Case Report / Olgu Sunumu

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Familial Mediterranean Fever Presenting with Perimenstrual Attacks and Infertility

Perimenstrüel Ataklar ve İnfertiliteyle Sunulan Ailesel Akdeniz Ateşi Olgusu

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Abstract / Özet

Familial Mediterranean fever (FMF) is a genetic disease, transmitted by an autosomal recessive gene prevalent among Turks, Armenians, Sephardic Jews and Arabs. FMF is manifested by short, self-limiting attacks of fever, peritonitis, pleuritis, and arthritis. Usually, patients also have attacks between menstruations. Infertility has been implicated by ovulatory dysfunction and peritoneal adhesions and reported in up to 30% of untreated women with FMF. A 34 year old woman presented to the emergency department with dysmenorrhea three times annually since 22 years of age. She had had infertility treatment for 3 years (three times in vitro fertilization therapy, which had not ended with pregnancy). We thought that this patient, who presented with painful perimenstrual attacks and who had infertility could have FMF.

Key Words: Familial mediterranean fever, infertility, dysmenorrhea

Ailesel Akdeniz Ateşi (FMF); Türkler, Ermeniler, Sefarad Yahudileri ve Araplar arasında yaygın olan ve otozomal resesif olarak iletilen bir genetik hastalıktır. FMF kısa süren ve kendini sınırlayan; ateş, peritonit, plevrit ve artrit ataklarıyla seyreder. Ataklar genellikle menstrüasyon dönemlerinin arasında olur. FMF'i olan ve tedavi almayan kadınlarda %30'a varan oranlarda görülen infertilite, ovulatuar bozukluk ve peritoneal yapışıklıklara bağlanmıştır. 34 yaşındaki bayan hasta acil servise 22 yaşından beri yılda 3 kez olan dismenore şikayetiyle başvurdu. Hasta 3 yıldan beri infertilite tedavisi almaktaydı ve hiçbiri gebelikle sonuçlanmayan 3 in vitro fertilizasyon tedavisi almıştı. Biz bu hastanın ağrılı perimenstrüel atakları olan bir FMF hastası olduğunu ve FMF'e bağlı infertilitesi olabileceğini düşündük.

Anahtar Kelimeler: Ailesel akdeniz ateşi, infertilite, dismenore

Introduction

The estimated prevalence of familial Mediterranean fever (FMF) in Turkey is 1/1000. With a population of more than 70 million inhabitants, therefore, a large proportion of all the FMF cases in the world live in Turkey (1). FMF is a recessively inherited disorder most commonly affecting Sephardic jews, Armenians, Arabs and Turks. Since large numbers of these people migrated from the Mediterranean coast during the 20th century, FMF cases may now be found more frequently all over the world, especially the countries of Western Europe.

The disease may occur at any age, with more than 80% of patients being symptomatic by the age of 20 years (2). Only 5% of the cases develop the disease after the age of 30. The male-to-female ratio has consistently been reported to be about 2:1, suggesting that the mutation has reduced the penetration in females. Despite the fact that the disease is often familial, in about 50% of cases a family history is not found (3).

Clinically, FMF is characterized by recurring, acute, self-limiting episodes of fever accompanied by serosal, synovial or cutaneous inflammation, lasting from 1 to 3 days, but occasionally up to 1 week. Between the attacks, the affected individual is usually free of symptoms and appears healthy.

In women, gynaecological evaluation is required to rule out rupture or torsion of ovarian cysts, bleeding from a follicle or corpus luteum cyst, ectopic pregnancy, endometriosis, septic abortion, myometritis or endometritis as well as pelvic inflammatory disease. Therefore, affected individuals have commonly undergone unnecessary emergency abdominal surgery including appendectomy, exploratory laparotomies, or laparoscopies.

Usually, patients also have attacks between menstruations. It was reported thatup to 15% of female patients with FMF experience perimenstrual attacks (4). FMF is also associated with infertility. In females, infertility was mainly related to oligomenorrhea, although the causes remain unclear. In pregnant FMF patients, an increased incidence of miscarriage has been found (5).

Case Report

A 34-year-old Turkish woman presented at the emergency department with dysmenorrhea, three times annually since 22 years of age. According to her history, she has dysmenorrhea, ankle joint

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pain and an erysipelas-like, well-demarcated, erythematous, painful rash on the dorsum of the foot after physical stress, since 8 years of age. Each event lasted approximately one day and healed spontaneously. The patient had had a pleuropericarditis attack and had no history of genital ulcers, rash or any thrombotic events. Her medications included various non-steroidal anti-inflammatory drugs.

In the family history; her brother has FMF and her father died because of renal failure at a young age. She also presented with a complaint of primary infertility of 6 years duration and she had undergone infertility treatment for 3 years. She had 3 IVF therapy sessions (in vitro fertilization) and none of them ended with pregnancy. She specified regular cyclic menstruation. Her husband's tests for infertility, such as a sperm analysis, Anti-Sperm Antibodies were in normal ranges. Therefore, to investigate the female infertility, she underwent a hysterosalpingogram and pelvic ultrasonography which revealed bilateral tubal patency.

All other laboratory tests, including thyroid stimulating hormone and serum prolactin, were normal. Her FSH level was 10.7 mIU/mL, LH level was 12.36 mIU/mL, Estradiol (E2) level was 112 pg/dl and progesteron level was 0,6 ng/mL.

She reported the presence of perimenstrual attacks, family history of FMF, pleuropericarditis, arthritis and erysipelas-like rash, which is diagnostic of familial Mediterranean fever. She also underwent a complete medical evaluation and had normal renal and liver function tests. Her complete blood count revealed a microcytic, microchromic anemia with a hemoglobin of 10.7 g/dl, hematocrit of 32.2%, MCV of 76.6 fl. Antinuclear antibody and Rheumatoid Factor assays were negative. A single M694V and E148Q mutations in the MEFV gene were identified as heterozygote. A C-reactive protein (CRP) of 46 mg/dL (normal 0-5) and an erythrocyte sedimentation rate (ESR) of 52 mm/h (1-12) were observed during a perimenstrual attack. Laboratory evaluation for CRP and ESR during a remittive period revealed normal ranges. Ultrasound of the abdomen and pelvic region were unremarkable.

After starting 0.5 mg colchicine three times daily, her ankle joint arthritis and "dysmenorrhea" ceased for the first time. She started IVF therapy again.

Discussion

According to the literature, two major mechanisms can be responsible for the menstruation-FMF relationship. The first is a suggestion for the underlying physiology for this relationship. It is proposed that hormonal changes may lead to the FMF attacks during menstruation. Support for this hypothesis may be found by two observations: (a) Hormone replacement therapy significantly lowered the expression of intercellular adhesion molecules; (b) Estrogen can inhibit tubulin assembly using a binding site analogous to colchicine sites. Based upon these two findings, it is tempting to speculate that estrogen may mimic the colchicine effect on tubulin and adhesion molecules. Colchicine inhibits the chemotaxis of neutrophils by inhibiting their microtubules and by suppressing the expression of adhesion molecules in granulocytes and endothelial cells. Because estrogen levels decrease significantly during menstruation, their protective effect disappears, leading to the acute attack. Another hypothesis may be suggested based upon the finding that colchicine and estrogens are substrates of the same cytochrome (3A4) in the liver. When levels of estrogens are decreased (during menstruation), more enzymes are available for colchicine metabolism, thereby decreasing its concentration and its protective effect (6, 7).

Until now, eighteen different genotypes have been characterized with the greatest diversity of genotypes observed among Turks and Armenians (8). In addition, several disease-associated mutations were identified in the distal part of exon 10 of the MEFV gene, but three of these (M6801, M694V, V726A) appear to account for the majority of clinical FMF cases (9, 10).

Familial Mediterranean fever, amyloidosis and colchicine may affect the reproductive system of male and female patients. The acute FMF episodes may cause miscarriage or early delivery in pregnancy. However, colchicine treatment may improve female fertility and the outcome of pregnancy by preventing the serosal adhesions and controlling the acute attacks. Amyloidosis may lead to male and female infertility through its deposition in the testis and ovaries.

As in our patient, a woman with FMF, the perimenstrual attacks can present with dysmenorrhea and it can be a rare cause of infertility. Colchicine is the drug of choice of that improves both conditions.

The exact mechanism of colchicine in the disease is not entirely known. However, it has been shown that colchicine prevents amyloidosis in all patients in whom treatment is started before amyloidosis is clinically manifest and may inhibit neutrophil chemotaxis, thereby decreasing the inflammatory process (11).

Conclusion

Colchicine may not affect female fertility in patients with FMF. On the contrary, it may control FMF attacks during pregnancy and prevent abortions and inhibit peritoneal adhesions and prevent infertility. Thus, overall, colchicine treatment improves the prognosis of patients with FMF and may increase their reproductive ability.

Conflict of Interest
No conflict of interest was declared by the authors.

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