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Clinicopathologic characteristics of pediatric tuberculous pleural effusion: a retrospective analysis of 112 consecutive cases

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Abstract. – OBJECTIVE: The aim of this study was to describe the clinicopathologic characteristics of pediatric tuberculous pleural effusion (TPE) patients to make an accurate diagnosis.

PATIENTS AND METHODS: Pediatric TPE patients who admitted to Shandong Provincial Chest Hospital were retrospectively reviewed from March 2006 to April 2015.

RESULTS: 112 pediatric TPE patients were enrolled. The mean age was 11.6 ± 3.2 years. 60 (53.6%) patients were diagnosed as TPE, 40 (35.7%) were TPE+Pulmonary tuberculosis (PTB). 96 (85.7%) patients had fever (> 37°C), 81 (72.3%) had dyspnea, 63 (56.3%) had cough. Radiological test results showed effusions on the right side in 58 patients (51.8%), on the left side in 50 patients (44.6%), and on both sides in 4 patients (3.6%). 6 (5.4%) patients were acid-fast bacilli (AFB) smear–positive. 16 (14.3%) PCR positive patients were identified. 41 (36.6%) TB patients were culture-positive. Almost all effusions (99.1%) had the biologic characteristics of exudates. In 91.2% of the effusions, more than 50% of leukocytes were lymphocytes. Pleural adenosine deaminase (40 U/L) was positive in 74.5% of the patients, and erythrocyte sedimentation rate was raised in 84.1%.

CONCLUSIONS: The usefulness of routine microbiological tests to diagnose pleural TB is limited by its poor sensitivity. Further studies should be performed to validate new techs and assays for pediatric TPE.

Key Words:
Children, Pleural effusion, Diagnosis, Tuberculosis.

Introduction

Tuberculosis (TB) is among the top 10 causes of death among children worldwide. According to World Health Organization (WHO) estimates, about one million children annually develop TB worldwide, accounting for about 11% of all TB cases[1,2]. However, children with TB are given low priority in most national health programs and are neglected in this epidemic[3]. TB can occur at different anatomic sites of the human body. The most common site of TB is pleura but pulmonary, with an incidence of 4.9%[4,5].

The diagnosis of pleural TB in children is based on medical history, clinical findings, chest x ray, tuberculin skin test (TST), microbiological tests (acid-fast bacilli (AFBs) in smear or mycobacterial culture), pleural effusion (PE) biochemical analysis and response to anti-TB treatment[6-8]. Due to the paucibacillary nature of pediatric TB, the AFB positivity was low and culture was a moderate diagnostic test, which takes 6-12 weeks[9,10]. Although pleural adenosine deaminase (ADA) was evaluated as a good biomarker in the diagnosis of tuberculous pleurisy for adults[11], the ADA that was associated with pleural *mycobacterial tuberculosis* burden may have limited diagnostic value in pediatric patients[12]. Recent technological advancements in diagnosis of TB in adults show limited diagnostic value in children. Such as, T-SPOT.TB assay have poor diagnostic accuracy in pediatric TB[13]. Although Interferon-γ and IP-10 release assays performed well in adults, the tests exhibited an equally poor performance in diagnosing active TB in children[14].

In recent studies[15,16], the multi-drug resistance (MDR) rates in children were 22%-80%. Late and inadequate treatment is an important factor for the high MDR-TB rate in children. To date, limited systematic research is available about pathologic information of pediatric TPE. We examined 112 consecutive pediatric TPE cases at Shandong Provincial Chest Hospital since 2006, and analyzed clinicopathologic features retrospectively to make a prompt diagnosis.

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Patients and Methods

This retrospective study was approved by the Shandong Provincial Chest Hospital Review Board. Patient records/information were anonymized and de-identified prior to analysis. The inpatient data banks were screened for pediatric cases with the diagnosis of TPE using key words such as children, tuberculosis, pleural, and effusion.

Clinical analysis included the age, gender, and medical history of each patient; clinical features; lab examination and the time before hospital admission. All PE sample was obtained with a needle at the same time as thoracocentesis, then was processed for AFB detection (Auramine O stain), mycobacterial culture (Bact/Alert 3D, Biomerieux Durham, NC, USA), ADA activity (Maker, Sichuan, China), TB real time-PCR analysis (TB RT-PCR kit, DAAN, China; LightCycler®480, Roche, Mannheim, Germany), biochemical tests (total protein, total bilirubin, lactate dyhydrogenase, and amylase) and pleural cytology. White blood cell, neutrophil and lymphocyte counts were performed on an XT 1800 Sysmex automated haematology analyser (Sysmex Corporation, Kobe, Japan).

Statistical Analysis

Statistical analysis was carried out using SPSS 17.0 software. Data were expressed as mean ± standard deviation (SD). Comparisons of data between different groups were performed using Kruskal-Wallis or Mann-Whitney tests. Associations between clinicopathologic features and age were assessed with Spearman's correlation coefficient analysis. $p < 0.05$ was considered as statistically significant.

Results

Between March 2006 and April 2015, 112 pediatric patients with a diagnosis of TPE were identified at our hospital, and then were grouped into Group 1 (0-6 years old, 10 (8.9%) patients, 80% of these were male), Group 2 (7-12 years old, 40 (35.7%) patients, 68% of these were male) and Group 3 (13-15 years old, 40 (35.7%) patients, 55% of these were male). The mean age was 11.6 ± 3.2 years for all patients, 4.7 ± 1.5 years for Group 1, 9.8 ± 1.8 years for Group 2, and 14.0 ± 0.9 years for Group 3. Clinicopathologic features are shown in Table I.

The time before hospital admission reflecting diagnostic delay was evaluated. The average time was 33.1 ± 61.9 days for all patients, 20.6 ± 8.7 days for Group 1, 19.9 ± 19.8 days for Group 2, 43.6 ± 80.3 days for Group 3.

In our study, 60 (53.6%) patients were diagnosed as TPE, 40 (35.7%) were TPE+ pulmonary TB (PTB), 8 were TPE+extra-pulmonary TB (EPTB), 4 were TPE+PTB+EPTB. TPE and TPE+PTB were comprised the majority of each group. In Group 1, 2 and 3, TPE accounted for 60%, 50% and 54.8%, respectively; TPE+PTB accounted for 30%, 42.5% and 32.3%, respectively.

96 (85.7%) patients had fever (> 37°C), 81 (72.3%) had dyspnea, 63 (56.3%) had cough. Group 2 and 3 had similar results as in all patients. But in Group 1 only 4 (40%) patients had dyspnea. This may contribute to poor communication skill of younger children. Radiological test results showed effusions on the right side in 58 patients (51.8%), on the left side in 50 patients (44.6%), and on both sides in 4 patients (3.6%). 17 patients had contact history with patients with TB with active disease, 7 patients were in Group 2, 10 were in Group 3.

6 (5.4%) patients were AFB smear-positive. 16 (14.3%) PCR positive patients were identified in Group 2 (7 patients) and Group 3 (9 patients). 41 (36.6%) TB patients were culture-positive, 2 in Group 1, 15 in Group 2 and 24 in Group 3.

Almost all effusions (99.1%) had the biologic characteristics of exudates, only one cases was categorized as transudate (Lights' criteria). In 91.2% of the effusions, more than 50% of leukocytes were lymphocytes. Pleural ADA (40 U/L) was positive in 74.5% of the patients, and ESR (male: 0-15 mm/h, female: 0-20 mm/h) was raised in 84.1%.

There were significant differences in WBC ($\chi^2 = 10.33$, $p < 0.01$) and lymphocyte ($\chi^2 = 11.89$, $p < 0.01$) counts among the three groups. This should be related with the influence of age on WBC and lymphocyte counts.

Mann-Withney test showed that female children had significant higher pleural levels of glucose ($p < 0.01$), and lower pleural levels of ADA ($p < 0.01$) and LDH ($p < 0.05$) than of male. There was low correlation between age and, pleural effusion levels of total bilirubin ($r = 0.225$, $p < 0.05$), LDH ($r = -0.278$, $p < 0.01$) and WBC ($r = 0.234$, $p < 0.05$); WBC ($r = -0.267$, $p < 0.01$) and lymphocyte ($r = -0.312$, $p < 0.01$).

Table I. The characteristics of Pediatric TPE.

	Group 1 (0-6 years old)	Group 1 (7-12 years old)	Group 1 (13-15 years old)	Total
Number	10	40	62	112
Number	10	40	62	112
Sex, Male (%)	80%	68%	55%	62%
Age (years)	4.7 ± 1.5	9.8±1.8	14.0±0.9	11.6±3.2
Disease				
TPE	6 (60.0%)	20 (50%)	34 (54.8%)	60 (53.6%)
TPE+PTB	3 (30.0%)	17 (42.5%)	20 (32.3%)	40 (35.7%)
TPE+EPTB	1 (10.0%)	3 (7.5%)	4 (6.5%)	8 (7.1%)
TPE+PTB+EPTB	0	0	4 (6.5%)	4 (3.6%)
Symptom				
Fever	10 (100.0%)	34 (85.0%)	52 (83.9%)	96 (85.7%)
Dyspnea	4 (40.0%)	31 (77.5%)	46 (74.2%)	81 (72.3%)
Cough	6 (60.0%)	25 (62.5%)	32 (51.6%)	63 (56.3%)
Time before hospital admission (days)	20.6 ± 8.7	19.9 ± 19.8	43.6 ± 80.3	33.1 ± 61.9
Contact history	0	7 (17.5%)	10 (16.1%)	17 (15.2%)
Effusion site				
Both	0	1 (2.5%)	3 (4.8%)	4 (3.6%)
Left	1 (10.0%)	17 (42.5%)	32 (51.6%)	50 (44.6%)
Right	9 (90.0%)	22 (55.0%)	27 (43.5%)	58 (51.8%)
Mycobacterial culture	2 (20.0%)	15 (37.5%)	24 (38.7%)	41 (36.6%)
AFB smear	0	3 (7.5%)	3 (4.8%)	6 (5.4%)
PCR	0	7 (17.5%)	9 (14.5%)	16 (14.3%)
Pleural effusion				
Total Protein (g/L)	46.2 ± 6.9	46.9 ± 8.3	49.3 ± 7.0	48.1 ± 7.5
Total Bilirubin (μmol/L)	8.2 ± 3.4	10.0 ± 6.7	10.2 ± 5.2	9.9 ± 5.7
Glucose (mmol/L)	2.58 ± 1.96	3.66 ± 1.99	3.87 ± 1.54	3.67 ± 1.78
LDH (U/L)	4535 ± 8180	1696 ± 3241	787 ± 791	1481 ± 3336
ADA (U/L)	65.9 ± 33.2	62.2 ± 39.9	54.9 ± 24.6	58.7 ±3 1.8
AMY (U/L)	165 ± 444	28 ± 10	59 ± 198	58 ± 199
WBC (10^6/L)	2.63 ± 2.95	2.85 ± 2.09	4.39 ± 3.34	3.69 ± 2.98
Lymphocyte (%)	90.8 ± 7.9	79.1 ± 25.7	83.0 ± 20.2	82.1 ± 21.7
Blood				
WBC (10^9/L)	13.1 ± 8.2	8.2 ± 4.2	6.8 ± 2.5	7.92 ± 4.32
Neutrophil (10^9/L)	8.34 ± 7.39	5.34 ± 3.71	4.46 ± 2.19	5.13 ± 3.64
Lymphocyte (10^9/L)	3.29 ± 2.22	1.75 ± 0.86	1.45 ± 0.58	1.73 ± 1.06
Monocyte (10^9/L)	1.37 ± 1.04	1.01 ± 0.62	0.94 ± 0.52	1.01 ± 0.63
ESR	46.9 ± 30.6	53.5 ± 26.3	42.0 ± 26.4	46.6 ± 27.1

TPE: tuberculous pleural effusion; PTB: pulmonary tuberculosis; EPTB: extra-pulmonary tuberculosis; AFB: acid-fast bacilli; LDH: lactate dehydrogenase; ADA: adenosine deaminase; AMY: amylase; WBC: white blood cell; ESR: erythrocyte sedimentation rate.

Discussion

TB contributes significantly to child morbidity and mortality. The World Health Organization (WHO) estimates that 550 000 children developed TB in 2013[6], but recent modeling studies suggest that the burden could be much higher[17,18]. Diagnosing pediatric TB is challenging, because of non-specific symptoms, difficulties in obtaining samples for microbiological examination and paucibacillary nature of their disease[19]. Few studies have described clinicopathologic features of pediatric TPE[6,20]. We reviewed pediatric TPE cases admitted to our hospital, and analyzed clinicopathologic features retrospectively. To our knowledge, the study is the first time that clinical features of pediatric TPE have been described on such a large scale.

In our work, the majority of patients (53.6%) had primary infection involving the pleura, 35.7% of patients get PTB and TPE. Meanwhile, only 17 patients with recent tuberculosis contact were identified. The results supported that TPE developed from PTB wasn't the major source of

pediatric TPE. Usually pleurisy with effusion develops in 2-38% of children with primary pulmonary tuberculosis[6,19,21].

In a report on clinical spectrum of pediatric TPE, fever (12/92%), cough (9/69%) and malaise (6/46%) were the most common symptoms[6]. Our study showed that fever (85.7%) was the most common symptoms in the study, following dyspnea (72.3%) and cough (56.3%). Few cases had malaise (data not shown). However, only 4 (40%) patients had dyspnea in Group 1 with younger age, this may contribute to poor communication skill of younger children. It was reported that effusions on the right side in 55.9% of adult TPE patients, on the left side in 42.5% of patients, and on both sides in 1.6% of patients[17]. Pediatric patients also have the tendency for TPE to occur preferentially on the right side (right *vs.* left, 51.8% *vs.* 44.6%), bilateral effusions are rare (3.6%).

The paucibacillary nature of pleural TB reduces the yield of positive stain and culture for acid-fast bacillus. Usually, the AFB positivity in the fluid is < 20% and fluid culture grows AFB in 18-38% of samples, which takes 6-12 weeks[9]. Comparing for adults, the sensitivity of AFB and culture was lower in detection of TPE for pediatrics[17]. The results was similar to that found in our previous study or others' reports in pediatric tuberculosis, suggesting that a need to find better biomarker or technologies in detection of pediatric TPE[10]. PCR technique can be a valuable diagnostic tool in the detection of *M. tuberculosis* from extra-pulmonary specimens for pediatrics[22,23]. Mishra et al showed that PCR for *Mycobacterium tuberculosis* was positive in 74% of tuberculous effusions, but in our study the PCR had low sensitivity (14.3%). The difference need to be further validated in a prospective study.

Due to increasing ADA in parapneumonic effusions, our previous study showed that pleural ADA wasn't accurate in detection of pediatric TPE[24]. Meanwhile, Recent study showed ADA was associated with pleural *mycobacterial tuberculosis* burden[12]. This may contribute to low positivity of ADA assay in detection of pediatric TPE. However, Light's criteria[25], ESR and pleural effusion lymphocyte proportion may be useful biomarker to differentiating TPE from other causes. Since age was associated with WBC and lymphocyte counts, caution should be used when interpreting elevated WBC and lymphocyte count in pediatric TPE patients.

Although pleural biopsy is a sensitive aid to the diagnosis of pleural tuberculosis in children, in this study pleural biopsies were not obtained because they were deemed higher risk than thoracentesis[18]. It was difficult to assess the utility of diagnostic assays such as IGARs and pleural IFN-γ in this study, as they were performed in few children. For some children, this might have been because TB was not suspected at the time the procedure was performed. In other instances, assays were not available at the time the child was being evaluated.

Conclusions

For detection of pediatric TPE, (1) fever and cough were the most two common symptoms; (2) Due to paucibacillary nature of pleural TB, microbiologic tests showed low positivity, many new techs or biomarkers that have been validated in adults need to be evaluated, such as IGARs, IFN-γ and IP-10[14,26-29]; (3) Light's criteria, ESR and pleural effusion lymphocyte proportion were useful biomarkers to differentiating TPE from other causes; (4) Pleural ADA had limited diagnostic performance; (5) Caution should be used when applying biomarkers that are strong associated with age.

Authors' Contributions

WMS and WXF conceived and designed the study. WJL collected data. ZGW supervised data collection. WJL, ZZQ and WMS have been involved in the analysis and interpretation of data. WMS and WXF wrote the manuscript. All authors read and approved the final manuscript.

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Conflict of Interest

The Authors declare that there are no conflicts of interest.

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