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Visceral Leishmaniasis as a Rare Cause of Granulomatosis Hepatitis: A Case Report

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SUMMARY: Visceral leishmaniasis (VL) is one of the parasitic infections causing different pathogeneses of various systems including intraabdominal solid organs. *L. donovani* and *L.infantum*, particularly in Turkey, have been diagnosed in systemic infections. In the present case study, a 43-year-old woman with left upper abdominal pain, persistent fever and splenic pathology according to the radiological findings was investigated. Laboratory findings showed elevated liver function tests and anemia while radiological studies revealed splenomegaly, and nodular infiltration and laceration of the spleen. Because of enlarged intraabdominal lymph nodes observed during surgery, a lymph node biopsy and a liver biopsy were also performed along with the splenectomy. Results from the pathological examination of the spleen were nonspecific and the liver biopsy confirmed a diagnosis of granulomatosis hepatitis. Further examination of the hepatic granulomatosis including parasitic evaluation and serological evaluation with the rK39 dipstick test revealed VL. In conclusion, in cases of visceral organ pathology accompanied by persistent fever, and hematological disorders, parasitic infections, particularly VL, should be considered in the differential diagnosis.

Key words: Parasitic infection, visceral leishmaniasis, granulomatosis hepatitis

Granülomatöz Hepatitin Nadir Bir Sebebi olarak Visseral Leishmaniasis: Olgu Sunumu

ÖZET: *Leishmania* vücutta birçok bölgeye yerleşebilen bir protozoondur. İç organların tutulumundan sorumlu türleri *L.donovani* ve özelikle ülkemizde *L. infantum*'dur. Bu olgu sunumunda da sol üst kadran ağrısı ve ateş şikayetleri üzerine tarama yapılan ve dalakta patoloji saptanan 43 yaşında bir olgu sunulmuştur. Karaciğer enzim değerlerinde yükseklik ve anemi tespit edilen hastanın yapılan radyolojik değerlendirmesinde fizik muayene ile uyumlu olan dalak boyutlarında artış ve çok sayıda nodüler infiltrasyonlarla laserasyon alanları saptandı. Hastaya yapılan operasyonda, splenektomi prosedürüne enzim yüksekliği nedeniyle karaciğer biyopsisi ve irilemiş lenf nodları nedeni ile lenf biyopsisi de eklendi. Karaciğerin patolojik incelemesinde granülomatöz hepatit tanısı alan hastanın şikayetleri gerilemeyince yapılan ileri incelemelerde- serolojik değerlendirme, rK39 dipstik testi- nadir görülen parazitik enfeksiyonlardan visseral leishmaniasis (VL) tespit edildi. Sonuç olarak, endemik bölgelerde ateş ve anemiye ek olarak karın içi organ patolojisi de tespit edilen hastalarda paraziter hastalıklar ve özellikle VL akılda tutulmalıdır.

Anahtar kelimeler: Paraziter infeksiyon, visseral leishmaniasis, granülomatöz hepatit

INTRODUCTION

Hepatic granulomatosis (HG) is an anatomo-pathologic feature, rising as a response of the liver to the various antigenic, toxic, and infectious substances with an incidence ranged between 2-15% (7, 14). One of the most frequent symptoms of this disease is the fever episodes, lasting several weeks. The most frequent etiology has been proved to be infectious, particularly tuberculosis, and sarcoidosis (10, 14).

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Leishmaniasis, one of the causes of hepatic granulomatosis, is an infectious disease caused by various strains of the protozoa. Even though the disease affects almost all countries, most of visceral leishmaniasis (VL) (90%) cases occur in few countries, in which this disease is endemic (e.g. Bangladesh, India, Nepal, Sudan, and Brazil) (13). Thus, in other countries where it is detected in few cases, it can be difficult to diagnose the leishmaniasis infection because it is not thought to be a reason of the pathology.

Leishmania infection is transmitted through the bite of female sand flies (phlebotomine). VL is caused primarily by *L. donovani, L. infantum*, *L. chagasi, L. amazonensis* and rarely *L. tropica* minor (13). Approximately 500,000 new cases of VL arise annually worldwide (18). Cardinal signs of VL

consist of prolonged fever, splenomegaly, anemia, leucopenia, or hypergammaglobulinemia, sometimes with a cutaneous nodule at the site of the bite. Differential diagnosis includes some infections, hematological diseases, liver diseases, and other entities.

In this study, A patient with leishmaniasis who presented with fever and left upper abdominal pain has been reported. Radiological investigations revealed laceration, infiltration, and enlargement of the spleen. Histological examination of spleen and liver were not adequate for diagnosis. Liver biopsy only showed HG. In the light of the detailed investigation due to HG, serological studies revealed active infection of VL. We emphasized the association between VL and HG and its importance for differential diagnosis.

CASE

A 43-year-old female was admitted to Ege University School of Medicine, Department of General Surgery due to symptoms of left abdominal pain and fever of one-month. It was learned that she had been living in a village since she was born. Although the antipyretics including acetaminophen were administrated, the fever did not respond. Her past medical history did not reveal anything significant (e.g. drug administration, concomitant diseases, frequent infections) except an orthopedic operation of the right foot due to spontaneous bone necrosis when she was 35 years old. The spleen was palpable on the abdominal examination. During hospital stay for two weeks, she had undulating fever with two or even three peaks in 24 hours and drenching sweats. In addition, chills, rigors, weight loss, fatigue, poor appetite, cough, abdominal pain, and joint pain were the other symptoms observed. She caught an upper respiratory infection and this significantly aggravated her cough. Laboratory findings well-matched to hemorrhagic fever showed elevated C-reactive protein (CRP), hypergammaglobulinaemia, hypoalbuminaemia, thrombocytopenia. Complete blood count (hemoglobin: 9.8 g/dl; white blood cells: 3600/mm^3; platelets: 158,000/mm^3) was therefore thought to be the result of a hematological disorder. Thus, bone marrow aspiration and biopsy were performed to find out whether a hematological problem was the underlying problem. Histological examination revealed hypercellular bone marrow with a content of 80% epithelial and histiocyte cells, and no protozoan (intracellular form-amastigot) was isolated. Mildly to moderately elevated aminotransferases (Aspartate amino transferase=AST: 200 IU/l, alanin amino transferase=ALT: 226 IU/) were observed during hospital stay. Computed tomography (CT) and ultrasonography (US) of the abdomen showed the spleen at upper limits of the normal and some structural abnormalities such as multiple nodular infiltrations and intracapsular lacerations within. On the elective surgical operation, splenectomy and the biopsy of both liver and enlarged intraabdominal lymph nodes were performed. She had an uneventful postoperative period and was discharged on postoperative day 4. The pathological examination of the spleen showed only hemophagocytosis. The histological examination of the lymph nodes did not reveal significant findings, except reactive hyperplasia, but liver biopsy result was reported as HG. Meanwhile, she was admitted to the hospital with persistent symptoms of fever, nausea, vomiting, fatigue, abdominal discomfort reflecting on her back and anorexia in the postoperative 3rd week. Radiological investigations including US and plain abdominal radiographs showed nothing abnormal. Thus, all the results were evaluated and consulted with the other related clinics such as infectious disease and gastroenterology. For causes of granulomatous liver disease, the cultures of bacteriologic identifications, purified protein derivative (PPD) skin test, tests for brucellosis and leishmaniasis, HBV, HCV markers were performed. In the laboratory of Parasitology of the Ege University School of Medicine, the serological examination including enzyme-linked immuno-sorbent assay (ELISA), indirect fluorescent antibody test (IFAT) confirmed the diagnosis of VL. The positive rK-39 dip-stick test supported active infection. Liposomal amphotericin B (AmBisome) was administered for treatment. Drug regimen was planned as 3 mg/kg for one week, with pre-medication each day with a non-steroidal anti-inflammatory agent. Follow-up period was 8 months, and so far, she has no complaints.

DISCUSSION

Although VL is considered endemic in the tropical and sub-tropical regions such as Africa, Asia, the Mediterranean, Southern Europe, South and Central America, whole parts of the world is under threat because of advanced intercontinental communication. According to our data, cutaneous leishmania is endemic in the east of Turkey, but VL is not as common both in the east and the west of the country, with a rate of 0.2% in the west (1, 4). L. infantum is responsible for human VL, which is seen mainly in the Aegean, Mediterranean, and Central Anatolia Regions. Children below the age of 15 years were at the highest risk and males were over three times more susceptible than females (16). In the epidemiological studies, the ratio of asymptomatic carriers was 7.4% in the west of Turkey and only a few adult cases of VL were reported from Turkey (3, 9, 15).

L. infantum causes a systemic form of leishmaniasis and the reticuloendothelial system consisting of a series of lymphoid organs such as liver, bone marrow, and spleen, which is the most severely infected part of the body (13). The symptoms of VL vary among individuals and according to geographical regions. The cardinal manifestations of the disease include gradual onset of fever that often rises and falls twice a day, fatigue, weight loss, dizziness, cough, diarrhea, generalized lymphadenopathy, acute tonsillitis, jaundice, and ascites (onset may also be acute) (2, 13). Without a doubt, some of these nonspecific symptoms may emerge due to various diseases

and thus, delayed diagnosis in this situation may be unavoidable. In addition, splenomegaly and hepatic disorders with mild changes in serum aminotransferases may be detected (8) as was in our patient. Anemia and fatigue associated with VL may also lead physician to a misdiagnosis of this serious infectious disease because of rarity and similarity to the other disorders such as malaria, relapsing fever etc. Presence of cardinal symptoms and demonstration of the pathologic organisms in the bone marrow, splenic aspirate, blood or secretions are useful for certain diagnosis (18).

Diagnosis of the infection depends on identification of amastigotes in tissues. Serologic examination [enzyme immunoassay (EIA), direct agglutination, IFAT] is also useful in immunocompetent individuals (17). Radiological investigations such as abdominal US and CT may reveal enlargement of spleen and liver. Liver biopsy can demonstrate the Leishmania amastigotes inside the reticuloendothelial cells. Splenic tissue is rich in amastigotes allowing a rapid and sensitive diagnosis. Although spleen biopsy is a highly sensitive method for diagnosis, it is not widely used because of the risk of hemorrhage. In addition, infection of the bone marrow may be pronounced, usually resulting in anemia, leucopenia and sometimes thrombocytopenia or even pancytopenia. The protozoon is isolated in bone marrow biopsy in 90% of the cases (13). In our case, some original clinical manifestations of VL were present: fever, and splenic and liver pathology. However, interestingly, none of the histological examinations was revealing. In spite of all the examinations, neither the bone marrow nor the lymph nodes and the skin seemed affected in the first step. However, because it is mostly seen in infants, we had no clinical suspicions for VL. Subsequently, the liver was thought to be involved because the liver biopsy showed HG accompanied by a mild elevation of serum aminotransferases. For the second step, to determinate the reason for HG, a detailed evaluation was performed. Thus, the diagnosis was confirmed by the serological studies, the results of which indicated a high serum anti-leishmanial antibodies titre by ELISA, and IFAT and rK-39 dip-stick test proved the active regeneration of the parasite. Although it is known that there can be appeared granulomatous hepatitis in the patients with visceral leishmaniasis, there have been a few reports about the combination of the visceral leishmaniasis and hepatic granulomatosis (11). The infectious etiology for HG is reported higher in Turkey and some Eastern countries (10).

Treatment with liposomal amphotericin B is less toxic than pentavalent antimony is and it is effective (4). It yielded very satisfactory results in our patient. It has been used successfully to treat VL patients unresponsive to standard drugs (12). Dietze et al recommended administration of Ambisome for all ages without toxic side-effects (5).

Although the frequency of the disease has been constantly decreasing due to improved standards of living, diet and the use of insecticides, nobody can deny its probable threat for all countries (6). Despite all the evaluations around the world, there are many countries where the leishmaniasis is still endemic. The main problem with the diagnosis is to determine the system that is affected by the organism. In case of granulomatous hepatitis, as in our patient, VL must be a part of differential diagnosis, especially in endemic regions. Although the principal treatment of VL is conservative, surgical intervention may be necessary for certain diagnoses, particularly in case of intraabdominal complications.

In conclusion, the unique essential part of the diagnosis depends on suspicion and therefore to overcome delayed or misdiagnosis in a patient with unresponsive fever and intraabdominal pathologic findings in endemic regions, we should consider the diagnosis of VL, which is one of the parasitic infections that cause different abnormalities in every system including intra-abdominal solid organs.

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