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ORIGINAL ARTICLE

Diagnostic Accuracy of Sonographic Septations in Tuberculous and Malignant Pleural Effusions

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ABSTRACT

Background: Discrimination between tuberculous (TB) and malignant pleural effusions is a real practical challenge because both exist as exudative lymphocytic type. Transthoracic ultrasonography not only identifies and quantifies pleural effusion but also displays sonographic septations, which are frequently seen in TB pleural effusions and can help in differentiation between tuberculosis and malignancy successfully, without any invasive procedure. We designed this study to determine the diagnostic usefulness of these septations for tuberculous and malignant pleural effusions.

Material and Methods: This prospective study was conducted in the OPD of Gulab Devi Chest Hospital Lahore, Pakistan, a 1500 bedded tertiary care hospital, from November 2016 to February 2018. Total of 339 consecutive cases, aged 14-83 years with radiological evidence of pleural effusion were included in the study. After detailed history, thorough physical examination, radiological, haematological and biochemical findings were recorded. Pleural fluid macroscopic, cytological, microbiologic and biochemical analysis results were also recorded. Ultrasonography was done, septated and non-septated pleural effusions identified and findings were noted. SPSS-16 was used for statistical evaluation. Fisher Exact test was utilized for comparison between TB and malignant cases with *P*-value < 0.05 taken as significant. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), diagnostic accuracy and positive likelihood ratio were calculated.

Results: Out of total 339 cases, 49 (14.45%) were malignant and 290 (85.55%) were non-malignant. In the malignant group, only 03 cases (6.12%) showed sonographic septations. In the non-malignant group, 259/290 (89.31%) cases showed tuberculous etiology and 187/259 (72.20%) of these cases displayed sonographic septations. By considering septations as predictor of TB, statistical analysis revealed a sensitivity of 79.23%, specificity of 92.85%, PPV of 98.42%, NPV of 44.31% and diagnostic accuracy of 81.29%, respectively.

Conclusions: Sonographic septations can be a valuable predictor of tuberculosis, in a population with high prevalence of the disease. We found it to be a useful feature in differentiating between a malignant and tuberculous etiology, in exudative lymphocytic pleural effusions. It can be used with confidence in patients who are unfit for interventional procedures.

Key words: Pleural effusion, Sonographic septations, Transthoracic ultrasonography, Tuberculosis

Authors' Contribution:
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Introduction

A pleural effusion (PE) is always abnormal and indicates the presence of an underlying disease. Many infective, neoplastic, inflammatory, metabolic or connective tissue disorders produce pleural effusions. It can be an exudate or transudate depending upon the protein content of the pleural fluid (PF). According to the Global Tuberculosis (TB) report by WHO, TB is endemic in Pakistan, which occupies the fifth position among the high burden countries.[1] The incidence of TB is 497/100,000 in Pakistan. TB is usually considered the sole cause of an exudative lymphocytic pleural effusion until proven by further work up. According to literature, TB is the most common cause of exudative pleural effusion.[2] Malignancy and acute infections are also significant contributors.[3] The Gold Standard for TB diagnosis is capturing acid-fast bacilli (AFB) in pleural fluid, but the yield is less than 20%.[4,5] About 40-70% cases can be diagnosed by an invasive procedure like pleural biopsy followed by histopathology.[6-8] In spite of utilizing all these tools, 10-20% cases still remain undiagnosed.[9] Similarly negative results on AFB smear, culture and histopathology reports do not rule-out TB.

The chest ultrasonography has been gaining popularity for the evaluation and management of lung cancer, consolidations, mediastinal tumors, and pleural diseases during the last decade.[10,11] It has emerged as an excellent imaging tool for assessing the quantity and nature of pleural effusions. Sonographic septations are frequently present in exudates and very commonly found in tubercular pleural effusions.[12] Current literature reports that tuberculous pleural effusions and empyema commonly have complex septated sonographic appearances.[13-15]

Pyogenic effusions (empyema and parapneumonic PE) can be isolated by typical clinicopathological findings but the discrimination between TB and malignancy still remains a practical challenge, because both exist as exudative-lymphocytic type of PE. The differentiation between tuberculosis and malignancy is made by pleural fluid cytology, adenosine deaminase levels and pleural biopsy. [16,17] Pleuroscopic biopsy is the standard widely-used technique, but requires special equipment and expertise.[18] It has its own complications and lacks cost-effectiveness.[19] In this scenario, there is a need for a safe, readily available and cost-effective tool capable of discriminating TB from malignancy. This study was designed with the primary objective of evaluating the diagnostic usefulness of sonographic septations in predicting tuberculosis. In order to achieve this objective, we first diagnosed pleural effusions on the basis of pleural fluid analysis and laboratory investigations, then identified the sonographic patterns in different types of PEs and finally compared the usefulness/efficacy of sonographic septations in differentiating between TB and malignant PE.

Material and Methods

This prospective study was conducted at Pulmonology OPD of Gulab Devi Teaching Hospital, Lahore Pakistan (a 1500 bed tertiary care hospital). Ethical approval was obtained from the IRB of the hospital (IRB No. Admin/GDEC/18-549) prior to the commencement of the study. Informed consent was taken from all the patients enrolled in the study. Sample size was calculated using the OpenEpi sample size formula for cross-sectional studies $[(Z_{1-a/2})^2 \times P(1—P)/d^2]$. Total of 339 consecutive patients, reporting from November 2016 to February 2018 (15-months period) were recruited. Patients with undiagnosed pleural effusions (on laboratory investigations and ultrasound), aged 14-83 years and willing for pleural aspiration/biopsy were included. The

exclusion criteria included minimal PE, pleural effusions with diagnosed etiology, previous pleural interventions and any contraindication to pleural aspiration.

The diagnostic tools included chest x-ray posteroanterior (PA) and lateral views, and ultrasound examination (Toshiba, Japan) with 3.5-5.5 MHz convex probes. After a thorough history and physical examination, patients were evaluated with grey scale ultrasonography machine (Toshiba, Japan) using 3.5-5.5 MHz convex probes. Anterior, posterior and lateral scans were obtained in sitting and supine positions. Both hemithoraces were scanned systematically. Pleural effusions, septations, loculations and pleural thickenings were diagnosed. Four main sonographic patterns were recognized: 1. Anechoic pattern having no echoes inside the effusion (simple effusion), 2. Complex septated pattern with fibrous bands running inside the complex effusion, 3. Complex non-septated pattern with effusion without any septation, 4. Homogenous echogenic pattern with effusion consisting of homogenous bright echoes.

Ultrasound-guided pleural fluid aspiration was done and sent for biochemistry, cytology, AFB smear, culture and sensitivity (C/S) and adenosine deaminase (ADA) levels. CBC, ESR, serum proteins, liver function tests (LFTs) and renal function tests (RFTs) were performed. Pleural fluid analysis results including macroscopic findings, cytological, microbiological and biochemical analysis were recorded. Exudates and transudates were classified by Light's criteria.[20] Exudates were further sub-classified into neutrophilic and lymphocytic by differential leukocyte count (DLC). Para-pneumonic effusions and empyema were diagnosed by typical short history, peripheral leukocytosis, neutrophilic exudate, homogenous echogenic pleural effusion, Gram staining and C/S results.

Tuberculosis was diagnosed by history, pyrexia of unknown origin (PUO), history of contact, lymphocytic exudates, caseating granulomas and by capturing AFB. Pleural fluid (PF) ADA level with a cut-off value of 40 IU/L was used for diagnosis of TB. Anti-TB treatment initiated according to DOTs protocol and response to treatment was considered for final diagnosis. Patients were followed up for six months at least. All observations were recorded in a proforma. Findings were tabulated, sonography patterns were compared with the final clinical diagnosis and statistical analysis was done.

SPSS-16 software package was used for statistical evaluation. Quantitative data was expressed as means with standard deviation and categorical variables were presented as percentages. Fisher Exact test was utilized for comparison between TB and malignant cases. *P*-value < 0.05 was considered significant. Patients with disease and also having septations were considered true positive (TP), cases with disease but without septations were false negative (FN), cases without disease but with septations were false positive (FP) and patients without any disease and with no septation were defined as true negative (TN). Sensitivity, specificity, PPV, NPV, diagnostic accuracy and positive likelihood ratio were calculated.

Results

Total 339 cases were enrolled with 233 (68.73%) male and 106 (31.26%) female patients, respectively (male-to-female ratio of 2.2:1.2). About 339 (62.24%) pleural effusions were on the right side while 128 (37.75%) were on the left side. The mean age of the patients was 48.5 ± 21.6 years (age range 14-83 years). The mean age for tuberculous and pyogenic effusion was 28 years while for malignant group it was 41 years. Forty-nine cases (14.45%) were found with a malignant etiology. Of the non-malignant (n=290; 85.55%)

cases, 259/290 (89.31%) had tuberculous etiology, while 31/290 cases (11.96%) had a pyogenic cause (parapneumonic PE and empyema). Regarding clinical presentation of the patients, 282 (83.18%) presented with chest pain, 264 (77.87%) with cough, 247 (72.86%) with fever, 210 (61.94%) with dyspnea, 200 (58.99%) with expectoration and 198 (58.4%) with loss of appetite, respectively. About 48 (14.15%) gave history of previous contact with TB patients, 36 (10.61%) cases had hemoptysis, 44 (12.97%) clubbing and 37 (10.91%) cases were found with known diabetes mellitus.

Table I: Pleural Fluid analysis and Laboratory investigations for diagnosis of Pleural effusions (n = 339)

S No	Diagnosis of PE (n=339)	Pleural Fluid Analysis n (%)						Mean Concentrations			
		Clot +ve	Mean Protein gm/dl	AFB	Pyogenic Culture	Infl Cells (Poly/ Lymph)	Cancer Cells	Serum Protein (gm/dl)	ESR (mm/1st hr)	TLC /mm^3	Hb (gm%)
1.	*TB (n=259)	251 (97)	5.3	0.00	0.00	Lymph 255 (98.43)	0.00	6.49	39.0	8,450	11.86
2.	*Pyogenic (n=31)	0.00	5.9	0.00	26 (83.9)	Poly 26 (82)	0.00	7.7	31.6	13,750	10.9
3.	*Malignant (n=49)	0.00	5.0	0.00	0.00	Lymph 42 (85.71)	38 (77.55)	7.2	69	10,220	8.2

*Percentages are calculated independently for each etiology.

PE-Pleural effusion; n-Number of patients; +ve-Positive; AFB-Acid-fast Bacilli; ESR-Erythrocyte sedimentation rate; TLC-Total leukocyte count; Hb-Hemoglobin; Infl cells- Inflammatory cells; Poly-Polymorphonuclear leukocytes/neutrophils; Lymph-Lymphocytes

Table II: Frequency distribution of sonographic patterns in different types of pleural effusions (n = 339)

S No.	Sonographic Patterns of PE	Types of pleural effusions n (%)			Total Cases n (%)
		Tuberculous (n=259)	Malignant (n=49)	Para-pneumonic (n=31)	
1.	Anechoic	23 (8.88)	5 (10.20)	2 (6.45)	30 (8.84)
2.	Complex septated	187 (72.2)	03 (6.12)	6 (19.35)	196 (57.81)
3.	Complex non-septated	49 (18.91)	39 (79.59)	7 (22.58)	95 (28.02)
4.	Homogenously echogenic	0.00	2 (4.08)	16 (51.61)	18 (5.3)

The details of pleural fluid analysis and laboratory investigations for tuberculous, pyogenic and malignant pleural effusions are shown in Table I.

On cytology, 308/339 (90.85%) showed lymphocytic infiltration, 31/339 (9.14%) neutrophilic infiltration and 38/339 (11.20%) were found with malignant cells. About 76.4% cases with lymphocytic infiltration were of tuberculous etiology and 14.45% were found in malignant cases. Table II shows the distribution of sonographic patterns in different types of pleural effusions. There were 278 cases of complex pleural effusions, 190 patients with complex septated PE and 88 cases with complex non-septated PE. All these cases had a TB and malignant etiology. By considering complex septated pattern as predictor of TB diagnosis, 187 cases were TP, 3 cases were

FP, 39 cases were TN and 49 cases were FN. Statistical analysis revealed a sensitivity of 79.24% (95% confidence interval 73.5% to 84.23%), specificity of 92.86% (95% CI 80.52% to 98.5%), PPV of 98.42% (95% CI 95.44% to 99.46%), NPV of 44.32% (95% CI 37.96% to 50.87%), diagnostic accuracy of 81.29% (95% CI 76.21% to 85.70%) and Positive Likelihood Ratio of 11.09 (95% CI 3.72 to 33.07). Similarly, sensitivity, specificity, PPV, NPV, positive likelihood ratio and diagnostic accuracy were also determined for malignancy by using sonographic septations. Comparative efficacy is depicted in Table III. By using sensitivity and specificity for TB and malignancy from Table III, the Fisher exact test *P*-value is 0.0418 which is statistically significant.

Table III: Comparative Efficacy of Sonographic Septations in TB and Malignant PE

Statistical Test	Tuberculous PE n = 236	Malignant PE n = 42
Sensitivity	79.23%	7.14%
Specificity	92.85%	20.76%
PPV	98.42%	1.57%
NPV	44.31%	55.68%
Positive likelihood ratio	11.15	0.089
Diagnostic Accuracy	81.29 %	18.70%

PPV: Positive predictive value, NPV: Negative predictive value.

*By using sensitivity and specificity for TB and malignant PE, p-value (by Fisher exact test) is 0.0418 which is statistically significant.

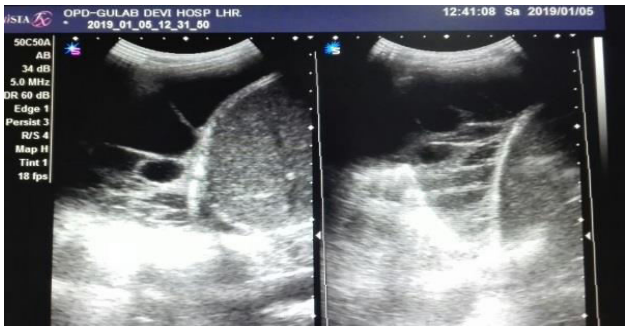

Figure 1: Transthoracic ultrasound image showing sonographic septations in Tuberculosis PE.

Discussion

We aimed to evaluate the usefulness of sonographic septations for the diagnosis of TB PE and its comparative efficacy in differentiating TB from malignant PE. Exudative lymphocytic pleural effusions are a diagnostic dilemma and TB is a common cause in high prevalence areas. That is why many undiagnosed patients with exudative lymphocytic pleural effusions are found on anti-TB drugs.[20] Pyogenic infections and malignancy are also significant contributors to this type.[21] Sonographic septations are found in all these entities (TB, pyogenic and malignant) but with different frequencies.

This study showed a male to female ratio of 2.19:1, indicating a male predominance in our population. The mean age for our study population was 48.5 years with an inter-quartile range of 40, which is higher than that reported by Hira et al. (48.5 vs 31.7 years).[8] The mean age for non-malignant group was 28 years. This group included pyogenic infections and mostly fresh cases of tuberculosis. The mean age for malignant group was 41 years. A small number of TB cases were also found in elderly age group, which comprised mostly of previously treated patients. These cases were either due to re-infection or reactivation of previously healed lesions, as shown by other authors as well.[22]

Chest pain, fever and cough were the predominant symptoms in this study, which are the usual, non-specific respiratory complaints. Dyspnea, expectoration and loss of appetite were also found in a significant number. These clinical features are consistent with the reports of Light[2] and Porcel et al.[3] The sudden onset pointed towards pyogenic infection, clubbing of finger suggested chronic suppurative processes like pyothorax and pyopneumothorax and positive history of contact with TB-patients raised a high index of suspicion for tuberculosis.

Maskell and Butland also reported tuberculous effusions as a predominant cause, followed by malignant and parapneumonic effusions.[23] This high percentage for TB is due to the fact that our region is endemic for tuberculosis with Pakistan ranked as fifth among the high burden countries with an annual incidence of 497/100000.[24] In short, tuberculosis is the commonest etiology, followed by malignancy and pyogenic infections (parapneumonic PE and empyema) which is compatible with reports from the current literature.[25]

In this study, out of 339 cases, 196 had septations and 6/196 pyogenic cases were isolated easily by acute onset, high blood and pleural fluid TLC count, culture sensitivity findings and homogenous echogenic pattern. Out of remaining 190 cases with septations, 3/190 (1.57%) were malignant while 187/190 (98.42%) had TB pleural effusion. Current researchers have tried the application of intra-pleural sonographic septations for early diagnosis of tuberculosis in exudative lymphocytic pleural effusions.[26] The intra-pleural fibrinous matrix formation is due to disordered fibrin turn-over. The dynamic equilibrium is lost and fibrin formation is up-regulated while fibrin dissolution is down-regulated. Furthermore, cytokines, such as TGF-β and TNF-α enhance the fibrin matrix formation. According to Kunter et al., high levels of pleural fluid glucose, alpha-1 acid glycoprotein (AAG) and C-Reactive protein, seen in these patients might be responsible for pleural thickening.[27]

Philip-Joet et al. and Hua et al. displayed significantly higher levels of plasminogen activator inhibitor and Von Willebrand factor in patients with tuberculosis than in those with cancer. They also reported increased levels of tissue-type plasminogen activators in some malignant pleural effusions. These findings reveal that fibrinolytic activity is higher in malignant pleural effusions than tuberculous pleural effusions.[28,29] Chen et al. also reported that complex septated pattern is a useful diagnostic tool for discriminating tuberculosis from lung cancer.[26] A number of authors reported pleural infections, including tuberculosis as a cause of intra-pleural fibrosis, in addition to other causes. In 1989 Martinez et al. reported that winding bands were seen by ultrasonography in 38% patients with TB pleural effusion.[30] These facts further confirm our findings that fibrin strands were more common in tuberculous than cancer-related pleural effusions, hence septations are more commonly encountered in tuberculous pleural effusions.

There were 190 cases of sonographic septations after excluding pyogenic cases (proven TB PE n=187; Malignant PE n=3) The frequency of TB effusion was 98.42% and that of malignancy was 1.57% with a wide gap between the two entities. The Fisher exact test was highly significant ($P< 0.00001$) and suggests that tuberculosis can be predicted with a high degree of confidence in complex, exudative lymphocytic PE just by finding sonographic septations, with no need for any invasive procedure. By group wise analysis, there were 3 cases of septated pleural effusions in 49 cases of malignancy, which is only 6.1% of total malignant group, indicating a very low chance of malignancy in septated pleural effusions. Similarly, there were 187 cases (79.23%) of septated pleural effusions out of 236 complex TB-pleural effusions, indicating that by finding sonographic septations, chance of malignancy is only 6.1%, while for tuberculosis it is 79.23%. It means we can correlate sonographic septations with tuberculosis by high level of confidence in clinical suspects.

Conventionally, the differentiation between TB and malignant pleural effusion is made by pleural fluid cytology, pleural biopsy, histopathology and immuno-cytology, which are invasive, costly, time-consuming and expertise-dependant procedures. Furthermore, the availability of these facilities is also an issue in resource limited populations. On

the other hand, sonographic septations do not have such disadvantages and can help in predicting tuberculosis immediately, without any delay, invasion and complication.

In the light of this discussion, it can be said that the finding of sonographic septations is useful in clinical practice for differentiating tuberculous from malignant pleural effusions with confidence, in high prevalence populations. It can be very useful in those areas where facilities for invasive procedures are not available or in patients who are not fit for invasive procedures.

The main limitation of our study was that this was a single centre study and the number of patients in malignant and pyogenic group was small as compared to TB group. This might be because the study is prevalence dependent. As 339 consecutive patients were included in the study, there is more probability of getting TB cases in larger number in an endemic population as compared to non-TB patients.

Conclusion

Sonographic septations are non-invasive, easily detectable, cost effective and valuable predictor of TB diagnosis in exudative lymphocytic pleural effusions, in high prevalence populations. It can be used with confidence for making differentiation between malignant and TB PEs. Furthermore, it can provide tremendous help for point of care diagnosis in non-ambulatory and serious patients.

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