THE DIAGNOSTIC VALUE OF PLEURAL EFFUSION Γ-INTERFERON RELEASE TEST AND ADENOSINE DEAMINASE ALONE AND IN COMBINATION FOR TUBERCULOUS PLEURISY

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ABSTRACT

Objective: *To investigate the diagnostic value for tuberculous pleurisy of performing the interferon-γ release assay (IGRA) and adenosine deaminase (ADA) assay on pleural effusion, either alone or in combination.*

Methods: *A total of 138 patients with exudative pleural effusion were admitted to the tuberculosis department of our hospital, from October 2018 to October 2019, and included in this study. According to the comprehensive clinical diagnosis, they were divided into a tuberculosis (TB) group (n = 92) and a non-tuberculosis group (n = 46). Within 24 hours of admission, 4 ml fasting venous blood was collected from all patients, and IGRA was performed after detection with an enzyme marker. During this period, 1 ml pleural effusion was collected from each patient, and ADA was assessed using a biochemical analyzer.*

Results: *The IGRA-positive rates were 32.61% in the non-TB group and 83.70% in the TB group. The ADA-positive rates were 10.87% in the non-TB group and 30.43% in the TB group. The IGRA- and ADA-positive rates of patients in the TB group were significantly higher than those in the non-TB group (P<0.05). Both the IGRA index and the ADA assay have value for the diagnosis of TB pleurisy. The sensitivity of the IGRA index for the diagnosis of tuberculous pleurisy was 83.70%, the specificity was 67.39%, and the coincidence rate was 83.70%. For the diagnosis of TB pleurisy, the ADA assay had a sensitivity of 68.96%, a specificity of 91.30%, and a coincidence rate of 92.75%. Non-TB patients demonstrated a systemic positive test rate of 10.87%, and the systemic detection rate of TB patients was 65.22%. The positive parallel detection rate among TB patients was 36.96%, whereas the parallel detection rate among TB patients was 85.87%. Both the systemic and parallel detection rates for TB patients were significantly higher than those for the non-TB group (P<0.05). The sensitivity, specificity, and coincidence rate for the systematic detection and diagnosis of tuberculous pleurisy were 65.22%, 89.36%, and 73.91%, respectively. The sensitivity, specificity, and coincidence rate for the parallel detection of tuberculous pleurisy were 92.39%, 83.33%, and 82.60%, respectively.*

Conclusion: *The positive IGRA and ADA rates in patients with tuberculous pleurisy were higher than those in patients with non-tuberculous pleurisy.*

Keywords: *Pleural effusion, interferon-γ release assay, adenosine deaminase, single, combined, diagnosis, tuberculous pleurisy.*

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Introduction

Tuberculous pleurisy refers to the inflammation that occurs due to direct or indirect infections with Mycobacterium tuberculosis, resulting in a late type of allergic reaction of the pleura to the Mycobacterium tuberculosis components[(1)]. Clinically, cough, chest pain, fever, and dyspnea may occur, and most patients experience a small amount of pleural effusion, although a small number of patients experience a large amount of pleural effusion[(2)]. At present, the primary clinical methods used to detect tuberculous pleurisy include performing Mycobacterium tuberculosis cultures and acid-fast bacilli smears on pleural effusion samples; however, the positive rates of these tests are low, and these tests are time-consuming, which can affect the diagnosis and treatment of patients[(3)].

Recent studies have shown that the interferon (IFN)-γ release assay (IGRA) is widely performed on pleural effusion samples in the field of tuberculosis (TB) treatment and diagnosis, and the IGRA has a significant auxiliary effect for the diagnosis of tuberculous pleurisy[4]. Adenosine deaminase (ADA) is an important enzyme involved in purine nucleoside metabolism, which can be widely distributed throughout the body and can catalyze the transformation of adenine nucleoside into hypoxanthine nucleoside, which is closely related to the cellular immunity of the body. Some studies have suggested a relationship between ADA levels and tuberculous peritonitis[5].

The purpose of this study was to evaluate the value of using IGRA and ADA assessment, either alone or in combination, during the diagnosis of tuberculous pleurisy.

Materials and methods

General information

A total of 138 patients with exudative pleural effusions, from October 2018 to October 2019, in the TB department of our hospital, were enrolled in this study, divided into the TB group (n = 92) and the non-TB group (n = 46).

The tuberculous pleurisy inclusion criteria were as follows:

• All patients met the published Chinese Medical Association guidelines for the clinical diagnosis and treatment of TB and the standard guidelines for the diagnosis of tuberculous pleurisy[6], which included:

(a) pleural effusion was found in the tissues, and a smear or culture revealed Mycobacterium;

(b) pathological examination revealed caseous caryodontia;

(c) the clinical symptoms of the patient were consistent with tuberculous pleurisy, with a positive tuberculin test;

(d) imaging findings for the patients were consistent with tuberculous pleurisy;

(e) after 2 months of anti-TB treatment, the clinical symptoms and imaging examination showed improvement. Patients who met either item (a) or (b), or met two or of criteria (c)–(e) were diagnosed with combined pleurisy.

• The patient had no other serious infection and no history of autoimmune diseases and other immune diseases;

• The patient and the patient's family knew and signed informed consent.

The exclusion criteria included:

• The patient's heart, liver, kidney, and other organs appeared serious dysfunction;

• Patients with hypertension, diabetes, and other chronic diseases;

• or the patient refused the test or had poor compliance.

The inclusion criteria for non-TB peritonitis included:

• Patients with pleurisy other than tuberculous pleurisy;

• The patient and the patient's family signed the informed consent.

The exclusion criteria for the non-TB group included:

• The patient's heart, liver, kidney, and other organs appeared to demonstrate serious dysfunction;

• Patients with hypertension, diabetes, and other chronic diseases;

• The patient refused the test or had poor compliance. A total of 92 patients were included in the TB group, including 47 males and 45 females, with an average age of 45.11±10.23 years and an average body mass index (BMI) of 20.05±0.98 kg/m^2. A total of 46 patients were included in the non-TB group, including 25 males and 21 females, with an average age of 45.15±9.78 years and an average BMI of 20.06±1.02 kg/m^2.

No significant differences in age, sex, or BMI were observed between the groups (P>0.05).

Observation indicators

IGRA

Fasting venous blood samples from all patients were collected within 24 hours of admission, for a total volume of 4 ml, within 2 hours. Samples were divided into the control culture tube, the test culture tube, and the negative control culture tube, mixed, and were maintained at 5°C for 22 hours. The tubes were then centrifuged at 3,000 r/min for 10 minutes, and the serum was carefully separated. The IFN-γ levels of each group were detected and calculated using an enzyme marker. The IGRA was considered positive when the IFN-γ level was >14 pg/ml and, at the same time, a quarter of the negative control tube value.

ADA detection

Pleural effusion was collected by a pleural puncture, and the ADA level was quantitatively analyzed using a biochemical analyzer. An ADA level >40 U/L was considered positive.

Systematic detection

Systemic detection was defined as a positive result for both the IGRA and the ADA level of the pleural effusion.

Parallel detection

Parallel detection was defined as a positive result for either the IGRA or the ADA level of the pleural effusion.

Statistical methods

The data in this study were analyzed using SPSS, version 20.0. Measurement data are reported as the mean ± standard deviation ($\bar{x} \pm s$), and the t-test was used to perform comparisons between groups. For statistical data expressed as percentages, the chi-square test was used to perform comparisons between groups. The grade data were compared using the Ridit test. The diagnostic value was evaluated by determining the sensitivities, specificities, positive and negative predictive values, and coincidence rates, for each test individually and the parallel combined test and systematic combined test. The results were considered significant if $P<0.05$.

Results

Comparisons between the IGRA and ADA positive rates between the two groups

The IGRA positive rates were 32.61% in the non-TB group and 83.70% in the TB group. The ADA positive rate for the TB group was 30.43%. The IGRA and ADA positive rates for the TB group were significantly higher than those for the non-TB group ($P<0.05$, Table 1).

Group	n	IGRA		ADA	
		Positive	Negative	Positive	Negative
TB group	92	77 (83.70%)	15 (16.30%)	64 (69.96%)	28 (30.43%)
Non-TB group	46	15 (32.61%)	31 (67.39%)	5 (10.87%)	42 (91.30%)
χ^2		36.016		42.212	
P		< 0.001		< 0.001	

Table 1: Comparison of the IGRA and ADA positive rates between the two groups.

The tuberculous pleurisy diagnostic value of using either the IGRA index or the ADA assessment, independently

Both the IGRA index and the ADA diagnosis have diagnostic value for tuberculous pleurisy. The sensitivity of the IGRA index for the diagnosis of tuberculous pleurisy was 83.70%, the specificity was 67.39%, and the coincidence rate was 83.70%. The ADA-based diagnosis of tuberculous pleurisy had a sensitivity of 68.96%, a specificity of 91.30%, and a coincidence rate of 92.75%. These results are shown in Table 2.

Index	Sensitivity	Specificity	Positive	Negative	Coincidence rate
IGRA	83.70%	67.39%	83.70%	67.39%	78.26%
ADA	69.96%	91.30%	92.75%	60.00%	74.81%

Table 2: Diagnostic value for tuberculous pleurisy of single IGRA index or ADA analysis.

Analysis of systemic and parallel detection using IGRA and ADA positive rates for tuberculous pleurisy diagnoses

Non-TB patients presented a systemic positive test rate of 10.87%, whereas the system detection rate of TB patients was 65.22%. The TB patients had a parallel detection rate of 36.96%, whereas the parallel detection rate of TB patients was 85.87%. Both the systemic and parallel detection rates of TB patients were significantly higher than those for the non-TB group ($P<0.05$, Table 3).

Group	n	Systematic detection		Parallel detection	
		Positive	Negative	Positive	Negative
TB group	92	60 (65.22%)	32 (34.78%)	85 (85.87%)	7 (14.13%)
Non-TB group	46	5 (10.87%)	42 (91.30%)	17 (36.96%)	29 (63.04%)
χ^2		37.222		34.654	
P		< 0.001		< 0.001	

Table 3: Analysis of IGRA and ADA systematic and parallel detection rates between the two groups of patients.

Value analysis of using IGRA and ADA for the diagnosis of tuberculous pleurisy

The sensitivity, specificity, and coincidence rate of systematic detection for the diagnosis of tuberculous pleurisy were 65.22%, 89.36%, and 73.91%, respectively. The sensitivity, specificity, and coincidence rate of parallel detection for tuberculous pleurisy were 92.39%, 83.33%, and 82.60%, respectively (Table 4).

Index	Sensitivity	Specificity	Positive	Negative	Coincidence rate
Systematic detection	65.22%	89.36%	92.31%	56.76%	73.91%
Parallel detection	92.39%	63.04%	83.33%	8.55%	82.60%

Table 4: Value analysis of the combined detection using IGRA and ADA for the diagnosis of tuberculous pleurisy.

Discussion

The early clinical symptoms of tuberculous pleurisy are atypical. The current methods for identifying tuberculous pleurisy are inefficient because the culture period required to identify Mycobacterium tuberculosis in pleural effusion is long, the positive culture rate is low, and the early positive rate of acid-fast bacilli smears from pleural effusion is low. In addition, the trauma associated with pleural biopsy is large and pleural biopsy cannot be performed in patients with especially poor conditions and has limited clinical applications. Therefore, the early diagnosis of tuberculous pleurisy is difficult, which can prolong the patient's condition and affect treatment[7]. Therefore, developing a method for the early diagnosis of tuberculous pleurisy has been a research focus.

The antigen expressed by Mycobacterium tuberculosis stimulates the peripheral blood mononuclear production IFN-γ, which can be detected by the IGRA. Clinical IGRA results can generally be obtained 12-18 hours after blood sample collection, with the reported results classified as positive, negative, or uncertain[8]. Recent clinical studies have shown that the probability of meaningful results obtained using IGRA detection was higher than 96%[9]. The guidelines established by the United States Centers for Disease Control and Prevention (US CDC) have suggested that IGRA alternatives can be used in all cases in place of the current tuberculin skin test[10]. IGRA detection can reduce the medical costs associated with false-positive skin test results in patients with latent TB and is not affected by the anti-TB vaccine Bacille Calmette-Guerin (BCG) or by most non-pathogenic Mycobacteria. IGRA detection may be significant in countries with high levels of TB burden, such as China, where BCG use is widespread[11]. At present, IGRA is widely used in clinical practice because of its rapid detection time, high sensitivity and specificity, and high cost-effectiveness[12].

ADA is a nucleic acid metabolic enzyme that has an important relationship with immune activity. Blood is primarily comprised of red blood cells, lymphocytes, and granulocytes, among which ADA enzymatic activity is higher in T lymphocytes than in B lymphocytes[13]. At present, ADA detection is significant for detecting diseases such as liver injury, chronic liver disease, liver fibrosis, differential jaundice, hematopathies, tumor, and meningitis[14]. In this study, the positive IGRA rates were 32.61% in the non-TB group and 83.70% in the TB group, whereas the positive ADA rats were 10.87% in the non-TB group and 30.43% in the TB group. The IGRA and ADA positive rates in the TB group were significantly higher than those in the non-TB group ($P<0.05$). The positive systemic detection rates were 10.87% in the non-TB group and 65.22% in the TB group, whereas the positive parallel detection rates were 36.96% in the non-TB group and 85.87% in the TB group. The positive rates for systemic and parallel detection in the TB group were significantly higher than those in the non-TB group ($P<0.05$). These results suggested that positive IGRA and ADA tests are closely related to patients with tuberculous pleurisy, similar to the results reported by fu hongyi's[15].

To further analyze the relationship between IGRA, ADA, and patients with tuberculous pleurisy, the receiver operator characteristic (ROC) curve was analyzed. The ROC curve showed that the IGRA index and the ADA diagnosis of tuberculous pleurisy have diagnostic value. The sensitivity of the IGRA index to diagnose tuberculous pleurisy was 83.70%, the specificity was 67.39%, and the coincidence rate was 83.70%, whereas the sensitivity of ADA to diagnose tuberculous pleurisy was 68.96%, the specificity was 91.30%, and the coincidence rate was 92.75%. The sensitivity, specificity, and coincidence rate of systematic detection for the diagnosis of tuberculous pleurisy were 65.22%, 89.36%, and 73.91%, respectively. The sensitivity, specificity, and coincidence rate of parallel detection for tuberculous pleurisy were 92.39%, 83.33%, and 82.60%, respectively. These results suggested that IGRA and ADA, either alone and in combination, have diagnostic value for tuberculous pleurisy, with combined parallel detection demonstrating the highest diagnostic value.

In summary, the IGRA and ADA positive rates for tuberculous pleurisy patients were higher than those for non-tuberculosis pleurisy patients. The diagnostic values of both tests, either alone or combined, were also higher for TB patients than for non-TB patients. The combined parallel diagnostic value was the highest among all possible combinations, suggesting that this parallel testing approach could be widely applied to clinical practice.

References

1) Zeng J, Wang GM, Wu BQ, Wang G, Zhang RL, et al. Diagnostic value of pleural effusion and blood γ-interferon release test in patients with tuberculous pleurisy. China Mod Med 2018; 25: 47-49.
2) Nieto JC, Zamora C, Porcel JM, Mulet M, Pajares V, et al. Migrated T lymphocytes into malignant pleural effusions: an indicator of good prognosis in lung adenocarcinoma patients. Sci Rep 2019; 9: 2996.
3) Tamura K, Suzuki M, Ishii S, Takasaki J, Naka G, et al. IgG4-related disease with elevated adenosine deaminase in pleural effusion diagnosed clinically using thoracoscopy under local anesthesia and FDG-PET-CT. Respir Med Case Rep 2020; 30: 101066.
4) Shen F, Han C, Wang MS, He Y. Poor agreement between repeated T-SPOT.TB in a short time period in a high TB burden country. Infect Dis (Lond) 2018; 50: 771-774.
5) Zervou MI, Goulielmos GN, Matalliotakis M, Matalliotaki C, Spandidos DA, et al. Role of adenosine deaminase 2 gene variants in pediatric deficiency of adenosine deaminase 2: A structural biological approach. Mol Med Rep 2020; 21: 876-882.
6) Wang J, Liu X. Application of the tow-interferon release test (tb-igra) in the diagnosis of tuberculous pleurisy. J Appl Med 2015; 32: 815-816.
7) Zathar Z, James S, Pressler N, Ho E. Constrictive pericarditis masquerading as hepatic sequestration crisis in a patient with sickle cell disease: a case report. Eur Heart J Case Rep 2020; 4: 1-5.
8) Xu M, Sun X, Liu Z, Zhong Y, Zhong QQ, et al. Clinical Significance of Positive TB-IGRA in Patients with Crohn's Disease and Intestinal Tuberculosis. Chin J Gastroenterol 2019; 24: 76-80.
9) Grinsdale JA, Islam S, Tran OC, Ho CS, Kawamura LM, et al. Interferon-Gamma Release Assays and Pediatric Public Health Tuberculosis Screening: The San Francisco Program Experience 2005 to 2008. J Pediatric Infect Dis Soc 2016; 5: 122-130.
10) Qi X, Wang YC, Guo YJ, Ma Q, Chen YY, et al. Analysis of the results of two detection techniques in screening latent TB infection in children with different risk factor levels. J Natl Def Tuberc 2018; 40: 9.
11) Wen A, Qu XH, Zhang KN, Leng EL, Ren Y, et al. Meta analysis of the diagnostic value of non-blood body fluids in patients with stuck interferon release test. Chin J Infect Dis 2019; 37: 179-182.
12) Serra S, Bologna C, Londono L, Wang L, Shepard M, et al. Abstract 5583: Pegylated adenosine deaminase 2 (PEG-ADA2) abrogates the cytoprotective effects of adenosine against chronic lymphocytic leukemia cells. Cancer Res 2017; 77: 5583.
13) Sun Q, Zheng W, Lin C, Shen D. A Low-Cost Micro-Volume Nephelometric System for Quantitative Immunoagglutination Assays. Sensors (Basel) 2019; 19: 4359.
14) Santosh UP, Renu GS, Abhilash S. Role of Adenosine Deaminase in Common Chronic ENT Infections. J Clin Diagn Res 2020; 10: 1-2.
15) Zhou M, Yang QL, Chen HX, Yu ZM, Gao L, et al. Diagnostic value of interferon-γ release assay of peripheral blood and pleural effusion for tuberculous pleurisy. Med J Chin Peoples Liberation Army 2018; 43: 64-68.

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