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Pleural tuberculosis: experiences from two centers in Brazil

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Abstract
Objective: This study aimed to describe the clinical and laboratory findings of patients diagnosed with pleural tuberculosis at two hospitals in southern Brazil.
Methods: Patients aged < 18 years were evaluated retrospectively. The patients' medical and epidemiological history, tuberculin skin test results, radiological and pathological findings, and pleural fluid analysis results were retrieved.
Results: Ninety-two patients with pleural tuberculosis were identified. The mean age was 10.9 years old. Twenty-one percent were children aged six years or less. The most common symptoms were fever (88%), cough (72%), and chest pain (70%). Unilateral pleural effusion was observed in 96% of the cases. Lymphocyte predominance was found in 90% of the pleural fluid samples. The adenosine deaminase activity of the pleural fluid was greater than 40 U/L in 85% of patients. A diagnosis of community-acquired pneumonia with antibiotic prescriptions was observed in 76% of the study population.
Conclusions: Tuberculosis etiology must be considered in unilateral pleural effusion in a child with contact with a case of tuberculosis. Pleural fluid biomarkers contribute to the diagnosis of pleural tuberculosis in children and adolescents.

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Introduction

Tuberculosis is a communicable disease that remains frequent and causes high mortality worldwide.[1] In 2017, the incidence of tuberculosis in the city of Porto Alegre, the capital of the southern Brazilian state of Rio Grande do Sul, was 90 cases per 100,000 population.[2]

Pulmonary tuberculosis is the most frequently observed manifestation of tuberculosis in the pediatric population. However, 30%-40% of children present with extrapulmonary tuberculosis.[3] Pleural tuberculosis is reported in 12%-38% of childhood thoracic tuberculosis cases.[4] Some studies have shown that pleural tuberculosis is the most common type of extrapulmonary tuberculosis in children and adolescents.[5-7] However, there is little data on the specific epidemiology and clinical characteristics of this form in children.[8]

Pleural tuberculosis may be a manifestation of primary or reactivated infection.[9,10] It is speculated that tuberculous pleural effusion is a result of the rupture of a subpleural caseous focus into the pleural space,[9-13] causing type IV delayed hypersensitivity reaction, in which different cytokines stimulate the antimycobacterial activity of macrophages, resulting in pleural exudates.[9-11,13] There are usually very few bacilli in pleural fluid, where they induce a granulomatous reaction.[4]

Pleural tuberculosis is defined by the identification of *Mycobacterium tuberculosis* on smear microscopy (Ziehl-Neelsen staining), a culture of pleural fluid, or pleural biopsy material, in association with clinical and/or imaging compatible with pleural infection. It can also be identified through the presence of *M. tuberculosis* complex DNA using the Xpert MTB/RIF method.[3,14,15] However, in children, due to the difficulty in isolating *M. tuberculosis*, diagnosis is often determined indirectly according to consistent epidemiological, radiological, clinical, and laboratory criteria.[16] Pleural tuberculosis should always be considered a differential diagnosis in children with isolated, non-toxemic pleural effusion, especially in those older than five years and those with a history of contact with an adult with pulmonary tuberculosis.[8,17] However, in countries where parapneumonic pleural effusions are widespread, suspicion of pleural tuberculosis can be delayed, causing prolonged admissions and unnecessary antibiotic treatment.

To demonstrate the authors' experience with the diagnosis and management of pediatric patients with pleural tuberculosis, this study describes the clinical and laboratory findings of patients diagnosed with pleural tuberculosis at two tertiary university hospitals in southern Brazil.

Methods

Cases of pleural tuberculosis were retrospectively evaluated at two tertiary university hospitals in southern Brazil. Patients below 18 years of age were admitted to the Pediatric Pulmonology Department of Hospital da Criança Santo Antônio (HCSA) between January 2007 and December 2016 and to the Hospital de Clínicas de Porto Alegre (HCPA) between January 2001 and June 2018 were included. Eligible participants were identified by reviewing their electronic medical records.

The diagnostic criteria for pleural tuberculosis were: a) suggestive clinical picture associated with the presence of alcohol-acid resistant bacilli (AFB) in smear or culture positive for *M. tuberculosis* in a sputum sample, gastric aspirate, pleural fluid, bronchoalveolar lavage, or biopsy specimens; b) suggestive clinical picture associated with the presence of granuloma with or without caseous necrosis on pleural biopsy specimen; c) suggestive clinical picture associated with the presence of skin tuberculin skin test (TST) $\geq$ 10 mm in patients with at least one of the following: history of contact with an adult with tuberculosis, or predominance ($>$ 50%) of lymphocytes in the pleural fluid, or pleural fluid adenosine deaminase (ADA) $\geq$ 40 U/L; and d) suggestive clinical picture associated with an improvement of clinical and radiological status after treatment with tuberculostatic drugs. The combination of at least two of the following clinical manifestations was considered suggestive of pleural tuberculosis: fever, chest pain, cough, dyspnea, night sweats, and weight loss. Pleural effusion was confirmed by radiography, computed tomography, or ultrasound. Radiography and computed tomography were retrospectively interpreted by the researchers. If any of the above criteria (a, b, c, or d) were satisfied, a diagnosis of pleural tuberculosis was made, and the patient was included in the study.

All children and adolescents started an antituberculosis regimen according to the Brazilian Ministry of Health protocol.

Demographic data, medical and epidemiological history, TST, radiological findings, pathological findings, and pleural fluid laboratory examinations were evaluated.

During the study period, lactate dehydrogenase (LDH) was analyzed by photometry, and ADA was determined using the colorimetric method described by Giusti and Galanti.[18]

Ethical approval was obtained by the Ethics and Research Committee of both hospitals.

For statistical analysis, the data were entered into Excel® and later exported to SPSS version 20.0. Categorical variables are described as frequencies and percentages. The chi-square test was used to determine differences in proportions between the groups. Quantitative variables with symmetrical distribution are presented as mean and standard deviation, and those with asymmetric distribution are presented as median and interquartile range. Quantitative variables with symmetrical distribution were compared using the Student's t-test. Variables with asymmetric distribution were compared using the Mann-Whitney test. Spearman's coefficient was used for a correlation analysis of the quantitative variables. A p-value of $<$ 0.05 was considered statistically significant.

Results

Ninety-two patients with pleural tuberculosis were identified between the two centers during the study period (59 patients from the HCSA and 33 from the HCPA). Among them, 51 (55%) were male. The mean age was 10.9 years old (10.9 $\pm$ 4.6). Twenty-one percent of the study population was represented by children aged six years or less. The most commonly reported symptoms were fever (88%), cough

(72%), and chest pain (70%). Only four patients were HIV-positive. Unilateral pleural effusion was observed in 95.7% of the patients. Fifty-eight percent had right pleural effusion. Concomitant parenchymal lung disease was observed in 23.9% of cases. A sputum examination was performed in 28 patients (30%). Pleural biopsies were performed in 69 patients (75%). Granulomas were found in 52 (75%) of the pleural biopsy samples. The detailed clinical findings are described in Table 1.

A pleural fluid sample and fluid analysis were performed on 84 children. However, not all pleural fluid tests were performed on all children. The pleural fluid results highlighted the importance of the cytological study as lymphocyte predominance was observed in 90% of the pleural effusion samples. The lymphocytes/neutrophils ratio of pleural fluid was greater than 0.75 in 93% of the cases. ADA activity of the pleural fluid was greater than 40 U/L in 57 patients (85%). The ADA levels did not vary with age (Spearman's coefficient = 0.075; $p = 0.54$). The pleural fluid lactate dehydrogenase/adenosine deaminase (LDH/ADA) ratio was below 16.2 in 83% of the patients. Almost one-third of patients (31.5%) required chest tube insertion. The pleural fluid results are summarized in Table 2.

In 76% of the study population, a diagnosis of community-acquired pneumonia and antibiotic prescriptions were observed. In 38% of the patients, two or more antibiotics were prescribed before a tuberculosis diagnosis was finally made.

Children aged six years or younger frequently underwent chest tube insertion (53%).

Discussion

The clinical features, laboratory characteristics, and radiological presentation of pleural tuberculosis have many similarities between children and adults. However, a definitive diagnosis of pleural tuberculosis is more challenging in pediatric patients because bacteriological confirmation or granuloma detection in pleural specimens occurs less frequently.[4,19-21] Therefore, pleural fluid biomarkers should be considered useful diagnostic tests for pleural tuberculosis in children. In the present study, lymphocytes predominated in 90% of the pleural fluid analyzed. Similar data have been reported in studies on children.[21-23] On the other hand, the ADA level in the pleural fluid has been well studied in adults

Table 1 Clinical information of the patients with pleural tuberculosis.

Data	TOTAL (HCSA+HCPA; *n* = 92)	HCSA (*n* = 59)	HCPA (*n* = 33)
	N (%) or Mean ± SD or Median (IQ)		
AGE (mean ± SD)	10.9 ± 4.6	10.9 ± 4.3	11.0 ± 5.2
0-6 years old	19 (20.7)	11 (18.6)	8 (24.2)
7-14 years old	49 (53.3)	33 (55.9)	16 (48.5)
15-18 years old	24 (26.1)	15 (25.4)	9 (27.3)
SEX			
Male	51 (55.4)	37 (62.7)	14 (42.4)
SYMPTOMS[a]			
Fever	79/90 (87.8)	50/59 (84.7)	29/31 (93.5)
Cough	63/88 (71.6)	41/59 (69.5)	22/29 (75.9)
Thoracic pain	58/83 (69.9)	43/59 (72.9)	15/24 (62.5)
Dyspnea	37/84 (44.0)	21/59 (35.6)	16/25 (64.0)[b]
Night sweats	18/70 (25.7)	15/58 (25.9)	3/12 (25.0)
Weight loss	30/79 (38.0)	18/59 (30.5)	12/20 (60.0)[b]
Hemoptysis	1/91 (1.1)	1/59 (1.7)	0
Time between the onset of symptoms and diagnosis of PT, days	16 (10-31)	14 (8-24)	22 (16-42)[b]
HISTORY OF CONTACT WITH TB[a]			
Yes	54/81 (66.7)	39 (70.9)	15 (57.7)
No	27/81 (33.3)	16 (29.1)	11 (42.3)
TUBERCULIN SKIN TEST[a]			
≥ 10 mm	37/61 (60.7)	27/41 (65.9)	10/20 (50.0)[b]
5- 9 mm	8/61 (21.3)	8/41 (19.5)	0/20 (0)[b]
< 5 mm	16/61 (18)	6/41 (14.6)	10/20 (50.0)[b]

HCSA, Hospital da Criança Santo Antônio; HCPA, Hospital de Clínicas de Porto Alegre; N, sample size; SD, standard deviation; IQ, interquartile range; PT, pleural tuberculosis; TB, tuberculosis.

[a] Denominators vary due to missing data.

[b] $p < 0.05$ for differences between hospitals.

Table 2 Pleural fluid analysis of patients with pleural tuberculosis.

Data	N	TOTAL (HCSA + HCPA) % or Mean ± SD or Median (IQ)	HCSA	HCPA
Leucocytes (cel/mm^3)	66	1525 (681-2420)	1445 (615-2153)	2050 (931-4000)
Lymphocytes (%)	68	74.9 ± 21.8	78.7 ± 19.4	63.7 ± 25.3[a]
Neutrophils (%)	68	6 (2-18.8)	6 (2-17)	8 (3-33)
pH	48	7.35 ± 0.13	7.38 ± 0.1	7.28 ± 0.17[a]
LDH (U/L)	81	559 (368-891)	519 (342-723)	663 (466-1116)[a]
Glucose (mg/dL)	80	68.2 ± 25.5	69.2 ± 24.7	66.4 ± 27.3
Protein (g/dL)	71	5.3 (5.0-5.7)	5.2 (5.0-5.7)	5.5 (2.0-6.0)
ADA (U/L)	67	86.0 (52-169)	60 (44-85)	160 (94-220)[a]
LDH/ADA	65	6.3 (3.3-14.1)	9.3 (4.8-16.8)	4.1 (2.7-7.7)[a]

HCSA, Hospital da Criança Santo Antônio; HCPA, Hospital de Clínicas de Porto Alegre; N, sample size; SD, standard deviation; IQ, interquartile range; LDH, lactate dehydrogenase; ADA, adenosine deaminase.
Note: A pleural fluid sample and fluid analysis were performed on 84 children. However, not all pleural fluid tests were done in all children.
[a] $p < 0.05$ for differences between hospitals.

but not in children. In the present study's population, the authors observed that 85% of the patients presented with an ADA level greater than 40 U/L.

The description of the LDH/ADA ratio represents an original aspect of the present case series. Local anecdotal observations have suggested that the LDH level in pleural fluid is generally lower in pleural tuberculosis than in other types of inflammatory pleural effusions in which ADA is elevated.[24] Two retrospective studies showed that the LDH/ADA ratios were significantly lower in adults with pleural tuberculosis than those with pleural effusion of other etiologies.[24,25] Wang et al. found that LDH/ADA is highly predictive of pleural tuberculosis in adults, with a suggested cut-off level of 16.2.[25]

The differential diagnosis of pleural effusion in children poses an additional challenge because of the similar clinical pictures of two etiologies: tuberculosis and community-acquired pneumonia.[8] As reported in prior studies, the most frequent clinical presentation was fever, cough, and chest pain.[15,21,26,27] A history of contact with adults with tuberculosis has been identified in most cases. Therefore, a detailed medical history should be taken when providing care to children with the above clinical presentation to detect contacts, which would make the diagnosis of pleural tuberculosis more probable than community-acquired pneumonia. The clinical suspicion of pleural tuberculosis is also based on the poor response to conventional antibiotic therapy in children with lung or pleural disease.[28] Boloursaz et al. found that 78% of patients had received antibiotic treatment before the final diagnosis, which is in accordance with the present study's results.[27]

Children aged six years or younger accounted for 21% of the study population, which is at least twice as high as previously described.[21,22,26] This may be explained by the aggressive diagnostic approach in the younger age groups in the studied centers. In addition, the study was hospital-based, and older children were more likely to be managed in primary care. In addition, there are more hospitals that treat adolescents than hospitals that treat pediatric patients in Porto Alegre. This could also explain why the percentage of young children in the present study was higher. This hypothesis is supported by the fact that the younger group frequently required chest tube insertion, which suggests that the disease had a severe clinical presentation in preschoolers in the present sample.

In this case series, involvement of the pulmonary parenchyma associated with pleural effusion was observed in only 24% of cases. In HCSA, this proportion was significantly smaller than in HCPA (12% vs. 46%), which may be partially explained because patients were more frequently subjected to chest ultrasound and chest tomography in HCPA. Most authors describe a frequency of parenchymal involvement of $>$ 59%.[22,26,27,29] Similar to other studies, unilateral pleural effusion was predominant.[22,23,26,29]

Sixty-one percent of the patients had a TST $\geq$ 10 mm, with similar results reported by other authors.[23,27,29] In contrast, the TST results were non-reactive in 18% of the study population. TST negativity has been reported in up to 30% of immunocompetent patients.[19] Furthermore, false-negative reactions may occur more frequently in infants and young children, early ($<$six to eight weeks) after infection, in individuals who have recently received viral vaccination, and after recent viral and bacterial infections.[30]

The present study had several limitations. The first limitation is the retrospective nature of this study. Retrospective studies lack homogeneity in patient care and data entry into electronic medical records, resulting in missing data. In addition, a descriptive study cannot test hypotheses and cannot be used to establish cause-and-effect relationships. Another limitation is that the study subjects may not be representative of the population, as the study was conducted in two tertiary care hospitals, which may not represent patients seen in primary care. On the other hand, children and adolescents with large pleural effusions are referred to tertiary care centers in Brazil. Finally, many patients did not undergo TST because of tuberculin distribution problems during some periods of the study interval.

Improving knowledge of epidemiology and manifestations of pleural tuberculosis in children is important to decrease tuberculosis-related morbidity and mortality. Early diagnosis of the disease facilitates timely initiation of treatment and reduces unnecessary therapeutic interventions, such as hospitalization and antibiotic therapy. In addition, it also

benefits patients and the community by minimizing the spread of pulmonary tuberculosis, thereby improving the plan of action for tuberculosis control and cost reduction generated by sub-diagnosis and delayed treatment.

Based on the present results, the authors suggest that tuberculosis etiology must be considered in unilateral pleural effusion in a child in contact with a case of tuberculosis and with a TST $\geq$ 10 mm. When feasible, ADA and cell count in pleural fluid should be analyzed. An ADA level $\geq$ 40 U/L and lymphocyte predominance contributed to enhancing the diagnosis.

Conflicts of interest

The authors declare no conflicts of interest.

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