Contradictory Pleural based Mass Occurred in Patients with Pleural Tuberculosis during the Treatment: A Clinical Observational Study in China

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Abstract

Background: Recent years pleural based mass newly occurred during anti-tuberculosis (TB) treatment had been observed in patients with pleural TB. Its occurrence is contradictory and unfavorable for the outcome of patients. This study aims to explore its clinical, pathological and bacteriological characteristics.

Methods: Patients newly diagnosed as pleural TB met included criterion were prospectively enrolled into the study. Patients were followed up throughout the treatment, clinical data were recorded. Percutaneous biopsy and surgical tissues from pleural based mass were pathologically and bacteriologically examined, related clinical factors were calculated by Fagan's nomogram and ROC curve.

Results: A total of 122 patients with pleural TB were enrolled. 34.4% of them (42/122) were newly observed pleural based mass during the treatment, 12 cases received surgical resection at the 12±0.5 months of treatment course, under surgical observation only 58.3% of them (7 /12) were located on pleura, 41.7% (5/12) of them were located in lung parenchyma. Pathological observations showed that pleural based masses were divided into three types: granulomatous inflammation, fibrous hyperplasia and necrosis type. Mycobacterium tuberculosis PCR was positive in 57.1% of cases (24/42), any first-line anti-TB drug resistance gene mutation was positive in only 9.5% (4/42). Besides 12 cases receiving surgical operation, there were 86.7% of patients (26/30) in which pleural based mass still existed at the end of 12 months course. Young age, pleural thickness and adhesion, higher LDH, ADA, TGF-β and PAI-1, lower GLU and t-PA in pleural effusion were risk factors of occurring pleural based mass.

Conclusions: Pleural based mass had been observed in about one third of patients with pleural TB, which were located in lung or pleura and divided into three pathological types. There are some clinical characteristics as its predictive risk factors.

Background

Tuberculosis (TB) remains one of the leading infectious diseases in the world. There were estimated 10.0 million new cases of TB worldwide in 2019 [1]. Pleural TB ranks the second most common form of extra-pulmonary TB [2,3]. Pleural based mass in patient with pleural TB had been observed by imaging recent years [4], most of them were newly developed during anti-TB treatment, which was “contradictory changes” under chemotherapy. There were several literatures reported its occurrence [5-8]. We described it in the following case shown in figure 1, which presented radiological changes during the process of the occurrence of pleural based mass. Figure 1A showed the mass pleural effusion in the right chest; Figure 1B showed pleural effusion was clear after the drainage of pleural fluid and starting the treatment; Figure 1C showed the occurrence of pleural based mass in the same site of the right chest after 4 months of chemotherapy; Figure 1D Pleural based mass resected by surgery was found no recurrence in a year's follow-up.

Patients with pleural based mass were frequently found in clinics in China. However, published studies only focus on case reports and mainly reported in Asian regions with high TB burden [5-7]. There had no unified treatment regimen for patients when pleural based mass was observed in imaging during patients received anti-TB treatment. Why does pleural based mass happen? How does pleural based mass show pathologically, which was located in pleural or lung? How should patients proceed to get treatment after pleural based mass occurred? Patients should maintain the origin regimen or change the regimen and how to change if changing the regimen was needed? However, all above questions still remain elusive.

In the present study, we conducted a clinical observational study to describe its clinical characteristics, explored the pathological findings and associated risk factors of pleural based mass in order to clear the recognition about the occurrence of pleural based mass in the patients with pleural TB.

Materials And Methods

1. Study design and patients' information

The study was conducted in a national pulmonary disease specialized hospital, and the patients were mainly from eastern six provinces and one municipality in China. From January 1, 2017 to June 30, 2018, patients diagnosed as pleural TB met include criteria were prospectively enrolled into the study, which was approved by the ethics committee of Shanghai Pulmonary Hospital, Tongji University School of Medicine (No. K16-131). Written informed consent was obtained from all enrolled participants. Included patients were collected pleural effusion which were sent for biochemical and cytokines tests, then followed up throughout the treatment, observed the treatment outcome, all patients with pleural based mass were obtained biopsy tissue via surgical resection or aspiration biopsy. Biopsy tissues were tested by anti-TB drug resistant genes mutation and pathological observation.

Inclusion criteria were as followed: newly diagnosed as pleural TB and pleural effusion could be punctured and obtained; and had no pleural based mass or nodules at the initiation of treatment; and negative in serum human immunodeficiency virus (HIV) and had no previous history of anti-TB treatment.

Excluded criteria were as followed: Patients had malignant tumor; or with immunosuppressive status; had other pulmonary diseases; could not be drawn pleural effusion.

The standard of diagnosis of pleural TB was according to the WHO guideline: patients were diagnosed as pleural TB if there was at least one of the following criteria [9,10]: (1) identification of mycobacterium tuberculosis (MTB) in pleural effusion by acid-fast bacilli (AFB) smear; (2) detection of MTB by culture or DNA PCR in pleural effusion; (3) typical pathological findings on a pleural biopsy; and (4) anti fast bacteria (AFB) stain or culture positive in sputum and chest radiology indicated abnormal lesions compatible with pulmonary TB; and clinical comprehensive standard in accordance with pleural TB (immunology, biochemical or histopathology and responsive to anti-TB treatment).

All patients included were followed up throughout the treatment course. Outcome of pleural based mass was evaluated and included obviously absorbed (lesion absorbed by more than 50%); partly absorbed (lesion absorbed less than 50%), no change and deteriorated (lesion enlarged or diffused).

2. Data and sample collection

All clinical characteristics including age, symptoms, complications, diagnosis, pleural thickness, pleural nodule, bacteriological tests and treatment regimen were recorded completely. Pleura thickness > 2 mm was considered as plural thickness [11].

Patients with pleural TB were performed percutaneous transthoracic puncture to collect pleural effusion sent to clinical laboratory for biochemical test, part of which was frozen at -20 °C. Biomedical examinations included adenosine deaminase (ADA), lactate dehydrogenase (LDH), protein and glucose. Meanwhile, IFN- γ , PAI-I, t-PA and TGF- β in pleural effusion were tested by enzyme-linked immunosorbent assay (ELISA) (ELISA kit was from eBioscience Corp, San Diego, CA). ELISA were detected on the reader with 450nm wavelength within 30 minutes after the end of operation. All procedures were performed in strict accordance with the product instructions.

Surgery and biopsy

Part of patients with pleural based mass were received surgical resection decided by surgeons, physicians and patients. Surgeons decided the operative approach and recorded the precise location of pleural based mass during the course of operation. Other patients with pleural based mass were performed by CT guided percutaneous biopsy to obtain the tissue. Biopsy tissues from surgery and aspiration were sent for pathology and bacteriological tests.

3. Pathological observation and immunohistochemistry (IHC)

The biopsy tissues were pathologically tested. Formalin fixation and paraffin embedding (FFPE) sections stained with hematoxylin-eosin (HE) were observed by two experienced pathologists, and another pathologist was invited to provide a diagnosis in cases of disagreement between two pathologists. Ziehl-Neelsen stain was used to examine AFB with 1000 times magnification. IHC using an envision detection system (Leica Biosystems Melbourne Pty Ltd., Melbourne, Australia) was carried out to estimate expression of PAI-1(ab226946, 1:200, Abcam, USA) and t-PA (ab157469, 1:50, Abcam, USA) in pleural based mass lesions comparing with pleural TB cases without pleural based mass. As a classic methodology [12], H-score was used to access IHC results. The score calculated using the formula $1 \times (\% \text{ of } 1 + \text{cells}) + 2 \times (\% \text{ of } 2 + \text{cells}) + 3 \times (\% \text{ of } 3 + \text{cells})$. Zero for 'no staining', 1 + for 'light staining visible only at high magnification', 2 + for 'intermediate staining' and 3 + for 'dark staining'.

4. Anti-TB drug resistance genes mutation detection in biopsy tissues

All biopsy tissues were sent for molecular pathological test, including real-time PCR and PCR-reverse dot blot to detect MTB and drug resistance gene mutations. Paraffin sections 4~5 μm thick, 8~10 pieces

were put into Eppendorf tube. And then total DNA was extracted by using an E.Z.N.A. FFPE DNA Kit (Omega Bio-tek, Inc., USA) according to the manufacturer's protocol. Four μ l of the extracted DNA was used for real-time PCR to detect specific gene sequence IS6110 of MTB on a Stratagene Mx3000P QPCR System (Agilent Technologies, Santa Clara, CA, USA). After the amplification, the data was analyzed on Mx3000P. Subject to quality control (no S type amplification curve in negative control PCR batch; S type amplification curve in positive control PCR batch with the Ct value < 30 ; in internal standard channel, DNA sample with the Ct value < 45), the MTB is positive if there is an S type amplification curve with the Ct value < 37 in MTB detection channel. Another 4 μ l of the extracted DNA was used for PCR-reverse dot blot to detect rifampicin, isoniazid, streptomycin and ethambutol resistance (*rpoB*, *katG*, *inhA*, *embB* and *rpsL* gene accordingly) by anti-TB drug resistance genes mutation detection kit (Yaneng Co, Shenzhen, China) according to the manufacturer's instructions. Clear blue dot indicates positive MTB drug resistance gene. Positive and negative controls were set up in all above test.

5. Statistics

The statistical analysis and data visualizing were performed using SPSS statistics version 25.0 (SPSS, Inc., Chicago, IL, USA), R 3.5.3 software (The R Foundation for Statistical Computing) and Stata/MP 14.0. Differences with $P < 0.05$ were considered significantly. The diagnostical value of each biomarker was calculated with the area under receiver operation curve (ROC) curve (AUC). The Fagan's nomogram was used to present pre-test probability and post-test probability which derived from Stata module (FAGAN: Stata module for Fagan's Bayesian nomogram).

Results

1. Patients characteristics

A total of 122 patients were finally enrolled into the study, median age was 34 (22 ~ 59) years old, males were 66.4% (81/122), 76 patients (76/122, 62.3%) had accompanied with pulmonary TB, 54 cases (54/122, 44.3%) showed pleural thickness with average diameter at 3.1 (2.0 ~ 4.3) cm. During the follow up of treatment, 42 patients were observed to develop pleural based mass with occurrence rate of 34.4% (42/122). In patients with pleural based mass, 64.3% (27/42) had single nodule, 26.2% (11/42) had two nodules, 9.5% (4/42) had more than 3 nodules. For occurrence time during the anti-TB treatment, 47.6% (20/42) occurred at 4 to 6 months of course (Table 1). Clinical characteristics and flow diagram of included cases were shown in figure 2.

Patients with occurring pleural based mass were younger (29 years old vs. 42 years old, $p=0.001$) and had higher rate of pleural thickness (78.6% vs. 26.3%, $p=0.001$) and pleural adhesion (47.6% vs. 18.8%, $p=0.001$) and higher proportion of packaged pleural effusion (47.6% vs. 18.8%, $p=0.001$) compared with those without occurring pleural based mass ($P=0.001$), however, MTB culture positive rates from any specimens were similar in both groups, $P>0.05$ (Table 2).

2. Biochemical and cytokines expression in pleural effusion

To further explore characteristics of patients with occurring pleural based mass, we tested biochemical and cytokines in pleural fluid at the initiation of anti-TB treatment, LDH and ADA were significantly higher and glucose was lower in patients with pleural based mass patients than those without pleural based mass, p value was 0.001, 0.001, 0.008, respectively. TGF- β and PAI-1 were statistically higher and t-PA was significantly lower in patients with pleural based mass than those in patients without pleural based mass (20.021 μ g/L vs. 16.386 μ g/L, P=0.044, 241.014 μ g/L vs 187.152 μ g/ L, P=0.048, 1.733 μ g/L vs 3.025 μ g/L, P=0.024), Detailed data were showed in Table 3.

3. Surgical findings

Among 42 patients occurred pleural based mass, 12 of them (12/42, 28.6%) were received surgical resection. 41.7% (5/12) of pleural based masses were actually located in parenchyma closed to the pleura and only 58.3% of them were located on pleura through the surgical findings (see in Figure 3A, B and C). Only 2 pleural based masses (2/12, 16.7%) showed encapsulated empyema exhibited as abundant pus wrapped in fibrous tissue. Others (10/12, 83.3%) were shaped as tuberculoma.

4. Pathological observations

Pathological diagnosis was made on 12 surgical and 30 biopsy specimens. According to pathological findings, pleural based masses had three pathological types: (1) granulomatous inflammation type, in which lesions mainly included inflammatory cells, epithelioid histiocytes, Langhans giant cells with or without necrosis. Most pleural based mass lesions (34/42, 81.0%) presented this type; (2) fibrous hyperplasia type, in which lesions mainly consisted of fibroblasts and fibrous proliferation without any granulomatous changes, few cases (3/42, 7.1%) presented this type; (3) necrosis type, in which lesions showed large area of caseous necrosis with or without infiltration of inflammatory cells, fibrous hyperplasia and granuloma were not obviously observed. Necrosis seemed as dominant morphology including 2 cases of encapsulated empyema, 5 cases (5/42, 11.9%) presented type 3(See in figure 4).

AFB stain was positive in 52.4% of cases (22/42,). IHC expression of PAI-1 (50 vs. 20, $p<0.05$) was higher and t-PA (100 vs. 160, $p<0.05$) was lower in patients with pleural based mass compared to patients without pleural based mass, which were in accordance with the cytokines change trend in pleural effusions tested by ELISA.

5. Anti-TB drug-resistance genes mutation detections

Specimens were extracted DNA and tested by rpoB, katG, inhA, embB and rpsL genes mutation. 57.1% (24 /42) of cases were found positive of MTB DNA, only 9.5% (4/42) of them were detected mutation of drug resistance gene, including 1 case (2.4%) with resistance to isoniazid, rifampicin and streptomycin, 2 cases (4.8%) with isoniazid resistance and 1 case (2.4%) with resistance to rifampicin (see in table 4).

6. Treatment and outcome:

We following all patients with pleural TB, all patients without pleural based mass had cured after full course of chemotherapy. Among 42 cases with pleural based mass, 12 cases received surgical resection got cure, 73.3% of cases (22/30) without received surgical resection had their pleural based mass no change after finished one year of chemotherapy, only 4 cases (4/30, 13.3%) got partly absorption and 4 cases (4/30, 13.3%) got obviously absorption, and no patient found their lesions deteriorated. All patients remained the anti-TB regimen no matter pleural based mass occurred or not.

Most pleural based mass (90.9%, 20/22) larger than 3 cm had no change after finished anti-TB treatment course, however, lesions with smaller than 1cm in diameter had absorbed, including 75% (3/4) of lesions obviously absorbed and 25% (1/4) of lesions partially absorbed after finished the treatment (see in table 5).

7. Analysis of predictive risk factors of pleural based mass

We found nearly 30% of patients with pleural TB occurred pleural based mass during the treatment. To explore the risk factors of occurring pleural based mass on patients with pleural TB, ROC curve was used to choose the best appropriate clinical characteristics, biochemical and cytokines indexes for association of occurrence of pleural based mass. After screening and calculating the value of AUC, age, glucose, ADA, LDH, protein, TGF- β , PAI-1 and t-PA were associated with the occurrence of pleural based mass, data were shown in table 6.

We further used Fagan's nomogram to evaluate the prognostic possibility of pleural based mass occurrence. We found the probability of pleural TB to develop pleural based mass can reach 99.7% when patients have pleural thickness, packaged pleural effusion, LDH>461.5IU/L, ADA>62.9IU/L, GLU<4.75mmol/L, TGF- β >15.235 μ g/L, PAI-1>180.720 μ g/L, t-PA<2.875 μ g/L and age<32.5 years old. There was no probability (0.0%) to develop pleural based mass when patients do not have above nine characteristics (see in table 6 and figure 5).

Discussion

In recent years physicians found patients with pleural TB had likelihood to develop pleural based mass during anti-TB treatment (see in figure 1). However, there is little study regarding the reason and deep characteristics of occurring pleural based mass. We performed a prospective observational study focused on clinical, immunological, bacteriological and pathological findings in order to get further knowledge on pleural based mass occurrence during the treatment.

During the follow-up of treatment on pleural TB, we found 34.4% of patients (42/122) developed pleural based mass. 12 cases were performed surgical resection due to failure absorption after months of anti-TB chemotherapy. Among the resting 30 cases, 73.3% of the patients (22/30) did not get pleural based mass any absorbed although finished enough course of anti-TB treatment; secondly, AFB positive was in

52.4% (22/42) of 42 cases within pleural based mass and MTB DNA positive was in 57.1% (24/42) of them; what is more, cases with pleural based mass in larger size (>3 cm) had more possibility (90.9%, 20/22) of not being absorbed than those with pleural based mass in smaller size (≤ 3 cm) (9.1%, 2/22), implying the poor outcome of cases once occurring the pleural based mass especially the larger lesions.

For further explore the characteristics of pleural base mass, we observed its location via surgical resection and pathological findings, we observed only 58.3% of “pleural based mass” were located on pleura, 41.7% of “pleural based mass” were actually located at lung parenchyma, which suggested that pleural based mass was observed by imaging methods, which actually were partly located at pleura and partly located in lung, indicating pulmonary lesions closed to the pleura and involvement with pleural TB.

We further observed the pleural based mass through pathological findings on biopsy specimens, they were three pathologically types: granulomatous inflammation type, fibrous hyperplasia type and necrosis type. The basic pathological change of TB was necrotizing granulomatous inflammation with varying numbers of accompanying non-necrotizing granulomas [13,14]. Our study showed granulomatous inflammation was the main type in pleural based mass (81.0%). However, the pathological morphology is various in different cases. MTB with strong virulence can cause massive necrosis without any granulomas in patients with hypo-immunity, and 11.95 of cases were as this type (necrosis type) in the present study. Despite two above pathological types, we found 7.1% of patients were exhibited as fibrous hyperplasia, which was thought to be more common in strong immunity environment.

We speculated pleural based mass was likely to be associated with treatment failure because MTB was positive within the lesions although patients had taken enough course of chemotherapy. How to treat the patients once occurring pleural based mass, our observation indicated that strengthen anti-TB regimens should be required because majority of pleural based masses were tuberculoma with positive MTB or AFB detected within lesions, majority of cases had treatment failure in absorbing the pleural based mass when they did not change their treatment regimen. Further studies should be designed to explore the optimal regimen for pleural based TB mass occurrence during anti-TB treatment.

In order to answer the question whether drug-resistance play an important role in the occurrence of pleural based mass, we performed the detection of anti-TB drug resistance gene mutation, the results showed that drug- resistance was not the main reason of occurring pleural based mass because only 9.5% of cases were detected having drug resistant gene mutation.

The occurrence of pleural based mass indicated the pleural TB contradictory change and make the further treatment complicated and bring dilemma. Therefore, exploring the predicted factors of pleural based mass is helpful for physicians to prevent its occurrence. We tested biochemical indexes and cytokines in pleural effusion before the treatment, we found that nine clinical and biochemical factors including LDH, plural thickness, ADA, glucose, t-PA, age, PAI-1, packaged pleural effusion and TGF- β were predictive risk factors of occurring the pleural based mass. Pleural thickness and packaged pleural effusion were indicator of local immune response [15,16]. Increased TGF- β was associated with the occurrence of pleural thickness. Increased PAI-1 and decreased t-PA was associated with pleural

thickness in pleural TB [17,18]. Previous study showed pleural thickness may be associated with lower glucose and higher ADA in pleural effusion [19-21]. Therefore, the present results regarding to higher ADA, PAI-1, TGF- β and lower glucose and t-PA associated with pleural based mass should be reasonable. These nine factors were able to help physicians to prevent occurrence of pleural based mass by some measures such as thoroughly drainage of pleural effusion as early as possible, injecting urokinase into packaged pleural effusion to reduce the pleural thickness.

In summary, pleural based mass was common in patients with pleural TB and had one third of occurrence rate, half of them were located in lung, presented as granulomatous inflammation, necrosis or fibrous hyperplasia pathologically. Nearly one half of cases had AFB positive and had lower resistant rate within the lesion, majority of cases did not get any absorbed if did not changing the regimens. Combination of 9 clinical and biochemical factors could be useful for physicians to predict occurrence of pleural based mass.

Declarations

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Author's contributions

L. F. and C. W. designed the research; Z. D. wrote the manuscript; Z. D., C. Y. and L. F. collected the clinical data; L. F., W. S. and S. Z. interpreted the clinical data; W. Z. and Z. D. analyzed the data.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the ethical guidelines of the institutional review board of Shanghai Pulmonary Hospital, Tongji University (project approval No. K16-131). All participants gave

written consent for use of their clinical information and tissue samples for research purposes. Specimens were anonymized.

Consent for publication

All authors have read the final version of the manuscript and agreed with the content and have agreed to be a co-author on this manuscript.

Competing interests

The authors have stated that they have no conflicts of interest.

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References

1. Organization GWH. Global tuberculosis report 2019. Geneva: World Health Organization; 2019.
2. Ruan SY, Chuang YC, Wang JY, et al. Revisiting tuberculous pleurisy: pleural fluid characteristics and diagnostic yield of mycobacterial culture in an endemic area. *Thorax*. 2012;67(9):822-7.
3. Porcel JM. Advances in the diagnosis of tuberculous pleuritis. *Ann Transl Med*. 2016;4(15):282.
4. Tang SJ, Xiao HP, Chen G, et al. [Clinical, pathological and radiological characteristics of 83 cases of pleural tuberculoma]. *Zhonghua Jie He He Hu Xi Za Zhi*. 2009;32(4):262-5.
5. Ariyurek OM, Cil BE. Atypical presentation of pleural tuberculosis: CT findings. *Br J Radiol*. 2000;73(866):209-10.
6. Hwang SM, Rho JY, Yoo SM, Jung HK, Cho SH. Atypical pleural tuberculosis presenting as an isolated pleural tuberculoma. *Acta Radiol*. 2012;53(1):49-52.
7. Patel A, Choudhury S. Pleural tuberculosis presented as multiple pleural masses: An atypical presentation. *Lung India*. 2013;30(1):54-6.
8. Choi YW, Jeon SC, Seo HS, et al. Tuberculous pleural effusion: new pulmonary lesions during treatment. *Radiology*. 2002;224(2):493-502.

9. World Health Organization (WHO). Treatment of tuberculosis: guidelines-4th ed. WHO/HTM/TB/2009
10. Tuberculosis Coalition for Technical Assistance. International Standards for Tuberculosis Care (ISTC). The Hague: Tuberculosis Coalition for Technical Assistance, 2006.
11. Barbas CS, Cukier A, de Varvalho CR, Barbas Filho JV, Light RW. The relationship between pleural fluid findings and the development of pleural thickening in patients with pleural tuberculosis. *Chest*. 1991;100(5):1264-7.
12. Mazieres J, Brugger W, Cappuzzo F, et al. Evaluation of EGFR protein expression by immunohistochemistry using H-score and the magnification rule: re-analysis of the SATURN study. *Lung Cancer*. 2013;82(2):231-7.
13. El-Zammar OA, Katzenstein AL. Pathological diagnosis of granulomatous lung disease: a review. *Histopathology*. 2007;50(3):289-310.
14. Ohshimo S, Guzman J, Costabel U, Bonella F. Differential diagnosis of granulomatous lung disease: clues and pitfalls: Number 4 in the Series "Pathology for the clinician" Edited by Peter Dorfmueller and Alberto Cavazza. *Eur Respir Rev*. 2017;26(145).
15. Philip-Joet F, Alessi MC, Philip-Joet C, et al. Fibrinolytic and inflammatory processes in pleural effusions. *Eur Respir J*. 1995;8(8):1352-6.
16. Tucker TA, Jeffers A, Alvarez A, et al. Plasminogen activator inhibitor-1 deficiency augments visceral mesothelial organization, intrapleural coagulation, and lung restriction in mice with carbon black/bleomycin-induced pleural injury. *Am J Respir Cell Mol Biol*. 2014;50(2):316-27.
17. Gerogianni I, Papala M, Tsopa P, et al. Could IFN-gamma predict the development of residual pleural thickening in tuberculous pleurisy? *Monaldi Arch Chest Dis*. 2008;69(1):18-23.
18. Seiscento M, Vargas FS, Antonangelo L, et al. Transforming growth factor beta-1 as a predictor of fibrosis in tuberculous pleurisy. *Respirology*. 2007;12(5):660-3.
19. Darooei R, Sanadgol G, Gh-Nataj A, et al. Discriminating Tuberculous Pleural Effusion from Malignant Pleural Effusion Based on Routine Pleural Fluid Biomarkers, Using Mathematical Methods. *Tanaffos*. 2017;16(2):157-65.
20. Haro M, Ruiz Manzano J, Morera J, Gallego M, Manterola JM, Ribas J. [Analysis of 90 cases of pleural tuberculosis in relation to adenosine deaminase levels]. *Med Clin (Barc)*. 1997;108(12):452-4.
21. Krenke R, Safianowska A, Paplinska M, et al. Pleural fluid adenosine deaminase and interferon gamma as diagnostic tools in tuberculosis pleurisy. *J Physiol Pharmacol*. 2008;59 (Suppl 6):349-60.

Tables

Table 1 Clinical characteristics of pleural based mass

Pleural based mass	cases (n=42)	Percentage (%)
Number (n)		
1	27	64.3
2	11	26.2
>=3	4	9.5
Size (in diameter)		
<1cm	0	9.5
1-3cm	0	9.5
>3cm	34	81.0%
Occurrence time(mo)		
<2	6	14.3
2-4	16	38.1
4-6	20	47.6

Table 2 Comparison of clinical factors between patients with pleural based mass (n=42) and patients without pleural based mass (n=80)

Demographic indices	pleural based mass	no pleural based mass	<i>P</i> Value
Age, y	29(22-47)	42(27-59)	0.001*
Male	29(69.0%)	52(65.0%)	0.341
Clinical factors			
Plural thickness	33(78.6%)	21(26.3%)	0.001*
Pulmonary TB	28(66.7%)	48(60.0%)	0.108
Pleural adhesion	20(47.6%)	15(18.8%)	0.001*
Culture positive (pleural)	4(9.5%)	4(5.0%)	0.247
Culture positive (sputum)	4(9.5%)	7(8.8%)	0.825
Packaged pleural effusion ^b	20(47.6%)	15(18.8%)	0.001*

MTB=Mycobacterium tuberculosis

* $P < 0.0$

Table 3 Biochemical tests and cytokines in pleural effusion between patients with pleural based mass and patients without pleural based mass

Index	pleural based mass (mean, range)	no pleural based mass (mean, range)	<i>P</i> Value
Biochemical tests in pleural effusion			
ADA (IU/L) ^c	69.55(60.075-83.675)	56.1(44.625-64.700)	0.001*
LDH (IU/L) ^c	530(359.75-715.5)	318(248-419.75)	0.001*
Glucose (mmol/L)	4.7(3.4-5.8)	4.9(4.625-6.200)	0.008*
Protein (g/L)	50(45-54)	47.0(42-53.75)	0.126

Cytokines			
INF- γ (μ g/L)	3.918(0.992-5.491)	2.458(0.958 -5.669)	0.806
TGF- β (μ g/L)	20.021(15.777-26.265)	16.386(14.363-23.423)	0.044*
PAI-1(μ g/L)	241.014(191.213-320.184)	187.152(134.645-297.537)	0.048*
t-PA(μ g/L)	1.733(1.069-2.876)	3.025(1.832-4.852)	0.024*
PAI-1/t-PA	135.06(36.876-286.603)	58.92(21.64-131.19)	0.012*

* $P < 0.05$

Table 4 MTB drug resistance detections in patients with pleural based mass (n=42)

Type of MTB drug resistance	Cases (n)	Percentage (%)
Isoniazid resistance	2	4.8
Rifampicin resistance	1	2.4
Multidrug resistance of for isoniazid, rifampicin and streptomycin	1	2.4
Total	4	9.5

Table 5 Status of pleural based mass with different diameters after one year's chemotherapy

Status of pleural based mass	>3cm	1-3cm	<1cm	Total
Completely absorbed	0	1	3	4
Partially absorbed	2	1	1	4
Stabilization	20	2	0	22
Total	22	4	4	30

Table 6 Value of clinical and laboratory indexes of pleural effusion in predicting occurrence of pleural based mass

Index	AUC Value	Best Cutoff Value
Age	0.651	32.5(y)
Glucose	0.621	4.75(<i>mmol/L</i>)
ADA	0.710	62.9(<i>UI/L</i>)
LDH	0.745	461.5(<i>UI/L</i>)
TGF- β	0.635	15.235($\mu\text{g/L}$)
PAI-1	0.632	180.720($\mu\text{g/L}$)
PAI-1/t-PA	0.668	98.972
t-PA	0.651	2.875($\mu\text{g/L}$)

Figures

Figure 1

Occurrence and change of pleural based mass was observed by Chest CT. A Massive pleural effusion in the right side of the chest. B It was clear in the right side of the chest after drainage of pleural effusion and initiated the chemotherapy. C The occurrence of a mass closed to the right plural after 4 months of s chemotherapy. D Pleural based mass resected by surgery was found no recurrence in a year's follow-up,

Figure 2

Flow diagram of included participants

Figure 3

Surgical findings of MSP. A Pleural based mass was located in lung, and one side of boundary was close to the pleura. B Pleural based mass was found on pleura adjacent to lung parenchyma. C Pathological morphology of case in the figure B, mass was based on pleura, and there was a clear boundary between pleural based mass and lung parenchyma (black circle).

Figure 4

Pathological subtypes of pleural based mass. A Granulomatous inflammation type: composed of inflammatory cells, epithelioid histiocytes, Langhans giant cells and necrosis. HE stain, *100 B Fibrous hyperplasia type: lesion mainly consisted of fibroblasts and fibrous proliferation. HE stain, *100 C Necrosis type: necrosis was dominantly occupied in the lesion. HE stain, *100

Figure 5

Fagan's nomogram for the 9 tests of 122 cohort. Which take in sequence of with LDH, plural thickness, ADA, GLU, t-PA, age, PAI-1, packaged pleural effusion, TGF- β .