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Case Report

Tuberculous pleurisy with false negative adenosine deaminase level- Case report.

Enes Ahmetoğlu[1], Dilek Karadoğan[1], Oğuzhan Okcu[2], Songül Özyurt[1], Ünal Şahin[1]

[1]Department of Chest Diseases, Recep Tayyip Erdoğan University, School of Medicine, Rize, Türkiye
[2]Department of Pathology, Recep Tayyip Erdoğan University, School of Medicine, Rize, Türkiye

Corresponding author:
Enes Ahmetoğlu,
Adres: Department of Chest Diseases, Recep Tayyip Erdoğan University, School of Medicine, Rize, Türkiye
Tel: 05058528418
E-mail: awt882013@gmail.com

Tuberculous pleurisy with false negative adenosine deaminase level- Case report.
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Abstract

Background and aim: Tuberculous pleural effusion is a common disease entity with a spectrum of presentations from a largely benign effusion, The World Health Organization (WHO) recognized 6.3 million new tuberculosis (TB) cases in 2017, 16% corresponding to extrapulmonary forms; pleural tuberculosis is the most common extrapulmonary form in adults. Diagnostic thoracentesis with thorough pleural fluid analysis including biomarkers such as adenosine deaminase (ADA) and gamma interferon achieves high accuracy in the correct clinical context. Definitive diagnosis may require invasive procedures to demonstrate histological evidence of caseating granulomas or microbiological evidence of the organism on smear or culture.

Case: We report the case of a 30- year old male patient admitted to the outpatient setting of the hospital with fever, nonproductive cough and pleuritic pain. He had these symptoms for four weeks. His chest x-ray revealed massive pleural effusion on the left hemithorax. The patient comes from an area with a high incidence of tuberculosis, so our diagnostic strategy was combined with a lymphocyte / neutrophil ratio of exudative pleural fluid greater than 0.75 plus closed needle biopsy tissue. Empirical anti-TB treatment was initiated due to the most likely diagnosis of TB.

Conclusion: In this patient who was negative for ADA, the diagnosis was obtained by pleural biopsy. TB should be considered in cases that may be false negative ADA, and pleural biopsy should be performed primarily for pathological diagnosis in all pleural effusions where clinical suspicion for TB persists. In cases where diagnostic delays may occur, empirical treatment should be started in the presence of strong diagnostic suspicion.

Introduction

Tuberculous (TB) pleural effusion is a common disease entity with a spectrum of presentations from a largely benign effusion, which resolves completely, to a complicated effusion with loculations, pleural thickening and even frank empyema, all of which may have a lasting effect on lung function. The pathogenesis is a combination of true pleural infection and an effusive hypersensitivity reaction, compartmentalized within the pleural space (1).

TB pleural effusion is one of the most common sites of extrapulmonary TB, although the incidence varies between regions. The incidence of pleural involvement in TB non endemic areas is 3–5% (2, 3). In TB endemic areas, however, the incidence approaches 30%, in part due to the high proportion of human immunodeficiency virus (HIV)-positive individuals, in whom TB is the most common cause of lymphocytic effusions (5). Tuberculosis pleural effusion (TPE) predominates in men, with an overall male-to-female ratio of 2:1 (2). In an epidemiological analysis from the United States, TPE occurs significantly more often than pulmonary tuberculosis among persons >65 years old, and the mean age of patients with TPE is 49 years: about 50% were younger than 45 years and 30% were over 65 years of age (3). In contrast, TPE affects mainly younger individuals (mean age =34 years) in higher tuberculosis burden areas, where primary infection accounts for a large percentage of patients with TPE (4). TB effusions typically present as acute to subacute illnesses, characterized by unilateral pleuritic chest pain (~75%), cough (~70%), fever (~85%), night sweats (~50%), dyspnea (~50%) and weight loss (25–85%). A small proportion of patients have only mild symptoms (3,6,7). TPE is usually unilateral and can be of any size. In one series of 333 patients, pleural fluid occurred only on the left side in 127 (38.1%), only on the right in 161 (48.4%), and both sides were affected in 45 (13.5%). In either unilateral or bilateral effusion, the percentages of small, moderate, and large size of pleural effusions were 20.4%, 19.2%, and 60.4%, respectively. Approximately 20% of patients with TPE have coexisting parenchymal disease on chest radiograph. However, computed tomography scanning offers a more sensitive method and can demonstrate parenchymal disease in 40–85% of cases (8,9,10). Pleural TB remains difficult to diagnose. The gold standard for diagnosis of a TB pleural effusion is isolation of Mycobacterium tuberculosis in pleural fluid or pleural tissue by culture, microscopy or a pleural biopsy that demonstrates caseating granulomas. However, a rational diagnostic approach. Begins with comprehensive pleural fluid analysis and, where appropriate, analysis of sputum. In high TB prevalence areas, a presumptive diagnosis may be made on the basis of a lymphocyte-predominant exudate with a high ADA (1), almost all patients with pleural TB have a pleural fluid ADA level above 40 U/L, which is the most widely accepted cutoff value for the diagnosis of pleural TB (14). The higher the level, the greater the chance of the patient having pleural TB while the lower the level the lesser the chance of the patient having plural TB (15).

CASE PRESENTATION:

A 30-years old man Asian background, was presented with a 4-week history of nonproductive cough and pleuritic chest pain, the patient had no symptoms otherwise, there was no history of fever, night sweat, fatigue, hemoptysis, and weight loss. He did not have any systemic condition or immunodeficiency diseases, The patient took antibiotics and nonsteroid antiinflammatory drugs (NSAID) for about two weeks without any significant improvement. Vital signs (heart rate – 82 beats/min, respiratory rate – 16 breaths/ min, blood pressure – 120/80

mmHg, body temperature – 36.6 Celsius) were within the normal range. An examination of the patient showed in auscultation of the respiratory system revealed left side respiratory sounds decreased, no rales or rhonchi. On percussion there was dullness in the lower region of the left hemithorax. A laboratory examination comprising routine blood and biochemical tests was normal except C-reactive protein level (CRP 131 mg/dl). A chest x-ray showed homogenous opacification in the left hemithorax (Figure 1). The chest was examined by ultrasound and left pleural effusion obtained by thoracentesis, effusion was determined. The fluid was an exudate with predominantly lymphocytes with negative cytology, culture and titer of adenosine deaminase was 10 IU/L. Pleural fluid glucose level was 80 mg/dL, lactate dehydrogenase (LDH) 420 U/dL, total protein 50.9 g/dL, pH was 7.35. The White blood cell count (WBC) differential of pleural fluid showed 93% lymphocytes, and 1.5% neutrophils. Serum LDH was 401 U/ dL, and total protein was 68 g/dL. In order to make a definitive diagnosis for the investigation of pleural effusions, a closed pleural biopsies with Abram's needle had been performed. Purified protein derivative test was measured as 16 mm. While waiting the biopsy results empirical antituberculosis treatment was initiated under suspicion of tuberculosis pleurisy. Treatment with anti-tuberculosis drugs was initiated. The patient was prescribed isoniazid 5 mg/kg, rifampin 10 mg/kg, pyrazinamide 25 mg/kg, and ethambutol 15 mg/kg daily for 2 months. The second phase of the treatment was planned to consist of isoniazid and rifampin daily for 4 months. After 2 weeks, histopathological examination of pleural biopsy showed necrotizing granulomatous inflammation with benign cytology (Figure 2, 3).

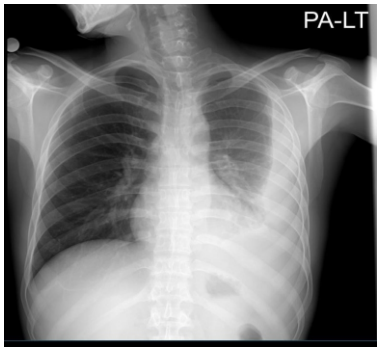

Figure 1. Pleural effusion in left hemithorax (Damoiseau line)

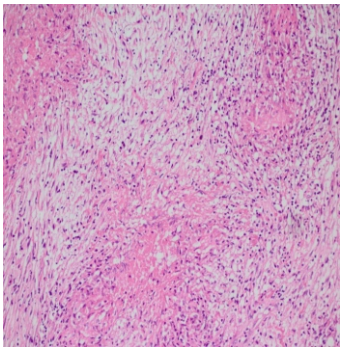

Figure 2. Necrotizing granulomatosis inflammation (hematoxylin eosin ×200)

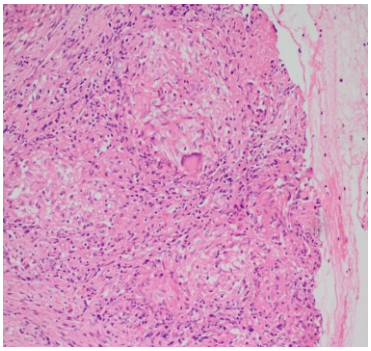

Figure 3. Multinuclear giant cells in granuloma structure (hematoxylin eosin ×200)

Discussion

The diagnosis of pleural tuberculosis was regarded as established when examination of pleural fluid revealed the presence of acid fast bacilli (AFB) by microscopy or M. tuberculosis by culture or when pleural biopsy specimens yielded a positive culture or granulomatous inflammation with caseous necrosis on histology (11). Pleural tuberculosis (TB) remains difficult to diagnose. In about two- thirds of the cases the diagnosis is reliant upon clinical suspicion along with consistent fluid biochemistries (i.e., lymphocytic predominant exudates) and exclusion of other potential causes for the effusion. Microbiological methods for a confirmatory diagnosis of pleural TB, which include acid-fast smears (Ziehl-Neelsen), cultures on solid media (Lowenstein-Jensen) and polymerase chain reaction tests from either pleural fluid or sputum samples, remain suboptimal since they are positive in only a minority of patients (11). The diagnostic evaluation of patients with tuberculous pleurisy includes a tuberculin skin test. In populations with a high prevalence of tuberculous infection, a positive skin test in a patient

with a pleural exudate strongly suggests the diagnosis of tuberculosis like our patient's case, whereas the diagnostic value of a positive tuberculin skin test in countries with a low prevalence of tuberculous pleurisy is lower. On the other hand, a negative tuberculin skin test does not rule out the diagnosis of tuberculous pleurisy. Negativity of the skin test has been reported in up to 30% of immunocompetent (12). Due to the financial conditions of the patient and his lack of health insurance, we could not conduct advanced research such as rheumatological tests and others, but during the taking of the medical history, it was found that the patient was not suffering from any diseases as far as he knew and did not have symptoms directed to rheumatic diseases, and despite his use of NSAIDs medications for a period of two weeks, he did not feel a decline in his symptoms. A number of pleural fluid biomarkers such as adenosine deaminase (ADA), interferonY, interferon-Y-induced protein of 10 KDa (IP-10) and interleukin-27 (IL-27), have shown promise for the rapid diagnosis of TB, but only ADA combines the accuracy and simplicity required to be considered a mainstay investigative tool for clinical decisions, particularly in areas with medium to high TB prevalence (11).

Since first reported in 1978 (16), the measurement of pleural fluid ADA has consistently demonstrated a high accuracy for diagnosing pleural TB (12). Five meta analyses have shown that pleural fluid ADA has a sensitivity of approximately 92%, a specificity of 90% (17-18). Even though the most widely accepted threshold ADA value is 35–40 U/L, some studies have reported that pleural fluid ADA decreases with age, therefore suggesting that lower cutoffs should probably be considered in older patients to reduce the number of false-negative results (19). Other than TB pleuritis, the main diseases associated with a high pleural fluid ADA level are complicated parapneumonic effusions, empyema and lymphomas (12). In geographical areas with moderate to high incidence of the disease, ADA has virtually substituted closed pleural biopsies for diagnostic purposes. In regions with low disease burden ADA is still of value in that a low level almost entirely rules out TB (i.e., the chance of an effusion with pleural fluid ADA under 35 U/L being of TB etiology is negligible) (12,13). Despite strong supporting evidence, nearly four decades later there is still some reluctance to accept ADA for expedited clinical decision making (12,13). In our case ADA is low 10 U\L, almost all patients with pleural TB have a pleural fluid ADA level above 40 U/L, which is the most widely accepted cutoff value for the diagnosis of pleural TB (14). An ADA level less than 40 U/L virtually rules out pleural TB and no further invasive diagnostic procedures should be necessary for diagnosing pleural TB (14). Nevertheless, if the patient has a typical clinical presentation of tuberculosis (i.e., febrile young patient from an endemic area of tuberculosis with a negative pleural fluid cytological investigation), especially with lymphocytic predominant pleural fluid, the possibility of pleural TB can be further evaluated with invasive diagnostic methods such as needle biopsy of the pleura, or medical thoracoscopy, or open pleural biopsy (14,15). However, interpretation of the result must take into account the patient profile and local TB prevalence. In high TB prevalence regions, in a patient with a high clinical suspicion of tuberculous effusion, an ADA value of >40 IU/L in a lymphocyte predominant exudate carries a positive predictive value (PPV) of 98% (20-21).

This is in contrast to its interpretation in low TB prevalence regions, where a pleural fluid ADA value of <30 IU/L has a negative predictive value (NPV) of 98.9% (22). Use of the ADA-2 isoenzyme assay increases the test's specificity for TB, which may be useful where there is the potential for a false positive result such as in bacterial pleural infection, chronic rheumatoid effusions, mesothelioma, lung cancer and hematological malignancies (24-25). One-third of parapneumonic effusions and two thirds of empyema have ADA levels exceeding 40 IU/L.8

These conditions are usually distinguishable from TB effusions by the neutrophil predominance in the pleural fluid, highlighting the fact that the ADA should not be interpreted in isolation. Tuberculous effusions are unlikely to elevate the ADA over 250 IU/L, and in this instance a bacterial empyema or lymphoid malignancy should be considered (26). Currently, pleural fluid ADA is routinely employed in the diagnostic workup of pleural effusions in high tuberculosis burden countries. However, the negative predictive value remains high even though the positive predictive value of pleural ADA declines in the developed countries. Therefore, when interpreting ADA levels, the clinician must additionally be aware of situations which may increase the likelihood of both the false-negative and false-positive ADA results (16). Previously, Lee et al. reported that pleural ADA could be lower than 40 IU/L in TPE patients who are in old ages or who are current smokers, which raises the number of false negative cases that can impair the sensitivity of ADA (29).

Histological analysis and mycobacterial culture of pleural biopsied tissue have traditionally been the gold standard diagnostic method. A closed needle biopsy of pleura using Cope's or Abrams' needle has been the most sensitive diagnostic test for tuberculous pleurisy. In one study of 248 patients with tuberculous pleurisy who underwent needle biopsy of the pleura, the biopsy showed granulomas in 198 patients (80%), the AFB stain of the biopsy was positive in 64 (25.8%) and the culture of the biopsy tissue was positive in 140 (56%) (30). The technique used to acquire pleural tissue is often dictated by the local expertise and resource availability, and while medical thoracoscopy has a sensitivity of up to 100% for tuberculous pleuritis, and is known to improve the yield for both culture and Xpert, it is not always available (32-33). In resource-limited settings, an ultrasound-guided closed pleural biopsy represents a reasonable alternative with a diagnostic yield of up to 90% (31). Necrotizing granulomatous inflammation is considered a distinctive sign for TB infection composed of central necrotic zone surrounded by epithelioid histiocytes with varied number of multinucleated giant cells and lymphocytes, multinucleated giant cells may contain Langhans type giant cells but Langhans type giant cells are not specific for TB infection.

Caseating granulomas even in the absence of acid-fast bacilli on smear or culture are considered adequate for diagnosis of pleural tuberculosis. Noncaseating granulomas can be seen on histologic examination of the pleura in sarcoidosis, as well as fungal infections and rheumatoid pleuritis (13). There is no data on the penetration of anti-TB drugs into pleural fluid or on their individual effectiveness in treating pleural TB. Regimens to treat pleural TB are per necessity adapted from the regimens for pulmonary TB; however, as the majority of pleural TB originates from a pulmonary focus, this seems a logical approach. The recommended therapy for all forms of extra-pulmonary TB (except meningitis, which requires a longer duration of therapy) is 6 months of standard anti-tuberculous treatment consisting of 2 months intensive phase with rifampicin, isoniazid, pyrazinamide and ethambutol (RHZE fixed-dose combination), followed by a 4-month continuation phase with RH only (1-4) In some situations, even when a presumptive diagnosis of pleural TB is made, antituberculosis chemotherapy should also be initiated, provided that the diagnosis occurs in a country with a moderate or high incidence of tuberculosis and low drug-resistance rates. Like our patient, empirical antituberculosis therapy was started under suspicion of tuberculosis pleuritis before biopsy results came out (3-5).

Conclusion

A combination of pleural fluid adenosine deaminase, differential cell count and closed needle biopsy has a high diagnostic accuracy in undiagnosed exudative pleural effusions in areas with high incidences of tuberculosis and might substitute medical thoracoscopy at considerably lower expense in low income countries.

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Address
Recep Tayyip Erdoğan Üniversitesi, Tıp Fakültesi, İslampaşa, 53020, Rize Türkiye
Faculty of Medicine, Recep Tayyip Erdogan University, Islampasa, 53020, Türkiye
Phone: (+90) 212 30 09, E-mail: rizetipdergi@erdogan.edu.tr
Web site: https://dergipark.org.tr/tr/pub/rizetip