Pediatric Pleural Tuberculosis

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Abstract

Background: Pleural tuberculosis (TB) diagnosis is sometimes controversial because the microbiologic confirmation ratio is very low in pleural fluid. There are few pediatric pleural TB case series in the literature. Methods: We retrospectively evaluated our TB cases below 18 years of age and extracted pleural TB cases. Results: Seven cases with pleural TB were identified. About 42.9% of the patients had isolated pleural TB whereas 57.1% of the patients had accompanying pulmonary TB. Lymphocytic pleural effusion and increased adenosine deaminase (ADA) (>40 U/L) level are found in 85.7% of the patients. Six patients had uncomplicated effusion (transudate) according to Light’s criteria and one had complicated effusion (exudate). Lung decortication was needed in three patients. All patients were given 6 months anti-TB medication and recovered completely. Conclusion: In the lymphocyte-predominant pleural effusion, an increased ADA level highly supported TB disease. The complicated effusion (exudate) in pleural TB is not rule; uncomplicated effusion (transudate) could be seen.

Keywords: Children, exudate, pleura, transudate, tuberculosis

INTRODUCTION

Tuberculosis (TB) remains an important infectious disease worldwide. Diagnosis of TB depends on the combination of compatible symptoms, contact history with active TB, radiological and pathological findings, and results of microbiological tests for Mycobacterium tuberculosis. In childhood, a definitive diagnosis may not be possible because of low bacillus load or the patients’ inability to provide adequate sputum specimens.[1] Pleural TB is reported in 12%–38% of thoracic TB cases in childhood.[2] Pleural TB can develop as a result of T-lymphocyte-related inflammatory response to a ruptured subpleural TB focus. This inflammatory response is type-4 hypersensitivity reaction and results in pleural exudates. There are very few bacilli in the pleural fluid, and this bacillus induces a granulomatous reaction. A pleural TB diagnosis is sometimes controversial because the microbiologic confirmation ratio is very low in pleural fluid. Further, pleural fluid findings in TB are easily confused with other causes of pleural effusion such as atypical pneumonia and malignancies. There are few pediatric pleural TB case series in the literature. Herein, we present our pediatric pleural TB patients.

METHODS

We retrospectively evaluated our TB cases below 18 years of age and extracted pleural TB cases seen between January 2014 and December 2016. Pleural TB diagnoses were divided into two classes as probable or definitive pleural TB. Probable pleural TB was considered in the presence of clinical and radiological findings compatible with TB, absence of neoplastic cells in the pleural fluid, contact history with an adult TB patient and positive tuberculin skin test (TST), QuantiFERON-TB Gold test (QFT) or T-spot test result, and an observed clinical response to anti-TB treatment. Definitive pleural TB was determined in the presence of pleural effusion with bacilli identified in the pleural fluid, sputum or pleural biopsy with acid-fast bacillus (AFB) staining or TB culture, or in the presence of epithelioid cell granulomas and/or caseating granulomas in pleural biopsy. Demographic data, medical and epidemiological history,
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physical examination findings, laboratory test results, TST, QFT and T-spot test results, pathologic examination results, and pleural fluid laboratory examinations and pleural fluid adenosine deaminase (ADA) level were evaluated. Results of the pleural fluid laboratory examination were evaluated according to Light’s criteria.[3] Anti-TB treatment regimen, requirement of video-assisted thoracoscopic surgery (VATS) or open decortication, the period of follow-up, and patient outcomes were recorded.

Results

Of the 65 TB cases, 7 (10.7%) cases with pleural TB (two females, five males) were identified. There were four definitive and three probable TB cases.

The mean age of our patients was 14 ± 1.4 years (minimum: 13; maximum: 15). The duration of complaints was 81.4 ± 61.1 days (minimum: 15; maximum: 180). Symptoms, household contact status, affected lung side, TST, and interferon-gamma-releasing assays (T-spot test and QFT in tube) results are shown in Table 1. Chest X-rays at presentation are shown in Figure 1. Laboratory examination revealed the following: white blood cell count was 8014 ± 1856/mm$^3$ (minimum: 1500; maximum: 10,800), C-reactive protein was (mg/L) 140.5 ± 124.8 mg/L (minimum: 4; maximum: 398), and erythrocyte sedimentation rate was 72.4 ± 30.8 mm/h (minimum: 35; maximum: 130). The chest X-rays of the patients at presentation are shown in Figure 1.

A total of 3 patients (42.9%) had isolated pleural TB whereas 4 (57.1%) had accompanying pulmonary TB. Massive pleural discharge (150–200 cc/day) from the chest tube was observed.

### Table 1: Patient’s symptoms, household contact, affected lung side, tuberculin skin test, and interferon gamma-releasing assays (Tspot test and QuantiFERON-TB Gold in tube) results

|                  | n (%) |
|------------------|-------|
| Symptoms         |       |
| Cough            | 7 (100) |
| Exhaustion       | 1 (14.3) |
| Dyspnea          | 3 (42.9) |
| Fever            | 5 (71.4) |
| Night sweats     | 2 (28.6) |
| Lose appetite    | 3 (42.9) |
| Weight loss      | 3 (42.9) |
| Chest pain       | 2 (26.8) |
| Household contact| 2 (28.6) |
| Lung side        |       |
| Right            | 3 (42.9) |
| Left             | 3 (42.9) |
| Bilateral        | 1 (14.3) |
| TST              |       |
| Positive         | 4 (57.1) |
| Negative         | 3 (42.9) |
| T spot test      |       |
| Positive         | 1 (14.3) |
| Negative         | 0 |
| Not studied      | 6 (85.7) |
| QFT              |       |
| Positive         | 4 (57.1) |
| Negative         | 0 |
| Not studied      | 3 (42.9) |

TST: Tuberculin skin test, QFT: QuantiFERON-TB Gold in tube, TB: Tuberculosis

Figure 1: The chest X-rays of the patients at the presentation are shown: (a) Patient 1, (b) Patient 2, (c) Patient 3, (d) Patient 4, (e) Patient 5, (f) Patient 6, (g) Patient 7
Table 2: Laboratory examination of pleural fluid

| Patient number | pH | Glucose (mg/dL) | Protein (g/dL) | LDH (U/L) | Lymphocyte ratio (%) | ADA (U/L) |
|----------------|----|----------------|---------------|-----------|----------------------|-----------|
| 1              | 7.5| 75             | 5.2           | 469       | 95                   | 50        |
| 2              | 7.6| 60             | 5.9           | 623       | 80                   | 54.2      |
| 3              | 7.33| 88            | 5.4           | 418       | 100                  | 37.5      |
| 4              | 7.4| 71             | 5.2           | 747       | 96                   | 41        |
| 5              | 7.9| 43             | 5.1           | 544       | 85                   | 44.5      |
| 6              | 8.3| 82             | 5.4           | 214       | 80                   | 54        |
| 7              | 7.1| 11             | 5.7           | 3628      | 5                    | 75        |

ADA: Adenosine deaminase, LDH: Lactate dehydrogenase

in six of seven patients (up to total 3500 cc). The pleural fluid laboratory examination results are shown in Table 2.

Mean ADA level in the pleural fluid was 50.8 ± 12.3 U/L, and ADA level was >40 U/L in all except one of our patients (Patient 3) (85.7%). Patient 3 was diagnosed with TB based on massive pleural effusion unresponsive to antibiotics and positive QFT result. Anti-TB treatment was initiated; however, the massive pleural discharge continued. Pleural biopsy was taken for definitive diagnosis of TB, and steroid was initiated; the pleural fluid rapidly recovered.

Sputum/fasting gastric aspirate and pleural fluid AFB staining, mycobacterium polymerase chain reaction (PCR), and culture were negative in all but one patient. Patient 5 had positive mycobacterium PCR test in the pleural fluid. Four patients underwent pleural biopsies, and all revealed caseating chronic granulomatous inflammation.

Lung decortication was needed in three patients. Patient 2 had pleural fluid with septations and insufficient drainage through the tube necessitating VATS. During the VATS procedure, multiple nodules on the pleural surface and intense pleural thickening of nearly 2 cm were seen, and decortication was performed. The patient’s follow-up was uneventful.

Patient 5 was diagnosed with pleural TB, and anti-TB treatment was commenced. As the patient’s fever persisted at the 40th day of anti-TB treatment, VATS was performed. Significant pleural thickening was observed during VATS, which progressed to an open decortication. During the surgery, pleural thickening of nearly 2 cm was present, causing lung collapse. Following complete decortication, the lung reexpanded. Areas of lung parenchyma were macroscopically clean with no parenchymal lesion. The patient’s fever subsided dramatically after surgery.

Patient 7 underwent lung decortication due to massive pleural effusion resulting in lung collapse. Pleural fluid findings were different in this patient. While the other six patients had uncomplicated effusion (transudate) according to Light’s criteria, Patient 7 had complicated effusion (exudate), and a neutrophilic predominance was present in the pleural fluid. Lymphocytic pleural effusion is found in 85.7% of the patients.

All patients were given 6 months’ anti-TB medication and recovered completely. Chest X-rays had returned to normal at the follow-up, and no residual pleural thickening developed in any patient.

**Discussion**

In childhood, pleural TB is more common in children >5 years than in those <5 years of age, and most commonly seen in adolescence. The mean age for pleural TB in childhood has been reported as 13 years.[2] Unilateral hemithorax involvement is typically seen in pleural TB, and pleural involvement without lung involvement is seen in 41%–53.6% of the cases.[2,4,5] Compatible with the literature, all our cases were of adolescent age; unilateral involvement was observed in six of our seven patients; and 42.9% had isolated pleural TB. Macroscopically, straw-colored fluid was seen in 80% of pleural TB cases, and massive pleural discharges are clues for pleural TB.[6] We observed massive pleural effusion in all except one patient. Unresponsiveness to the antibiotic treatment and persistent massive effusion may alert clinicians to screen for TB in pleural effusion.

In pleural TB, the pleural fluid bacilli load is very low, generally resulting in negative AFB staining and mycobacterium culture. In the pleural fluid, AFB stain positivity is reported in <20%, M. tuberculosis culture positivity in 18%–38%, and PCR positivity in 14.3%. In the pediatric population, this ratio is even lower.[4,7] Furthermore, especially in isolated pleural TB without pulmonary involvement, microbiologic examination in gastric fasting aspirate and sputum samples is very rarely helpful.[8] However, in one pediatric case series, one-third of the pleural TB patients had positive M. tuberculosis culture results in gastric fasting aspirate and sputum samples, and the authors recommended M. tuberculosis culture test of gastric fasting aspirate and sputum samples even in the absence of pulmonary involvement in pleural TB.[3] Our one case with isolated pulmonary TB had positive M. tuberculosis PCR result in fasting gastric aspirate.

As a pleural TB diagnosis is difficult, the pleural fluid chemical and Gram-staining examinations are critical. Pleural fluid features in pleural TB are generally compatible with exudates according to Light’s criteria. In one pediatric case series, 99.1% of the patients had exudate, and only one case was characterized as transudate.[3,4,8] Lymphocyte predominance (>50% of leukocytes) is very commonly seen (91.2%), and lymphocytic pleural effusion alone had a sensitivity of 88%, but specificity is low.[4,8] We found the lymphocytic pleural effusion ratio similar to that reported in the literature; however, in contrast with the literature in regard to transudate/exudate discrimination, all of our patients except one were characterized as transudate.

Pleural fluid ADA level is investigated in detail in TB. Pleural ADA levels increase, and levels >40 U/L generally indicate pleural TB disease.[4,8,10] In a study which included microbiologically or histologically confirmed TB pleural effusion cases, ADA sensitivity and specificity were reported as 95% and 89%, respectively. When the pleural ADA level is combined with a lymphocyte: neutrophil ratio ≥0.75, specificity increased to 100%, and sensitivity dropped to 89%.[8] ADA is also increased in parapneumonic pleural

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effusion and emphysema; however, in these diseases, the clinical presentation is very different from TB; furthermore, there is a neutrophil predominance in the pleural fluid in emphysema.\[9\] Malignancies can cause lymphocytic pleural effusion. In studies comparing malignant and tuberculous pleural effusion, a lower ADA level was found in malignancy than TB pleural effusion.\[10\] ADA examination is a simple, rapid, and low-cost test that can be used to efficiently confirm the diagnosis of TB in the absence of microbiologic confirmation. In all our cases, ADA level was >40 U/L, and high ADA level was an important finding pointing to TB diagnosis in our cases.

Pathological examination of the pleura is helpful in the diagnosis of TB, with very high sensitivity up to 80%.\[4\] In one case, we presumed a TB diagnosis based on compatible symptoms, no response to antibiotic treatment and positive QFT result, and anti-TB treatment was commenced. However, due to continued massive pleural discharge, steroid treatment was needed, and exclusion of malignancy was required. Pathological examination of the pleura is beneficial for both confirming the TB diagnosis and excluding malignancies.

Lung decortication is removal of the thickened layer from the pleural surface and is indicated if pleural fluid cannot be drained efficiently despite thoracentesis, tube drainage, and VATS or if there is severe pleural fibrosis or fibrothorax.\[6,12\] Pleural fibrosis or fibrothorax is an important complication of pleural TB, causing impairment in lung function, chronic chest pain, and dyspnea.\[6\] Pleural TB sometimes remains undiagnosed until severe pleural fibrosis develops. The late diagnosis is an important risk factor for pleural fibrosis.\[4\] Two of our patients had severe pleural fibrosis up to 20 mm and decortication was applied in both. In one patient, fever persisted despite anti-TB treatment; hence, we considered that severe fibrosis could cause persistent fever in pleural TB. Lung decortication was performed in three of our cases, and no complication or adverse effect of the procedure was observed.

**Conclusion**

Pleural TB can present in the form of transudates. Lymphocytic pleural effusion and elevated ADA level strongly point to TB; in other lymphocytic pleural effusion, ADA level is generally found <40 U/L. However, as neither high ADA level nor lymphocyte predominance always presents in pleural TB, pleural biopsy is highly encouraged in the diagnosis of pleural TB.

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**Conflicts of interest**

There are no conflicts of interest.

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