

Validity of pleural fluid protein in differentiating tuberculous from malignant pleural effusion

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MU AJ conceived idea, MU ZI MYK drafted the study, MU AB collected data, MU AJ MYK did statistical analysis & interpretation of data, AJ MU MYK ZI critical reviewed manuscript, All approved final version to be published

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The Authors declares that there is no conflict of interest.

Abstract

Introduction: Tuberculosis (TB) and malignancy are the most common causes of exudative pleural effusion (PE) in our country. Despite the development of new diagnostic methods, closed pleural biopsy and pleural fluid analysis remain the most common ways of establishing diagnosis of tuberculous or malignant PE.

Objective: The objective of the study was to determine the validity of pleural fluid protein in differentiating tuberculous from malignant pleural effusion keeping histopathology as gold standard.

Methodology: The cross sectional validation study was carried on patients referred from in/out door patient departments. Total duration was 6 months, from 1st January 2017 to 31st June 2017. Those patients fulfilling inclusion criteria were subjected to Abrams needle biopsy after taking informed written consent according to standard protocol and pleural tissue was examined by one histopathologist In order to know the significant difference of pleural fluid protein level between tuberculous and malignant PE, three categories were made i.e. category-A (3-4 g/dl), Category-B (4-5 g/dl) and Category-C (>5 g/dl).

Results: Among total number of 179, males were 114 (63.69%) and females were 65 (36.32%). Age limit was from 15 to 80 years. 60.9% were tuberculous and 39.1% were malignant PE. Among malignant PE the primary were 20 (11.2%) and secondary were 50 (27.9%). Tuberculous PE was more common in younger age group while malignant PE in older age group 88 (49.2%) of the patients were falling in category A, 59 (33%) in category B, and 32 (17.9%) in category C.

Conclusion: Pleural fluid total protein level is a valuable tool in reaching to the diagnosis of suspected tuberculous or malignant pleural effusion provided it is used in addition to the adequate clinical scenario.

Key words: Tuberculous; Pleural effusion; malignant pleural effusion; exudates; pleural biopsy; pleural fluid protein.

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Introduction

Pleural effusion (PE) is common¹ clinical problem both in developed and developing countries and presents both to respiratory and non-respiratory specialists.

The first step in the etiological investigation of a pleural effusion is to determine whether the effusion is a transudate or an exudate. Transudates reflect the presence of systemic disease with repercussions on

the mechanisms of pleural fluid production and resorption.² In contrast, exudates reflect the presence of primary pleural disease and require etiological investigation.³ So 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.⁴⁻⁵ Disease in any organ can cause exudative PE through a variety of mechanisms

including infection, malignancy, immunologic response, lymphatic abnormality and noninfectious inflammation.⁶

The Annual prevalence rate of exudative PE is 9% in hospitalized patients in tertiary level teaching hospital at Peshawar, Pakistan.⁷

Like many areas of the world, tuberculosis (TB) and malignancy are the most common causes of exudative PE in our country. Although TB is the most common cause of exudative PE 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

The gold standard for diagnosis of pleural tuberculosis is the identification of Mycobacterium tuberculosis in pleural fluid or tissue¹¹ however, in clinical practice this identification is problematic because of the low identification rate of the bacillus (less than 30% in pleural fluid and approximately 50% in the pleura) and the slow growth of mycobacterium in culture (about 60 days).¹¹

At present, several tests are of great interest for diagnosing tuberculous pleural effusion such as ADA¹² interferon,¹³ lysozyme,¹⁴ the polymerase chain reaction,¹⁵ and specific c antibodies.¹⁶ Lymphocytic predominance in pleural fluid is the rule in tuberculous effusions.¹⁷ However, the tests mentioned above need specific and/ or expensive equipment that is not available in most laboratories particularly in developing countries.

Closed pleural biopsy^{18,19} and pleural fluid analysis²⁰ remain the most common ways of establishing diagnosis of tuberculous or malignant PE.

In our setting due to lack of awareness, expertise and financial constraints, simultaneous pleural biopsy along with pleural fluid protein level is not routinely

practiced. Mostly pleural fluid protein, total cell count, different cell count and occasionally lactic dehydrogenase are measured to differentiate between transudative and exudative PE and most of the exudative PEs are then treated as tuberculous PE.

This study was aimed to explore the role of pleural fluid protein in differentiating tuberculous from malignant PE.

Objective

The objective of the study was the validity of pleural fluid protein to differentiate tuberculous from malignant pleural effusion keeping histopathology as gold standard.

Methodology

This cross sectional validation study was conducted on 114 patients at Lady Reading Hospital Peshawar from 1st January 2017 to 31st June 2017. All patients with pleural effusion coming to Pulmonology unit from out patient department (OPD), emergency department or private clinics were evaluated. Detailed history and clinical examination was carried out.

Patients with exudative pleural effusion were subjected to Abrams needle biopsy after taking informed written consent. The biopsy specimen was sent for histopathological examination. The biopsy report was collected and recorded on the structural proforma designed for the study. For control of confounding variables, following steps were taken

- (a) One standard laboratory was used for pleural fluid analysis and pleural tissue will be examined by one histopathologist
- (b) Pleural biopsy was done by the researcher himself and only one standard Abrams needle be used for collection of pleural tissue.
- (c) Standard tubes/bottles with standard chemicals

Table 1: Age wise distribution of study cases

Age	Biopsy		Total
	Tuberculous	Malignancy	
< 20 years	11 (10.1%)	1(1.4%)	12 (6.7%)
20-40	67 (61.5%)	5(7.1%)	72 (40.2%)
41-60	22 (20.2%)	45(64.3%)	67 (37.4%)
61-80	9 (8.3%)	19(27.1%)	28 (15.6%)
Total	109 (100.0%)	70(100.0%)	179 (100.0%)

were used for transport of all specimens to the laboratory

Those patients fulfilling inclusion criteria were enrolled in the study after taking informed consent. Baseline clinical data like age, sex etc including the pleural fluid protein level was collected and entered into the proforma.

In order to know the significant difference of pleural fluid level between tuberculous and malignant pleural effusion three categories were made i.e. category-“A” having pleural fluid protein level ranges from 3-4 g/dl, Category-“B” having range from 4-5 g/dl.,Category-“C” having range from >5 g/dl.

Table 2: Gender wise distribution of study cases

Gender	Biopsy		Total
	Tuberculous	Malignancy	
Male	76 (69.7%)	38(54.3%)	114 (63.7%)
Female	33(30.3%)	32(45.7%)	65(36.3%)
Total	109(100.0%)	70(100.0%)	179(100.0%)

Biopsy result was analysed as n=109 (60.9%) of cases were tuberculous PE and n=70 (39.1%) were malignant PE.

Tuberculous vs. Malignant PE (pleural biopsy result)

Malignant PE was analyzed and 20(11.2%) patients were malignant mesothelioma, the primary malignant pleural disease and 50 (27.9%) were metastases to pleura.

The categories of pleural fluid protein were analyzed as 32 (17.9%) of patients were having pleural fluid protein level of category “A”, 59 (33%) were in the

Results

A total of 179 patients were included in our study. Gender distribution shows that 114 (63.69%) patients were male and 65 (36.32%) patients were female.

Age rang was 15-80 years. Most of the patients were in the age group of 20-60 years, in which majority were tuberculosis

57 + 13.13 SD years. Tuberculosis PE was common in younger age group while malignant PE, as expected, in older age group (Table 1)

Gender wise distribution shows that TPE is significantly common in male (p=0.036) (Table 2).

category “B” and 88 (49.2%) of the patients were having protein level in the category “C” The sensitivity and specificity of pleural fluid protein of various categories was analysed as that at category “C” the sensitivity was highest while for the category “A” the sensitivity was the lowest. (Table 3) The positive (PPV) and negative predictive (NPV) values were analysed for the three categories of pleural fluid protein as that PPV was lowest for category A having value of 2.7% while NPV was 58.57%. For category B, PPV was 26.6% while the NPV was having value of 52.87%. The PPV was highest for category C reaching to the value 73.4% similarly the PPV was also highest in this category reaching to the value of 88.57%.

Table 3: Sensitivity versus Specificity of plural Fluid Protein

Categories	Sensitivity	Specificity
C	100.000	0.000
B	97.200	41.430
A	73.30	90.600

Discussion

A systematic approach to the classification of pleural effusion permits the diagnosis of a large number of pleural diseases, especially when considering the high incidence of tuberculosis and cancer in Pakistan. Diagnostic exploration is based on the analysis of clinical variables (gender, age and symptoms),

imaging characteristics (volume and location of fluid), and laboratory (biochemical and cytological) data.

The distinction between tuberculous and malignant pleural effusions poses a diagnostic challenge to the physician. This is mainly due to the large proportion of cases in which no confirmatory diagnosis of pleural tuberculosis is achieved by microbiological methods, and the sensitivity of cytological studies for

malignancy is inadequate. Closed needle biopsy of the pleura is more useful than pleural fluid in establishing tuberculosis as the etiology of the effusion, but for malignant effusions adds little diagnostic yield to fluid cytology alone.²¹

Tuberculosis and malignancy are the most important and commonest causes of lymphocytic exudative pleural effusion. But the ratio is different in developed and developing countries.

In areas where the tuberculosis is not prevalent, MPE is more common than TPE.

In a study, conducted in Spain (2003)²² on 392 patients 73% cases were MPE and 27% were TPE.

Similarly another study which was carried out in Thailand on Lymphocytic exudative pleural effusion showed that 40.6% of cases were MPE, 37.2% were TPE and 22.3% were nonspecific pleuritis.²³

In areas where tuberculosis is prevalent, TPE is more common than MPE as shown in a study¹⁹ conducted in Brazil on 326 patients. TPE cases were 55.9% while MPE were 44.1% of total cases.

Many studies carried out in our country have shown the fact that tuberculosis is the leading cause of lymphocytic exudative pleural effusion followed by malignancy. Javaid A et al²⁴ conducted a study, in collaboration with Pakistan Medical Research Council, on patients with Lymphocytic exudative pleural effusion. Out of total 150 patients, 45% were Tuberculous PE, 24% malignant PE and 31% were cases of chronic non specific pleuritis.

Another local study⁸ from Peshawar carried out on 74 patients who underwent percutaneous pleural biopsy, showed that 52.71% were cases of TPE, and 18.91% were MPE. The pleural biopsy yield was 71.62%.

Similarly in the study²⁵ of Rizwan M, tuberculous pleural effusion was the commonest cause of lymphocytic exudative PE (75%) followed by MPE (22.5%).

Our study also showed the fact that TPE was commoner than MPE, accounting for 60.9% of total cases. Rest of cases (39.1%) was malignant PE.

Age has also been an important complementary variable while deciding about tuberculous or malignant PE.

In our study the TPE was commoner in younger age group than MPE, which was more in older age group. The mean age for TPE was 35.8+ 15.43SD while 57 + 13.13SD was the mean age for MPE. Our findings were comparable with the international studies.

Porcel JM et al (2003) reported in their study,²² the mean age of 30 years (range 22 – 40) in TPE while the mean age was 68(58 – 76) years in MPE cases.

Antonangelo et al¹⁹ reported in their study that patients with tuberculous PE were significantly younger than those with MPE. The mean age was 36 years in tuberculous while in malignant PE the mean age was 58 years.

With respect to gender, it is known²⁶ that men are more predisposed to both tuberculosis and lung cancer, though the incidence of cancer has been increasing among women over the last few decades.

The predominance of females among patients in MPE was observed in our study. This finding is in contrast to international epidemiological data. This bias is easily explained by the tertiary character of our hospital, which is a referral center for cancer with pleural involvement, particularly that secondary to breast Cancer.

Closed pleural biopsy with Abram needle is the main diagnostic tool in exudative pleural effusion in our country and in this regard national and international studies are available showing different diagnostic yield for TPE and MPE. In the study of Javaid et al,²⁴ the diagnostic yield was 69%. 45% cases were tuberculous and 24% malignant PE. Magsi,1 JA et al reported 60% diagnostic yield. Fishman AP et al²⁷ reported 40% diagnostic yield in their patients. Baum GL et al²⁸ reported 51% diagnostic yield in their Meta analysis of 14 studies including 2893 patients. In the study of Heidri et al,²⁹ the diagnostic yield was 70% for TPE and 54% for MPE.

In developed centers various parameters are used for differentiation between tuberculous and malignant PE including (PV) pleural viscosity; (CRP) C-reactive protein ;(CEA) carcinoembryonic antigen; (IL) interleukin; (IFN): interferon; (VEGF): vascular endothelial growth factor; (TNF) tumour necrosis factor and pleural fluid T-cells but no national study has been done on any one of them understandably due to lack of afford ability and availability. Keeping in view these limitations, the total pleural fluid protein was utilized in the present study. It is cheaper, easily available and routinely done in PE cases. This study is the first ever study across the country focusing on the utility of total pleural fluid protein for discrimination between tuberculous and malignant PE.

In our study we showed that pleural fluid protein level was higher in TPE than MPE and the difference was statistically significant at $\geq 5\text{g/dl}$ (category "C"). At $\leq 4\text{g/dl}$ (category "A"), the MPE was commoner than TPE and the differences was significant. These

findings were consistent with international data.

Porcel-perez JM et al (2004)²⁰ reported that 73% of TPE were having pleural fluid protein level $\geq 5\text{g/dl}$. This value was the cutoff point for considering tuberculous etiology of the lymphocytic exudative PE.

In another Spanish study conducted on 105 patients of TPE, 57% of patients showed pleural fluid protein level above 5g/dl .³⁰

Antonangelo et al (2007) reported higher protein level in TPE than MPE. The protein level was $5.3 \pm 0.8\text{g/dl}$ in Tuberculous PE while 4.2 ± 1 was the level in MPE. The difference was statistically significant.¹⁹

Along with other laboratory parameters, protein level was utilized for discrimination between tuberculous and malignant PE. The same findings were found in the study conducted by Liam et al (2000) on patients having tuberculous or malignant PE.³¹

Melo et al proposed 4.5g/dl as cutoff value for diagnostic presumption of TPE.³²

Porcel JM et al (2003) reported protein level of 5.4g/dl in tuberculous while the level was 4.2g/dl in malignant pleural effusion. The difference was statistically significant.²²

Conclusion

Despite the development of advanced investigatory tools in developed countries, the diagnosis of tuberculous or malignant PE has been challenging. These two etiologies still remain the most common causes of undiagnosed lymphocytic exudative PE.

Due to lack of modern and costly investigations, closed pleural biopsy is the main stay of diagnosis in our country but the yield is not high. Due to these limitations total pleural fluid protein, in addition to adequate clinical picture, can be used in decision making to differentiate between tuberculous and malignant pleural effusion.

References

- Magsi JA, Khan SU, Awan SR. Pleural biopsy in the diagnosis of lymphocytic exudative pleural effusion. *Ann King Edward Med Coll* 2005;11:572-4.
- Maskell NA, Butland RJA. BTS Guidelines for the investigation of a unilateral pleural effusion in adults. *Thorax* 2003;58:8-17.
- Storey DD, Dines DE, Coles DT. Pleural effusion: a diagnostic dilemma. *Am J Med Assoc* 1976;236:2183-6.
- Gannels JJ. Perplexing pleural effusion. *Chest* 1978;47:390-3.
- Keshmiri M, Hashemzadeh M. Use of cholesterol in differentiating of exudative and transudative pleural effusions. *Med J Iran* 1997;2:187-9.
- Sahn SA. Pleural anatomy, physiology and diagnostic procedures. In: Baum GL et al. (edi). *Textbook of pulmonary diseases*. 6th ed. Philadelphia: Lippincott-Raven; 1998:255-65.
- Ahmad N, Aamir AH, Hussain I, Ghulam S. Annual prevalence of various diseases in hospitalized patients in tertiary level teaching hospital at Peshawar, Pakistan. *J Med Pes* 2004;43:4.
- Anwar R, Farooqi JI. Causes of lymphocytic exudative pleural effusion as revealed by percutaneous pleural biopsy: experience from Peshawar. *Pak J Med Sci* 2005;21:39-43.
- Kalaajieh WK. Etiology of exudative pleural effusion in adults in north Lebanon. *Can Respir J* 2001;8:93-7.
- Golshan M et al. Common causes of pleural effusion in referral hospital in Isfahan, Iran. *Asia Cardiovasc Thorac Annals* 2002;10:43-6.
- Gopi A, Madhavan SM, Sharma SK, Sahn SA. Diagnosis and treatment of tuberculous pleural effusion in 2006. *Chest* 2007;131:880-9.
- Valdes L, Alvarez D, San Jose E, et al: Value of adenosine deaminase in the diagnosis of tuberculous pleural effusion in young patients in a region of high prevalence of tuberculosis. *Thorax* 1995;50:600-3.
- Ribera E, Ocana I, Martinez-Vazquez JM, Rosell M, Español T, Ruibal A: High level of interferon gamma in tuberculous pleural effusion. *Chest* 1988;93:308-11.
- Verea Hernando HR, Masa Jimenez JF, Dominguez Juncal L, Perea Garcia-Buela J, Martin Egana MT, Fotan Bueso J: Meaning and diagnostic value of determining the lysozyme level of pleural fluid. *Chest* 1987;91:342-5.
- Villena V, Rebollo MJ, Aguado JM, Galan A, Lopez Encuentra A, Palenque E: Polymerase chain reaction for the diagnosis of pleural tuberculosis in immunocompromised and immunocompetent patients. *Clin Infect Dis* 1998;26:212-4.
- Caminero JA, Rodriguez de Castro F, Carrillo T, Lafarga B, Diaz F, Cabrera P. Diagnosis of pleural tuberculosis by detection of specific IgG anti-antigen 60 in serum and pleural fluid. *Respiration* 1993;60:58-62.

- 17 Valdes L, Alvarez D, San Jose E, et al. Tuberculous pleurisy: a study of 254 patients. *Arch Intern Med* 1998; 158:2017–21.
- 18 Chakrabarti B, Ryland I, Sheard J, Christopher J, Warburton, Earis EJ. The role of Abrams percutaneous pleural biopsy in the investigation of exudative pleural effusion. *Chest* 2006;129:1549-55.
- 19 Antonangelo L, Vargas FS, Seiscento M, Bombarda S, Teixeira L, Sales RK. Clinical and laboratory parameters in the differential diagnosis of pleural effusion secondary to tuberculosis or cancer. *Clinics* 2007;62:585-90.
- 20 Porcel-Perez JM, Vives SM, Esquerda SA, Jover SA. Cutoff values of biochemical tests on pleural fluid: their usefulness in differential diagnosis of 1040 patients with pleural effusion. *An Med Interna* 2004;21:113-7.
- 21 Ferrer J: Tuberculous pleural effusion and tuberculous empyema. *Semin Respir Crit Care Med*, 2001;22:637-46.
- 22 Porcel JM, Vives M. Differentiating tuberculous from malignant pleural effusion: A scoring model. *Med Sci Monit* 2003;9:175-80.
- 23 Chierakul N, Kanitsap A, Chaiprasert A, Virivataveekul R. A simple C- reactive protein measurement for the differentiation between tuberculous and malignant pleural effusion. *Respirology* 2004;9:66-9. Javaid
- 24 Javaid A, Amjad M, Shah N, Samad A, Ullah Z. Diagnostic evaluation of exudative pleural effusion, the value of pleural biopsy. *Pak J Chest Med* 2001;7:12-20.
- 25 MR. Khaliq Pleural biopsy by Abrams punch needle pattern and frequency of histopathological lesions encountered in patients with exudative pleural effusion. *Ann Abbasi Shaheed Hosp Karachi Med Dent Coll* 2003;8:6-11.
- 26 Parkin DM. Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *Cancer J Clin* 2005;55:4-108.
- 27 Fishman AP, Elias JA, Fishman JA, Grippi MA, Kaiser LR, Senior RM. Disorders of pleural space. In: *Fishman's pulmonary diseases and disorders*. 3rd ed. Washington DC: McGraw-Hill; 1997:1389-1452.
- 28 Baum GI, Crop JD, Celli BR, Karlinsky JB. Pleural anatomy, physiology, and diagnostic procedures. In: *Textbook of pulmonary diseases*. 6th ed. New York: Lippincot-Raven; 1997:255-65.
- 29 Heidari B, Bijani K, Eissazadeh M, Heidari P. Exudative pleural effusion: effectiveness of pleural fluid analysis and pleural biopsy. *East Meditter Health J* 2007;13:765-73.
- 30 Haro M, Ruiz-Manzano J, Gallego M, Abad J, Manterola JM, Morera J. Pleural tuberculosis: analysis of 105 cases. *Enferm Infecc Microbiol Clin* 1996;14:285-9.
- 31 Liam CK, Lim KH, Wong CM. Differences in pleural fluid characteristics, white cell count, biochemistry of tuberculous and malignant pleural effusions. *Med J Malaysia* 2000;55:21-8.
- 32 Melo AF, Santos ML. Diagnóstico da tuberculose pleural pela ada, isolada ou combinada a outras variáveis, inclusive em hivpositivos. *Folha Med* 2000;119:19-21.