The Unusual Cause of Abdominal Pain in a Patient with Coexistence of Behçet's Disease and Familial Mediterranean Fever: Cyst Hydatid Disease: Case Report

Behçet Hastalığı ve Ailesel Akdeniz Ateşinin Birlikte Görüldüğü Bir Hastada Karın Ağrısının Nadir Bir Nedeni: Kist Hidatik Hastalığı

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ABSTRACT Behçet's disease (BD) is a rheumatologic disorder of unknown etiology. Familial Mediterranean fever (FMF) is another inflammatory disease which occurs due to the mutations in the MEFV gene. Both diseases have some common signs and symptoms, such as fever, arthritis, abdominal pain and cutaneous signs. Echinococcosis or hydatid disease is a zoonotic infection which mainly involves the liver and may cause abdominal pain accompanied by a large cystic mass. We report a case of 23-year-old male patient applied to our clinic with the complaints of recurrent pain and swelling in the left knee with abdominal pain. After the diagnosing coexistent BD and FMF in our patient we started colchicine treatment. Although knee pain and swelling improved, abdominal pain did not improve after this treatment. Therefore, we investigated other reasons for abdominal pain. In conclusion, concomitant occurrence of BD, FMF and also hydatid disease which may also cause abdominal pain was discussed in this case report.

Key Words: Behçet's disease, familial Mediterranean fever, arthritis, abdominal pain

ÖZET Behçet hastalığı (BH) nedeni bilinmeyen romatolojik bir hastalıktır. Ailevi Akdeniz ateşi (AAA) ise MEFV genindeki mutasyon nedeniyle oluşan diğer bir inflamatuar hastalıktır. Her iki hastalık da ateş, artrit, karın ağrısı ve cilt bulguları gibi bazı ortak semptom ve bulgulara sahiptir. Ekinokokkozis veya hidatik kist hastalığı başlıca karaciğeri tutan ve büyük kistik kitleye bağlı karın ağrısı da yapabilen zoonotik bir enfeksiyondur. Biz burada sol dizinde tekrarlayan ağrı, şişlik ve karın ağrısı şikayetleri ile kliniğimize başvuran 23 yaşındaki bir erkek hastayı sunmaktayız. Hastamızda BH ve FMF birlikteliği teşhis edildikten sonra kolşisin tedavisine başladık. Bu tedaviden sonra dizdeki ağrı ve şişlik gerilediği halde, karın ağrısı rahatlamadı. Bunun üzerine karın ağrısının diğer nedenlerini araştırdık. Sonuçta, bu olgu sunumunda BH, AAA ve yine karın ağrısına neden olabilecek kist hidatik hastalığının birlikteliği tartışıldı.

Anahtar Kelimeler: Behçet hastalığı, ailesel akdeniz ateşi, artrit, karın ağrısı

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In 1937, Behçet's Disease (BD) was first described by Hulusi Behçet as triple complex of oral and genital ulcers and recurrent uveitis with hypopyon formation.[1] Then, it has been shown that, BD is a chronic, multisystemic disorder. Besides orogenital ulcers and uveitis; it may involve arteries and veins of all sizes, skin and locomotor, central nervous, pulmonary and gastrointestinal systems. Joint involvement in BD is usually recurrent and inflammatory mono/oligoarthritis is seen especially in major joints of the lower extremities. It may be symmetrical or asymmetrical.[2]

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Familial Mediterranean fever (FMF) is an autosomal polyserositis with an unknown etiology.[3] Serositis usually appears in forms of peritonitis, pleuritis and is synovitis and self-limited. Joint involvement in FMF manifests with acute attacks of pain accompanied by swelling of one joint at the same time, and affects most frequently the major joints of the lower extremities.

Behçet's Disease and FMF are inflammatory diseases which have similar clinical and laboratory findings with same geographic and etiopathogenetic properties.

Echinococcosis or hydatid disease (HD) is a zoonotic infection caused by the tapeworm *Echinococcus granulosus*. HD mainly affects the pulmonary and digestive systems. The first and the most frequently involved organ is the liver and it may cause abdominal pain accompanied by a large cystic mass. The lungs, heart, spleen, kidneys and brain can be less frequently involved.[4] It may also cause mono, oligo or polyarthritis in course of the liver HD.[5-7]

All of these three diseases have similar symptoms, such as arthritis and abdominal pain. In FMF and BD, colchicine is an effective medical treatment. Apart from this, total excision of the hydatid cyst[5-7] and albendazole therapy are necessary for recovery in HD.[7]

In this case report, we aimed to explain the existence of BD, FMF and HD in a patient with arthritis and abdominal pain.

CASE REPORT

A 23-year-old male admitted to our clinic with complaints of pain and swelling of his left knee, fever and loss of apetite. It was learned that the swelling and pain at his left knee had started five years ago. The fluid in the knee joint was aspirated in a state hospital without any relief in his complaints at that time. Since swelling persisted, an arthroscopy was performed one year ago, and the same procedure was repeated in a university hospital 5-6 months after this procedure due to recurrence. Joint fluid of the knee was analyzed. According to his medical records, there was no growth in synovial fluid culture. No microorganisms including *Mycobacterium tuberculosis* were seen on dricet microscopic examination. His laboratory test results were: C-reactive protein (CRP): 15.1 (0-7) mg/dl, erythrocyte sedimentation rate (ESR): 70 mm/h and white blood cell count (WBC): 9600 /mm^3. His urine analysis was found normal and HLA-B27 test was negative. Magnetic resonance imaging (MRI) of the left knee showed joint effusion and an alteration in the intensity of bone marrow of distal femur. He was diagnosed as (suspected to have) Behçet's arthritis or reactive arthritis because of the existence of oral aftous ulcers and dysuria. He was examined by ophthalmology and dermatology clinics and was found to be normal. Indomethasine 75 mg/day was started during the control visits due to lack of any relief after knee joint puncture. After the medical treatment, the patient did not recover. ESR was still high at a level of 95 mm/h and CRP was 11.5 mg/dl during his control visit.

The patient was hospitalized for further investigation and treatment in the university hospital. Swelling and pain of his left knee persisted (Figure 1). Furthermore, he complained of pain in his right

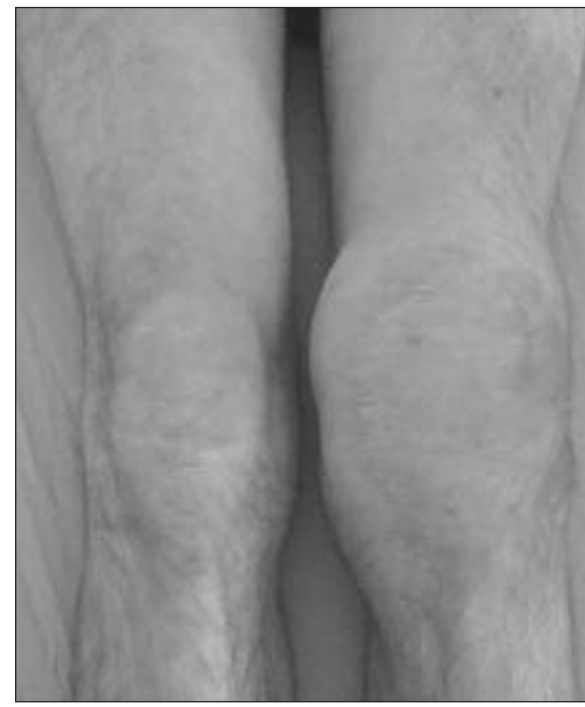

FIGURE 1: Knee photograph before treatment: It shows the clear swelling of the left knee in comparison with the right.

hip which wor sened with movements. He had no difficulty of movements in the morning. He lost weight (10 kg in 3 months) and was also sweating at nights. In his medical history, it has been learned that he had suffered from oral aphthous lesions 3-4 times in a year and had eruptions on his chest. Moreover, he also had recurrent abdominal pain and diarrhea for one year. When the patient's history was obtained again, it has been found out that his recurrent abdominal pain and diarrhea complaints were seen every 30-45 days and recovered in a couple of days spontaneously. Patient gave a history of fever occasionally, but he mentioned that he could not recognize whether it was related to his abdominal pain or not. He had no cough but had sputum in white color. He had a history of smoking 1 pack of cigarettes/day for 15 years. He had no genital ulcerations but dysuria and a genital discharge yellow in color. His familial history revealed that his father used indomethacin for his arthritis without any diagnosis.

In his physical examination, there were a few fissures at the border of his lips, two aphtous lesions in the oral mucosa and papullopustular lesions on chest. We detected 1-2 lymphadenopathies in his axillary region, 1 x 1 x 1.5 cm in size bilaterally. Liver was palpable approximately 2 cm inferior to the costal margin. His musculoskleletal system examination revealed that, left knee was swollen and a scar was seen due to the latest arthroscopy. There was an effusion in his left knee and movements of this knee were painful and restricted. Movements of his right hip were unrestricted but minimally painful. Fabere test was positive for right hip. Examinations of other joints and his neurological examination were normal. A scar was seen on the scrotal skin during his genital examination.

Laboratory tests were performed for the differential diagnosis of Behçet's arthritis, reactive arthritis, tuberculous arthritis, inflammatory bowel disease and malignancy. His routine biochemistry tests were normal. Hemoglobin (Hgb): 13.6 g/dl, ESR: 94 mm/h, CRP: 12.5 mg/dl and all Brucella agglutination tests including Brucella IgM and IgG and prostate spesific antigen were negative. Mild increases in alpha-1, alpha-2 and gamma globulin fractions were determined in protein electrophoresis. His peripheral blood smear was rich in atypical lymphocytes and hyperpigmented leucocytes. Hypochro- mic microcytic anemia was also detected. HLA-B51(08) was positive, while HLA-B27 was negative. There was no evidence of growth in his urine culture. 1500/mm^3 lymphocytes and PNL dominance with 50% were reported in the cytological examination of the synovial fluid of his knee. No microorganisms were seen in direct smear and no growth was seen in the culture.

The patient was consulted to different clinics for further examination. The patient was seen by urology department because of his genital discharge and dysuria. They diagnosed chronic prostatitis and suggested a medical treatment. Pathergy test was found negative after the dermatological consultation. No evidence for rheumatic diseases was found in ophthalmolgy consultation. The tuberculin skin test with PPD (purified protein derivative), ARB (acid-resistant bacteria) in mucus, tuberculosis (TBC) culture and thorax computerized tomography (CT) were recommended by the clinics of pulmonary diseases. The laboratory tests were found negative. In his thorax CT, there were bilateral several non-pathological lymph nodes in the axilla and paratracheal area. A fibrotic band was detected at the superior segment of the lower lobe of the right lung. TBC was excluded according to these findings. Right sacroiliac and hip MRI of the patient were also reported as normal.

Fecal occult blood test, fecal culture and examination for parasites were performed because of the abdominal pain with diarrhea and results were found negative. His colonoscopy was also normal.

The patient was diagnosed as BD. We also suspected of FMF and detected M680I heterozygous mutation after analysis of the MEFV (MEditerranean FeVer) gene. Our findings support the existence of both BD and FMF in our patient. We started colchicine 1 mg/day. For complete recovery (since pain did not improve completely), the dose increased to 1.5 mg/day. His pain and swelling improved with this treatment (Figure 2). During the follow-up, the patient suffered from pain localized at midline and quarter part of the abdomen. In BD, aort aneurysm may be one of the ca-

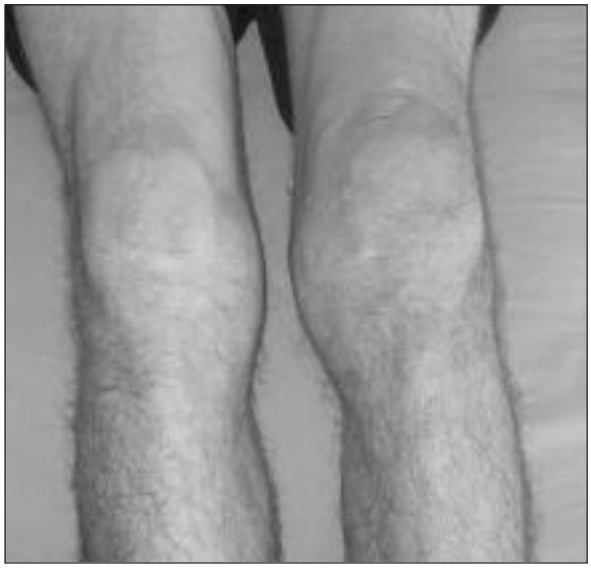

FIGURE 2: Knee photograph after medical treatment: It shows the improvement of left knee swelling after the colchicine therapy.

usative factors for abdominal pain. MRI angiography was performed to exclude aort aneurysm and found as normal. On abdominal ultrasonography, total vertical length of the liver was found as 162 mm, bigger than normal and a cyst with a size of 21 x 18 mm was detected in the liver. General surgery department consultation was performed and a 3D CT was requested. In 3D CT, a lobulated 25 x 15 mm cyst was detected in the 4b segment of the liver (Figure 3). Hydatid cyst agglutination test was positive. Albendazole treatment was started for HD.

The patient was discharged with the diagnosis of BD, FMF and HD. After one month the patient did not have hip, knee or abdomanital pain. Colchicine dose was lowered to 1mg/day and patient was invited for outpatient controls. To use the data and his photos for the scientific purpose, we obtained written consent of the patient.

DISCUSSION

BD and FMF are inflammatory, periodical, multisystemic and ethnically related disorders. Both diseases have been highly prevalent in the Middle Eastern and Mediterranean populations, namely Turks, Arabs and non-Ashkenazi Jews.[8] Because of the geographical and ethnic characteristics, both diseases may appear in our country. There are similarities in FMF and BD for skin, gastrointestinal and muscoloskeletal system involvements. In addition, both diseases have common etiopathogenetic mechanism. It has been demonstrated that the chemotaxis of neutrophils was increased and the level of serum interleukin was elevated in both diseases. Furthermore, colchicine is an effective choice in preventing FMF attacks and some of clinical manifestations of BD.[9]

In literature, it has been investigated whether FMF and BD have a causal relationship. Schwartz et al.[8] conducted a retrospective study which included approximately 4000 registered FMF patients also suffering from BD. The aim of that study was to define and characterize the coexistence of FMF and BD. At the end, they emphasized that the prevalence of BD was higher in FMF patients than in populations known to be rich in BD (controls), and FMF-BD patients and patients suffering from each of the diseases alone were clinically and demografically comparable. In another study, it has been reported that although coexistence of FMF and BD was higher than expected, two diseases were two separate entities and there was no mutual effect of FMF in BD or BD in FMF.[9]

MEFV gene is the main factor in FMF etiopathogenesis.[10] Mutations in MEFV gene have been investigated in various BD and FMF patient co-

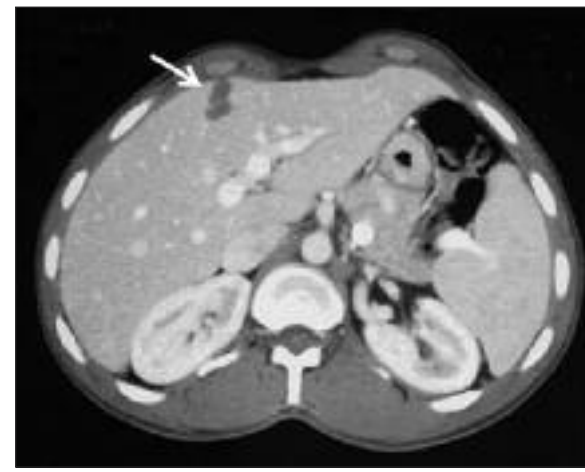

FIGURE 3: 16 cross-section multislice 3D abdominal CT: It has been demonstrated a lobulated cyst which is 25 x 21 mm in size, liquid dencity in the 4b segment of the liver .

horts. Although high mutation rates were found in MEFV gene in many studies for BD,[10-12] some studies did not find this result. Espinosa et al.[13] studied a cohort of fifty Spanish patients with BD and they concluded that FMF and BD were not genetically related diseases. Dursun et al.[14] similarly conducted a study on 54 Turkish patients to investigate whether mutations in pyrin domain of MEFV gene were involved in BD. At the end of the study, they reported that pyrin domain was not mutated. Atagündüz et al.[15] investigated the presence of MEFV mutations in 57 BD patients from Turkey. They found that BD patients carrying MEFV gene mutations tend to experience vascular manifestations in a significantly higher frequency compared to non-carriers. Touitou et al.[16] conducted a multicenter study for common MEFV mutations in BD patients, FMF patients and healthy controls. They studied a cohort of definite and probable BD patients from an ethnically mixed population for common MEFV mutations, and screened an ethnically-matched cohort of FMF and healthy individuals parallelly. They discovered that the M694V, V726A and E148Q mutations tended to be more frequent in BD than in controls and suggested that MEFV mutations might act as additional susceptibility genetic factors in BD. They also emphasized that M694I and M680I mutations, usually found in more than 10% of the FMF patients, were not detected in BD. Ayesh et al.[17] studied 42 Palestinian patients with BD. They found nine different MEFV mutations and the E148Q was the most prevalent mutation in their study. They determined that only the M680I mutation was not detected in any of their patients. In contrary, we detected M680I mutation in our patient. This mutation type was fairly rare and interesting in BD. İmirzalioglu et al.[18] screened 42 patients with BD and 66 healthy controls for common MEFV mutations (E148Q, M680I, M694V and V726A). They found 15 (36%) MEFV mutations in BD patients and one of them was M680I mutation.

M694V is the most prevalent mutation in FMF.[19] It has also been demonstrated that the incidence of arthritis is related to presence of M694V mutation. Brik et al.[3] screened 136 pediatric patients with FMF who were evaluated for a variety of musculoskeletal symptoms. In that study, the frequency of acute monoarthritis was found as 71% in Sephardic Jewish children (all of them carried M694V mutation) and 40% in Arab children (who carried mostly the V726A and M680I mutations). A multicenter study included 2838 FMF patients from Turkey.[20] One thousand ninety of them were examined genetically. At the end of the study, it was reported that the most prevalent mutation in FMF was M694V (51.4%), followed by M680I (14.4%) and V726A (8.6%) mutations. Furthermore, M694V mutation was found to be related to earlier age of onset and higher frequency of arthritis and arthralgia. In another study from Turkey, it has been reported that patients with M680I mutation were associated with lower frequency of arthritis than the ones with M694V mutation in FMF patients.[21] Türkçapar et al.[22] similarly reported that M694V mutation was related to a higher frequency of arthritis.

In our patient, we found out M680I mutation, which was encountered fairly rare in BD and associated with a lower frequency of arthritis. The main complaint of the patient was recurrent monoarthritis. On the other hand, Diri et al.[23] reported that papulopustular skin lesions were seen more frequently in BD patients who had arthritis. This result was similar to our case because our patient had papulopustular lesions at his chest which accompanied arthritis.

Echinococcosis, which has highest prevelance in Mediterranean region and Middle East, is another reason of abdominal pain and arthritis. Large cystic mass in the abdominal organs such as liver and spleen may cause abdominal pain which is not recurrent.[4] Arthritis accompanied with HD has been reported only rarely. In these studies, it has been reported that arthritis resolved completely after excision of the hydatic cyst[5-7] and albendazole therapy.[7] We thougt it was different in our patient, because the arthritis improved after colchicine treatment.

As a conclusion, FMF and BD are multisystemic and inflammatory diseases which similar to each other for some clinical and genetic properties,

and appear in definite geographical regions and ethnical groups. The M680I mutation which was determined in our patient is interesting because it is encountered rarely. Furthermore, in our case it was shown that other reasons of abdominal pain should be certainly considered even in the presence of diseases which can cause abdominal pain like FMF and BD. It is also shown that, sometimes abdominal pain may originate from a different disease, especially in countries where HD is endemic.

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