Coexistence of Familial Mediterranean Fever and Juvenile Idiopathic Arthritis with Osteoporosis Successfully Treated with Etanercept

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Abstract

Familial Mediterranean fever (FMF) is an autoinflammatory disorder characterized by recurrent febrile polyserositis and arthritis attacks. Accompanying seronegative spondyloarthropathy has been reported in FMF in addition to its own joint involvement. However, the coexistence of FMF with juvenile idiopathic arthritis (JIA) is very rare, only three cases with severe joint involvement and mortal outcome have been reported in the literature. Here, we present another case with FMF and JIA with osteoporosis, successfully treated with etanercept with a four-year follow-up.

Key words: FMF, JIA, osteoporosis, etanercept


Introduction

Familial Mediterranean Fever (FMF) is an autosomal recessive disorder that is prevalent among eastern Mediterranean region inhabitants, mainly in non-Ashkenazi Jews, Armenians, Turks and Arabs (1). Recurrent peritonitis, fever, arthritis, pleuritis, myalgia and erysipelas-like erythema are the clinical features. Secondary amyloidosis is among the serious complications of FMF.

Juvenile idiopathic arthritis (JIA) is the most common chronic disease of childhood and an important cause of disability. It begins under the age of 16 years and persists for more than six weeks. It has various clinical features like systemic arthritis, oligoarthritis, rheumatoid factor positive and negative polyarthritis, enthesitis-related arthritis, psoriatic arthritis and undifferentiated forms (2).

Both FMF and JIA are systemic diseases of childhood; the coexistence of FMF with JIA is a very rare condition with a poor prognosis (3). Here, we report a case with FMF and JIA with osteoporosis that was successfully treated by etanercept.

Case Report

A 27-year-old male patient with FMF and JIA with osteoporosis has been followed-up for four years in our rheumatology department. JIA was diagnosed when he was 10 years old. His first symptoms were pain and swelling in his knees. After a few months, arthritis of wrists and small joints of the hands were added. He had morning stiffness for over an hour, pain at night, and minimal growth retardation. He was given various non-steroidal anti-inflammatory drugs and corticosteroids with partial response. In the subsequent years he developed deformities in the wrists and in the small joints of the hands.

He was 23 years old when he was first evaluated in our clinic. He had pain and swelling in various joints which lasted for months. He had morning stiffness for over an hour and he had severe fatigue, and was unable to walk because of knee, ankle and feet involvement. He also had a history of abdominal pain and fever attacks since he was 19 years of age. Severe abdominal pain had persisted for three days, and was completely resolved in a week. Fever accompanied these abdominal pain attacks. His joint symptoms were not deteriorating at the time of these attacks. Appen-
dectomy was planned but was not performed as his symptoms were resolved a few times. He was experiencing these attacks at least five times a year, sometimes two times a month. His brothers’ daughter was diagnosed as FMF. He and his family were from Sivas, which is located in the middle-eastern part of Turkey where FMF incidence is high. He had no uveitis attacks or any organ involvement.

On physical examination he had active arthritis in his knees, ankles, feet, wrists and hands. There were z-deformity and flexion deformity in the fifth digit on the right hand and ulnar deviation in both hands. Range of motion was severely limited in the wrists. There were deformities in the feet. Systemic evaluation was normal. Laboratory results were as follows; C-reactive protein (CRP): 35 mg/L, erythrocyte sedimentation rate (ESR): 55 mm/hr, WBC: 10.0×10^3/μL, platelet count: 301×10^3/μL, Hb: 11.8 g/dL, RF: <20 mg/dL, ANA: (-), ds DNA: (-). Urinary analysis did not reveal any pathology including proteinuria. Radiological evaluation showed erosions at the wrists and metacarpophalangeal joints, pencil-in-cup, and z-deformity, joint space narrowing between the carpal bones and metacarpophalangeal joints and deformities in his hand (Fig. 1). Genetic examination revealed mutations of M694V/V726A in the 10th exon of the MEFV (Mediterranean Fever) gene located on the short arm of the 16th chromosome.

The present patient was already diagnosed as JIA (at age 10) and we also diagnosed him as FMF according to Tel Hashomer criteria (4). He was started on methotrexate (MTX) 15 mg/week, folic acid 5 mg/day two times a week, and colchicine 0.5 mg tid. He was already using corticosteroids and we continued prednisolone 16 mg/day.

After six months of treatment, leflunomide was added 20 mg/day as there was only a partial response to MTX. DEXA scan demonstrated osteoporosis. DEXA t-score of the neck of femur, L1-L4 and L4 were -2.43, -2.82 and -3.09, respectively. Risedronate (35 mg/week), calcium (1,000 mg/day) and vitamin D (800 IU/day) were added to the therapy. Abdominal pain and fever attacks responded to colchicine treatment and the frequency of the attacks were decreased however he was not totally attack free.

At the 7th month of MTX and leflunomide treatment we decided to start him on etanercept as joint inflammation did not subside despite MTX and leflunomide, and tapering off of corticosteroids was not successful. He had active polyarthritis, severe fatigue, and prolonged morning stiffness. DAS-28 score was 5.7, CRP was 84.8 mg/L, ESR was 65 mm/hr, WBC was 8.9×10^3/μL, platelet count was 409×10^3/μL and hemoglobin was 11.5 g/dL. Kidney and liver function tests and urine analysis were within normal limits. The results of control DEXA were as follows: DEXA t-score of the neck of femur, L1-L4 and L4 were -1.90, -2.87 and -3.47 respectively.

He was started on etanercept 25 mg/twice a week. MTX was continued as 15 mg/week. Leflunomide was stopped. He continued to take risedronate, calcium, vitamin D and colchicine.

By the 3rd dose of etanercept, the patient began to feel well and we were able to taper off and stop prednisolone at the end of 2nd month of etanercept treatment. At the end of the first year, he started to gain weight and his quality of life was better. On physical examination he had no joint pain, swelling or warmth but there were deformities of small joints of the hand. Systemic examination was also normal. CRP was 2.3 mg/L, ESR was 18 mm/hr, WBC was 8.8×10^3/μL, platelet count was 208×10^3/μL and Hb was 15.6 g/dL. DAS-28 score was 2.8. DEXA t-score of neck of femur, L1-L4 and L4 were -1.51, -1.8 and -1.99, respectively.

He is still receiving etanercept, MTX, colchicine, calcium and vitamin D treatment since three years previously. He had fatigue and arthralgia once in a while, but never had a true synovitis. His FMF attacks were also dramatically improved; he had only one attack of abdominal pain after the onset of etanercept treatment.

**Discussion**

The present patient has three interesting points to be discussed. First he had a rare coexistence which worsened his clinical picture, second he responded well to etanercept treatment both regarding JIA and FMF and third, his osteoporosis also responded dramatically to etanercept.

MEFV gene mutations are observed in systemic onset JIA and RA. In addition to increasing the risk of RA development, they seem to worsen the disease prognosis (5, 6). This may have resulted from unsuccessful suppression of inflammation by pyrin, a protein known to be encoded by MEFV gene (3). Due to MEFV mutations, in addition to the defect in pyrin functions, uncontrolled production of active IL-1β was also suggested (6). Thus, in RA or JIA patients with MEFV mutations, these mechanisms contribute to inflammation which further worsen the clinical progression. It may also be speculated that the coexistence of JIA and FMF in the present case may have resulted from these mutations.

The present patient had MEFV gene mutations, and more-
over he had FMF, and a resistant destructive arthritis of JIA. Seronegative spondyloarthropathy have been described in FMF in various cases. The coexistence of FMF with RA or JIA has only been reported in three cases in the literature (3). The common features of these three cases were the poor prognosis and M694V mutation of the MEFV gene. Two of these patients had erosive polyarthritis and they underwent bilateral hip joint replacement in their early thirties. The third one had bilateral knee joint replacement because of avascular necrosis, and small bowel resection due to repeated ileal obstruction. He also had amyloidosis and osteoporotic fractures. This patient died at 42 years of age. These patients were under colchicine and non-biological DMARD therapies like MTX and sulfasalazine. The genotype of the present patient was M694V/V726A; El-Shanti et al suggested that patients with M694V/M694V and M694V/V726 A genotypes tend to have a severe clinical course (7).

JIA has different clinical forms and especially the systemic form with fever, serositis, and rash may be confused with FMF. The present patient had rheumatoid factor negative polyarthritis. This is the most heterogeneous subtype of JIA. It has at least three distinct subtypes, one of them progresses with ANA positivity and increased risk of iridocyclitis, and an association with HLA-DRB1*0801. The second subset is a form with negligible joint swelling but there is stiffness and it could follow a destructive course. The third one is similar to adult-onset rheumatoid factor-negative RA and is characterized by symmetric synovitis of the large and small joints. It usually starts in school age, ANA is negative and it has variable outcome (2). The present patients’ clinical features were in accordance with this third subtype.

In FMF, arthritis typically involves the lower extremities and tends to be monoarticular. Tenderness, swelling and redness over the joint may be seen. Attacks usually subside in a few days however protracted arthritis, involvement of the upper extremities and seronegative spondyloarthropathy have been reported (8). Arthritis is asymmetrical and nondestructive with the exception of the sacroiliac and hip joints (1). In the present patient, in addition to his history, he had bilateral and symmetric destructive arthritis in the small joints of the hands and feet indicating the presence of JIA.

MTX is the most preferred disease modifying anti-rheumatic drug (DMARD) for the treatment of JIA because of its effectiveness and acceptable side effects. We have started to treat our patient with MTX and a second DMARD, lefunomide was also added on with a partial response. Arthritis was resistant to DMARD therapy. For those patients resistant to conventional DMARD therapy, biological agents are new therapeutic options. Among them, etanercept is the first agent registered for the pediatric use (2). It also has a lower tuberculosis risk (9). It is well known that infliximab is the choice of treatment in FMF however the reason to start TNF-α blockers was resistant JIA in the present case. So, our choice was etanercept for the present patient. Anti-TNF-α blockers have been previously used in FMF patients. In a study which analyzed the cytokine levels during acute attack of FMF, sIL-2r, IL-6 and TNF-α were found to be higher than during the silent period and in the healthy controls (10). This may explain the successful results observed in the case reports, pointing out treatment of FMF with biological therapies. Infliximab was used in seven patients with FMF arthropathy, resistant to treatment with colchicine, salazopyrin, and methotrexate with good results (11-14). The only patient to receive etanercept was a 35-year-old Jewish man with recurrent episodes of abdominal and articular pain (15). He was resistant to colchicine treatment and improved after etanercept injections. In the present case, we administered etanercept for joint symptoms of JIA, and obtained a good response for FMF symptoms as well as joint involvement of JIA.

The present patient had secondary osteoporosis. There are three possible reasons in this case for osteoporosis. First, he was given corticosteroids for a long time, second he had a sedentary life due to the active arthritis of his lower extremities, and finally the cytokins secreted in JIA and FMF during the attacks increased bone resorption. Among these cytokins, TNF-α effects bone metabolism by stimulating osteoclast development and activity therefore TNF-α blockers seem to be an efficacious treatment for osteoporosis (16). For the treatment of osteoporosis in our patient we started risedronate, calcium and vitamin D. After seven months of treatment, another DEXA was performed as it is suggested for follow-up of steroid osteoporosis which revealed an increase in BMD of femur neck but the BMD values worsened in the lumbar vertebrae. We continued treatment with these medications and etanercept was started at this point. Etanercept was given because of uncontrolled arthritis, nevertheless after 12 months of treatment with etanercept, BMD was dramatically increased both in femur and lumbar vertebrae. In addition to blocking TNF-α, etanercept enabled us to discontinue steroids and allowed the patient to gain mobility which further attenuated bone healing. So it may be possible that osteoporosis was actually treated by etanercept.

In conclusion, disease progression can be more serious in JIA patients with accompanying FMF. In JIA patients with symptoms like abdominal pain, chest pain, fever or resistant arthritis, FMF should be considered in the differential diagnosis. A modifier role of pyrinc could be responsible for this severe involvement and resistance to DMARD therapy. The possible role of TNF in both JIA and FMF renders the early use of anti-TNF treatment reasonable in these patients to prevent further deformities.

References


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