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CASE REPORT

Tuberculous meningitis together with systemic brucellosis

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Abstract We present a case of a 57-year-old woman admitted with findings of meningitis. Cerebrospinal fluid (CSF) tests revealed a pleocytosis together with a low CSF glucose concentration. Empirically, antituberculosis treatment was started. Rose Bengal and Wright tests were performed to exclude brucellosis with central nervous system involvement. These tests were positive in serum but not in CSF. Antibrucellosis treatment with doxycycline and ceftriaxone was started without withdrawing the antituberculosis treatment because of the possibility of simultaneous infection with both tuberculosis and brucellosis agents. Finally, this approach was shown to be correct when tuberculosis was isolated from the culture of CSF. Clinicians in endemic regions for brucellosis should be careful while diagnosing subacute/chronic meningitis. Other possible similar etiologies such as *Mycobacterium tuberculosis* must be ruled out before attributing the meningitis to brucellosis.

Keywords Tuberculosis · Brucellosis · Meningitis

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Introduction

Tuberculosis and brucellosis, both of which are endemic in Turkey, are included in the differential diagnosis of subacute/chronic meningitis. Herein we present a case of a 57-year-old woman admitted with meningitis and positive Rose Bengal and Wright tests (1/320). At first look, this case might be interpreted as systemic brucellosis with central nervous system (CNS) involvement, but the possibility of concurrent infection of both brucellisis and tuberculosis suggested we wait for the results of the culture of the cerebrospinal fluid samples.

Case report

A 57-year-old woman was admitted with severe headache, altered consciousness, hallucinations, high fever, nausea and vomiting of 2 weeks duration. At physical examination, cooperation and orientation were not present, and she had strabismus, possibly caused by third cranial nerve palsy, neck stiffness, and positive Kernig and Brudzinski signs. Otherwise, neurological and general medical examinations were normal. Lumbar puncture was performed; cerebrospinal fluid (CSF) revealed 63 polymorphonuclear cells (PNL)/μl, 63 lymphocytes/μl, CSF glucose at 12 mg/dl (simultaneous serum glucose, 95 mg/dl), and total protein in CSF was 1,275 mg/dl. Cranial computed tomography (CT) and magnetic resonance imaging (MRI) results were normal. Gradual onset of irritability, anorexia, fever followed by headache, vomiting, and low glucose, high protein, and low total cell count (126 cells/μl) in CSF suggested a pleocytic-aseptic meningitis, especially, tuberculosis and brucellosis meningitis, both of which are endemic in Turkey. The high PNL count of the CSF was

considered to indicate the early phase of infection. Although she had no past history of tuberculosis, family history of tuberculosis, or contact with a person with tuberculosis, empirical antituberculosis therapy was administered (rifampin 600 mg/day, isoniazid 300 mg/day, pyrazinamide 1,500 mg/day, ethambutol 1,500 mg/day). Because of altered mental status and third cranial nerve palsy, dexamethasone 16 mg/day was also given. Acid-fast stain of CSF was negative. Because neurobrucellosis is included in the differential diagnosis of CSF pleocytosis, serum Wright test was performed, and repeated absolute agglutination titer was greater than 1:320. When asked for the possible infection routes of brucellosis, consumption of fresh dairy products from the eastern part of Turkey, where brucellosis is endemic, was revealed. These findings were compatible with the diagnosis of systemic brucellosis. Doxycycline and ceftriaxon were added to the present antituberculosis treatment. Although the entire clinical picture of this patient might be explained by systemic brucellosis with CNS involvolvement, antituberculosis treatment was not withdrawn without excluding evidence of tuberculosis meningitis (TBM) because of the possiblity of simultaneous infection with both tuberculosis and brucellosis. After about a week, lumbar puncture was repeated and CSF showed 22 PNL/μl, 57 lymphocytes/μl, glucose 25 mg/dl, and total protein 923 mg/dl. Wright and Rose Bengal tests of the CSF were negative. Finally, *Mycobacterium tuberculosis* was isolated in the culture of the CSF. Ophtalmoscopic examination showed bilateral choroidal metastatic foci of infection, also consistent with the diagnosis of miliary tuberculosis. Because she had dysuria, acid-fast stain of a urine specimen was performed, with negative results, but culture of the urine revealed *M. tuberculosis*. Doxycycline and ceftriaxone as the treatment of systemic brucellosis was completed and withdrawn after 3 weeks. After 50 days of antituberculosis treatment, she had hypertransaminasemia (AST, 313 U/l, ALT, 300 U/l), total serum bilirubin, 17 mg/dl, direct bilirubin, 12 mg/dl; prothrombin time was prolonged. Antituberculosis treatment had to be stopped because of toxic hepatitis. Pancytopenia (leukopenia, anemia, thrombocytopenia) appeared in the peripheral blood count. Peripheral blood smear revealed poikilocytosis and erythrocytes with teardrop shape. Bone marrow biopsy revealed lymphohistiocytic infiltration and three granulomatous foci, compatible with bone marrow involvement of miliary tuberculosis. Acid-fast stain of bone marrow aspiration was negative. She was diagnosed as miliary tuberculosis with meningeal, ocular, and bone marrow involvement. She had no sign or radiologic finding of pulmonary involvement of tuberculosis. When the liver function tests returned to normal (AST, 90; ALT, 80 U/l; total bilirubin, 2 mg/dl), streptomycine, oflaxocin, ethambutol, and isoniazid were added to the treatment gradually. Currently, she is followed by antituberculosis treatment.

Discussion

Tuberculosis and brucellosis are great imitators with the potential to present with every clinical picture. Both diseases are endemic in Turkey, so these two entities must be kept in mind in the differential diagnosis of nearly all diseases, including meningitis.

Tuberculosis meningitis (TBM) is the most severe clinical form of tuberculosis. It has remarkably decreased in developed countries but remains a serious health problem in developing countries for children and adults. TBM still often results in residual sequelae and mortality in 15–51% of the cases [1]. The prompt diagnosis and antibiotic treatment of TBM saves lives [2]. In fact, as many as 60% of patients with TBM die despite anti-tuberculosis treatment[3].

Although the gold standard for the diagnosis of TBM is the isolation of *M. tuberculosis* from CSF, the culture is positive in only about 40% of cases [4]. The isolation of *M. tuberculosis* by culture is time consuming, and return of a positive result may take up to 6 weeks. Thus, the decision to treat patients for TBM is often made empirically. In our case, antituberculosis therapy was already started in the first day of admission to our clinic.

Differential diagnosis of this case also includes brucellosis with CNS involvement. Brucellosis is a systemic infectious disease caused by gram-negative bacilli, the genus *Brucella* (*B. abortus, B. melitensis, B. suisa*, and *B. canis*). The disease has diverse clinical features including fever, fatigue, sweating, arthralgia, loss of appetite, myalgia, lumbar pain, weight loss, headache, hepatomegaly, splenomegaly, and arthritis [5].

Although brucellosis is a controlled disease in developed countries, it still remains as a health problem in developing ones. The prevalence is higher in the Mediterranean area, the Arabian Peninsula, Mexico, and Central and South America [5]. Brucellosis is endemic in Turkey, which is located between Asia and Europe and is also a Mediterranean country. During the last decade (between 1991 and 2000), 9,000 cases yearly were reported to Turkish Ministry of Health (incidence: 14/100,000). Seropositivity of human brucellosis in rural endemic areas in eastern Turkey was detected in 5.4% according to the standard tube agglutination test, rising to 11.9% when the Rose Bengal test was used [6].

In daily practice, the diagnosis of brucellosis is established by a positivity of Wright test in a titer of 1/160 in association with appropriate clinical setting. Agglutination tests currently used in the diagnosis of brucellosis are very

sensitive and specific. In a study, both sensitivity and specificity of Wright's test at a dilution of 1/160 were 100%, so brucellosis can be effectively excluded from the diseases having similar clinical features by the use of agglutination tests [7]. The exact diagnosis is possible after isolation of the agent in various samples (especially blood and bone marrow).

Neurological manifestations of brucellosis include meningitis, encephalitis, myelitis, radiculoneuritis, intracerebral abscess, epidural abscess, demyelination, and meningovascular syndromes [1]. CNS involvement occurs in less than 5% of patients and usually presents as acute or chronic meningitis [5].

Neurobrucellosis has neither a typical clinical picture nor specific CSF findings. The diagnosis is made by acute or chronic meningitis symptoms and abnormal CSF findings, e.g., increased protein, decreased glucose levels, lymphocytosis, and a high *Brucella* agglutination titer. The detection of any titers of antibodies in CSF provides evidence of neurobrucellosis, but CSF agglutinins may be absent in some cases [8].

Specimens from cases of tuberculosis, typhoid, rheumatoid arthritis, and bacterial endocarditis should also be screened for brucellosis and vice versa [9]. Specifically, because brucellosis and tuberculosis are both endemic in developing countries, the consideration of either disease in a case should raise the suspicion of the other; however, rarely both may be present in a single patient simultaneously. In a case from Turkey [10], the patient was initially diagnosed as *Brucella* meningitis based on her history (stockbreeding, consuming raw milk products), physical examination, and positive tube agglutination test of 1/640 titer. Antibiotic therapy with ceftriaxone, rifampicin, and doxycyclin was started, but there was no clinical improvement. Subsequently, *M. tuberculosis* was isolated in the culture of the CSF. The patient was considered to have meningitis with double etiology and recovered with the addition of antituberculous treatment. In another case report [11], the CSF of a patient with meningitis was examined with a prediagnosis of tuberculous meningitis because the patient was from a region endemic for tuberculosis. Eventually, *Brucella melitensis* was grown in the CSF culture. In a similar report [12], a patient with peritonitis, intestinal obstruction, granulomatous hepatitis, and meningitis was diagnosed as a case of disseminated tuberculosis and treated accordingly. However, the serological tests for brucellosis were strongly positive, and the patient was subsequently treated as a case of brucellosis and recovered fully.

In conclusion, in endemic areas, the possibility of simultaneous infection with both tuberculosis and brucellosis must be kept in mind. Treatment must be arranged according to culture results. Because the sensitivity and specificity of agglutination tests for brucellosis are very high, patients with high titers with proper clinical findings must be given antibrucellosis treatment. Clinicians in regions endemic for brucellosis should be careful while diagnosing subacute/chronic meningitis, and other possible similar etiologies such as *M. tuberculosis* must be ruled out before attributing the meningitis to brucellosis.

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