THE VALUE OF ADA LEVEL AND MONOCYTE RATIO IN PLEURAL EFFUSION TO DIFFERENTIATE TUBERCULOUS PLEURISY FROM MALIGNANT EFFUSION AND EMPYEMA

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ABSTRACT

Objective: *To analyze the value of adenosine deaminase (ADA) level and monocyte ratio in pleural effusion to differentiate tuberculous pleurisy from malignant effusion and empyema.*

Methods: *One hundred fifteen patients with pleural effusion admitted to our hospital from January 2019 to January 2020 were selected and divided into the tuberculous pleurisy group (n = 68), the malignant pleural effusion group (n = 25), and the empyema group (n = 22) by pathological examination. After admission, all patients underwent pleural puncture and drainage or catheterization. The first pleural effusion was collected and placed in the collection tube for ADA, CA125, nucleated cell count and single-factor analysis. The values of ADA, CA125, nucleated cell count and monocyte ratio in each group were compared. An ROC curve was used to analyze the value of ADA and CA125 in differentiating tuberculous pleurisy from malignant effusion and empyema.*

Results: *The proportion of monocytes in pleural effusion of the tuberculous pleurisy group and the malignant pleural effusion group was significantly higher than that of the empyema group, and the number of nucleated cells was significantly lower than that of the empyema group; the proportion of monocytes in pleural effusion of the tuberculous pleurisy group was significantly higher than that of the malignant pleural effusion group, and the number of nucleated cells was significantly lower than that of the malignant pleural effusion group (P<0.05). The ADA of the tuberculous pleurisy group and the malignant pleural effusion group was significantly lower than that of the empyema group, and CA125 was significantly higher than that of the empyema group; ADA of the tuberculous pleurisy group was significantly higher than that of the malignant pleural effusion group, and CA125 was significantly lower than that of the malignant pleural effusion group; the difference was statistically significant (P<0.05). ROC curve analysis showed that the AUC of ADA in the diagnosis of tuberculous pleurisy was 0.785, the AUC of monocyte ratio in the diagnosis of tuberculous pleurisy was 0.685, the AUC of combined diagnosis of tuberculous pleurisy with ADA was 0.845, the AUC of ADA diagnosis of malignant effusion was 0.815, the AUC of monocyte ratio in the diagnosis of malignant effusion was 0.715, and the AUC of combined diagnosis of malignant effusion was 0.925.*

Conclusion: *The level of ADA and the proportion of monocytes in pleural effusion can be used as important test indexes to distinguish tuberculous pleurisy from malignant effusion and empyema, and the combination of the two has the highest value and can be widely used in clinical practice.*

Keywords: *Pleural effusion, ADA, monocyte ratio, differential diagnosis, tuberculous pleurisy, malignant effusion, empyema, value.*

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Introduction

Pleural effusion is a common clinical symptom characterized by pathological fluid accumulation in the pleural cavity, which is relatively common in the elderly[(1)]. At present, the clinical diagnosis mainly depends on X-rays, CT scans, and other means of imaging examination. Tuberculous pleurisy is a pleural inflammation caused by the entry of Mycobacterium tuberculosis and its autolytic products and metabolites into the pleural cavity of the hypersensitive body, and is a common cause of pleural effusion[(2)]. At present, skin biopsy, acid-fast bacilli smear, and culture in pleural fluid have become the gold standard for the diagnosis of tuberculous pleurisy. However, smears and

cultures are time-consuming and less sensitive, and may lead to missed diagnoses and misdiagnoses. Two-puncture biopsy is an invasive operation that is prone to infection and other complications[3-5]. Therefore, it is of great importance to find a simple, quick, repeatable, and non-invasive method for the diagnosis of tuberculous pleurisy in early diagnosis and treatment. Adenosine deaminase (ADA) is a nucleic acid converting enzyme that is closely associated with cellular immunity in the body[6].

Recent studies have found that ADA is abnormally expressed in patients with tuberculous pleurisy, and it is speculated that there is a connection between the occurrence and the development of tuberculous pleurisy[7]. Nucleated cells in pleural effusion include lymphocytes, mesothelial cells, neutrophils, eosinophils, plasma cells, and others, among which mononuclear cells can be significantly increased in the presence of nucleobacter infection[8]. In this study, 115 patients with pleural effusion admitted to the Department of Respiratory Medicine in our hospital from January 2019 to January 2020 were selected as the observation objects. The purpose of this study was to analyze the value of ADA level and monocyte ratio in pleural effusion in differentiating tuberculous pleurisy from malignant effusion and empyema.

Materials and methods

General information

A total of 115 patients with pleural effusion admitted to the Department of Respiratory Medicine in our hospital from January 2019 to January 2020 were selected.

Inclusion criteria were as follows:

• All patients were diagnosed with pleurisy;

• There were signs of pleural effusion by X-ray and ultrasound examination;

• All patients had no other serious underlying diseases;

• The patients were informed and signed the informed consent form.

Exclusion criteria were as follows:

• Severe dysfunction of the heart, liver, kidneys, or other vital organs;

• Allergic constitution;

• Or refusal of this experiment or termination of the experiment for other reasons.

The patients were divided into the tuberculous pleurisy group (n=68), the malignant pleural effusion group (n=25), and the empyema group (n=22) by pathological examination. There were 68 patients in the tuberculous pleurisy group, composed of 35 males and 33 females, with an average age of (45.06±9.78) years old and an average BMI of (20.05±0.98) Kg/m^2. In the malignant pleural effusion group, there were 25 patients, composed of 13 males and 12 females, with an average age of (45.11±9.85) years old and an average BMI of (20.11±0.85) Kg/m2.

There were 22 patients in empyema group, composed of 11 males and 11 females, with an average age of (45.01±9.84) years old and an average BMI of (20.12±0.25) Kg/m^2. There was no significant difference in age, sex, or BMI among all groups (P>0.05). See Table 1.

Group	n	Age	Gender		BMI
			M	F	
Tuberculous pleurisy group	68	45.06±9.78	35	33	20.05±0.98
Malignant pleural effusion group	25	45.11±9.85	13	12	20.11±0.85
Empyema group	22	45.01±9.84	11	11	20.12±0.25
F		0.000	0.021		0.080
p		0.999	0.989		0.924

Table 1: Analysis of general data of each group ($\bar{x}\pm s$).

Observation indexes

All patients received pleural aspiration or catheterization after admission, and the first pleural effusion was collected and placed in the collection tube for the numerical test of ADA, CA125, nucleated cell count and mononuclear cell proportion. ADA was used with ZN2005 human adenosine deaminase (ADA) ELISA kit provided by Beijing Biolabo Technology Co., Ltd. CA125 was tested by KIT test kit provided by Hangzhou Washeng Biological Technology Co., Ltd., and the nucleated cell count and mononuclear cell proportion were tested by Cellometer Auto T4 provided by Nilon Biological Instruments (Shanghai) Co., Ltd.

Statistical methods

The SPSS 20.0 software package was used for the statistical analysis of data in this study. The normal distribution of all measurement data was expressed as ($\bar{x}\pm s$) after testing.

One-way ANOVA was used for comparison between multiple groups, and an LSD t-test was used for pair comparison between groups. Enumeration data were expressed as percentages, and a χ^2 test was used for comparison between groups. ROC curve was used to analyze the value of ADA and CA125 in

differentiating tuberculous pleurisy from malignant effusion and empyema. The statistical results were considered statistically significant if P<0.05.

Results

Comparison of the proportion of mononuclear cells in pleural fluid and nucleated cell count in each group

The percentage of mononuclear cells in pleural fluid in the tuberculous pleurisy group and the malignant pleural effusion group was significantly higher than that in the empyema group, and the count of nucleated cells was significantly lower than that in the empyema group. The percentage of mononuclear cells in pleural effusion in the tuberculous pleurisy group was significantly higher than that in the malignant pleural effusion group, and the nucleated cell count was significantly lower than that in the malignant pleural effusion group, with statistical significance (P<0.05). See Table 2.

Group	Percentage of mononuclear cells in pleural fluid (%)	Count of nucleated cells (n/L)
Tuberculous pleurisy group	86.35±20.45	2546.31±1850.37
Malignant pleural effusion group	75.52±18.16[a]	1862.58±1785.34[a]
Empyema group	33.56±20.15[ab]	72546.39±16528.52[ab]
F	58.450	812.200
p	<0.001	<0.001

Table 2: Comparison of the proportion of mononuclear cells in pleural fluid and nucleated cell count in each group ($\bar{x}\pm s$).

Note: a indicates compared to the tubercular pleurisy group, P<0.05, and b indicates compared to the malignant pleural effusion group, P<0.05.

Comparison of ADA and CA125 levels in each group

ADA in the tuberculous pleurisy group and the malignant pleural effusion group was significantly lower than the empyema group, and CA125 was significantly higher than the empyema group. ADA in the tuberculous pleurisy group was significantly higher than that in the malignant pleural effusion group, and CA125 was significantly lower than that in the malignant pleural effusion group, with statistical significance (P<0.05). See Table 3.

Value analysis of ADA and CA125 in the diagnosis of tuberculous pleurisy

ROC curve analysis showed that the AUC, sensitivity, and specificity of ADA in the diagnosis of tuberculous pleurisy were 0.785, 82.46%, and 85.69%, respectively. The AUC, sensitivity, and specificity of monocyte ratio in the diagnosis of tuberculous pleurisy were 0.685, 72.54%, and 69.67%, respectively. The AUC of tuberculous pleurisy was 0.845, the sensitivity was 89.67%, and the specificity was 85.45%. See Table 4.

Group	n	ADA (U/L)	CA125 (μg/L)
Tuberculous pleurisy group	68	62.15±32.15	459.61±452.31
Malignant pleural effusion group	25	20.64±12.45[a]	877.69±845.21[a]
Empyema group	22	155.67±133.25[ab]	77.84±64.38[ab]
F		28.440	13.650
p		<0.001	<0.001

Table 3: Comparison of ADA and CA125 levels in each group ($\bar{x}\pm s$).

Index	AUC	Sensitivity	Specificity
ADA	0.785	82.46%	85.69%
Monocyte ratio	0.685	72.54%	69.67%
ADA + monocyte ratio	0.845	89.67%	85.45%

Table 4: Value analysis of ADA and CA125 in diagnosis of tuberculous pleurisy.

Value analysis of ADA and CA125 in diagnosis of malignant effusion

ROC curve analysis showed that the AUC of ADA diagnosis of nodal malignant effusion was 0.815, the sensitivity was 83.25%, and the specificity was 85.41%. The AUC of the diagnosis of malignant effusion was 0.715, the sensitivity was 73.47%, and the specificity was 73.54%. The AUC of the combined diagnosis of malignant effusion was 0.925, the sensitivity was 93.01%, and the specificity was 92.85%. See Table 5.

Index	AUC	Sensitivity	Specificity
ADA	0.815	83.25%	85.41%
Monocyte ratio	0.715	73.47%	73.54%
ADA + monocyte ratio	0.925	93.01%	92.85%

Table 5: Value analysis of ADA and CA125 in diagnosis of malignant effusion.

Discussion

China has a large population, and there are many kinds of respiratory diseases, among which pleural effusion is one of the most common. At present, most are caused by tuberculosis, empyema, and tumors[9]: China is a country with a high incidence

of tuberculosis, ranking second in the world. If pleural effusion is not diagnosed and treated in time, it will lead to a high rate of disability, which will seriously affect the quality of life of patients and can even endanger their lives[10]. Currently, there are many methods to diagnose tuberculous pleurisy, but the clinical effects are different. Thoracoscopy is an invasive examination method, but it carries certain requirements regarding patients and the environment and cannot be widely used[11].

ADA is a nucleic acid metabolic enzyme required for the conversion of adenine to hypoxanthine, and it plays an important role in the immune response of the body[12]. Acid-fast bacilli can cause specific immunity when they invade patients. When tuberculous pleurisy was present, acid-fast bacilli induced the differentiation and proliferation of T-lymphocytes in the pleural cavity, and ADA increased to varying degrees. There is a certain degree of inflammation in empyema patients, and the stimulation of T-lymphocytes will also lead to the increase of ADA level. Tumor cells in patients with malignant pleural effusion will attack T-lymphocytes, and ADA is expressed at a low level[13]. CA125 is a protein commonly found in the epithelial tissues of the ovaries, uterus, peritoneum, and other coelomic tissues, and is widely used as a tumor marker in clinic.

The cell count in pleural effusion can be used as an important reference index to judge the nature of disease. Monocytes are derived from the mononucleus-macrophage system and can enter the blood. After entering various tissues in the body with the blood flow, they change morphologically and become macrophages. The membrane of mononuclear macrophages has many receptors with different functions, which can bind to many factors secreted by lymphocytes; the membrane itself has a variety of biological functions as well. Mycobacterium tuberculosis cell wall protein stimulation in patients with tuberculous pleurisy can enhance the killing power of macrophages against Mycobacterium tuberculosis cells and play a defensive role in local Mycobacterium tuberculosis infection. Therefore, a significant increase in monocytes can be observed in the pleural fluid of patients with tuberculous pleurisy[14]. In this experiment, the proportion of mononuclear cells in pleural effusion in the tuberculous pleurisy group and the malignant pleural effusion group was significantly higher than that in the empyema group, and the count of nucleated cells was significantly lower than that in the empyema group. The percentage of mononuclear cells in pleural effusion in the tuberculous pleurisy group was significantly higher than that in the malignant pleural effusion group, and the nucleated cell count was significantly lower than that in the malignant pleural effusion group. ADA in the tuberculous pleurisy group and the malignant pleural effusion group was significantly lower than the empyema group, and CA125 was significantly higher than the empyema group. ADA in the tuberculous pleurisy group was significantly higher than that in the malignant pleural effusion group, while CA125 was significantly lower than that in the malignant pleural effusion group. It is suggested that the expression of ADA level and mononuclear cell ratio in pleural effusion has certain rules in patients with tuberculous pleurisy, malignant effusion, and empyema, which may provide strong test support for the identification of tuberculous pleurisy, malignant effusion, and empyema, which is similar to the research results of Yuan Meirong et al[15].

In order to further analyze the value of ADA level and mononuclear cell ratio in pleural effusion in differentiating tuberculous pleurisy from malignant effusion and empyema, an ROC curve analysis in this study showed that the AUC of ADA in diagnosing tuberculous pleurisy was 0.785, and the AUC of mononuclear cell ratio in diagnosing tuberculous pleurisy was 0.685. The AUC of combined diagnosis of tuberculous pleurisy was 0.845; that of ADA diagnosis of malignant effusion was 0.815, that of mononuclear cell ratio diagnosis of malignant effusion was 0.715, and that of combined diagnosis of malignant effusion was 0.925. Prompt, level of ADA in pleural effusion, the proportion of mononuclear cells to identify tuberculous pleurisy and malignant effusion, pyothorax have good predictive value, the joint detection from single parameter to the diagnosis of tuberculous pleurisy have better predictive value, help physicians in the early diagnosis of tuberculous pleurisy and take corresponding measures, has extremely important significance in patients with effective treatment.

In conclusion, ADA level and mononuclear cell proportion in pleural effusion can be used as important test indexes to distinguish tuberculous pleurisy from malignant effusion and empyema, among which the combination of the two has the highest value and can be widely used in clinical practice.

References

1) Mitrouska I, Klimathianaki M, Siafakas NM. Effects of pleural effusion on respiratory function. Can Respir J 2004; 11(7): 499-503.
2) Gu Y, Zhai K, Shi HZ. Clinical Value of Tumor Markers for Determining Cause of Pleural Effusion. Chin Med J (Engl) 2016; 129(3): 253-8.
3) Yang L, Hu YJ, Li FG, Chang XJ, Zhang TH, et al. Analysis of Cytokine Levers in Pleural Effusions of Tuberculous Pleurisy and Tuberculous Empyema. Mediators Inflamm 2016; 2016: 3068103.
4) Kawaguchi T, Oda K, Kido T, Kawanami T, Kawabata Y, Yatera K. Bilateral Tuberculous Pleurisy with Subsequent Upper Lobe Predominant Pulmonary Fibrosis Mimicking Pleuroparenchymal Fibroelastosis. Intern Med 2018; 57(1): 85-89.
5) Aoki Y, Katoh O, Nakanishi Y, Kuroki S, Yamada H. A comparison study of IFN-gamma, ADA, and CA125 as the diagnostic parameters in tuberculous pleuritis. Respir Med 1994; 88(2): 139-43.
6) Akinyemi AJ, Adedara IA, Thome GR, Morsch VM, Rovani MT, et al. Dietary supplementation of ginger and turmeric improves reproductive function in hypertensive male rats. Toxicol Rep 2015; 2:1357-1366.
7) Schepp J, Bulashevska A, Mannhardt-Laakmann W, Cao H, Yang F, et al. Deficiency of Adenosine Deaminase 2 Causes Antibody Deficiency. J Clin Immunol 2016; 36(3): 179-86.
8) Eo WK, Kwon S, Koh SB, Kim MJ, Ji YI, et al. The Lymphocyte-Monocyte Ratio Predicts Patient Survival and Aggressiveness of Endometrial Cancer. J Cancer 2016; 7(5): 538-45.
9) Akinyemi AJ, Thomé GR, Morsch VM, Bottari NB, Baldissarelli J, et al. Dietary Supplementation of Ginger and Turmeric Rhizomes Modulates Platelets Ectonucleotidase and Adenosine Deaminase Activities in Normotensive and Hypertensive Rats. Phytother Res 2016; 30(7): 1156-63.
10) Barranco T, Rubio CP, Tvarijonaviciute A, Rubio M, Damia E, et al. Changes of salivary biomarkers under different storage conditions: effects of temperature and length of storage. Biochem Med (Zagreb) 2019; 29(1): 010706.
11) Schepp J, Bulashevska A, Mannhardt-Laakmann W, Cao H, Yang F, et al. Deficiency of Adenosine Deaminase 2 Causes Antibody Deficiency. J Clin Immunol 2016; 36(3): 179-86.
12) Antonangelo L, Vargas FS, Seiscento M, Bombarda S, Teixera L, et al. Clinical and laboratory parameters in the differential diagnosis of pleural effusion secondary to tuberculosis or cancer. Clinics (Sao Paulo) 2007; 62(5): 585-90.
13) Fellmann F, Angelini F, Wassenberg J, Perreau M, Arenas Ramirez N, et al. IL-17 receptor A and adenosine deaminase 2 deficiency in siblings with recurrent infections and chronic inflammation. J Allergy Clin Immunol 2016; 137(4): 1189-1196.e2.
14) Li W, Tao L, Zhang L, Xiu D. Prognostic role of lymphocyte to monocyte ratio for patients with pancreatic cancer: a systematic review and meta-analysis. Onco Targets Ther 2017; 10: 3391-3397.
15) Verma A, Abisheganaden J, Light RW. Identifying Malignant Pleural Effusion by A Cancer Ratio (Serum LDH: Pleural Fluid ADA Ratio). Lung 2016; 194(1): 147-153.

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