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Diagnostic Utility of Adenosine deaminase 1–2, and Interferon-γ in the Diagnosis of Pleural Tuberculosis

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Abstract

Pleural tuberculosis is the most common cause of pleural effusion (PE) worldwide. To date, diagnosis of pleural TB relies on either insensitive, unspecific, or time consuming methods often leading to defer initiation of therapy. A search for reliable least invasive diagnostic test for tuberculosis has resulted in identification of many diagnostic tests over the years, the most qualified one is adenosine deaminase (ADA). The best cut-off value of pleural ADA may vary depending on the incidence of tuberculosis pleural effusion (TBE). Using a cut off value of 35 U/L is reported that the sensitivity of ADA in diagnosis of tuberculous pleural effusion was 85.7%. Another biomarker widely using for TB PE is interferon-gamma (IFN-γ) cytokine. T-SPOT.TB has very high sensitivity in detection of TPE and is widely used for investigating the prevalence of TB infection.

Tuberculosis (TB) remains as an important health problem worldwide, and a pleural effusion occurs in approximately 5% of patients with tuberculosis[1]. Moreover, pleural tuberculosis is the most common cause of PE worldwide. Extra-pulmonary (EPTB) was estimated at 10-20% of TB patients, and tuberculous pleural effusion was the most common form of EPTB[2]. Compared with data from European studies where pleural tuberculosis accounted for 3–5% of cases, in developing countries the incidence of pleural tuberculosis has been documented to be as high as 30%[3,4]. Pleural TB effusion is thought to occur when a sub-pleural parenchymal lesion ruptures, releasing a small number of tuberculous bacilli into the pleural space, which in turn triggers a local immunological response. A neutrophilic influx takes place, which is followed by monocyte migration and a strong T-helper type 1 lymphocyte reaction[5].

To date, diagnosis of pleural TB relies on either insensitive (acid fast bacilli smears), unspecific (cell count, biochemical levels), or time consuming (culture) methods often leading to defer initiation of therapy. The paucity of bacilli in pleural fluid leads to low sensitivity of direct bacillary detection such as Ziehl-Neelsen staining, culture, and also PCR. It is known that diagnostic yield of ZN is <5%, culture is 35%, and PCR in PF is <20%. The diagnostic yield of pleural biopsy is 60–95% in case of tuberculous pleural effusions[6]. Diagnostic performance of closed biopsy is 55% by culture and 80% by histopathology. However, traditional pleural biopsy using Abram's or Copes needle is a blind procedure and is associated with certain limitations such as a lower diagnostic yield as well as a comparatively higher rate of complications when compared with VATS or thoracoscopic biopsy[7,8]. Diagnostic yield of these tecniques are 70% by culture and 100% by histopathology.

A search for reliable least invasive diagnostic test for tuberculosis has resulted in identification of many diagnostic tests over the years and these tests range from amplification of mycobacterial DNA via polymerase chain reactions to measurement of C-reactive protein (CRP), pleural viscosity, pleural fluid interferons, interleukins, carcinoembryonic antigen (CEA), tumour necrosis factor (TNF), pleural fluid T-lymphocytes and the vascular endothelial growth factor (VEGF). Although many have been evaluated during the last decades, the most qualified is adenosine deaminase (ADA), a predominant T-lymphocyte enzyme.

The levels of ADA is mostly found in the cell cytoplasm, are ten-times higher inside T-lymphocytes. So makes it useful for diagnosis of immune-related disorders because it is released from T-lymphocytes as well as macrophages during immune responses[9]. It must be kept in mind that high ADA level in pleural TB comes mostly from pleural macrophage. Ever since ADA was first reported to be of value in diagnosis of tuberculosis in 1978[10]. A meta-analysis showed that pleural effusion ADA had sensitivity 0.92 and specificity 0.90 in the diagnosis of tuberculous pleurisy[11]. In a recent study, the sensitivity and specificity of ADA in diagnosis of tuberculous pleural effusion were 88.88% and 77.04% respectively[12]. Another recently published study from Peshawar reported that the pleural fluid ADA levels were 90.47% sensitive and had a specificity of 76.66% when it came to diagnosis of tuberculous pleural effusions[6]. On the other hand, a study from Lahore reported that pleural fluid ADA levels more than 40 U/L had a sensitivity and specificity of 95.77% and 92.31% respectively in diagnosing tuberculous pleural effusions[9]. Other reports of the sensitivity and specificity of ADA for the diagnosis of tuberculous pleural effusion include 94.29% and 92.16% respectively, from India[13], 78% and 86% respectively from Turkey[14] and a range of 87–100% and 81–97% respectively from Spain[15]. Some old reports have even reported a sensitivity approaching 100% for ADA in diagnosis of tuberculous pleural effusion[16,17].

Different cut-off values have been used in the research on utility of ADA in predicting tuberculous pleural effusion. The best cut-off value of pleural ADA may vary depending on the incidence of TBE. From values as low as 27 U/L to as high as 77 U/L has been used. Using a cut off value of 35 U/L a recent study from South West England reported that the sensitivity of ADA in diagnosis of tuberculous pleural effusion was 85.7%[18]. Authors pointed out that ADA in pleural fluid is more valid than expected for the diagnosis of pleural tuberculosis in intermediate and low prevalence settings like western countries. Similarly, researchers from Egypt reported that the sensitivity, specificity and diagnostic accuracy of ADA levels in pleural effusion were 80%, 85%, and 83.3% respectively for diagnosis of tuberculous pleural effusion. However, the cut-off value they used was 30 U/L[19]. 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[20,21]. In our recent study, taking a cut-off value of 40.68 U/L for total pleural ADA, the sensitivity and the specificity were found to be 88.37% and 88%, respectively[22].

The diagnostic accuracy of ADA can be improved by measuring different ADA isoenzymes. ADA-2 is increased in TB effusions, while ADA-1 is increased in other bacterial empyemas[23,24]. Distinguishing between these two principal isoenzymes can increase the specificity of ADA for diagnosing TB. Although ADA-2 slightly increases the sensitivity and specificity of the total ADA in diagnosing TB pleuritis, it probably adds little in the majority of cases[25]. Use of the ADA-2 isoenzyme measurement increased the specificity for TB from 91% to 96% (16) and 92.1% to 98.6%[26], in two different studies. In our recent study, the best cut-off value for pleural ADA-2 was 20.37 U/L and it yielded a sensitivity and specificity of 95.35% and 86%, respectively[22]. It can be concluded that, the improvements or increments mentioned are not small at all.

PE ADA usually is higher in the TBE patients compared to non-TBE patients, but sometimes may elevate in some other patients. For example, more than 40% of parapneumonics and half of lymphomatous effusions exceeded the cutoff set for pleural TB[27]. Pleural ADA has been occasionally reported to be elevated in cases of empyema, legionnaires' disease, pleural brucellosis, and mycoplasma pneumoniae pneumonia[28-30]. As many as 9% of patients with lung cancer and 15% of those with mesothelioma showed high ADA activity and were false-positive with ADA cutoff setting[31]. Although PE ADA has good performance in detection of TPE in adults, it isn't accurate in detection of pediatric TPE[32]. In this study, there was no difference in pleural ADA between TPE (62.1 ± 4.2 U/L) and non-TPE patients (87.7 ± 10.0 U/L). Compared with empyema patients (183.8 ± 30.0 U/L), pleural ADA was lower in parapneumonic effusion (PPE) patients (63.4 ± 3.8, $p < 0.01$), or TBE patients ($p < 0.01$). Moreover, ADA levels can be affected by mycobacterial load. In a retrospective study, authors concluded that ADA would detect smear- or culture- positive TPE patients more easily, but negative TPE patients may be missed[33]. Another limitation restricting its use in clinical practice is other biomarkers are necessary to aid improving the performance of ADA in detection of TBE, such as IL-33, IL-27, and lymphocyte proportion[34-36].

In recent years, blood-based in vitro interferon-γ release assays (IGRAs) have been developed for the immunodiagnosis of *M. tuberculosis* infection. The novelty of IGRAs is based on the in vitro stimulation of peripheral

blood T-cells specific for the *M. tuberculosis*-specific antigens early secretory antigenic target (ESAT)-6 and culture filtrate protein (CFP)-10. The presence of reactive T-cells is assessed by the induction of interferon (IFN)- γ. In pleural TB, more CD4+ T lymphocyte subgroups are found in the pleural fluid than in peripheral blood, and also the level of IFN-γ secreted by T lymphocytes in pleural fluid are more than the level of IFN-γ in peripheral blood[37]. Two commercialised systems are available, the QuantiFERON-TB1 Gold in-tube assay, and the T-SPOT.TB1 assay. Two reports from China showed that the T-SPOT.TB assay have high sensitivity in detection of TBE. Therefore, the negative result can be read as exclusion criteria of TBE[38,39]. T-SPOT.TB has very high sensitivity in detection of TPE and is widely used for investigating the prevalence of TB infection[40]. But T-SPOT.TB has no capability for discrimination of active and latent TB infection. Poor specificity in detection of TPE was reported in several studies[38].

In a recent study, the sensitivity, specificity, positive predictive value, and negative predictive value of the IGRA ELISPOT assay for the diagnosis of pleural TB were 100%, 88.89%, 97.5%, and 100%, respectively[41]. Authors concluded that as sensitivity of T-SPOT.TB was 100%, theoretically this test is appropriate for screening purpose. As specificity of T-SPOT.TB was only 88.89%, positive test results should always be furtherly evaluated with caution because there is a chance of 11.11% of false positive. As PPV of T-SPOT.TB was 97.5%, if a patient with presumptive pleural TB gets positive result, the chance of this patient to be really sick is 97.5%. As NPV of T-SPOT.TB was 100%, negative result of patients with presumptive pleural TB always ruled out a diagnosis of active pleural TB. In a meta-analysis of 22 studies, totaling 2,101 patients with pleural effusions (of whom 782 had TB), IFN-γ measurements yielded 89% sensitivity, 97% specificity and area under the ROC curve of 0.99 for the diagnosis of TB[42]. In our recent study, ROC curve identified 110 U/L as the best cut-off value for IFN-γ, the sensitivity and the specificity were 74.42% and 68%, respectively[22].

Conclusion

In conclusion, the quantification of IFN-γ and the measurement of ADA have shown high sensitivity and specificity in pleural TB, especially in the areas of high prevalence. The ease of performance, cost and time-effectiveness of ADA assays mean that ADA can be used as a reliable marker for diagnosis of tuberculosis. High cost and lack of a broadly accepted discriminative cutoff for IFN-γ, still makes ADA the test of choice.

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