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LETTER TO THE EDITOR

Successful treatment with anti-tumor necrosis factor (anti-TNF)-alpha of proteinuria in a patient with familial mediterranean fever (FMF) resistant to colchicine: anti-TNF drugs and FMF

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Abstract Familial mediterranean fever (FMF) is an autoinflammatory disease characterized by recurrent attacks of fever, peritonitis, pleuritis, and genetically by autosomal recessive inheritance. The major renal involvement in FMF is the occurrence of amyloidosis that can be prevented by a daily regimen of colchicine. About 5–10% of cases with familial mediterranean fever may be resistant to colchicine. In literature, there is a controversy about the treatment of FMF patients resistant to colchicine. We describe a case with FMF, proteinuria, and bilateral sacroiliitis, which responded to anti-TNF (tumor necrosis factor)-alpha therapy with infliximab and etanercept.

Keywords Familial mediterranean fever (FMF) · Proteinuria · Anti-TNF (tumor necrosis factor) alpha treatment

Introduction

Familial mediterranean fever (FMF) is an autoinflammatory disease characterized by recurrent attacks of fever, peritonitis, pleuritis, and genetically by autosomal recessive inheritance [1]. The major renal involvement in FMF is the occurrence of amyloidosis that primarily affects the kidneys causing proteinuria but can be prevented by a daily regimen of colchicine [2]. Colchicine is the drug of choice in controlling the attacks and preventing the development of amyloidosis [3]. About 5–10% of cases with familial mediterranean fever may be resistant to colchicine [4].

The typical arthritis of FMF is characterized by mono-oligoarthritis predominantly involving the large joints of the lower extremities [5]. Permanent joint disease can be related to either FMF or to a coexisting chronic inflammatory disease usually a spondyloarthropathy [6]. FMF patients have an increased rate of certain rheumatic diseases that might be related to the increased inflammatory milieu [7]. In literature, there is a controversy about treatment of FMF patients resistant to colchicine. In a case report, infliximab treatment has been shown to be effective in decreasing FMF related proteinuria [8].

We describe a case with FMF, proteinuria and bilateral sacroiliitis, which responded to anti-TNF-alpha therapy with infliximab and etanercept.

Case report

A 35-year-old male patient presented with fever, abdominal pain, malaise, and low back and ankle pain. When he was first examined for his severe back pain, he was demonstrated to have bilateral sacroiliitis at 1995 and non-steroid anti-inflammatory treatment was given. At that time, he started to suffer from severe abdominal attacks almost twice a week, back and ankle pain and morning stiffness of 2 h and diagnosed as FMF and colchicine 1 mg/day and sulfasalazine 1 g/day, and indometasine 0.2 g were started.

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Abdominal attacks were continued despite decreased in frequency and severity. At 2007, he was suffering from abdominal attacks, back and ankle pain, morning stiffness, severe myalgia, and malaise. He was a hospital staff and unable to work. The family history was negative for both spondiloarthritis and FMF. On physical examination, sacroiliac joints were painful and fabere test was bilaterally positive. Lomber schober was 3 cm and chest expansion was 4 cm. Direct radiography and computerized tomography demonstrated bilateral sacroiliitis. Laboratory evaluation yielded as erythrocyte sedimentation rate (ESR): 66 mm/h, C- reactive protein(CRP): 37 mg/l, albumin: 2.1 g/dl, hemoglobin(Hb): 10.8 g/dl, ferritin: 948 ng/ml 24 h, urinary protein extraction(UPE): 3,306 mg/day (0–150) and 244.8 mg/dL (0–11.9). MEFV mutation test was homozygous for M694 V. ANA and HLA B27 were negative, and rheumatoid factor was 10 IU/ml. He was hospitalized, and colchicine and sulfasalazine dosage was increased to 1.5 g and 2 g/day, respectively. Skin and duodenal biopsies were negative for amyloid deposition, and methyl prednisolone at a dosage of 16 mg and methotrexate 10 mg were added to treatment regimen. Since the clinical symptoms of the patient were not recovered with this treatment, he was then started a treatment with 5 mg/kg/g infliximab at weeks 0, 2, 6, and repeat infusions every 8 weeks. The general status of the patient improved in parallel with a decrease in the severity of symptoms after the third dose of infliximab. At the sixth dose, allergic symptoms like fever, chills, and skin rash appeared and infliximab infusion stopped. The patient refused to continue treatment with infliximab and etanercept was commenced in a few weeks. The patients also responded well to etanercept. After 1 year, etanercept injection rate was decreased. Febrile abdominal attacks and joint symptoms didnot recur. According to the last laboratory findings, urinary proteinuria was 144 mg/24 h and 9.6 mg/dl and acute phase proteins returned to normal limits. He uses etanercept twice a month and is in excellent condition 4 years after the start of anti-TNF-alpha therapy.

Discussion

FMF, also known as recurrent polyserositis, periodic disease is the most prevalent periodic fever syndrome, which affects more than 10,000 patients worldwide [8]. The most prominent common clinical feature is a recurrent fever lasting from several days to several weeks interspersed with symptom-free intervals of unpredictable duration. Colchicine is widely used for the treatment FMF with regard to its ability to strongly inhibit neutrophil chemotaxis [1]. The gene responsible for FMF, MEFV gene is expressed in the cells of myelomonocytic lineage, especially granulocytes. The expression of MEFV gene is stimulated by proinflammatory mediators such as IL-1, TNF-alpha and interferon-gamma [9].

It has been proposed that proinflammatory stimuli, such as inflammatory cytokines, the autonomic nervous system, hormones, or some types of stress, are normally balanced by marenostrin/pyrin expressed on mature neutrophils. Disruption of this balance by mutations in the MEFV gene could easily cause microtubule activation and migration of neutrophils resulting in FMF attacks [1]. According to a recent report, mutations at position 694 of the MEFV gene have a crucial role in the development of FMF but also in showing a severe phenotype [1]. Our patient also was homozygous M694 V mutation and showed a progressive clinical course of the disease.

The protracted arthritis of FMF is characterized by a long duration. Although colchicine is the unique drug effective in FMF, arthritis may be less responsive than fever and serositis [9]. In patients with FMF, a less likely involvement can be in the form of HLA B27 negative spondyloarthritis. These patients usually have unilateral or bilateral sacroiliitis, recurrent enthesitis, and inflammatory neck/low back pain with minimal radiologic spinal involvement [10]. Our patient also has similar findings and may be considered to have FMF with some overlap of spondyloarthritis features.

The role of anti-TNF agents in FMF has to be clarified. In a report, it was hypothesized that marenostrin/pyrin on neutrophils can adequately regulate the activity of caspase-1, which increases the production of IL-1 beta in response to the proinflammatory cytokines like TNF-alpha. Mutations in the MEFV gene may impair the regulatory function of marenostrin/pyrin resulting in febrile attacks through excessive production of inflammatory cytokines [1].

The presence of amyloidosis determines the prognosis of FMF patients. Regression of amyloidosis with anti-TNF-alpha treatment was shown in a case report [8]. Although we could not demonstrate the presence of amyloidosis in this patient, disappearance of proteinuria after the anti-TNF-alpha treatment was significant.

This is one of the few reports about successful treatment of FMF with proteinuria with anti-TNF-alpha therapy. TNF-alpha blockade may represent a possible alternative on adjuvant treatment of FMF patients resistant to colchicine. Further prospective studies are needed for long-term efficacy of anti-TNF drugs in FMF patients.

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