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Distinguishing tuberculosis pleural effusion from parasitic pleural effusion using pleural fluid characteristics
A case control study

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Abstract
Tuberculosis pleural effusion (TPE) and parasitic pleural effusion (PPE) present with similar clinical manifestations. We evaluated the pleural fluid features of TPE and PPE.

A total of 76 patients with pleuritis, including 25 patients with TPE and 51 patients with PPE were retrospectively studied. Pleural fluid was sent for analyses of protein, cytology, cell count, acid fast bacilli (AFB) staining, Gram stain, culture, sensitivity, and adenosine dehydrogenase (ADA).

The proportion of eosinophilia present in the PPE group was significantly higher than that in the TPE group ($P < .001$). However, the proportion of lymphocytes found in the TPE group was significantly higher than that in the PPE group ($P < .001$). The mean level (SD) of ADA was 46.99 ± 22.09 U/L in the TPE group and 39.08 ± 23.03 U/L in the PPE group. No difference was detected between the study groups in terms of the ADA level of the pleural fluid ($P > .05$).

When the results of pleural fluid testing reveal marked eosinophilia and a low proportion of lymphocytes, physicians should consider a diagnosis of PPE, especially for patients who live in or have traveled to endemic areas.

Abbreviations: ADA = adenosine dehydrogenase, PPE = parasitic pleural effusion, TB = tuberculosis, TPE = tuberculosis pleural effusion, ZN = Ziehl Neelsen.

Keywords: parasitosis, pleural effusion, tuberculosis

1. Introduction

Tuberculous pleural effusion (TPE) is one of the most common forms of extrapulmonary tuberculosis.[1] On a global scale, tuberculosis (TB) remains one of the most frequent causes of pleural effusion.[2] TPE occurs in approximately 5% of patients with *Mycobacterium tuberculosis* infection.[3] In the same way, pleural effusion can also be caused by some parasitic infections, such as paragonimiasis, infections by amoeba, and *Echinococcus granulosus*. With increasing travel and migration, the rates of parasitic pleural diseases are also increasing.[4] Parasitic pleural

effusion (PPE) and TPE present with similar clinical manifestations, but the prognosis and therapy for each are quite different. Therefore, rapid differentiation of the 2 types is important. However, the differential diagnosis of PPE and TPE remains a challenge.

The gold standard for diagnosing TPE includes the Ziehl Neelsen (ZN) acid-fast bacilli stain and a laboratory culture of *Mycobacterium tuberculosis*. However, *Mycobacterium tuberculosis* is rarely observed on direct examination by acid fast bacilli (AFB) staining in pleural fluid. Less than 30% of cultured pleural fluid samples are positive for *Mycobacterium*.[2] Furthermore, laboratory culture of *Mycobacterium tuberculosis* requires 8 weeks to yield a positive result.[5] The other method considered for diagnosing TPE is a pleural biopsy, which is an invasive procedure that requires a high level of expertise.[6] For parasitic pleural diseases, the basic and most easily available diagnostic tool is finding ova in the pleural fluid. However, although eggs may be present in the pleural fluid,[7] they can be hard to observe.[8] We find that the pleural fluid features of TPE and PPE are quite different clinically. Therefore, we retrospectively evaluated the pleural fluid features of TPE and PPE in an attempt to help differentiate them.

2. Materials and methods

A total of 76 patients with pleural effusion, including 25 patients diagnosed with TPE and 51 patients with PPE admitted to the West China Second University Hospital between January 2011 and December 2017, were retrospectively studied. The children in the PPE group were further grouped according to etiology of PPE. The study was undertaken to compare the pleural fluid features between the TPE and PPE groups and to identify the following:

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the pleural fluid albumin/blood albumin ratio, total protein and albumin levels, adenosine dehydrogenase (ADA) level, and the proportions of eosinophils and lymphocytes. These characteristics were studied for clues to the differences between TPE and PPE. TPE was diagnosed if ZE stains or Lowenstein-Jensen cultures of pleural fluid, sputum or pleural biopsy specimens were positive or if granulomas were present in the parietal pleural biopsy specimens. The diagnoses of PPE were based on seropositivity and/or the detection of eggs (in sputum, aspirated pleural effusion, or feces) as well as pleuropulmonary involvement. The exclusion criteria for this study included

1. patients were suspected of having both tuberculosis and parasitic diseases,
2. underlying diseases such as bacterial pneumonia and rheumatic disease were present,
3. age was greater than 14 years, and
4. disease history or clinical data were incomplete.

The study protocol was approved by local ethics committee (Research Ethics Review board of Sichuan University).

2.1. Investigations

A complete hemogram and tests for liver function were completed, and pleural fluid was sent for analyses of protein, cytology, cell count, AFB staining, Gram stain, culture, sensitivity, and ADA.

2.2. Statistical analysis

The statistical analysis was performed using IBM SPSS Statistics 20.0. Continuous variables were expressed as the mean ± standard deviation. The Pearson chi-square test was used for categorical variables. The independent samples t test and paired t test were used for continuous variables. The Pearson correlation test was used to find a correlation. A 2-sided P value ≤.05 was considered statistically significant.

3. Results

A total of 76 patients (54 males and 22 females) were included in the study. The TPE group consisted of 18 males and 7 females; the mean (SD) age was 10.32 ± 3.67 years. The PPE group consisted of 36 males and 15 females; the mean (SD) age was 6.99 ± 3.22 years. The mean age of the TPE group was significantly higher than that of the PPE group ($P < .001$). There was no statistically significant difference between the 2 groups in sex distribution ($P > .05$). Distribution of the etiological causes in the PPE patients are given in Table 1. Paragonimiasis is the most common cause of PPE. In TPE group, effusion was detected in 6 patients (24%) on both sides and in 19 patients (76%) on 1 side. The pleural fluid features of TPE and PPE are given in Table 2. In the PPE group, pleural effusion was most commonly unilateral (72.5%). No significant difference in the ratio of lymphocytes in the blood was found between the 2 groups ($P > .05$). The mean pleural fluid L/N ratio of TPE was 4.91 and the mean pleural fluid L/N ratio of PPE was 0.50. The pleural fluid albumin/blood albumin ratio and the total protein and albumin levels in effusion were not significantly different between the TPE group and PPE group ($P > .05$). The mean level (SD) of ADA was 46.99 ± 22.09 U/L in the TPE group and 39.08 ± 23.03 U/L in the PPE group. No difference was detected between the study groups in terms of

Table 1

The characteristics of TPE and PPE.

	TPE	PPE	P
Mean (SD) age	10.32 ± 3.67 years	6.99 ± 3.22 years	.001
Male/Female	18/7	36/15	.05
Position of pleural effusion (unilateral/bilateral)	19 (76%)/6 (24%)	37 (72.5%)/14 (27.5%)	.05
Etiology	—		
Paragonimiasis (Paragonimus westermani)	—	41	
Myiasis (Larvae of flies)	—	6	
Schistosomiasis (Schistosoma)	—	2	
Cysticercosis (Cysticercus)	—	1	
Clonorchiasis (Clonorchis sinensis)	—	1	

PPE = and parasitic pleural effusion, TPE = tuberculosis pleural effusion.

ADA level of the pleural fluid ($P > .05$). The mean blood eosinophil ratio of PPE compared to TPE was $37.57\% \pm 21.31\%$ vs $2.02\% \pm 2.86\%$. The eosinophil proportion of the pleural fluid in the PPE group was significantly higher than that in the TPE group ($P < .001$). However, the lymphocyte proportion in the TPE group was significantly higher than that in the PPE group ($P < .001$).

4. Discussion

The purpose of this study was to distinguish between the pleural effusion of tuberculosis and that caused by parasitic infection. In our study, paragonimiasis was the most common cause of PPE. According to relevant reports in the literature, the prevalence of pleural effusion in patients with pleuropulmonary paragonimiasis varies greatly.[8,9] Misdiagnosis of paragonimiasis and TB seems to be common throughout the world.[10,11] Distinguishing between paragonimiasis and tuberculosis can be sometimes difficult especially in area where tuberculosis and paragonimiasis coexist.[12]

All patients with a newly discovered pleural effusion should undergo thoracentesis. In this study, we found that the major differences in the pleural fluid of patients with pleural tuberculosis and those with pleuropulmonary paragonimiasis are the proportions of lymphocytes and eosinophils. In our study, the mean blood eosinophil ratio of PPE was significantly higher than TPE ($37.57\% \pm 21.31\%$ vs $2.02\% \pm 2.86\%$). The majority of patients with PPE had low levels of lymphocytes ($7.27\% \pm 5.61\%$) and significant eosinophilia ($78.13\% \pm 21.60\%$) in their pleural fluid. These are characteristic findings of pleural fluid analysis that can contribute to the diagnosis of PPE. Other studies have shown that most patients with pleuropulmonary paragonimiasis have significant eosinophilia in their pleural

Table 2

The pleural fluid features of TPE and PPE.

Group	PPE	TPE	P value
Eosinophil ratio	78.13% ± 21.60%	1.67% ± 2.87%	.000
Lymphocyte ratio	7.27% ± 5.61%	82.08% ± 23.67%	.000
ADA	39.08 ± 23.03	46.99 ± 22.09	.357
Total serum protein	76.71 ± 9.77	67.98 ± 16.86	.006
Pleura fluid albumin/ Blood albumin ratio	1.11 ± 0.30	1.74 ± 1.26	.097
Nucleated cell count	12,006 ± 14,590	1387 ± 1544	.000

ADA = adenosine dehydrogenase, PPE = parasitic pleural effusion, TPE = tuberculosis pleural effusion.

fluid.[13] Eosinophilic pleural fluid is a very important characteristic of pleuropulmonary paragonimiasis. It can also be found with other parasitic pleural effusions, such as echinococcosis.[14] The epidemiological contact history, and the pathogenic inspection are needed to further distinguish them. But we should also note that it lacks specificity and has been described in many different diseases, including nonparasitic diseases such as TB, lymphoma and cancer.[15] Although eosinophilia may be prominent in the early stage but relatively low eosinophilia in the late stage,[16] its presence should increase the suspicion for paragonimiasis when we differentiate the cause of pleural effusion.[9]

The determination of ADA is an inexpensive and easy test that we now consider in the early routine evaluation of patients with pleural effusion. ADA is an essential enzyme in purine nucleoside metabolism, and its activity is related to the infiltration of T lymphocytes in pleura and pleural effusion.[17] Tuberculosis involves a T-lymphocyte-mediated cellular immune response; therefore, the level of ADA increases accordingly. ADA has been reported to be a sensitive and specific marker for diagnosing TPE. A meta-analysis included 63 studies reveals that the sensitivity and specificity of ADA in the diagnosis of pleural TB were 92% and 90%.[18] A meta-analysis review of 40 articles on ADA in pleural fluid shows that test results for ADA with a cut-off value >40 U/L was 92.2% for both sensitivity and specificity.[19] However, elevated levels of ADA in pleural fluid can also be caused by autoimmune disease, emphysema.[20] In this study, the mean level (SD) of ADA was 46.99 ± 22.09 U/L in TPE and 39.08 ± 23.03 U/L in PPE. The ADA levels of the TPE group were higher than those of the PPE group. However, no difference was detected between the study groups in terms of ADA levels in the pleural fluid ($P > .05$). This indicates that the single application of ADA to identify TPE may be not reliable. Research shows that combined use of the total ADA in pleural fluid of >40 U/L with a pleural fluid L/N ratio >0.75 is a more efficient means of diagnosing TPE than the use of ADA alone.[21] In their study, a total number of 120 patients with exudative pleural effusion were analyzed. Total ADA was found to be >40 U/L in all cases of TB effusion. All cases of TB effusion were lymphocyte predominant with L/N ratio > 0.75 and non-tuberculous etiology L/N ratio was <0.75 (P value <.0001). In our article, the mean pleural fluid L/N ratio of TPE was >0.75 (4.91) and the mean pleural fluid L/N ratio of PPE was 0.50. The combined use of the results of pleural fluid testing in terms of lymphocyte and eosinophil counts and patient histories were helpful in diagnosing pleuropulmonary paragonimiasis despite the elevated ADA levels.

This study has some limitations. The primary limitation is that it is a retrospective study. Selection bias possibly influenced the significance of our findings. The second limitation is that the study was from a single institution and had a small sample size, which limits the extension of our findings to the general population. A large-scale study is needed in the future.

In conclusion, pleuropulmonary paragonimiasis with pleural effusion may be confused with TPE. In patients with unexplained pleural effusion, pleural fluid should be obtained by thoracentesis. The single application of ADA to identify TPE may be not reliable. However, the mean eosinophil ratio and L/N ratio of PPE (in blood or pleura fluid) was significantly different from TPE. When the results of pleural fluid testing reveal a marked proportion of eosinophilia, pleuropulmonary paragonimiasis should be considered. When the results of pleural fluid testing reveal a marked L/N ratio, TPE should be considered. The epidemiological contact history should be inquired and the pathogen should be sought repeatedly to identify the diagnosis. Biopsy or diagnostic therapy can be taken if necessary.

Author contributions

Shuai Tong conceptualized and drafted the manuscript. Shuai Tong, Yu Zhu and Chaomin Wan drafted sections of the manuscript, reviewed and revised the manuscript, and approved the final manuscript as submitted. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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