Exudative pleural effusion: effectiveness of pleural fluid analysis and pleural biopsy

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الانصباب الجنبي النضحي: فعّالية تحليل السائل الجنبي والخزعة الجنبية

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الخلاصة: قارن الباحثون في هذه الدراسة بين تحليل السائل الجنبي، وتحليل الخزعة الجنبية، في تشخيص 100 حالة لمرضى مصابين بانصباب جنبي نضحي، في بابول، بجمهورية إيران الإسلامية. وقد تأكّدت الإصابة بالالتهاب الجنبي السلّي، أو الانصباب الجنبي الخبيث من خلال كشف عصيات صامدة للحمض في سوائل الجسد، أو خلايا ورمية في عينات نسيجية. وتبيَّن أن الأمراض الخبيثة كانت سبب الانصباب الجنبي النضحي في 43٪ من المرضى، في حين كان السل هو سبب الانصباب الجنبي في 33٪ من المرضى. وبلغت نسبة الحساسية التشخيصية للخزعة الجنبية لدى المرضى بالالتهاب الجنبي السلّي 70٪ ولدى المرضى بالانصباب الجنبي الخبيث 54٪، كما بلغت نسبة الحساسية التشخيصية لتحليل السائل الجنبي لدى مرضى الالتهاب الجنبي السلّي 33٪ ولدى مرضى الانصباب الجنبي الخبيث 70٪. وجاءت نتائج التحليل المشترك للخزعة والسائل الجنبي إيجابية في 99٪ من حالات الانصباب الجنبي السلّي، و91٪ من حالات الانصباب الجنبي الخبيث.

ABSTRACT The study compared pleural fluid analysis and pleural biopsy in the diagnosis of 100 patients with exudative pleural effusion (PE) in Babol, Islamic Republic of Iran. Tuberculous pleurisy and malignant pleural effusion were confirmed by the identification of acid-fast bacilli from body fluids or tumour cells from tissue specimens. Malignant diseases and tuberculosis were the causes of exudative PE in 43% and 33% of patients respectively. The diagnostic sensitivity of pleural biopsy in patients with tuberculous PE and malignant PE was 70% and 54%, and the diagnostic sensitivity of pleural fluid analysis was 33% and 70% respectively. Combined pleural biopsy and pleural fluid analysis were positive in 97% of tuberculous PE cases and 91% of malignant PE.

Pleurésie exsudative : efficacité de l'analyse du liquide pleural et de la biopsie pleurale

RÉSUMÉ L'étude a comparé l'analyse du liquide pleural et la biopsie de la plèvre dans le diagnostic de 100 patients présentant une pleurésie exsudative (PE) et résidant à Babol (République islamique d'Iran). La pleurésie tuberculeuse et la pleurésie exsudative maligne ont chacune été confirmées par identification de bacilles acidorésistants isolés dans le liquide pleural ou les cellules tumorales issues d'échantillons tissulaires. Malignité et tuberculose se sont avérées être respectivement à l'origine de 43 % et 33 % des cas. En ce qui concerne la sensibilité diagnostique de ces deux tests, la biopsie pleurale atteignait respectivement 70 % et 54 % dans la PE tuberculeuse et la PE maligne contre respectivement 33 % et 70 % pour l'analyse du liquide pleural. La combinaison biopsie pleurale/analyse du liquide pleural a obtenu des résultats positifs dans 97 % des cas de PE tuberculeuse et 91 % des cas de PE maligne.

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Introduction

Pleural effusion (PE) is a common problem in internal medicine practice. In cases with transudate PE, the diagnosis is usually made without any difficulties but exudative PE requires careful differential diagnosis that includes tuberculosis (TB) and metastatic cancers, which are often found to be the cause in a large number of patients [*1–3*].

Disease in any organ can cause exudative PE through a variety of mechanisms including infection, malignancy, immunologic response, lymphatic abnormality and noninfectious inflammation [*4*].

In many areas of the world, TB is the most common cause of exudative PE [*5–7*], but in regions with a low prevalence rate of TB, and also in patients aged over 60 years, malignant diseases should be considered the most probable cause, although in older patients a reactivation of previous TB may also present as exudative PE [*8–10*].

Despite the development of new diagnostic methods, closed pleural biopsy and pleural fluid analysis remain the most common ways of establishing a diagnosis of tuberculous PE or malignant PE [*10–12*]. However the value of these procedures is limited in establishing the cause of PE that results from either malignant or nonmalignant diseases. Although thoracoscopic biopsy and lavage has increased the diagnostic rate, the cause for many patients with exudative PE remains unknown or obscure. In these patients, detection of a treatable cause is very important. Even in patients with a known malignancy, accurate diagnosis of the cause of PE is essential, as the treatment and prognosis may vary.

Since TB and malignancy are among the most frequent causes of PE, in particular exudative PE, in most parts of the world previous studies have focused on the diagnosis of TB or malignancy [*5,6,9–12*]. Although the value of pleural fluid analysis and pleural biopsy in diagnosis of malignant or tuberculous PE has been shown in several studies [*10–12*], their diagnostic performance for identification of TB or malignancy in patients with the exudative type of PE has not been studied or compared yet.

The aim of the current study was to assess the effectiveness of pleural fluid analysis and pleural biopsy and the efficacy of combining both procedures in the diagnosis of TB and malignancy in patients with exudative PE.

Methods

This study was carried out on 100 consecutive patients with PE admitted to the pulmonary division of Shaheed Beheshti Hospital in Babol, Islamic Republic of Iran between 1997 and 2001.

Etiological diagnosis of exudative PE was confirmed according to appropriate clinical and/or laboratory findings or criteria. All patients were given a clinical examination, chest radiograph, blood chemistry and thoracentesis. Pleural biopsy with Abrams needle was performed in all patients except those with an obvious clinical diagnosis of congestive heart failure or bacterial pneumonia. Pleural fluid analysis was performed for protein concentration, lactic dehydrogenase (LDH), cultures, as well as cytologic study for tumour cells. Bacteriological examination of pleural fluid as well as examination for acid-fast bacilli (AFB) were also performed. Diagnosis of exudative PE was confirmed according to pleural fluid protein and LDH level, and the size of the effusion was determined on the basis of chest radiographs [*13*].

Other diagnostic methods such as bronchoscopy and bronchoalveolar lavage were done as clinically indicated. Bronchoalveo-

lar lavage fluids were examined for AFB by smears and culture, as well as for tumour cells. In patients with bloody sputum or those suspected for TB, 3 samples of stained sputum smears as well as 3 sputum samples for cultures were taken and sent to the TB ward of Babol health centre for examination of AFB. Standard tuberculin skin test was also performed for all patients.

Definitive diagnosis of TB was confirmed by identification of AFB from the cultures of the pleural fluid, bronchoalveolar lavage fluid, or from the pleural biopsy samples by direct examination. Presence of granulomas with caseous necrosis in biopsy specimens was confirmative of TB if clinical and radiological findings of TB were also available.

Diagnosis of malignant PE was confirmed by identification of tumour cells from the pleural fluid or pleural tissue samples.

Diagnosis of malignant mesothelioma was confirmed on the basis of histologic examination of pleural biopsy specimens, diffuse thickening of pleura on CT scanning, and bloody pleural fluid, defined as $\geq$ 100 000 red blood cells/mm^3 of pleural fluid and exclusion of metastatic disease.

The sensitivity of diagnostic tests was calculated as the proportion of diseased individuals with positive test results, i.e. diseased with positive test divided by all diseased. The gold standard for diagnosis of tuberculous PE and malignant PE was demonstration of AFB from body fluids and tumour cells from tissue biopsy samples respectively.

Results

The mean age of patients was 57 years (standard deviation 17 years) (range 12–82 years); 62% were males and 72% were aged over 50 years.

Causes of exudative PE

PE was right-sided in 51% of cases, left-sided in 44% and bilateral in 5% of patients.

Malignant diseases accounted for 41% and TB for 33% of the 100 cases of exudative PE; 2 patients (2%) had coexistence of TB and malignancy and were analysed with the malignant group. Para-pneumonia effusions were found in only 6% of cases. Other reasons were: congestive heart failure, 3%; complication of coronary bypass surgery, 2%; rheumatoid arthritis, 2%; systemic lupus erythaematosus, 1%; chronic renal failure, 1%; acute cholecystitis, 1%; unknown etiology, 8%. Large pleural effusions were found in 24% of patients, moderate in 58%, and mild effusions in 18%. In 15% of cases, the pleural fluid was bloody.

The majority of cases of malignant PE were due to metastatic cancers (95%). In this study the origins of primary cancers were determined in only 39% of patients, which included lung cancer (22%), breast cancer (7%), gastric carcinoma (5%) and lymphoma (5%). Malignant mesothelioma was diagnosed in only 2 patients.

Characteristics of tuberculous PE and malignant PE

The characteristics and the presenting features of tuberculous PE and malignant PE are summarized in Table 1. The most common presenting features of exudative PE for tuberculous and malignant pleurisy respectively were: dyspnoea (82%, 72%), cough (82%, 65%) and pleuritic chest pain (64%, 49%).

The presenting features of non-TB and non-malignant effusions were pleuritic chest pain, cough and dyspnoea in 71%, 54% and 38% of patients respectively. In 8% of patients the causes of exudative PE were not determined over a mean follow-up period of 3 months.

Table 1 **Patient characteristics and presenting features of tuberculous and malignant pleural effusions**

Characteristic	Tuberculous pleurisy (*n* = 33)		Malignant pleurisy (*n* = 43)		*P*-value[a]
	No.	%	No.	%	
Male	25	76	23	53	NS
Bloody pleural fluid	2	6	12	28	< 0.01
Bilateral effusion	1	3	1	2	NS
Left-sided effusion	20	61	15	35	< 0.05
Large effusion	4	12	19	44	< 0.05
Clinical presenting features					
Dyspnoea	27	82	31	72	NS
Cough	27	82	28	65	NS
Pleuritic pain	21	64	21	49	NS
Radiographic findings					
Pulmonary infiltrates	6	18	0	0	
Cavitation	2	6	0	0	
Pulmonary mass and atelectasis	0	0	5	12	
Mean age (SD) (years)	51.3	(20)	61.2	(13)	< 0.01

[a]*Chi-squared test and Fisher exact test.*
n = *total number of patients; SD = standard deviation; NS = not significant.*

Pleural biopsy versus pleural fluid analysis

Pleural biopsy was the most sensitive diagnostic measure for tuberculous PE with a sensitivity of 70%, whereas pleural fluid analysis was positive in only 33% of patients with tuberculous PE (Table 2). The sensitivity of pleural fluid analysis and pleural biopsy for diagnosis of malignant PE was 70% and 53.5% respectively, whereas the diagnostic sensitivity of both pleural biopsy and pleural fluid analysis in patients with tuberculous and malignant PE was 97% and 91% respectively.

The results of alveolar lavage testing are presented in Table 3. Sputum smears and cultures were not helpful for diagnosis of tuberculous PE and tuberculin skin test was positive in only 25% of patients with TB.

In patients with malignant PE who had cytology-negative pleural fluid, pleural biopsy was positive in 9 out of 13 patients (70%). In the remaining 4 cytology-negative cases 3 patients were diagnosed by bronchial biopsy and 1 patient by lymph node biopsy. In 14 cases of malignant PE, both pleural biopsy and pleural fluid analysis were positive. Patients with malignant PE were older, with higher frequency of large and bloody pleural effusions as well as higher frequency of right-sided effusions than patients with tuberculous PE.

In conclusion, pleural fluid analysis was more sensitive for diagnosis of malignant

Table 2 **Patients with positive test results, and the diagnostic value of pleural biopsy, pleural fluid analysis, and alveolar lavage fluid examination, in tuberculous and malignant pleurisy**

Diagnostic method	Tuberculous pleurisy[a] (*n* = 33)			Malignant pleurisy[b] (*n* = 43)			Total (*n* = 76)		
	No. of tests	No. positive	%	No. of tests	No. positive	%	No. of tests	No. positive	%
Alveolar lavage fluid	10	1	10	15	1	7	25	2	8
Pleural fluid analysis (cytology/cultures)	33	11	33	43	30	70	76	41	54
Pleural biopsy	33	23	70	43	23	54	76	46	61
Combined pleural biopsy + pleural fluid analysis	33	32	97	43	39	91	76	71	93

[a]*Tuberculosis confirmed by the identification of acid-fast bacilli or granulomas from the body fluids or biopsy samples.*
[b]*Malignant pleurisy confirmed by the identification of tumour cells, in body fluids or tissue samples (2 cases with coexistence of tuberculosis and malignancy were included in this group).*
n = *total number of patients.*

PE than tuberculous PE, whereas pleural biopsy was more sensitive for diagnosis of tuberculous PE. Combined pleural fluid analysis and pleural biopsy were positive in 97% and 91% of cases with tuberculous PE and malignant PE respectively.

Characteristics of the malignant and non-malignant pleural fluids

Characteristics of the malignant and non-malignant pleural fluids are shown in Table 3. In malignant PE the mean pleural fluid protein concentration was significantly higher but the mean pleural fluid LDH level was significantly lower than in non-malignant effusions ($P < 0.02$ for both).

Discussion

This study examined the effectiveness of pleural fluid analysis and pleural biopsy in diagnosis and differentiation of TB and malignancy in 100 hospitalized patients with exudative PE. The results revealed that malignancy was the leading cause of exudative

Table 3 **Comparison of malignant and non-malignant exudative pleural fluids**

Pleural fluid characteristics	Malignant effusion			Non-malignant effusion			*P*-value[a]
	No. of tests[b]	Mean	SD	No. of tests	Mean	SD	
Protein (g/dL)	57	5.1	1.1	43	4.5	1.2	< 0.02
Lactic dehydrogenase (IU/L)	57	344	362	42	637	681	< 0.02

[a]*t-test.*
[b]*Number of patients with available data.*
SD = standard deviation.

PE in this group of patients in Babol (43%), while TB accounted for only 33% of cases. Furthermore, these findings indicate that despite the development of new diagnostic procedures, pleural fluid analysis and pleural biopsy, and in particular combinations of both procedures, remain valuable diagnostic methods for establishing the etiology and differentiating tuberculous PE from malignant PE in patients with exudative PE.

The causes of exudative PE vary according to geographic region as well as the study population. Several factors including, age, smoking habits, exposure to environmental factors or occupational risk factors may increase the risk of malignancies, whereas crowding, poverty and malnutrition are associated with increased risk of TB.

Our study contrasts with 2 epidemiological studies from TB-endemic areas, where TB was the most common cause of exudative PE (43.7% and 44.1% of patients), whereas malignant diseases accounted for 32.1% and 29.6 % of patients respectively [*5,6*]. However, in 2 other studies from TB-endemic areas, malignant diseases were more frequent than TB [*9,10*]. In another study of patients with exudative or transudative pleural effusions in the Islamic Republic of Iran, malignant diseases were more frequent than TB [*8*].

In this study we have investigated a cohort of patients with exudative PE who underwent diagnostic thoracentesis. The majority of these patients were referred from other health centres for further investigation because of persistent PE. The population of this study did not include all cases of PE because several cases of tuberculous PE or malignant PE with obvious clinical and radiological findings who did not require further diagnostic measures were not referred. Therefore, the present study entailed only inpatients, mostly with longstanding and probably advanced disease. The study population of the present study differs from the epidemiological-based study population regarding patient selection.

The low prevalence of parapneumonia effusions and congestive heart failure in this study was also due to exclusion of patients with obvious clinical findings of pneumonia and congestive heart failure who did not require diagnostic pleural fluid analysis and pleural biopsy. However, in this study, the causes of exudative PE were undetermined in 8% of patients after follow-up for a mean period of 3 months; this value is lower than that reported by Zabokis et al. [*9*].

We obtained a yield of 70% for pleural biopsy in diagnosis of tuberculous PE and 54% for malignant PE. The diagnostic yield of pleural fluid analysis was 33% for tuberculous PE and 70% for malignant PE. The yields of either pleural fluid analysis or pleural biopsy or both for diagnosis of tuberculous PE and malignant PE were 97% and 91% respectively. The etiological diagnosis in 93% of the entire population was established by performance of pleural fluid analysis and pleural biopsy.

The diagnostic yields of pleural biopsy and pleural fluid analysis for diagnosis of tuberculous PE and malignant PE vary according to published studies [*9–12,14–18*]. Salazar-Lezama et al. found pleural biopsy to be the most effective method in diagnosis of pathology in 87% of cases with tuberculous PE [*16*], whereas in another study of patients with tuberculous PE the diagnostic yield of pleural biopsy was 47.4% which was lower than our study [*17*]. In a study by Christopher et al. the diagnostic yield of pleural biopsy was 75% in tuberculous PE and 71% in patients with malignant PE [*11*]. Mohamed et al. obtained a diagnostic yield of 60% in tuberculous PE and 50% in malignant PE, but the yields for thoracoscopic biopsy were 93% and 94% respectively [*10*]. In a study by Jain et al. the diagnostic

yields of visceral pleural biopsy in tuberculous PE and malignant PE were 69.7% and 81.3%, and parietal pleural biopsy were 42.3% and 31.3% respectively [*18*].

The proportion of patients with malignant PE who had positive pleural fluid analysis in these studies ranged from 62% to 76% [*9,10,12*] and the positivity rate of pleural fluid cultures in patients with tuberculous PE ranged from 7.9% to 73% [*12,14–17,19*].

Chen et al. compared the diagnostic value of echo-guided pleural biopsy with that of pleural fluid analysis in patients with malignant PE [*12*]. They obtained a diagnostic yield of 55% with pleural biopsy and 64% with pleural fluid analysis. Combining both methods increased the diagnostic rate to 88% in patients with malignant PE, which compares with 91% for our study. In another study of patients with malignant PE, the diagnostic yields of lavage cytologic analysis and fluid cytologic analysis were 84% and 62% respectively whereas the diagnostic yield of combined thoracoscopy and lavage cytologic analysis was 96% [*10*].

In addition to the present study, several previous studies have shown a higher sensitivity of pleural fluid analysis than pleural biopsy in the diagnosis of malignant PE and superiority of pleural biopsy in diagnosis of tuberculous PE [*19–24*].

The diagnostic yields of combined pleural fluid analysis and pleural biopsy in 3 previous studies for diagnosing malignant PE ranged from 64.7% to 94% and for diagnosis of tuberculous PE ranged 86% to 93% [*20–22*].

Furthermore in this study, 9 out of 13 (70%) cytology-negative pleural fluid samples were diagnosed as having malignant PE by pleural biopsy. In a study by Prakash et al. [*20*] the diagnostic sensitivity of pleural biopsy in cytology-negative malignancy was 7.1%. In the current study, the yields of pleural fluid analysis for diagnosis of malignant PE and pleural biopsy for diagnosis of TB, in particular the sensitivity of combined pleural fluid analysis and pleural biopsy, was higher. This may be due to advanced cases of malignant disease with extensive involvement of the parietal pleura.

In this study tuberculin skin test, sputum smears and cultures were not helpful for diagnosis of TB. However, the low positive rate of these tests was also reported in previous studies [*12,15,17,25*].

With regard to the clinical data presented here, large, bloody and right-sided PE with a high protein concentration favours the diagnosis of malignant PE rather than TB.

In summary, the findings of the present study in confirmation with previous studies indicate that TB and malignancy are the most probable causes of exudative PE. Additionally, these results confirm that, despite the development of new diagnostic procedures, pleural fluid analysis and pleural biopsy remain the best diagnostic methods for evaluation of PE, as well as for determining the etiology in patients with exudative PE.

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World Health Assembly resolution on TB

On 23 May 2007, the 60th World Health Assembly passed a resolution urging WHO Member States to develop and implement long-term plans for TB prevention and control aimed at accelerating progress towards halving TB deaths and prevalence by 2015, through the full implementation of the Global Plan to Stop TB, 2006–2015. WHO is requested to strengthen its support to countries affected by TB, in particular those heavily affected by Multidrug-Resistant TB (MDR-TB) and Extensively Drug-Resistant TB (XDR-TB), as well as TB/HIV. Member States are also urged, where warranted, to declare TB an emergency.

The Global Plan to Stop TB 2006–2015 is a comprehensive assessment of the action and resources needed to implement the Stop TB strategy and make an impact on the global TB burden. The plan can be downloaded in Arabic, English, French and Spanish from the homepage. *Actions for Life*, a flash film about the Global Plan can be accessed on the same page, URL http://www.stoptb.org/globalplan/