Artigo Original

Efficiency of clinical, radiological and laboratory testing in the diagnosis of pleural tuberculosis*

DENISE DUPRAT NEVES, RICARDO MARQUES DIAS, ANTÔNIO JOSÉ LEDO ALVES DA CUNHA, ANTONIO MONTEIRO DA SILVA CHIBANTE(TE SBPT)

Background: In Brazil, tuberculosis is the major cause of pleural effusion. In more than 50% of cases, treatment has been initiated prior to confirmation of the diagnosis. Our objective was to identify factors that can contribute to the diagnosis.

Method: We studied 215 consecutive patients with pleural effusion: 104 from tuberculosis (TB) and 111 from other causes (41 were from malignancies, 29 involved transudation, 28 were parapneumonic and 13 were from other etiologies). Clinical, radiological and laboratorial variables were evaluated for differences between the two groups, individually or in combination.

Results: Male gender and PPD > 10 mm were significantly more frequent in the tuberculosis group. Radiological features were similar in both groups. Among the continuous variables, adenosine deaminase (ADA), percentile of cells, protein and age performed better as isolated diagnostic criteria. Between the group with tuberculosis and that with pleural effusion from other causes, no significant differences were found in Lactate dehydrogenase, total leukocytes or duration of disease. The correlation of ADA with any other well-developed continuous variable showed an LR+ > 10 and an LR- < 0.1, which effectively confirmed or ruled out a diagnosis of tuberculous pleural effusion.

Conclusions: In patients with ADA levels > 39 at 95% sensitivity, the specificity can be improved to more than 90% if we consider non purulent effusion or effusion with a predominance of lymphocytes (> 50%).

Key words: Tuberculosis, pleural/diagnosis. Adenosine deaminase/diagnosis use. Sensitivity and specificity.

*Study carried out at the Hospital Universitário Gaffrée e Guinle (Gaffrée and Guinle University Hospital) - Universidade Federal do Estado do Rio de Janeiro (UNIRIO, Rio de Janeiro Federal University) in Rio de Janeiro, RJ.

Correspondence to: Denise Duprat Neves. Rua Mariz e Barros 775, Hospital Universitário Gaffrée e Guinle, DEMESP, Pneumologia. Tijuca, Rio de Janeiro. Brazil. CEP 20270-004. Phone: 55 21 2569 7610. E-mail: dduprat@unirio.br

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INTRODUCTION

Incidence of pleural effusion by cause varies according to the prevalence of those diseases in a given area. Tuberculosis is responsible for approximately half of the cases of pleural effusion in the city of Rio de Janeiro[1,2].

Culture and identification of species is the gold standard for etiologic diagnosis of pleural effusion, although time consuming and of moderate sensitivity[3-5]. As a result, the presence of granuloma combined with caseous necrosis is accepted as a diagnostic criterion and has been considered definitive, especially in areas where tuberculosis is highly prevalent(3,5-7). Even if we consider these two criteria, that is, culture and histopathological examination, a definitive diagnosis is only made in approximately 85% of cases[8]. In practice, efficiency can be even lower. Data from the city of Rio de Janeiro revealed that, in a great number of cases (approximately 50%), treatment was initiated prior to confirmation of the diagnosis[9].

Among other new diagnostic methods, determination of adenosine deaminase (ADA) activity has been highlighted in the diagnosis of pleural tuberculosis because of its high sensitivity (> 90%). Most studies have confirmed the usefulness of this method and have recommended its use in the routine investigation of pleural tuberculosis, even in patients infected with human immunodeficiency virus (HIV), especially in areas where prevalence of the disease is high[10,11]. However, due to its moderate specificity (approximately 85%), this diagnostic method cannot be used in isolation. Therefore, in order to improve the efficiency of the test, its has been suggested that it be used in combination with other clinical and laboratory criteria[2,7,10-19]. Unfortunately, these criteria, as well as an acceptable probability value, have yet to be established.

The main objective of the present study was to evaluate the efficiency of clinical, radiological and laboratorial testing in the diagnosis of pleural tuberculosis.

METHOD

This was a transversal study in which consecutive patients submitted to routine testing for the diagnostic investigation of pleural effusion at the *Hospital Universitário Gaffrée e Guinle* (Gaffrée and Guinle University Hospital) of the *Universidade Federal do Estado do Rio de Janeiro* (Rio de Janeiro Federal University) were included. Patients for whom ADA could not be determined or for whom a definitive diagnosis could not be made, as well as those patients who had been previously included in the study, were excluded.

Siglas e abreviaturas utilizadas neste trabalho:
ADA – Adenosine deaminase
HIV – Human immunodeficiency virus
NTB– Nontuberculous
PMN – Polymorphonuclear
PPD – Purified protein derivative
ROC – Receiver operating characteristic
TB – Tuberculosis

The group of patients diagnosed with tuberculosis (TB) comprised those who met at least one of the following criteria: detection of TB bacilli by direct microscopy or culture from pleural fluid or sample; granuloma in the pleural sample (with or without caseous necrosis if tuberculosis had been bacteriologically confirmed in another area); verified absence of other granulomatous diseases.

The group of patients not diagnosed with nontuberculous pleural effusion comprised patients whose pleural effusion was due to other causes than tuberculosis: this involved transudation[20] and exudation, infection (especially in the case of parapneumonic effusions and empyema), and other diagnoses in accordance with criteria described in the literature[5,21].

From among the variables routinely obtained during the investigation of pleural effusion, we selected some based on recognized discriminatory power in the differential diagnosis of pleural effusion and reliability of the available data. The variables chosen included gender, age and duration of disease (data obtained from the interview). In addition, we considered radiological findings regarding presence, location and volume of the effusion-induced lesion (evaluated by a pulmonologist on the day of thoracocentesis). Furthermore, results of pleural fluid cytometry and determination of protein, lactate dehydrogenase and ADA (all performed in routine testing), as well as from purified protein derivative (PPD) skin tests, were included. All laboratory testing was performed in accordance with recommended guidelines[2,22-25]. Technicians blinded as to the diagnoses carried out the tests.

The determination of ADA levels in pleural fluid was performed in duplicate in accordance with the technique described by Giusti[26]. After centrifugation, supernatant was stored at -20°C in a freezer, with no addition of anticoagulants. A blank was prepared for every sample. Blanks for the control of substrate and reagents were prepared daily.

We calculated the frequency of nominal variables, as well as central measures, dispersion, and range of continuous variables for the presentation of sample characteristics and of variables per group. The chi-square test was used for nominal variables and Mann-Whitney or Kruskal-Wallis tests were used for continuous variables. Values of $p < 0.05$ were considered statistically significant (rejection of the null hypothesis). Odds ratios and the properties of diagnostic testing were calculated from 2X2 contingency tables, and the greatest discriminatory power was determined using the receiver operating characteristic (ROC) curve.

The Ethics Research Committee of the Hospital Universitário Gaffrée e Guinle approved this study in 1998, in accordance with resolution 196/96 released by the Department of Health. This study was unsponsored and there was no conflict of interest.

RESULTS

The study comprised 294 consecutive pleural effusion patients submitted to pleural puncture. Of these, 42 were excluded because ADA levels could not be determined, and 5 were excluded because they had been previously included. Another 32 patients were excluded because the diagnosis was unconfirmed, although 17 of these were considered probable cases of tuberculosis.

Of the 215 cases included in the study, 104 (48%) were diagnosed with tuberculosis (TB group), and the remaining 111 (52%) were diagnosed with other diseases that were nontuberculous (NTB group). In the NTB group, pleural effusion resulted from malignancies in 41 patients (19.1% of the total sample: 7 with lymphoma and 34 with metastases) and transudation in 29 (13.5%). In the same group, 28 patients (13%) were parapneumonic (12 simple cases and 16 with complications), which resulted in their pleural effusion. The remaining 13 NTB patients (6%) presented other etiologies: 3 with systemic lupus erythematosus, 2 with pulmonary thromboembolism, 2 with pancreatitis, 1 with hemithorax, 1 with chylothorax, 1 with Dressler's syndrome, 1 with endometriosis, 1 with chronic renal disease, and 1 with liver disease).

Frequency of nominal variables in the groups is shown in Table 1. There was a predominance of males in the sample (male/female ratio of 2.7:1 in the TB group and 1.1:1 in the NTB group). A higher proportion of males was also found in the subgroups, such as in patients with parapneumonic effusion. However, there was no significant difference between this subgroup and the TB group ($p = 0.4988$).

Radiological findings revealed that effusion due to tuberculosis was typically unilateral and mostly present in the right hemithorax. However, there was no significant difference between the TB and NTB groups. In patients with transudation, most effusions (69%) were found in the right hemithorax, and the incidence was significantly higher than in the TB group ($p < 0.0001$). Bilateral effusions were two and a half times more frequent in the NTB group, especially in the cases involving transudation and those secondary to systemic diseases. No significant difference was found in effusion volume between the TB and NTB groups ($p = 0.1802$), although massive effusions were more frequent in the NTB group. Incidence of parenchymal lesions was higher in the NTB group, but there was no significant difference in comparison with the TB group ($p = 0.0753$). Radiography revealed lesions in 16 (40%) of the 41 cases involving malignancies (4 cases of lymphoma and 12 of metastasis), which was significantly higher than in the TB group ($p = 0.0056$). Lesions were also present in 33% of patients in the parapneumonic subgroup, although this incidence was not higher than in the TB group ($p = 0.1384$).

Only 52 patients (41%) were submitted to PPD skin tests. The few weak responses were studied concomitantly with negative results. Incidence of strong reaction (induration > 10 mm) was significantly higher in the TB group (76%) than in the NTB group ($p = 0.0008$).

Table 2 shows significant differences of central measures between TB and NTB groups, as well as the greatest discriminatory power and the area below the ROC curve for continuous variables.

Mean age was lower in the TB group, and the difference was significant in comparison with the NTB group. In comparing the TB group with NTB subgroups, we found no significant difference

between the TB group and the parapneumonic subgroup (p = 0.1120). Incidence of tuberculosis is higher (68%) among patients younger than 40. On the other hand, 80% of those older than 50 were diagnosed with etiologies other than tuberculosis, especially malignancies and transudation.

Although median disease duration was the same in both TB and NTB groups, there were extreme values in the NTB group, shorter in the parapneumonic subgroup (median of 18 days), and longer in the case of malignancies (median of 60 days). When we established two ranges with a discriminatory power of 45 days, there was shorter time to symptom relief in the TB group and parapneumonic subgroup, as well as in those with effusions resulting from other infectious diseases, than in those with malignancies or transudation.

Protein levels in pleural fluid were higher in the TB group than in the NTB group. This difference was significant even if we exclude the cases involving transudation (p = 0.0007). Within the malignancy subgroup, protein levels were the lowest in the case of lymphomas and were

TABLE 1
Nominal variables in the TB and NTB groups

Variable	TB group		NTB group	
	N	%	N	%
GENDER				
Male	76	35,35%	60	27,91%
Female	28	13,02%	51	23,72%
X-RAY (SIDE)				
Right	57	26,51%	64	29,77%
Left	43	20,00%	36	16,74%
Bilateral	4	1,86%	11	5,12%
X-RAY (VOLUME)				
≤ 1/3 HT	39	18,14%	51	23,72%
Between 1/3 and 2/3	35	16,28%	25	11,63%
≥ 2/3 HT	30	13,95%	35	16,28%
X-RAY (LESION)				
Absent	84	40,38%	75	36,06%
Present	18	8,65%	31	14,90%
PPD				
Non-reactive	9	11,24%	19	21,35%
Weak response	5	5,62%	5	5,62%
Strong response	38	42,70%	12	13,48%

PPD: purified protein derivative; TB: tuberculosis; NTB: nontuberculous; HT: hemithorax

TABLE 2
Characteristics of continuous variables

Variable	TB group	NTB group	p	Value	AUC	95% CI
Age	80,02	134,21	0,0001	≤ 45	0,752	0,689 a 0,808
Time	97,61	113,7	0,0558	≤ 45	0,576	0,507 a 0,644
Protein	133,28	83,13	0,0001	> 4,1	0,734	0,670 a 0,792
LDH	108,08	86,7	0,0079	> 298	0,611	0,538 a 0,680
Leukocytes	99,99	98,12	0,8179	≤ 6000	0,491	0,419 a 0,563
Lymphocytes	136,91	77,76	0,0001	> 81	0,799	0,717 a 0,833
PMN	78,53	132,93	0,0001	≤ 18	0,757	0,693 a 0,813
ADA	152,72	66,1	0,0001	> 39	0,903	0,855 a 0,939

TB: tuberculosis (median); NTB: nontuberculous (median); AUC: area under the receiver operating characteristic curve; 95% CI: 95% confidence interval; LDH: lactate dehydrogenase. PMN: polymorphonuclear; ADA: adenosine deaminase

significantly different than in the TB group (p = 0.0017). Lactate dehydrogenase levels varied among the groups and subgroups. Significantly higher values were found in the TB group. However, this difference was due to those cases involving transudation. When the transudation subgroup was excluded from the NTB group, the difference was not significant (p = 0.9748).

Total leukocyte counts and lactate dehydrogenase levels showed wide ranges, and there were no statistically significant differences between the TB and NTB groups. In the transudation and parapneumonic subgroups, cytometry values were significantly different than those found in the TB group ($p < 0.0001$). In most TB group patients (97%), leukocyte counts were lower than 6000 cells/ mm^3, whereas they were higher than that in 68% of parapneumonic patients.

Lymphocyte counts were significantly higher in the TB group than in the NTB group or in any NTB subgroup: transudation (p = 0.0051), malignancy (p = 0.0007), parapneumonic ($p < 0.0001$) and others ($p < 0.0001$). Lymphocytes predominated in 99% of TB group patients (more than 50% in the differential count), 59% with lymphocyte counts higher than 90%. Only 20% of the cases had lymphocyte counts higher than 90% in the NTB group. Polymorphonuclear (PMN) cells exhibited complementary behavior in relation to lymphocytes. All 9 cases with PMN counts higher than 90% were in the NTB group (with complications or empyema).

Higher ADA activity was found in the TB group, constituting significant differences in comparison to the NTB group and to the NTB subgroups ($p <$ 0.0001 for the malignancy, transudation, and other subgroups; p = 0.0005 for the parapneumonic subgroup). The ADA values were higher than 39 U/L in 98 patients from the TB group and in 19 patients from the NTB group: 13 in the parapneumonic subgroup (1 simple, 1 with complications and 11 with empyema), 3 with malignancies (2 with lymphoma and 1 with metastasis), 1 with transudation, and 2 with other etiologies (pancreatitis and systemic lupus erythematosus).

Table 3 summarizes power of the variables to discriminate between TB and NTB using the chi-square test and odds ratio, as well as the main properties as diagnostic testing. We found that the incidence of strong reaction to PPD skin test and the proportion of males were higher in the TB group. However, only PPD skin test presented accuracy higher than 70%. Continuous variables – especially ADA levels, cytometry, protein levels, and age – proved more efficient indicators of pleural tuberculosis.

Table 4 presents combinations of tests used in the diagnosis of pleural tuberculosis, including ADA levels (which was the most efficient) and those that had better individual efficiency. The best combination was that of ADA levels and leukocyte counts. When effusions resulting from empyema were excluded, specificity increased considerably (from 83% to 92%), with no loss of sensitivity.

TABLE 3
Comparison of efficiency in the differentiation between TB and NTB

	X^2	p	OR	95%CI	Accuracy	SE	95%CI	SP	95%CI
Gender	7,561	0,006	2,31	1,25-4,26	59,1	73,1	66-80	45,9	39-52
XR side	0,753	0,386	0,75	0,41-1,37	51,6	57,0	49-64	36,0	29-43
XR U/B	2,179	0,140	2,75	0,77-10,64	46,5	96,2	92-99	9,9	3-12
XR volume	0,078	0,780	1,14	0,61-2,12	50,7	71,2	64-78	31,5	25-38
XR lesion	3,266	0,070	1,93	0,95-3,93	55,3	82,4	76-88	29,2	23-35
PPD	12,062	0,001	5,28	1,94-14,67	70,0	71,7	62-79	67,6	54-79
Age	39,042	0,0001	6,90	3,56-13,50	71,2	80,8	74-87	62,2	56-68
Time	7,944	0,005	2,69	1,32-5,53	57,8	84,2	78-90	33,6	28-39
Proteín	39,022	0,0001	7,66	3,77-15,78	70,5	85,6	79-91	56,4	50-61
LDH	11,834	0,001	2,99	1,56-5,76	62,2	74,2	67-81	51,0	44-57
Leukocyte	11,755	0,001	10,17	2,18-65,23	55,8	97,9	93-99	18,3	14-20
Lymphocyte	47,333	0,0001	10,39	4,85-22,64	72,6	88,4	82-93	57,8	52-62
PMN cells	41,013	0,0001	8,95	4,19-19,45	70,8	88,4	82-93	54,1	48-59
ADA	129,046	0,0001	95,87	31,89-310,57	88,8	95,2	90-98	82,9	78-86

X^2: chi-square test; OR: odds ratio; 95% CI: 95% confidence interval; SE: sensitivity; SP: specificity; XR: X-ray; U: unilateral; B: bilateral; PPD: purified protein derivative; LDH: lactate dehydrogenase; PMN: polymorphonuclear; ADA: adenosine deaminase

DISCUSSION

The tuberculosis bacillus was identified more than 100 years ago. Since then, its characteristics have been described in detail, and effective therapeutic measures have been available for decades. Since early diagnosis is important for the control of the disease, diagnostic methods should be simple, rapid, inexpensive and easily performed, allowing them to be widely used, even in areas with poor socioeconomic conditions. Speed and precision are mutually exclusive characteristics in current tuberculosis testing methods[27]. This problem is compounded in cases of extrapulmonary tuberculosis, in which confirmation of diagnosis is more difficult.

Age, protein levels, lymphocyte counts, PMN counts and ADA levels proved to be consistently useful as diagnostic tests in isolation. In differentiating between tuberculosis and other causes of pleural effusion, these variables presented significant differences in central measures between groups, higher values in the area under the ROC curve (> 0.7), higher accuracy (over 70%), higher odds ratio (above 5) and higher minimal 95% CI (greater than 3.5). These findings are quite similar to those described in the literature, especially when compared to a study carried out in São Paulo[10], which identified the same tests as relevant for the diagnosis of pleural effusion. Other authors have suggested the use of these tests, both in isolation and in combination[10,14,15,27-30].

Determination of ADA levels was the most efficient test and the only one that could possibly be used in isolation for the diagnosis of pleural tuberculosis. The sensitivity of ADA determination was 95% (95% CI of 90% to 98%), which is in accordance with what has been described in the literature (95% CI of 88% to 100%). If we consider that tests with high sensitivity allow the exclusion of a diagnostic hypothesis, the diagnosis of tuberculosis should be considered very unlikely if ADA levels are low. However, since specificity of ADA was 83% (95% CI of 78% to 86%, compared with 81% to 97% in the literature), we should not use this test in isolation to confirm the diagnosis of tuberculosis[2,7,10-19,31]. Therefore, it is important that we identify the possible causes for the increase of ADA activity so that these causes are taken into consideration when there is an increase in enzyme levels. Increased ADA levels have been related to pleural effusions resulting from tuberculosis, rheumatoid effusion (which is rare), as well as to some cases of pleural effusion secondary to lymphoma or leukemia, and in most cases of pleural effusion caused by empyema[1,32-35].

Since parapneumonic effusions resulting from empyema, as well as effusions resulting from tuberculosis, are most often related to increased ADA levels, they have been excluded from case analyses by some authors because they are easily identified and do not significantly affect the use of this test in clinical practice[10,11,36,37]. When we excluded these cases from analysis in the present study, specificity increased and sensitivity was unaffected.

In order to exclude complicated parapneumonic effusions, ADA levels have been used concomitantly with lymphocyte counts or lymphocyte count/neutrophil count ratios[10,30,35,36,38]. We should be aware of the fact that we are excluding, in addition to empyema, some uncomplicated parapneumonic effusions and pleural effusions related to pancreatitis or systemic lupus erythematosus, as well as pleural effusions secondary to pulmonary thromboembolism, in which neutrophils are often predominant[5,39]. Occasionally, we may mistakenly rule out a diagnosis of tuberculosis because neutrophil counts are not as

TABLE 4
Efficiency of ADA in effusions not caused by empyema in combination with other variables

	N							
	TB	NTB	D	AUC	SE	SP	LR+	LR-
No pus	104	97	38,5	0,965	95,2	91,7	11,54	0,05
LYM > 50	102	74	38,5	0,967	95,1	94,6	17,59	0,05
LYM > 80	91	47	38,5	0,989	97,8	97,9	45,92	0,02
PTN > 4,1	89	48	39	0,869	94,4	77,1	4,12	0,07
Age < 45	84	42	30,5	0,868	98,8	76,2	4,15	0,02

ADA: adenosine deaminase; TB: tuberculosis; NTB: nontuberculous; AUC: area under the receiver operating characteristic curve; D: discriminatory power; LYM: lymphocyte count; PTN: protein; SE: sensitivity; SP: specificity; LR: likelihood ratio

high in initial effusions[39]. Using high ADA values, lymphocyte proportions higher than 80% and greatest discriminatory power (determined from the ROC curve and used by other authors)[40,41], we ruled out tuberculous effusion in 12 cases, and other types (including parapneumonic effusion involving complications, as well as pleural effusion resulting from pancreatitis, thromboembolism or empyema) in 47 cases. Due to its lower sensitivity, this combination reduced the chance for making a definitive diagnosis of tuberculosis, although there was a significant increase in specificity (to more than 97%), with only one false positive diagnosis (lymphoma). Using the criteria of high ADA values combined with lymphocyte proportions higher than 50% has been reported to increase specificity with no loss of sensitivity[30]. In the present study, leukocyte proportions were higher than 50% in the differential counts of 99% of the TB group patients. Sensitivity of ADA levels remained the same (95%) in this group, and specificity increased to 94.6%, with 4 false-positive diagnoses (2 lymphomas, 1 metastasis, and 1 parapneumonic effusion).

The combination of ADA levels and protein levels in pleural fluid and their relationship with serum protein levels could be used in the differential diagnosis between tuberculosis and malignancies, especially lymphomas[10,28]. The incidence of tuberculosis was higher in those cases with protein levels higher than 4 g/dL in the present study. This finding has been considered suggestive of effusion due to infection[3,5]. However, there was no increase in the specificity of ADA levels when it was combined with protein levels higher than 4 g/dL, probably due to the fact that empyema was present in 9 of the 10 false-positive diagnoses.

The presence of pleural effusion in young adults is suggestive of a tuberculous etiology, especially in those regions where there is high prevalence of the disease. There was no increase in specificity of ADA determination in the group of patients younger than 45 because there were several patients who presented with empyema at this age. This has also been reported in other studies[11,19,42]. The combination of these parameters has been recommended in medical practice in order to increase efficiency in the diagnosis of pleural tuberculosis[10,18,19,43] since it increases the probability of diagnosis prior to other tests, and since empyema can be easily diagnosed through macroscopic evaluation of the pleural fluid.

When we choose the criterion that one test or another should be positive, the likelihood of making an accurate diagnosis will vary, increasing sensitivity at the expense of specificity. When we decide that both tests should be positive, a correct diagnosis is more likely to be achieved. Unless both tests are very sensitive, specificity increases and sensitivity decreases in the latter case[44].

Currently, diagnostic tests may represent the best means of conserving health care resources. Rapid and accurate tests are essential for effective treatment and cost reduction. Determining ADA levels is simple, rapid, inexpensive and easily performed. This method can be widely used, especially in poor areas. There are no additional risks, since it is performed using fluid obtained during thoracocentesis, a routine procedure in the investigation of all cases of pleural effusion. We suggest that ADA testing be adopted as a routine procedure in medical practice since there is much consistent evidence of its usefulness.

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