (T values for L2–4 vertebrae and femur neck were –1.5 and –1, respectively). His 24-h urinalysis for possible renal amyloidosis was normal. As he had received continuous colchicine therapy, and there was no evidence of amyloidosis, no biopsy was performed.

In the light of these findings we diagnosed the patient as having seronegative spondyloarthropathy of FMF. He was hospitalized for 3 weeks in our clinic. His colchicine dose was altered to 1.5 g daily. During the course in the treatment program, including specific exercise and physical therapy modalities, an increase in his lumbar movements with an apparent reduction in his low back and buttock pain was observed.

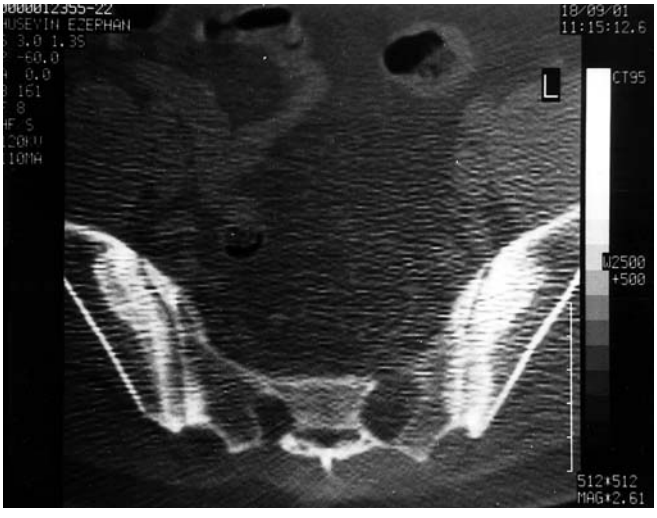

Fig. 1 Computed tomography images of both sacroiliac joints revealed marked sclerosis, apparent narrowing, and erosive changes predominantly on the iliac side; bilateral sacroiliitis

Discussion

FMF is characterized by recurrent self-limited febrile episodes and polyserositis with a predilection for persons of Mediterranean ancestry. Between attacks the patients are free of symptoms and appear healthy [9]. While the acute inflammation typically involves the peritoneum, pleura, and joints, patients report symptoms at almost every location in the body [3, 10, 11]. Although no specific triggers of the episodes have been discovered, the attacks may be precipitated by menses, emotional stress, strenuous physical activity, fat-rich diets, insignificant trauma, or tuberculin injection [5, 12]. Some patients report a prodromal period preceding an attack. The frequency of the attacks is variable and often unpredictable. The severity of the attacks and their frequency usually decrease throughout the person's lifespan [9]. The diagnosis of FMF is relatively easy in patients with typical clinical manifestations, family history and appropriate ethnic origin. Diagnosis is based mainly on clinical criteria. There are two sets of criteria, those of Sohar et al. [5] and those of Livneh et al. [11] (see also [2, 8]). The patient described here met the requirements of both sets of diagnostic criteria. The attack pattern of this patient and his relatives is typical, with abdominal pain and fever lasting 3 days and dissolving without any medication in the absence of any sequela. None of them report an acute articular attack.

The articular disease is the second most common manifestation after abdominal pain. It occurs in 70–75% of the patients, and in one-third of these patients it is the first presenting sign [2]. The arthritis of FMF consists of acute attacks of pain and swelling of one articulation at a time, most frequently affecting the large joints of the lower extremities. The shoulder, temporomandibular, and sternoclavicular joints may also be involved [7, 13, 14]. Small joint involvement is exceptionally rare [14, 15]. The radiographic appearance is not specific and is characterized by soft tissue swelling and transient osteoporosis; in chronic cases joint space narrowing, osteophytic formation and sclerosis are observed [12, 15]. Articular inflammation that lasts more than 1 month has been referred to as protracted arthritis, and its average duration is 6 months [12]. Approximately 5% of patients develop protracted arthritis, mostly in the hips or knees. Residual joint damage is uncommon, but an exception may be the hip joint which appears to be particularly prone to avascular necrosis [1]. Spinal involvement is rare; however, there have been case reports of joint fusion in the cervical and lumbar spine [6].

Sacroiliac joint involvement has been reported in some patients with FMF. Brodey et al. [13] reviewed 43 patients with FMF, 6 of whom presented radiographic changes in the sacroiliac joints. These changes were

reported despite the absence of clinically symptomatic joint disease. The relationship between FMF and seronegative spondyloarthropathy (SNSA) was investigated by Langevitz et al. [16] who studied the features of SNSA in 3000 FMF patients. Patients were considered to suffer from SNSA if they had chronic arthritis, inflammatory back/neck pain, and sacroiliitis. Eleven patients in this series met the criteria for diagnosis of SNSA in FMF; the authors concluded that these findings suggest SNSA to be one of the musculoskeletal manifestations of FMF that may occur despite colchicine therapy and requires specific treatment [16].

Our patient had a radiographically confirmed lumbar disc herniation which may have caused the low back pain, but there were no neurological findings in his examination. After having his history of FMF and in the light of our examination suggesting a sacroiliac joint pathology, we considered ankylosing spondylitis (AS) and SNSA for differential diagnosis. The patient's manifestations satisfied the modified New York (1984) criteria for AS as well as the spondyloarthropathy criteria of European Spondyloarthropathy Study Group, but there were conflicting points. Knockhaert et al. [17] have observed that AS may accompany FMF. In these patients, however, diagnosis of AS was based on the radiographic presence of sacroiliitis and spine involvement, and in the absence of HLA B27 it is likely that the cases reported were not true AS. Patients with FMF may have abnormal sacroiliac joints without other features of AS. This may be a source of diagnostic confusion in the association of sacroiliitis with FMF.

Our patient lacked some characteristic manifestations of AS, including syndesmophytes, bamboo spine, trolley track sign and uveitis. His chest expansion was within normal limits. He was negative for RF and HLA-B27. AS is almost always associated with HLA-B27 positivity. Also other causes of spondyloarthropathy (e.g., Reiter, inflammatory bowel disease) are commonly seen with higher HLA-B27 incidence than normal population [18]. On the other hand, HLA-B27 was not generally present in FMF patients with sacroiliitis as in the case of Besbas et al. [19]. Also multiple reports have failed to find any correlation with the HLA system and FMF. Hamza and Weisman [12] reviewed 14 FMF and AS cases in the literature and could not find any positive results for any of the patients. We also reviewed the literature, and to our knowledge there is only one case presented with HLA-B27 positive ankylosing spondylitis [20]. For our patient, although his features confirm AS diagnosis, it seemed reasonable to consider his condition as one of SNSA of FMF. This diagnosis depended on the clinical course of his disease: recurrent fever accompanied by abdominal pain attacks together with a positive family history and his ethnic origin and sacroiliitis. This case is presented to review the common manifestations of FMF and to remind physicians that sacroiliac joint involvement must be kept in mind in the presence of articular symptoms in a FMF patient.

References

1. Steuer A, Leonard N, Ahmed FB, Price AB, Gumpel JM (1997) An unusual case of familial Mediterranean fever. Br J Rheumatol 36:1118–1121
2. Yalçınkaya F, Tekin M, Tümer N, Özkaya N (1997) Protracted arthritis of familial Mediterranean fever. Br J Rheumatol 36.1228–1230
3. Majeed HA, Al-Qudah AK, Qubain H, Shahin HM (2000) The clinical patterns of myalgia in children with familial Mediterranean fever. Semin Arthritis Rheum 30:138–143
4. Siegal S (1945) Benign paroxysmal peritonitis. Ann Intern Med 23:1–21
5. 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
6. Samuels J, Aksentijevich I, Torosyan Y, Centola M, Deng Z, Sood R, Kastner DL (1998) Familial Mediterranean fever at the millennium. Clinical spectrum, ancient mutations, and a survey of 100 American referrals to the National Institutes of Health. Medicine (Baltimore) 77:268–297
7. Brik R, Shinawi M, Kasinetz L, Gershoni-Baruch R (2001) The musculoskeletal manifestations of familial Mediterranean fever in children genetically diagnosed with the disease. Arthritis Rheum 44:1416–1419
8. Livneh A. Langevitz P, Zemer D, Zaks N, Kees S, Lidar T, et al (1997) Criteria for diagnosis of familial Mediterranean fever. Arthritis Rheum 40:1879–1985
9. Nir-paz R, Ben Chetrit E, Pikarsky E, Hassin D, Hasin Y, Chajek-Shaul T (2000) Unusual presentation of familial Mediterranean fever: role of genetic diagnosis. Ann Rheum Dis 59:836–838
10. Gedalia A, Zamir S (1993) Neurologic manifestations in familial Mediterranean fever. Pediatr Neurol 9:301–302
11. Ozen S (1999) Pediatric rheumatology review. New interest in an old disease: familial Mediterranean fever. Clin Exp Rheumatol 17:745–749
12. Garcia Gonzales A, Weisman MH (1992) The arthritis of familial Mediterranean fever. Semin Arthritis Rheum 22:139–150
13. Uthman I, Hajj-Ali RA, Arayssi T, Masri AF, Nasr F (2001) Arthritis in familial Mediterranean fever. Rheumatol Int 20:145–148
14. Heller H, Gafni J, Michaeli D, Shahin HM, Sohar E, Ehrlich G, et al (1966) The arthritis of familial Mediterranean fever. Arthritis Rheum 9:1–17
15. Shahin N, Sohar E, Dalith F (1960) Roentgenologic findings in familial Mediterranean fever. Am J Roentgenol 84:269–275
16. Langevitz P, Livneh A, Zemer D, et al (1997) Seronegative Spondyloarthropathy in familial Mediterranean fever. Semin Arthritis Rheum 27:67–72
17. Knockhaert DC, Malysse IG, Peetersman WE (1989) Ankylosing Spondylitis: an unusual manifestation of familial Mediterranean fever: report of a case complicated by amyloidosis and polyneuropathy. Clin Rheumatol 8:408–412
18. Lehman TJ, Hanson V, Kornreich H, Peters RS, Schwabe AD (1978) HLA B27 negative sacroiliitis: a manifestation of familial Mediterranean fever in childhood. Pediatrics 61:423–426
19. Besbas N, Özdemir S, Saatçi I, Bakkaloğlu A, Özen S, Saatçi Ü (1999) Sacroiliitis in familial Mediterranean fever. An unusual presentation in childhood. Turk J Pediatr 41:387–390
20. Kaushik P, El-sobkie NI, Shehab D, Malaviya AN (1999) Familial Mediterranean fever. with HLA B27 positive ankylosing spondylitis in a young Armenian men. Clin Exp Rheumatol 17:387–388