Bone Marrow Edema and Pseudocyst as a Very Rare Complication of Familial Mediterranean Fever: A Case Report

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ABSTRACT
Familial Mediterranean fever (FMF) is one of the most common autoinflammatory diseases. FMF is a disease that characterized by recurrent fever, transient and self-limiting polyserositis, responds well to the treatment of colchicine. In 95% of patients, the first attack occurs with severe abdominal pain. The first attack frequency that starts with pleuritic chest pain, pleural effusion and fever are lower than 10%. Ninety percent of the cases are younger than 20 years old. After 40 years old, it is rarely diagnosed (1.25%). In this case report; we wanted to present an FMF case diagnosed after 40 years old in the context of the patient’s clinical follow-up, treatment, and literature, since it is very rare to diagnose in this age group, and unexpected complications can occur.

Keywords: Familial Mediterranean Fever, bone marrow edema, pseudocyst

Introduction
Familial Mediterranean fever is an autosomal recessive genetic disorder characterized by recurrent episodes of fever and accompanying attacks of peritonitis, pleuritis, arthritis, or erysipelas-like erythematous skin lesions. Abdominal pain is caused by peritonitis and continues for 12 to 72 hours with fever. Joint pain may be long-lasting. FMF’s cause is Mediterranean Fever (MFEV) gene mutation in the short arm of chromosome 16 (1). The pyrin protein, which plays a role in neutrophil activity, is synthesized from the MEFV gene found in 16p13.3 and plays an etiologically important role. MEFV gene is a large gene including 10 exons. 20 different mutations have been described in the literature for this gene. It is known that these mutations are localized to a small area in the 10th exon, their incidence in Turks, Armenians, Arabs, and Jewish communities is significantly higher compared to other populations. FMF’s incidence among Turks is approximately 1/1000, the carrier rate is 1/5. Family history must be questioned. Today, only 5% of patients with FMF have been diagnosed and their treatment has been started (2). In this case; a female patient had applied to the emergency service because of intermittent abdominal and chest pain, subsequently bone marrow edema and pseudocyst. The patient was diagnosed with FMF as a result of a long process and genetic testing, we aimed to emphasize the clinical follow-up results and treatment processes of the patient in the light of the literature.
Case Report

A forty-three year-old female patient works as a nurse and administrator in a healthcare facility. Her complaints were increasing severe pain in her both legs, especially in his right leg and right pelvis. She was unable to sit and her pain was increasing significantly at nights. Complaints were present for the last 6-7 months. The patient indicated severe muscle cramps, pain, and weakness, which started shortly after beginning to work, even requirea little effort. There was no muscle disease, effort intolerance and cramp history in patient’s family, according to her systematic anamnesis. The patient had applied to the hospital 2-3 times in last year due to severe abdominal pain, hospitalized with acute appendicitis preliminary diagnosis, and discharged after a good response to fluid replacement and medical treatment. Patient-applied to the emergency service because of 3-4 months of intermittent pain in left chest, shoulder and arm. This pain was not accompanied by fever. After continues hip and leg pain for 4-5 months, it had restricted walking and daily activities. The patient had admitted to a rheumatology clinic, pelvic X-ray, computed tomography, magnetic resonance imaging (MRI) and whole-body bone scintigraphy tests were done. As a result of these examinations, various preliminary diagnoses have been made. Primarily, the patient was diagnosed with osteoid osteoma and bone marrow edema at the right femoral head and neck and acetic salicylic acid and anti-inflammatory drug treatment were started (Figure 1-2). The patient was referred to a more advanced healthcare facility because of the treatment failure. The patient was diagnosed with Ischiofemoral Impingement Syndrome and bone marrow edema at next facilities, and physical therapy, analgesics and bed rest were recommended. Symptoms have not been reduced thereafter. Hemogram, biochemistry, C-reactive protein, procalcitonin, sedimentation, thyroid hormones, tumor markers, serology (rheumatoid factor, C3, C4,
all immunoglobulins), immunoblots, immunofluorescent and FMF-gene mutation scan tests were done. All of the patients results were normal and there is no relief.

The patient went to another facility on her own decision. The patient has been hospitalized, because of her muscle weakness, fatigue and recurrent abdominal pain of unknown etiology and recently increased chest pains. Along with the fact that routine laboratory tests and FMF-gene mutations screening were normal, MEFV gene mutation component and new pelvic MRI were requested. MEFV gene mutation in the patient was identified as heterozygous R202Q gene. This gene mutation results in a delayed FMF diagnosis. Pseudocyst and bone marrow edema, which are very rarely seen in FMF, were seen in the head of the right femur in MRI. Colchicum-Dispert tablets (0.5 mg colchicine) 3x1 were started along with rheumatology. Patient's pain declines dramatically within 15 days, the patient returns to her daily activities. Pseudocyst and bone marrow edema seems to disappear in a 1st-month control pelvic MRI (Figure 3).

The patient has a history of right salpingectomy due to ectopic pregnancy rupture, 15 years ago. The patient also has allergic asthma. Mother and father are not relatives, there is no disease history.

**Discussion**

The FMF typically occurs in childhood or young adulthood. The attack occurs in first 10 years in 75% of the patients, 20 years in 80% of the patients, the first occurrence of the attack after 40 years is very rare (1.25%) (3). FMF is more common in males than females (M/F: 1.8/1) (4). Our case was female, older than 40 years, and she was evaluated as a rare case according to literature findings. The late age of the onset of the disease indicates a clinically benign illness. Cold, greasy food and also the pregnancy could trigger attacks. Attacks typically continue for 1-3 days. About half of the patients have 10-30 attacks per year. The asymptomatic period is present between attacks. It was reported that R202Q gene mutation, which is in the 2nd exon of MEFV gene, is in cis position with M694V mutation. It was reported as 15% in chromosomes that do not carry mutations, and as 16% in chromosomes that carry mutations outside of 10th exon, and thus it is suggested that R202Q may be a common polymorphism (5). In our case, R202Q gene mutation was present, heterozygous, and compatible with the gene polymorphism in literature.

Abdominal attacks are one of the most common symptoms in patients and are observed in approximately 90% of patients. It may be widespread abdominal pain or muscle pain in the abdominal region and appendicitis-like pain extending to the whole abdomen. This symptom usually decreases in 2-20 hours and disappears in 24-48 hours (6). In our case, the abdominal pain has been occurred 2-3 times, then spread to chest and shoulder.

Articular attacks are the second most common symptom. Generally, they acutely continue for 24 hours accompanied by a high fever. It is present in knee and ankle less frequently, as well as areas such as shoulder, elbow, and wrist, and disappears within 24-48 hours (7). It is quite painful in held regions and it restricts the joint motion. Partial redness and heat increase

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**Figure 3: Magnetic resonance imaging, A. Hypotenseedema in T1A, B. In the T2A, the right femur head is laterally hyperintense in the subcortical area**
may be observed. Attacks emerge more often after mild trauma and walking with intensive effort. Synovial fluid is sterile and rich in neutrophil content. In our case, fever, knee and foot pain never occurred. The patient was not able to perform daily activities due to the widespread leg and pelvic pain. Despite the literature that implied symptoms reduce in 48 hours, our case could not walk for 3-4 months.

Moderate muscle pain is present in 10% of child patients. Especially in the legs below the knee, pain occurs for one day or less after physical exercise. Febrile myalgia syndrome has been defined in patients with FMF. This syndrome is characterized by abdominal pain, fever, myalgia, high sedimentation rate, leukocytosis and hyperglobulinemia without peritoneal irritation (8). In our case, sedimentation, leukocytosis and fever were not present, widespread muscle pain, and cramps were present, also significant atrophy was seen in the right leg compared to the left.

FMF is a genetic disease for which treatment is started with consideration of clinical diagnostic criteria and molecular methods. There are three different groups of criteria that are developed for clinical diagnosis. Most valid and useful of these is Tel-Hashomer diagnostic criteria (9).

Tel-Hashomer Criteria for FMF:

**Major criteria:**
- Recurrent episodes of fever accompanied by peritonitis, pleuritis or synovitis
- Type AA amyloidosis without a predisposing disease
- Good response to regular colchicine treatment

**Minor criteria:**
- Recurrent febrile episodes
- Erysipelas-like erythema
- First-degree relative history of the FMF.

In the case of patients with 2 major or 1 major and 2 minor criteria, definitive diagnosis is reached; in the case of patients with 1 major and 1 minor criteria, possible diagnosis is reached; and definitive diagnosis is reached by whether the patient responds to colchicine (10). In our case, only one criterion, good response to colchicine treatment, was present. Also, mutation was detected in gene analysis.

**Conclusion**

FMF is a common disease in the world and has difficulties in diagnosis. In recent years, molecular genetics methods in the diagnosis of the FMF have gained importance. Our case supported heterogeneity in MEFV gene mutation in patients with FMF and in this report emphasized importance FMF in the differential diagnosis in adults with recurrent abdominal pain.

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**References**