Brucellosis with Associated Granulomatous Hepatitis: Case Report

GRANÜLOMATÖZ HEPATİT İLE SEYREDEN BİR BRUSELLOZİS OLGUSU

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Abstract

Brucellosis is an infectious disease characterized by fever, joint pain, and hepatosplenomegaly. The clinical signs vary because the disease involves many organs. This condition rarely causes granulomatous hepatitis. Brucellosis is diagnosed mainly on the basis of serological testing, and false-negative results may cause delays in treatment. This report describes a pediatric case of brucellosis with associated granulomatous hepatitis. The patient presented with prolonged fever of unknown origin.

Key Words: Brucellosis, fever of unknown origin, granulomatous hepatitis, children

Özet

Brusellozis ateş eklem ağrıları ve hepatosplenomegali ile karakterize bir enfeksiyon hastalığıdır. Hastalık birçok organ sistemini etkilediği için klinik bulgular değişkendir. Nadiren granülomatöz hepatite neden olur. Brusellozisin tanısı serolojik testler ile konulur. Yalancı negatif sonuçlar tedavide gecikmeye neden olur. Bu yazıda granülomatöz hepatit ile seyreden, bir olgu sunulmuştur. Hasta uzamış nedeni bilinmeyen ateş ile başvurmuştur.

Anahtar Kelimeler: Brusellozis, nedeni bilinmeyen ateş, granülomatöz hepatit, çocuk

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Fever of unknown origin (FUO) is the term used to describe increased body temperature (> 38°C) at least twice a week during 3 weeks with no accompanying signs of infection or other disease.[1] Recent advances in serology, imaging, and microbiological investigations have led to enhance of diagnoses in FUO cases.

Brucellosis is a zoonotic disease caused by *Brucella* species that is characterized by fever, excessive sweating, joint pain, and hepatosplenomegaly. Some cases become chronic.[2] This condition tends to involve many organs and systems, and therefore has a wide variety of clinical signs. The prognosis varies with host response, host age, the type and virulence of the causative agent, and the time to appropriate antimicrobial treatment.[3] Brucellosis rarely causes FUO and granulomatous hepatitis. Here we describe the case of a 13-year-old boy who presented with FUO and was subsequently diagnosed with granulomatous hepatitis based on a liver biopsy. Five months after the onset of granulomatous hepatitis, brucellosis was diagnosed.

Case Report

A 13-year-old boy presented to our hospital with the complaint of undiagnosed fever episodes of several months' duration. His mother and father were second-degree relatives. There were three children in the family, and both the patient's siblings were healthy. The patient's father was a farmer who raised sheep and cows. His aunt had been treated for tuberculosis 15 years earlier. The boy had experienced his first episode of fever and left flank pain 5 months earlier. Medical examination at that time revealed enlargement of the liver

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and spleen, and the patient was referred to a university hospital for further work-up. He remained at that center for 20 days, during which time various tests were conducted. Laboratory assessment revealed hemoglobin 9.9 g/dL, white blood cell count 6.300/mm^3, erythrocyte sedimentation rate 18 mm/hour, aspartate aminotransferase 276 IU/L, alanine aminotransferase 131 IU/L, and alkaline phosphatase 790 IU/L. Serum levels of blood urea nitrogen, creatinine, albumin, and ceruloplasmin were normal. Results of tests for viral markers of hepatitis (HBsAg, anti-HBs, HBeAg, anti-HBe, HBcAg, anti-HBc, anti-HCV, anti-HAV immunoglobulin IgM and IgG, cytomegalovirus IgM and IgG, and Epstein-Barr virus) were negative. Abdominal computed tomography demonstrated hepatosplenomegaly and diffuse thickening of the wall of the proximal jejunum. Blood, urine, stool and a throat swab were cultured, but no pathogen microorganisms were isolated. Serological tests for *Salmonella* spp. and *Brucella* spp. were negative. A smear of bone marrow aspirate showed normal cells; no Gaucher cells or Leischman-Donovan bodies were observed. Examination of a liver biopsy revealed non-caseous granulomatous hepatitis. However, no definitive diagnosis was established and the patient was discharged without treatment. During 4 months of follow-up, he experienced one or two febrile episodes, approximately 38^{o}C, each day.

When the patient was admitted to our center with fever, he was weak and appeared slightly pale. Physical examination revealed body weight 31 kg (3rd percentile), height 137 cm (3rd percentile), body temperature 38.5^{o}C, and blood pressure 105/55 mmHg. Cardiac auscultation indicated normal sinus rhythm. No cervical or axillary lymphadenopathy was detected. The liver was palpable 2 cm below the costal margin, and the spleen was palpable 6 cm beyond its normal limits. No other abnormalities were detected.

Laboratory investigation revealed hemoglobin 11 g/dL, white cell count 6.000/mm^3 (47% lymphocytes), erythrocyte sedimentation rate 31 mm/hour, C-reactive protein 16 mg/L, aspartate aminotransferase 251 IU/L, and alanine aminotransferase 155 IU/L. Tests for the above-mentioned viral hepatitis markers and, blood and urine cultures were all negative. Investigations for tuberculosis were also negative, and he had two vaccine scars. A standard tube agglutination (STA) test for brucellosis was also negative, which suggested the presence of blocking antibodies. Blood culture for brucellosis was also negative. However, a subsequent Coombs' antiglobulin test was positive (titer 1:80), and the patient was therefore diagnosed with brucellosis.

The initial treatment was a 2-week course of a combination of intramuscular streptomycin 30 mg/kg/day and oral doxycycline 200 mg/day, followed by a 4-week course of doxycycline alone. Within the first week of therapy, the patient's body temperature normalized. After 1 month of treatment, the boy's liver enzyme levels were normal and he had gained 2 kg of weight. By 6 weeks, all the patient's symptoms had disappeared, he had gained 4.5 kg of weight, and there was no evidence of hepatosplenomegaly. No relapses were observed during 1 year of follow-up.

Discussion

The definitive diagnoses in cases of FUO vary according to geography, levels of industrial development, and sophistication of laboratory facilities. As in the rest of the world, the underlying problem in most cases of FUO in Turkey is infection. Specifically, research on FUO in our country has identified infection as the most frequent cause (42%-65% of all cases), followed by rheumatologic diseases (6%-34%), neoplasms (8%-26%), miscellaneous conditions (4%-16%), and unknown illness (4%-35%).[3,4] Studies from industrialized nations have revealed similar ranking, with infections responsible for 21%-58% of FUO cases, followed by rheumatologic conditions (13%-24%), neoplasms (6%-31%), miscellaneous diseases (4%-16.5%), and unknown illness (7%-38%).[5,6] Tuberculosis is the underlying illness in 15%-65% of FUO cases in Turkey, whereas the corresponding reported range in industrialized countries is only 5%-10%.[5] Other infections known to be linked with FUO include infective endocarditis; brucellosis; typhoid fever;

leptospirosis; Epstein-Barr virus, cytomegalovirus, and human immunodeficiency virus infections; malaria; toxoplasmosis; and amoebiasis.[3,4]

Brucellosis is a zoonotic disease that affects all ages, has no sex predilection, and can involve many organs and systems. This condition is endemic to Turkey. Patients present with a variety of symptoms and clinical signs, thus brucellosis may be mistaken for many other conditions.[7] During diagnostic work-up, it may not be possible to isolate the responsible agent from blood or other tissues because these bacteria are normally scarce in the blood and difficult to culture, and because affected individuals may already have received antibiotics. Also, it is particularly difficult to isolate *Brucella* spp. at certain stages of the disease.[8] Therefore, serological tests are used more frequently than cultures to diagnose brucellosis, as they provide rapid results. The most widely used serological assessment is the STA test (Wright's test), in which titers of 1:160 or higher are considered diagnostically significant. In cases of brucellosis, the rate of STA positivity is high. One study of by Gotuzzo et al. documented 91.7% positive results in acute brucellosis, 75% in subacute brucellosis, 70% in chronic brucellosis, and an overall positivity rate of 86%.[9] Ozkurt et al. reported an overall STA positivity rate of 96% in a series of 50 patients.[8] They noted rates of 100% in the 30 cases of acute brucellosis, 94.1% in the 17 cases of subacute brucellosis, and 66.6% in the 3 cases of chronic brucellosis. In line with culture results, both these studies indicated high rates of STA positivity in acute disease, and lower rates in subacute and chronic stages.

In general, STA is more sensitive than culture for identifying brucellosis, and is safe. However, diagnosing brucellosis with indirect methods like serology has certain limitations. Serological results can only support the preliminary diagnosis. Prozone phenomenon and blocking antibodies can lead to false-negative STA results in the acute phase of brucellosis. Furthermore, the diagnosis may be missed because levels of agglutinins sometimes remain low in subacute and chronic brucellosis.[8,9] In our case, serological testing and routine culturing was done at the initial work-up 5 months earlier (when granulomatous hepatitis was identified), and was then repeated during the investigation at our center. No *Brucella* spp. were isolated from the initial culturing, and STA was negative at both stages of serological assessment. We suspected that the negative STA result might have been due to blocking antibodies, and thus performed a Coombs' antiglobulin test. The patient was positive, with a titer of 1:80.

Granulomatous hepatitis is a condition in which granulomas form in the liver. The many possible causes of these lesions include infectious and parasitic diseases (such as tuberculosis, brucellosis, schistosomiasis, Q fever, leishmaniasis, hepatitis C, sarcoidosis, histoplasmosis, listeriosis, tularemia, secondary syphilis, cytomegalovirus, Epstein-Barr virus, toxoplasmosis and visceral larva migrans); primary biliary cirrhosis; various drugs (such as allopurinol, alpha-methyldopa, sulfamide, quinidine, phenylbutazone, and penicillin); various neoplasms (such as lymphoma, non-Hodgkin's lymphoma, and carcinoma); and some autoimmune diseases (such as primary sclerosing cholangitis and Crohn's disease).[10,11] Granulomatous hepatitis can also be idiopathic.[11,12] Brucellosis is not common etiology of granulomatous hepatitis. The etiology has been reported as Brucellosis in 7.4% of cases.[13] Villaverde et al. documented a case of myocarditis caused by brucellosis, and noted that a liver biopsy from this patient showed granulomatous hepatitis.[14] Our patient presented with FUO and was initially diagnosed with granulomatous hepatitis. The underlying cause of this was not able to identify, but brucellosis was diagnosed 5 months later.

In conclusion, diagnosing the underlying cause of FUO requires knowledge, experience, and thorough laboratory investigation. Brucellosis is endemic to many geographical regions, including Turkey. When a patient from such a region presents with FUO, serological tests and a full range of blood, urine, and bone morrow cultures are indicated. Brucellosis should still be considered a possibility even when the STA result is a titer below 1:160, and cannot be ruled out in seronegative cases. As our case demonstrates, brucellosis should

be included in the differential diagnosis when the underlying cause of FUO is not clear and a liver biopsy shows granulomatous hepatitis. In addition, we suggest that the cases with negative STA test should routinely underwent Coomb's antiglobulin test if there is suspicion of brucellosis.

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