A case of tuberculous pleural effusion with low pleural fluid adenosine deaminase levels

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ABSTRACT

Traditionally, *Mycobacterium tuberculosis* or granulomas have to be evidenced in the pleural cavity in order to establish a diagnosis of tuberculous pleuritis. In recent years, adenosine deaminase has aided tremendously in the diagnosis of tuberculous pleural effusion, often obviating the need for microbiologic or histologic verification of the diagnosis. However, the fact that the sensitivity of pleural fluid adenosine deaminase levels for tuberculous pleurisy, although high, is incomplete is often overlooked. To emphasize this, we present a case of a young male adult who presented with fever and a right-sided exudative bloody lymphocytic pleural effusion. While pleural fluid adenosine deaminase levels were low (22 U/L) and all other tests were inconclusive, tuberculin skin test conversion within the first two weeks of observation provided the clue for a clinical diagnosis of tuberculous pleurisy. The patient responded promptly to a four-drug regimen including isoniazide, rifampin, ethambutol, and pyrazinamide and had a normal chest X-ray at one month post-therapy initiation. He is well after two years of follow-up. Not all patients with a tuberculous pleuritis will have elevated adenosine deaminase levels in pleural fluid, and low pleural fluid adenosine deaminase levels do not rule out tuberculous pleuritis, especially in areas of high tuberculosis incidence.

INTRODUCTION

The diagnosis of a tuberculous pleural effusion (TPE) has traditionally rested on the detection of Mycobacterium tuberculosis in sputum, pleural fluid, or pleural tissue, or the demonstration of granulomata in pleural tissue (1). During the last

two decades, it has been established that the diagnosis of TPE can also be made with certainty by finding elevated levels of adenosine deaminase (ADA) in a pleural fluid with lymphocytic cellular predominance (2-10). This has been tremendously helpful for clinicians by obviating invasive diagnostic procedures and by aiding in timely therapy initiation.

However, the sensitivity of pleural fluid ADA for TPE, although ranging between 90 and 100 % in various series, is not absolute, meaning that a small proportion of patients with a TPE will have low pleural fluid ADA levels (2-10). In other words, although the negative predictive value of low pleural fluid ADA levels for the presence of a TPE is extremely high, ranging from 89 to 100 %, it is not absolute, especially in countries of high incidence of tuberculosis (8,11,12). In general, the test performs best in areas of intermediate incidence, while its specificity is lower in areas of low incidence, and its sensitivity is lower in areas of high incidence (8,11-13).

To exemplify the pitfalls of pleural fluid ADA misinterpretation, herein we report a case of a young man with clinical TPE with low ADA, who was successfully treated with antituberculous therapy.

CASE REPORT

A 35-year-old Greek actively smoking (10 pack-years) male presented with acute-onset fever (38° C), malaise, non-productive cough, shortness of breath and right-sided pleuritic chest pain. His past history was unremarkable for medications or immune-compromise. During admission the patient was mildly ill, with normal vital signs and a body temperature of 38.1°C. Electrocardiography, arterial blood gases, and electrolytes were unremarkable, while breath sounds and vocal repercussion were decreased at the right lung base. There were no signs of lower extremity deep-venous thrombosis and no palpable lymph nodes.

An isolated, free-floating, medium-sized pleural effusion without lung parenchymal abnormalities were evident on chest X-ray and computed tomography (CT) (images not shown). Routine laboratory work-up showed elevated white blood cell count (12.000/mm^3), erythrocyte sedimentation rate (35 mm in the first hour), and C-reactive protein (25 U/l). Human immunodeficiency virus and viral hepatitis antigens/antibodies/DNA were not detectable in serum. Rheumatoid factor, antinuclear and anti-DNA antibodies were also negative.

A tuberculin skin test done at admission was negative (0 mm enduration). Examination of sputum, urine, and gastric fluid for mycobacteria or other organisms was negative. Thoracentesis yielded an odorless, bloody pleural exudate (pH = 7.22, hematocrit = 1 %, glucose = 78 mg/dL, LDH = 704 U/L, protein = 4.6 g/dL, nucleated cells = 6400/mm^3 consisting of 80% polymorphonuclear, 10% lymphoid, and 10% eosinophil leukocytes). Pleural fluid adenosine deaminase was 19 U/L, while smears, cultures, cytology, and flow cytometry were negative. Lower extremity venous ultrasound and multi-detector computed tomography after intravenous contrast material administration ruled out deep-venous thrombosis and pulmonary embolism.

Repeat thoracentesis five days post-admission revealed lymphocyte predominance (80%) with no additional findings and ADA levels of 18 U/L. A third thoracocentisis was performed with once more the same findings (low ADA levels, lymphocytic exudate with pH = 7.3, negative cultures and cytology). Blood cultures also turned out negative.

A repeat tubercullin skin test was done two weeks later; this time the result was positive (15 mm enduration). The patient refused to undergo medical thoracoscopy or closed needle biopsy of the pleura. Based on the tuberculin skin test conversion in a patient with lymphocytic exudative pleural effusion coming from a high-incidence area fro tuberculosis, a clinical diagnosis of TB pleuritis was deemed most likely; the patient was adminis-

tered daily oral isoniazide (300 mg), rifampin (600 mg), ethambutol (1200 mg), and pyrazinamide (1500 mg).

The fever, pleural and constitutional symptoms resolved within five days, the chest X-ray was normal after two months into therapy, and the patient remains well after two years of follow-up.

DISCUSSION

Tuberculous pleural effusion (TPE) is more common than malignant pleural effusion in areas of high incidence of tuberculosis, which co-segregate with areas of poor socio-economic status (1,14). The differential diagnosis from malignancy, as well as timely and cost-effective diagnosis and institution of therapy are essential, especially in the deprived areas of high incidence. The diagnosis of TPE has traditionally rested on the detection of Mycobacterium tuberculosis in sputum, pleural fluid, or pleural tissue, or the demonstration of granulomata in pleural tissue (1,15). However, the results of pleural fluid staining for acid-fast bacilli are virtually always negative, and pleural fluid cultures are positive for mycobacteria in < 25 % of cases. On the other hand, a pleural biopsy specimen will demonstrate granulomatous pleuritis in 80 % of patients with TPE, and when a culture of a biopsy specimen is combined with histologic examination, the diagnosis can be established in approximately 90 % of cases (1,15). Hence the microbiologic and/or histologic diagnosis of TPE is time-consuming and expensive, and is not always achieved.

To fill this gap, a new, non-invasive, cheap, and readily accessible determination has acquired popularity as a diagnostic test for TPE: The levels of adenosine deaminase (ADA), an enzyme found in most cells, are increased in tuberculous pleural effusions (2-10). Several groups have suggested that an elevated pleural fluid ADA level predicts tuberculous pleuritis with a sensitivity of 90 to 100 % and a specificity of 89 to 100% (2-10,16). The reported cut-off value for ADA varies from 45 to 60 U/L. Specificity is increased when the lymphocyte/neutrophil ratio in the pleural fluid (of > 0.75) is considered together with an ADA concentration of > 50 U/L (1,5,11,15,16). As a result, in the recent couple of decades pleural fluid ADA has gained widespread use as a cheap and effective means of establishing a diagnosis of TPE (1).

In these years significant experience on the pitfalls of pleural fluid ADA interpretation have emerged, mostly concerning the specificity of the test. It has been found that ADA is elevated in pleural effusions caused by alternative *aetiologies*, such as malignancy (eg, *adenocarcinoma, lymphoma*), collagen vascular diseases (eg, *rheumatoid pleuritis* and systemic *lupus erythematosus*), and other infectious processes (eg, *empyema, brucellosis, legionellosis*) (5,7,9,11,17-19). Hence it has been proposed that a positive ADA test result is most useful in ruling in the diagnosis of a TPE in countries with high prevalence of tuberculosis (11-14).

However, criticism has relatively spared the sensitivity of pleural fluid ADA for TPE, which ranges from 90 and 100 %in various series (2-10). The negative predictive value of a negative ADA test has been considered so accurate as to warrant exclusion of TPE in the setting of low-incidence countries (8,11). However, problems with ADA sensitivity have not to be overlooked, especially in high-incidence areas, where the absolute number of TPEs with low ADA levels, although a small fraction of TPEs, becomes significant (8,11-14). In other words, although the negative predictive value of low pleural fluid ADA levels for the presence of a TPE is extremely high, ranging from 89 to 100%, it is not absolute, resulting in a significant number of TPEs with low pleural fluid ADA in countries of high incidence of tuberculosis (8,11-14). The case reported herein exemplifies the above-detailed facts. Although unfortunately Greece does not provide data on tuberculosis to the World Health Organization, local and regional expertise rules in favour of relatively high tuberculosis incidence in the country (14). In this setting we encountered a

patient with a lymphocytic pleural effusion with low pleural fluid ADA. A clinical diagnosis of TPE was made, and was confirmed by a full response to antituberculous treatment.

In conclusion, we encountered a TPE with low pleural fluid ADA, an occurrence which is to be expected in a region with high tuberculosis incidence. Pleural fluid ADA interpretation has to be undertaken with caution, especially in areas with low or high tuberculosis incidence.

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