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Highly Elevated Adenosine Deaminase Level in Brucellar Pleural Effusion

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Abstract: Pleural involvement is a rare presentation of brucellosis. There are only a few case reports in the literature presenting with pleural involvement due to brucellosis. In this report, we present a case with exudative pleural fluid first considered as tuberculous pleurisy due to lymphocyte predominance and elevated level of pleural adenosine deaminase, but later diagnosed as brucella pleurisy with positive serologic and microbiologic test results. In conclusion, in the differential diagnosis of pleurisies, routine serologic and bacteriologic methods appear to be more important than pleural adenosine deaminase elevation, especially in regions endemic for both tuberculosis and brucellosis.

Key Words: Adenosine deaminase, *Brucella melitensis*, pleural effusion

Brusellar Plevral Efüzyonda Çok Yüksek Adenozin Deaminaz Seviyesi

Özet: Bruselloza bağlı plevral tutulum oldukça nadir bir tutulumdur. Literatürde sadece birkaç plevral tutulumla seyreden olgu sunumu mevcuttur. Bu olgu sunusunda exudatif plevral sıvısı olan ve lenfosit hakimiyeti ve adenozin deaminaz yüksekliği nedeniyle tüberküloz plörezi düşünülen, ancak serolojik ve kültür yöntemleriyle brusella plörezi tanısı konulan bir olgu sunuldu. Sonuç olarak tüberküloz ve brusellozun endemik olarak görüldüğü bölgelerde plörezilerin ayırıcı tanısında ADA yüksekliğinden çok rutin serolojik ve bakteriyolojik yöntemlerin daha önemli olduğu anlaşılmaktadır.

Anahtar Sözcükler: Adenozin deaminaz, *Brucella melitensis*, plevral efüzyon

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Introduction

Brucellosis is a zoonotic disease with a worldwide distribution. Its high degree of morbidity is an important cause of economic losses and represents a serious public health problem in many developing countries (1,2). The most common route of transmission of the disease is consumption of unboiled/unpasteurized milk and milk products of infected animals. Brucellosis is a multi-system infectious disease that may affect many tissues and organs. Pleural involvement due to brucellosis is a very rare manifestation limited to only a few case studies in the literature (3,4). Clinical and laboratory findings of patients with brucellar pleurisy can be similar to those in tuberculous pleurisy; therefore, differential diagnosis can be problematic in regions endemic for both diseases.

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Case Report

An otherwise healthy, 26-year-old male was admitted to our clinic with the complaints of fever rising in the afternoon, pleuritic chest pain in the left hemithorax, malaise, night sweats, dry cough and abdominal pain lasting for one month. The patient had initially presented to a general practitioner with the same symptoms in this period and was given antibiotic treatment with the diagnosis of urinary infection and

nephrolithiasis. Afterwards, he was referred to our department as there was no improvement in his symptoms. The patient, who gave a history of consumption of local fresh herbaceous cheese made from unboiled milk and of a 5-kg weight loss in one month, was hospitalized in our clinic. On admission, his temperature was 38°C and clinical examination revealed no pathology except for dullness on percussion and reduced breath sounds on auscultation in the left lower hemithorax.

Laboratory results revealed: erythrocyte sedimentation rate (ESR) 25 mm/h, white blood cell count 11,700/mm³, with 64% neutrophils, 25% lymphocytes and 8% monocytes, and C-reactive protein (CRP) 155 mg/dl. Biochemistry of blood was in normal limits. Chest radiography revealed moderate pleural effusion blunting the left costodiaphragmatic angle (Figure 1), and computerized tomography of the thorax showed massive pleural effusion in the left hemithorax, with left lower lobe atelectasis. The pleural fluid obtained by ultrasound-guided thoracentesis was serous in appearance. Analysis of pleural fluid revealed: white blood cell count 1,020/mm³, with 58% lymphocytes, lactate dehydrogenase (LDH) 1,609 IU/L, protein 5 g/dl, glucose:

35 mg/dl, and adenosine deaminase (ADA) level 193 IU/L. Pleural fluid protein-serum protein ratio was 0.625 (5 vs 8 g/dl) and pleural fluid LDH-serum LDH ratio was 3.17 (1.609 vs .507 IU/L). Mantoux reaction was positive (12 mm) to 5 IU of human tuberculin purified protein derivative (PPD), but smears stained with Ziehl-Neelsen and cultures of the pleural fluid and sputum were found negative.

Serological studies of blood and pleural fluid subsequently confirmed the diagnosis. Standard Wright test was positive in blood at a titer of 1/320 and Wright test with Coombs at 1/1280, while standard Wright test in pleural fluid was positive at a titer of 1/160. After blood cultures were taken from the patient in the febrile stage, treatment was commenced with rifampicin 600 mg/day and doxycycline 200 mg/day for 8 weeks.

Brucella melitensis was isolated in blood culture (Bact-ALLERT) on the fifth day of treatment. The patient was discharged from the hospital after 15 days of hospitalization because of excellent improvement in his clinical and laboratory findings. At the end of the treatment period, and also at the end of 12 weeks, full recovery with significant clinical and radiological improvement was observed (Figure 2).



Figure 1. Chest radiograph revealed moderate pleural effusion on the left side.



Figure 2. After antibiotic therapy, chest radiograph revealed complete resolution of the pleural fluid.

Discussion

Although the reported frequency of respiratory symptoms such as cough is high (about 16%), true lung involvement confirmed by radiological evaluation is very rare (0.6-1%) in brucellosis (3,5). Hilar and paratracheal adenopathy, peribronchial infiltrates, pneumonia, bronchopneumonia, pleural effusion, empyema, solitary nodules, granulomas, lung abscess and miliary patterns are all described (3,6). In a prospective study performed on 110 brucellosis patients by Hatipoğlu et al. (7) from our country, while 20.9% of the cases had cough, pulmonary involvement was reported as 10%. In another prospective study performed on 400 brucellosis patients by Lulu et al. (8), while 17% of the cases complained of cough, only 1% were reported to have pulmonary brucellosis. This means that the presence of a dry or scarcely productive cough does not imply the existence of pulmonary involvement (2). True pulmonary involvement is quite rare, limited to only a few case studies in the literature (3,4,9-11).

The similarity between clinical and laboratory findings of brucellosis and tuberculosis, which have the common features of being intracellular pathogens and causing exudative pleural effusion with lymphocytic predominance, diminished level of pleural glucose and elevated level of pleural ADA, has led to diagnostic problems in regions endemic for both diseases (3,11). ADA is essentially a predominant T lymphocyte enzyme, and its plasma activity is high in diseases in which cellular immunity is stimulated. Therefore, pleural fluid ADA is elevated in both tuberculous and brucellar pleurisy, which are caused by intracellular agents. Measurements of especially high ADA levels in pleural fluid is a useful method in establishing the diagnosis of tuberculous pleurisy (3,12). ADA level was below 70 IU/L (65 and 50 IU/L) in the study of Dikensoy et al. (3), who reported two cases of brucellar pleurisy presenting with ADA elevation. Based on this, Dikensoy et al. (3) suggested that a pleural fluid ADA level above 70 IU/L virtually establishes the diagnosis of tuberculosis. However, ADA level in the pleural fluid of our case was very high (193 IU/L). This is an important finding showing that an ADA level alone is not useful in the differential diagnosis of tuberculous and brucellar pleurisy. As seen in our case,

a level above 70 IU/L is not pathognomonic for tuberculous pleurisy, and may also be seen in brucellosis.

Findings of lymphocytic predominance, elevated LDH, protein and ADA levels, and reduced glucose in pleural fluid in our case led us to first consider tuberculosis as the primary diagnosis. However, the final diagnosis was made with the positive Wright test results both in blood and pleural fluid followed by isolation of *B. melitensis* in blood, which provided the differential diagnosis. This is valuable for establishing the importance of routine serologic and bacteriologic methods rather than ADA level in pleural fluid in the differential diagnosis of the two entities (3,4). We did perform thoracentesis; however, because we considered tuberculous pleurisy in our patient, we did not send the culture for brucella but only for tuberculosis, so isolation of *B. melitensis* from the pleural fluid was not possible. Therefore, we think that taking brucella and tuberculosis cultures in such patients would be more reasonable.

Rifampicin, which is mainly used for tuberculosis, is also known to be effective in brucellosis. Thus, initiation of empirical antituberculous treatment will cause a partial regression in the patient with pleural effusion due to brucellosis. In addition, because neither brucellosis nor tuberculosis agents will be able to grow on cultures in that condition, the patient will be subjected to long-term unnecessary use of antituberculous drugs. Therefore, especially in regions endemic for these two entities, reconsideration of and ruling out the evidence of brucellosis in patients with pleural effusion is necessary before making the diagnosis of tuberculous pleurisy and initiating the antituberculous treatment.

In conclusion, clinical and laboratory findings of brucellar pleurisy are similar to those of tuberculous pleurisy and, therefore, differential diagnosis is frequently problematic. Furthermore, an increased ADA level is not significant in the differentiation of these two entities. Therefore, brucellosis should also be considered in the differential diagnosis of pleurisy especially in regions endemic for brucellosis. Serologic and bacteriologic tests appear to be the most important tools in the differential diagnosis in regions endemic for both diseases.

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