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# Diagnostic dilemma in tuberculous pleural effusion

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ABSTRACT

*Aim:* To evaluate the clinical use of interferon gamma release assays (QuantiFERON-TB Gold (In-Tube Method)) for the diagnosis of pleural tuberculosis and comparing it with ADA as a method for diagnosis TB effusion.

*Patients and methods:* 40 patients presenting with pleural effusions were classified according to their final diagnosis in two groups.

*Group I:* Include 20 cases with tuberculous pleural effusions, *group II:* Control group: 20 cases divided into 2 subgroups: Subgroup11a: para pneumonic pleural effusions: 8 cases, Subgroup11b: malignant pleural effusions: 12 cases.

*Results:* Tuberculous pleural effusion showed statistically significantly lower mean age than non-tuberculous effusion. Tuberculous group showed statistically significantly highest mean ADA. This was followed by para pneumonic group then malignant group. ADA showed sensitivity (98%), specificity (55%), diagnostic accuracy (75%), negative predictive value ($PV^-$) (67.9%) and positive predictive value ($PV^+$) (91.7%) in diagnosing tuberculous effusion QuantiFERON-TB Gold showed sensitivity 65%, specificity 70%, PPV (68.4%), NPPV (66.7%) and diagnostic accuracy (67.5%) in diagnosing tuberculous effusion.

*Conclusion:* It was concluded that ADA measurement in the pleural fluid is an appropriate, fast diagnostic tool for the diagnosis of tuberculous pleural effusion, with higher sensitivity (98%) and diagnostic accuracy (75%). QuantiFERON-TB Gold which is technically more complicated, expensive and has lower sensitivity (65%) and diagnostic accuracy (67.5%) than ADA.



## Introduction

Tuberculous pleuritis remains one of the major causes of pleural effusion in many countries [1]. The diagnosis of pleural tuberculosis (TB) is hampered by its paucibacillary nature. Less than 10% of pleural fluids are smear positive, and culture is only positive in 20–50% [2]. Elevated ADA levels were found in tuberculous effusions at levels >40 U/L, strongly suggestive of TB in areas of high incidence and prevalence. In this situation, ADA has a reported sensitivity of 92% and a specificity of 90%. In general, 40 U/L is the accepted cut-off level when measuring ADA in pleural fluid [3]. M. tuberculosis–specific protein antigens as early secretory antigenic target 6 (ESAT-6) and culture filtrate protein 10 (CFP-10), which are absent from the genomes of all bacilli Calmette-Guerin sub strains and most nontuberculous mycobacteria, have been identified [4]. A specific method for detection of tuberculous infection has been developed in which IFN-g production is measured after stimulation blood T cell with these antigens in vitro [5]. Advances in the immunopathology of tuberculosis have led to the development of novel T-cell interferon-γ release assays (IGRAs),which are now licensed as blood tests for the diagnosis of latent tuberculosis. Extending the use of IGRA for diagnosing TPE has been the focus of a growing number of publications [6]. Normally, IGRAs tests use peripheral blood mononuclear cells (PBMCs), but they can be used with pleural fluid mononuclear cell [7].

### *Subjects and methods*

The study was conducted on 40 patients with pleural effusion, admitted to Chest Department BeniSueif University and El-Giza Chest Hospital during the period fromMay 2011–September 2012.

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These patients were classified according to their final diagnosis in two groups:

Group1

Include20 cases with tuberculous pleural effusions

Group11

Control group: 20 cases divided into 2subgroups
Subgroup11a .malignant pleural effusions: 12cases
Subgroup11b. Para pneumonic pleural effusions: 8 cases

*Inclusion criteria*

- The diagnosis of tuberculous pleuritis was made if any one of the following was satisfied: (a)Mycobacterium tuberculosis identified by culture from pleural fluid or pleural biopsy specimen; (b) Caseating granuloma was present on biopsy specimen, with or without positive staining for acid-fast bacilli (AFB) (c) Positive sputum culture for M .tuberculosis with no alternative explanation for exudative pleural effusion (d) Clinical features were compatible with TB and there was clear response to anti-TB drugs [8].
- Malignant pleural effusion was diagnosed in patients with positive pleural fluid cytology and/or positive histology of pleural biopsy [9].
- Para pneumonic effusion or pleural empyema was diagnosed in patients who had: (i) grossly purulent pleural effusion, (ii) the presence of microorganisms in pleural fluid, or (iii) sign and symptoms of pneumonia accompanied by pleural effusion which resolved following antibiotic treatment and/or local pleural drainage [10].

*Exclusion criteria*

(1) Clinical diagnosis of heart failure, renal failure, liver cirrhosis, and nephrotic syndrome and other transudative effusions.
(2) Other causes of exudative effusions.

All patients were subjected to the following:

1- Full clinical examination.
2- Routine labs: (renal function – liver function – complete blood picture).
3- Chest x-rays.
4- Tuberculin test [11].
5- Thoracentesis.
   - Routine pleural fluid analysis, including:

A- The measurements of physicochemical parameters (protein, LDH, and glucose) and total and differential cell counts. *With Light's criteria*, a pleural effusion is an exudate if one or more of the following criteria are met:
   1- Pleural fluid lactic dehydrogenase activity is greater than 200 IU or greater than two thirds of the laboratory's upper normal limit for serum LDH.
   2- Pleural fluid/serum lactic dehydrogenase ratio is greater than 0.6.
   3- Pleural fluid/serum protein ratio is greater than 0.5.

If all three criteria are met with, the effusion can be classified as an exudate, with a sensitivity of 99%& a specificity of 98% [12].

This required determination of a total protein concentration and LDH activity not only in pleural fluid, but also in peripheral blood samples.

**B-**cytological and microbiological examinations of pleural fluid were performed.
**C-**QuantiFERON–TB Gold (In-tube method test).

*Principle of the test*

The QFT-G system uses two specialized collection tubes that contain antigens representing certain *M. tuberculosis* proteins (ESAT-6, CFP-10, and TB7.7) and negative (Nil) controls [13].

Interpretation of QFT-G results is based on interferon-γ concentrations in test samples. A test is considered positive if IFN-γ response to the TB Antigen tube is significantly above the Nil IFN-γ IU/ml value.

A positive result suggests that *M. tuberculosis* infection is likely; a negative result suggests that infection is unlikely and indeterminate result suggests QFT-G results cannot be interpreted [14].

*Specimen collection and handling*

1. 1 mL of effusion was taken directly into each of the collection tubes.
2. Shaking the tubes vigorously for 5 s (or 10 times) was done to ensure that the entire inner surface of the tube has been coated with effusion.
3. The tubes were then transferred to a 37 °C incubator within 16 h of collection.
4. Incubation of the effusion occurred in the tubes for 16 to 24 h, after which the effusion was centrifuged then supernate was kept at -20 °C till time of work and tested for the presence of IFN-gamma produced in response to the peptide antigens [14].
5. Measurement of IFN-γ by ELISA.

D-The measurement of ADA:

Principle:
ADA activity was measured by a spectrophotometric method described by Guist and Galanti (1984) [14].

## Results

*Discussion*

Tuberculous pleuritis is a common manifestation of extra pulmonary tuberculosis and is the most common cause of pleural effusion in many countries. Conventional diagnostic tests, such as microscopic examination of the pleural fluid, biochemical tests, culture of pleural fluid, sputum or pleural tissue, and histopathological examination of pleural tissue, have known limitations. Due to these limitations, newer and more rapid diagnostic tests have been evaluated. [15]

In the current study, it was shown that the age (Mean ± SD) of tuberculous group (group1) was 28 ± 10.4 while those of nontuberculous group (group11) were 48.4 ± 13.3. Group1 showed statistically significantly lower mean age ($p < 0.001$) than group11.There was no statistically significant difference between gender distributions in the two groups as shown in Table 1.

This result was in accordance with Krenkei R et al. [16] who found that a comparison of some demographic and clinical data found in patients with tuberculous and non-tuberculous effusions was consistent with other author's observations in that the mean age of patients with Tuberculous pleural effusion(TPE) was significantly lower than that of patients with non-TPE ($P < 0001$).

This is similar to Awad et al. 2011 [17], who reported that a highly significant statistical difference between patients with different causes of pleural effusions regarding their age where tuberculous effusion patients have the lowest mean age