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The Level of Expression and Diagnostic Value of Biomarkers in Tuberculous Pleurisy

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Abstract: *Objective:* Observe and analyze the clinical significance of the differences in the expression levels of sCD163, haptoglobin and cytokines. *Methods*: 120 patients with tuberculous pleural effusion diagnosed in our hospital from January 2019 to December 2021 were randomly selected as the experimental group. On the other hand, 40 patients with non-tuberculous pleural effusion admitted in the same period were selected as the control group. The expression levels of sCD163, haptoglobin and cytokines were observed and analyzed. *Results:* The expression levels of sCD163 (μg/mL), haptoglobin (g/L), IL-6 (pg/mL) and IL-12 (pg/mL) of the control group were 31.26 ± 14.12, 32.14 ± 18.79, 401.23 ± 24.36 and 1.32 ± 0.14, respectively. As for the experimental group, the expression levels of sCD163 (μg/mL), haptoglobin (g/L), IL-6 (pg/mL) and IL-12 (pg/mL) were 74.12 ± 14.78, 113.25 ± 19.45, 612.12 ± 36.98 and 4.12 ± 0.56 respectively, and $p < 0.05$ which shows that the data was statistically significant. *Conclusion:* The level of inflammatory cytokines in the pleural fluid of tuberculous pleural effusion patients are higher, which can be used for the diagnosis of auxiliary tuberculous pleurisy. Tuberculous pleural effusion patients has a significantly increased expression levels of sCD163 and haptoglobin in the pleural fluid. The combination of sCD163 and haptoglobin in the diagnosis of tuberculous pleural effusion has higher clinical diagnostic value, and sCD163 and haptoglobin are not interfered by inflammatory factors in the diagnosis of tuberculous pleural effusion

Keywords: Tuberculous pleurisy; Biomarkers

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1. Introduction

Pleurisy is pleural inflammation caused by various factors such as inflammation and tumor stimulating the pleura. Its main causes are tuberculosis and malignant tumors [1]. The early identification of tuberculous pleurisy and malignant pleurisy is of great significance for clinical intervention to improve prognosis. At present, the identification of tuberculous pleurisy and malignant pleurisy mostly depends on Mycobacterium tuberculosis detection or pleural tissue biopsy. However, there are few Mycobacterium tuberculosis in pleural effusion, which is difficult to be detected by routine detection methods; Pleural puncture biopsy will bring certain trauma to patients, and it is difficult to collect samples and has poor repeatability [2]. In recent years, biomarkers have been gradually applied to the diagnosis of pleurisy. Although at present, no single and effective biomarker has been found in our country as well as abroad to identify benign and malignant pleurisy. Hence, the combined detection of multiple biomarkers is expected to significantly improve the accuracy of differential diagnosis of benign and malignant pleurisy [3]. Tuberculosis is a widespread infectious disease in the world, mainly caused by Mycobacterium tuberculosis

through air transmission [4]. About 30% of the world's population is infected with Mycobacterium tuberculosis, of which 5% to 10% will develop into tuberculosis [5]. According to the report of the World Health Organization, in 2020, more than 7 million new TB cases were reported worldwide, of which extrapulmonary tuberculosis accounted for nearly 1/6. Tuberculous pleurisy (TP) is one of its most common manifestations [6]. TPE is the main symptom of TP, which is mainly caused by the invasion of Mycobacterium tuberculosis into the pleura or the recurrence of tuberculosis foci in the chest. However, not all patients can be diagnosed through typical imaging findings [7]. In China, nearly half of hospitalized patients with pleural effusion are diagnosed as TPE [8]. TPE cases of elderly patients are often complicated with a variety of basic diseases. Due to the weakened immune function of the elderly, the body's ability to fight tuberculosis bacilli is reduced, and they often do not show typical symptoms of tuberculosis infection. At the same time, they are prone to false negative TB related tests, and are often misdiagnosed as infection or other diseases, causing delayed treatment [9]. At present, the molecular immunological indicators related to tuberculosis are constantly updated, and these indicators can help diagnose TPE to a certain extent, but about 1/5 patients still cannot be diagnosed accurately [10]. Therefore, further studies need to be done to develop diagnosis methods on the causes of pleural disease followed by formulation of clinical treatment plans.

2. Data and methods

2.1. General information

120 patients with tuberculous pleural effusion diagnosed in our hospital from January 2019 to December 2021 were randomly selected as the experimental group, and 40 patients with non-tuberculous pleural effusion admitted in the same period were selected as the control group.

2.2. Methods

Both groups of patients underwent thoracentesis under sterile conditions. Before operation, the puncture needle was guided by ultrasonic positioning, routinely disinfected and papered. Under local anesthesia, the puncture needle was inserted into the chest, about 10ml of pleural effusion was extracted, test tube heparin was anticoagulated, the effusion was centrifuged at 3000 r/min speed for 10 min, the centrifugation radius was r = 12cm, standing at room temperature for 60min, and the separated supernatant was placed in -80 ℃ refrigerator for testing. The levels of sCD163 and haptoglobin in pleural effusion of patients in the two groups were detected by enzyme-linked immunosorbent assay. The operation process was carried out according to the instructions of human sCD163 kit and human haptoglobin kit.

2.3. Observation indicators

The expression levels of scd163, haptoglobin and cytokines was observed and analyzed.

2.4. Statistical methods

All data were processed by SPSS16.0 statistical software, and the measurement data were expressed as mean ± standard deviation, using t-test; the counting data is expressed in percentage (%), using χ^2 test, with $p < 0.05$ indicating statistical significance

3. Results

sCD163 in the control group (μg/mL), haptoglobin (g/L), IL-6 (pg/mL) and IL-12 (pg/mL) were 31.26 ± 14.12, 32.14 ± 18.79, 401.23 ± 24.36 and 1.32 ± 0.14, respectively. sCD163 of the study group (μg/mL), haptoglobin (g/L), IL-6 (pg/mL) and IL-12 (pg/mL) were 74.12 ± 14.78, 113.25 ± 19.45, 612.12 ± 36.98 and 4.12 ± 0.56 respectively, and $p < 0.05$ was statistically significant, as shown in **Table 1**.

Table 1. Comparison of expression levels of sCD163, haptoglobin and cytokines

Group	sCD163 (μg/mL)	Haptoglobin (g/L)	IL-6 (pg/mL)	IL-12 (pg/mL)
Control group (n = 40)	31.26 ± 14.12	32.14 ± 18.79	401.23 ± 24.36	1.32 ± 0.14
Research group (n = 120)	74.12 ± 14.78	113.25 ± 19.45	612.12 ± 36.98	4.12 ± 0.56
t	16.0572	23.0314	33.6768	31.2380
p	0.0000	0.0000	0.0000	0.0000

4. Discussion

Tuberculosis is a curable infectious disease caused by Mycobacterium tuberculosis, also known as acid fast bacilli. It can also involve other organs or tissues, known as extrapulmonary tuberculosis. The thorax is one of the most common lesions, which is manifested as pleural effusion in most cases. It is mainly an immunological process containing a small amount of MTB, which usually leads to negative AFB staining and culture. In addition to microbiological culture results, traditional diagnostic methods, it is of little diagnostic value [11]. The most direct evidence of MTB infection is etiology, but it has low sensitivity and is time-consuming (4-6 weeks) [12]. The gold standard for diagnosing TPE is still to isolate MTB from pleural effusion or pleural tissue through culture, microscope or nucleic acid amplification test; or the histology shows caseous granuloma containing AFB [13-14]. Due to the nature of oligobacilli in pulmonary tuberculosis, the sensitivity of MTB detection in PE is low [15]. 40-70% of TPE can be confirmed by invasive examinations such as pleural biopsy and histopathology [16-18]. The results of negative AFB smear/culture and histopathological reports cannot exclude the possibility of tuberculosis, although the pathological examination of pleural biopsy has a satisfactory positive rate with sensitivity and specificity close to 98%. However, biopsy is an invasive operation, which will inevitably cause complications such as trauma and infection. In previous studies, about 43.2% of patients have transient chest pain, and 9% of patients have subcutaneous emphysema. In addition, the accuracy of biopsy results largely depends on the skills of doctors, the operating environment and the quality of recovered samples. Despite performing all these examinations, there are still 10%−20% of patients who cannot be diagnosed accurately.

Haptoglobin is an acidic glycoprotein. Some scholars have studied the level of haptoglobin in pleural effusion and found that compared with non-malignant pleural effusion, the content of haptoglobin in malignant pleural effusion is significantly increased. CD163 is a transmembrane glycoprotein with a molecular weight of 130 KD and a member of the scavenger superfamily

IL-6 is a type of cytokine produced by T lymphocytes and monocyte macrophages. It participates in the communication between multiple cells, such as cell proliferation and differentiation, and plays a key role in inflammation and immune response. When Mycobacterium tuberculosis attacks the lung tissue, a strong immune response occurs locally, and antigens induce the activation of monocyte macrophages in the lung, which produces inflammatory cytokines such as tumor necrosis factor and interleukin. These cytokines can act on bronchial epithelial cells and pulmonary macrophages to increase the expression of IL-6. Studies show that BCG vaccination in mouse macrophages can significantly increase TNF- α and IL-6 levels, suggesting that the expression of IL-6 can be significantly increased in the process of tuberculosis infection. Besides, some studies have confirmed that the level of IL-6 in patients with active tuberculosis is significantly higher than patients with latent tuberculosis infection, disease control group, and healthy people. The mechanism may be that the body is infected with tuberculosis, and lipopolysaccharide stimulates the cell signal pathway mediated by toll like receptor family members (TLR2), thereby stimulating IL-6 and TNF- α. In addition, some studies have shown that IL-6 is involved in the immune

response, hematopoietic and other functions of the body, and is related to inflammation, autoimmune diseases and malignant tumors. Some studies have also shown that with the formal anti-tuberculosis treatment of tuberculosis patients, the level of IL-6 in their bodies gradually decreases, and when the patient's condition worsens, the level of IL-6 in the body increases accordingly. The current research is still focused on the diagnostic value of IL-6 for TPE, and there is a lack of research on the correlation between the expression level of IL-6 and the severity of tuberculosis, and the clinical outcome of tuberculosis infection. IL-12 participates in the immune response of the body by regulating Th1 cells after tuberculosis infection. Some studies have proved that MTB infection can stimulate and strengthen the innate immunity of mice, make adult mice secrete more IL-12, further regulate the immune response in the body, and inhibit the reproduction of MTB. Moreover, some studies have also proved that the phagocytic capacity and killing activity of neutrophils and polymorphonuclear cells in peripheral blood of patients with tuberculosis can be enhanced by IL-12, so as to effectively improve the immune function of the body against tuberculosis infection.

Pleural effusion can produce a variety of proteins. With the rapid development of proteomics, it has laid a solid technical foundation for exploring the protein expression level in tuberculous pleural effusion. Some scholars have proposed that haptoglobin (HP) and free CD163 (solid-CD163, sCD163) have obvious changes in the expression of tuberculous pleural effusion. The results shows that the expression level of sCD163 and haptoglobin in the pleural fluid of tuberculous pleural effusion patients is significantly higher. The combination of sCD163 and haptoglobin in the diagnosis of tuberculous pleural effusion has higher clinical diagnostic value, and sCD163 and haptoglobin are not interfered by inflammatory factors in the diagnosis of tuberculous pleural effusion. Further analysis showed that the proportion of Th1 cells, the content of tumor necrosis factor-A and C-reactive protein were significantly higher in patients with tuberculous pleurisy, and the combination of inflammatory and immunological indicators in pleural fluid was of high diagnostic value for tuberculous pleurisy.

5. Conclusion

In conclusion, the level of inflammatory cytokines in the pleural fluid of tuberculous pleural effusion is higher, which can be used for the diagnosis of auxiliary tuberculous pleurisy. The expression level of sCD163 and haptoglobin in the pleural fluid of tuberculous pleural effusion patients is significantly higher. The combination of sCD163 and haptoglobin in the diagnosis of tuberculous pleural effusion has higher clinical diagnostic value, and sCD163 and haptoglobin are not interfered by inflammatory factors in the diagnosis of tuberculous pleural effusion.

Disclosure statement

The author declares no conflict of interest.

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