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Diagnostic tools in tuberculous pleurisy: a direct comparative study

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ABSTRACT: Thoracoscopy is the most accurate yet most expensive tool for establishing the diagnosis of tuberculous (TB) pleurisy. However, most high TB-incidence regions have limited financial resources, lack the infrastructure needed for routine thoracoscopy and require an alternative, cost-effective diagnostic approach for pleural effusions.

Altogether, 51 patients with undiagnosed exudative pleural effusions were recruited for a prospective, direct comparison between bronchial wash, pleural fluid microbiology and biochemistry (adenosine deaminase (ADA) and cell count), closed needle biopsy, and medical thoracoscopy.

The final diagnosis was TB in 42 patients (82%), malignancy in five (10%) and idiopathic in four patients (8%). Sensitivity of histology, culture and combined histology/culture was 66, 48 and 79%, respectively for closed needle biopsy and 100, 76 and 100%, respectively for thoracoscopy. Both were 100% specific. Pleural fluid ADA of $\geqslant$50 U·L^{-1} was 95% sensitive and 89% specific. Combined ADA, lymphocyte/neutrophil ratio $\geqslant$0.75 plus closed needle biopsy reached 93% sensitivity and 100% specificity.

A combination of pleural fluid adenosine deaminase, differential cell count and closed needle biopsy has a high diagnostic accuracy in undiagnosed exudative pleural effusions in areas with high incidences of tuberculosis and might substitute medical thoracoscopy at considerably lower expense in resource-poor countries.

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Tuberculous (TB) pleurisy remains a diagnostic challenge. A high regional incidence for TB often correlates with poor financial resources necessitating a cost-effective diagnostic strategy. Pleural fluid staining for acid fast bacilli (AFB) and culture of *M. tuberculosis* has a poor yield and sputum or bronchial sampling *via* bronchoscopy can diagnose only a minority of cases with additional open lung tuberculosis. Closed needle pleural biopsy has a yield of 60–80% for TB pleurisy and 50% for malignancy [1, 2]. Its role is controversial, as pleural fluid cytology has a high yield in malignancy and medical thoracoscopy is diagnostic in >90% of TB and malignant pleural effusions [3]. Adenosine deaminase (ADA) is raised in TB pleural effusions and has gained popularity in high-incidence areas for TB. High diagnostic accuracy has been reported and the test is cheap and readily available [4]. The drawbacks of relying on ADA alone are the low number of TB cultures yielded on pleural fluid and the possibility of false positives. Specificity can be improved by including the lymphocyte/neutrophil-ratio (L:N) into the test [5].

Although the different diagnostic options have been studied alone, this study is the first prospective head-to-head comparison of bronchial wash, pleural fluid microbiology, pleural fluid biochemistry and closed needle biopsy *versus* thoracoscopic biopsy in a series of patients with undiagnosed exudative pleural effusions. The study was conducted at Tygerberg Hospital, Cape Town, South Africa, situated in a region with a very high incidence of TB (588 cases per 100, 000 inhabitants per year in 1999) [6].

Methods

Before inclusion, all patients had undergone a clinical work-up for pleural effusion, including chest radiograph (CXR), sputum smears for AFB, pleurocentesis for biochemistry, cytology and microbiology, without the establishment of a diagnosis. All patients with an exudative pleural effusion according to Light′s criteria were included, irrespective of ADA and lymphocyte counts. Patients with severe immunocompromising conditions or a positive human immunodeficiency virus (HIV)-screening were not included. Written informed consent was obtained. The study was approved by the local ethical committee.

All pleural biopsies were performed by experienced investigators in a standardised fashion. Local anesthesia was applied at a suitable location at the dorso-lateral thoracic wall with the patient in sitting position. Pleural fluid was sampled *via* Abrams needle and three to six biopsy specimens were cut off with an inward motion of the closed biopsy pouch. Flexible bronchoscopy with bronchial wash on the side of the effusion and thereafter rigid thoracoscopy with biopsies from areas with visible inflammation were performed in supine position. Thoracoscopy was employed as a "medical" procedure with a

single incision. An intercostal drain was inserted for up to 48 h. No serious complications occurred.

Pleural biopsies were stored in saline solution for TB culture and in 4% formaline for histology and AFB-staining. The Ziehl-Neelsen method was used for AFB-staining, and mycobacteria were cultured on solid media in addition to the standard Bactec method. Bronchial wash was processed for AFB-staining and TB culture. Pleural fluid was analysed for pH, biochemical markers, Gram stain, bacterial and TB culture, as well as for cytology and differential white blood cell (WBC) count using standard cytospin procedures and haematoxylin-eosin or Papanicolau stains. ADA was determined with the method of Giusti and Gallati [7].

The diagnosis of TB pleurisy was regarded as established when examination of pleural fluid or bronchial wash revealed the presence of AFB by microscopy or *M. tuberculosis* by culture or when pleural biopsy specimens yielded a positive culture or granulomatous inflammation with caseous necrosis on histology. Malignancy was diagnosed on pleural biopsy or bronchoscopy specimens. When no diagnosis could be made with all available information the effusion was deemed idiopathic.

Based on the results of all investigations, patients with malignancy were referred for palliative treatment. All patients with TB pleurisy were treated with a standard 6-month, directly observed anti-TB treatment regimen and followed up until 6 months after completed therapy. Based on local policy, TB treatment was also given to patients with idiopathic exudative pleuritis.

Results

Altogether, 51 patients were included, with a mean age of 34 yrs (range: 15–63 yrs) and 59% were male. One HIV-positive patient was included, whose HIV-test result was not available at enrolment. A final diagnosis of TB was made in 42 of 51 included patients. On follow-up, 40 of these recovered on completed anti-TB treatment, one patient died in a motor vehicle accident after good initial response and one was lost to follow-up. This patient had been positive for TB on histology, AFB stain and culture. Malignancy was diagnosed in five patients (adenocarcinoma: three; mesothelioma: two). One patient was clinically diagnosed to suffer from coronary bypass graft-related effusion and recovered under observation. The three remaining patients with idiopathic effusion received empirical anti-TB treatment and two recovered fully. One patient with a bloody effusion suggesting malignancy did not improve and was later lost to follow-up.

Radiologically, patients with TB pleurisy featured moderate effusions of one-third to one-half of a hemithorax in 38% and large effusions of more than one-half of a hemithorax in 52% of cases. Parenchymal lung involvement was seen on chest radiograph in seven patients (17%). Three had an ipsilateral infiltrate that disappeared on follow-up, four had cavitations and one had a sero-pneumothorax. The TB effusions were all exudative with a mean lymphocyte fraction of 86% (range: 43–100%). The mean pH was 7.33 (range: 7.13–7.46) and mean ADA 102 $U \cdot L^{-1}$ (range: 36–167 $U \cdot L^{-1}$).

The diagnostic accuracy of the different methods is shown in table 1. Pleural fluid, sputum and bronchial wash culture had a poor yield for TB of 7% each. An L:N of $\geqslant 0.75$ had a sensitivity of 88%, but specificity was poor. All cases with a definite diagnosis of TB pleurisy could be histologically diagnosed on thoracoscopic biopsies and 76% of these biopsies were culture positive. In contrast, histology was positive on only 67% on the Abrams needle biopsies, but five histologically nondiagnostic Abrams needle biopsies were culture positive for mycobacteria with 48% positive cultures in total. Of the 33% nondiagnostic Abrams needle biopsies, half provided insufficient or traumatised tissue or no pleura and the other half showed normal pleura. Two of the five malignancies were diagnosed on medical thoracoscopy only, one on Abrams needle only, one on both and one on bronchoscopy only. All methods based on histology or microbiology had a specificity of 100%.

ADA had a sensitivity of 95% with a specificity of 89% when used alone. With the addition of L:N, the specificity reached 100%, but sensitivity dropped to 89%. An approach combining Abrams needle, ADA and L:N reached a sensitivity of 93%, a specificity of 100% and a mycobacterial culture rate of 48%.

Discussion

This study prospectively determined the value of a range of diagnostic tests for TB pleurisy in a series of patients with exudative pleural effusion of unknown origin in a high incidence area for TB. Medical thoracoscopy had the highest diagnostic accuracy with 100% on histology and 76% positive cultures. Of note is the very good result of the combined

Table 1. – Accuracy of all methods for tuberculous pleurisy

	Positive (false) n	Negative (false) n	Sensitivity %	Specificity %	Positive PV	Negative PV
Bronchial wash	3 (0)	48 (39)	7	100	1	0.19
Pleural fluid						
Culture	3 (0)	48 (39)	7	100	1	0.19
ADA $\geqslant 50 U \cdot L^{-1}$	37 (1)	9 (2)	95	89	0.97	0.8
L:N $\geqslant 0.75$	41 (4)	10 (5)	88	56	0.9	0.5
ADA $\geqslant 50$ $U \cdot L^{-1}$ and L:N $\geqslant 0.75$	33 (0)	13 (4)	89	100	1	0.69
Abrams needle						
Histology and AFB stain	28 (0)	23 (14)	67	100	1	0.39
Culture	20 (0)	31 (22)	48	100	1	0.29
Overall	33 (0)	18 (9)	79	100	1	0.5
Medical thoracoscopy						
Histology and AFB stain	42 (0)	9 (0)	100	100	1	1
Culture	32 (0)	19 (10)	76	100	1	0.47
Overall	42 (0)	9 (0)	100	100	1	1
Combined Abrams needle, ADA $\geqslant 50 U \cdot L^{-1}$ and L:N $\geqslant 0.75$	39 (0)	12 (3)	93	100	1	0.75

PV: predictive value; ADA: adenosine deaminase; L:N: lymphocyte/neutrophil ratio; AFB: acid fast bacilli. ADA available for n=46.

approach with pleural fluid ADA and L:N plus closed needle biopsy histology and culture, which came very close to thoracoscopy.

The strength of this study is the prospective comparison of a wide range of diagnostic tests all applied to the same subjects, who had undergone an unsuccessful routine work-up for pleural effusion. Since a high percentage of TB patients in Southern Africa must be expected to be HIV-positive, the under-representation of HIV-disease in this study warrants discussion. The inclusion of HIV-positive subjects would call for stratification for CD4-counts and clinical stages of HIV disease. This would require a much larger study population and was considered not feasible at Tygerberg Hospital. Moreover, it has been shown that pleural fluid characteristics are similar in HIV-positive and negative patients with TB pleurisy [8, 9], and that particularly ADA is not affected by HIV-status [4]. HIV-positive patients with TB pleurisy tend to have a higher rate of positive pleural fluid smear [10] and the authors speculate that the combined alternative approach to medical thoracoscopy would have an even higher yield in HIV-positive patients.

A diagnosis remained elusive in three cases in the current study even after thoracoscopic biopsy, for which the authors still claim a diagnostic yield of 100% under the assumption that none of these cases had TB. This is a notorious problem with undiagnosed exudates. In a study in a low-incidence area for TB on 51 patients with idiopathic exudative pleural effusion after diagnostic thoracotomy, more than half had a benign course under observation [11]. In the present study, patients with idiopathic exudative pleuritis were empirically treated for TB. Whether the improvement in the three idiopathic cases in this series is spontaneous or due to therapy is speculative. However, even if all these patients were classified with TB pleurisy, the sensitivity and specificity of medical thoracoscopy would still be very good at 93% and 100%, respectively. Closed needle biopsy with a histological yield of 67% fared better in the present study than in many other reports but fell slightly short of the recent large study of VALDES *et al.* [1] reporting 80% histological yield for TB pleurisy in 248 patients. Operator skill is the key to good results in closed needle biopsy and experienced physicians performed the biopsies in the present study. Since 16% of cases had lung involvement on chest radiograph it is surprising that the bronchial wash only had 7% sensitivity. Referral bias caused by repetitive testing for sputum AFB in primary and secondary healthcare facilities leading to an over-representation of sputum negative cases in the study population offers a possible explanation.

The combination of ADA with the differential pleural fluid WBC count increases specificity. A cut-off of $\geqslant 50 U \cdot L^{-1}$ for ADA was used, combined with an L:N $\geqslant 0.75$ for which a sensitivity of 88% and a specificity of 95% were recently shown in a population from the same geographical area as in the present study [5]. However, in that study not all cases diagnosed as TB pleurisy had microbiological or histological proof of TB. With the present report this approach was prospectively validated with a sensitivity of 85% and specificity of 100% in biopsy or culture proven subjects.

ADA with L:N comes close to an ideal test for TB pleurisy because it is of low cost, minimally invasive, of high accuracy and gives swiftly available results. However, the ideal test should also deliver a reasonable proportion of positive cultures enabling sensitivity testing, which is not the case when pleural fluid only is available for culture. Therefore, the value of a combined strategy of pleural fluid biochemistry (ADA, L:N) and closed needle biopsy (histology with AFB stain and mycobacterial culture) was calculated for the present series, which was clearly the next best diagnostic test to medical thoracoscopy, with a sensitivity and specificity of 93% and 100%, respectively. However, the yield in mycobacterial cultures of 48% was significantly lower than with thoracoscopy (76%, $p<0.01$, paired sign test), which is of importance for regions with high antibiotic resistance.

In conclusion, this study allows the authors to propose recommendations for the work-up of undiagnosed exudative pleural effusions in a high incidence area for tuberculosis. For patients with a typical clinical presentation for tuberculous pleurisy, combined pleural fluid adenosine deaminase level and lymphocyte/neutrophil ratio is an accurate first step. If this test is negative despite a high clinical suspicion of tuberculous pleurisy, if antibiotic resistance is of concern or if other possible diagnoses are considered, medical thoracoscopy is the method of choice. If thoracoscopy is not available, closed needle biopsy should be performed in combination with pleural fluid analysis for adenosine deaminase and the lymphocyte/neutrophil ratio. This approach provides a high diagnostic yield with affordable, minimally invasive methods that can be performed in outpatient settings.

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