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Ultrasound Guided Complete Thoracentesis, Precluding Residual Pleural Thickening in Pleural Tuberculosis: A Case-Control Study

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ABSTRACT

Introduction: Pleural effusion is the commonest extra-pulmonary manifestation of tuberculosis in endemic populations. This is managed in routine, by diagnostic aspiration and treated with anti-TB medicines. A significant number of treated patients remain visiting pulmonology and thoracic surgery departments, for chest pain, abnormal chest x-ray, and shortness of breath due to residual pleural thickening (RPT).
Aims &Objectives: The study was conducted to determine the usefulness of complete thoracentesis under ultrasound guidance over diagnostic aspiration in preventing residual pleural thickening.
Place and duration of study: This case-control study was conducted from 01-07-21 to 30-06-2022 at Pulmonology-OPD of Gulab Devi Teaching Hospital Lahore-Pakistan.
Material & Methods: After approval from IRB and informed consent, 300 consecutive patients with age 14-85 years, diagnosed TB-pleural effusion, willing for intervention and participation in study were included in the study while pediatric patients, non-TB effusions and unwilling for aspiration or participation were excluded. Two groups of 150 each were allocated through odd and even numbers. Therapeutic aspiration under ultrasound guidance for interventional group and diagnostic aspiration of 50-100 ml for control group was performed. All patients were treated with same standard and followed up according to the principles of DOTS. Pleural thickness was measured utilizing ultrasonography at day 0, 60 and 180. Outcome was compared in both groups. SPSS-24, software was utilized for analysis. $p \leq 0.05$ was taken as significant.
Results: Only 31/150 patients (20.66%) from interventional group displayed residual pleural thickening while148/150 cases (98.66%) with residual pleural thickening were noted in control group. The P-value was 0.00001
Conclusion: Complete thoracentesis under ultrasound guidance is a tremendous tool for precluding residual pleural thickening in tubercular pleural effusions.

Keywords: Effusion, Pleural, Residual pleural thickening (RPT), Tuberculous, Thoracentesis, Therapeutic

INTRODUCTION

Tuberculosis (TB) remains a challenging public health issue in resource limited countries[1]. About 1/3rd of the globe is infected with Mycobacterium and TB is the leading infectious cause of death worldwide[2]. According to National Institute of Health Pakistan study 2022, pleura is the commonest extra-pulmonary site involved by tuberculosis and disease is manifested as pleural effusion. When a sub-pleural tubercular focus ruptures into pleural space, inflammation is triggered by mycobacterium tuberculosis and its metabolites and evoked by hypersensitivity phenomenon. The pleural inflammation starts with neutrophilic response which is followed by macrophage influx and later on T-helper lymphocyte driven immune reaction occurs, resulting in granuloma formation[3].

Inflammation evolves an increased capillary permeability, influx of proteins and fluid into pleural space, resulting in accumulation of protein rich fluid in pleural space. If patient is not treated timely with appropriate strategy, fibrin protein deposition occurs on pleural surfaces. The lymphatic stomata in parietal pleura are blocked, resulting in a decreased rate of fluid absorption. In this way, the dynamic equilibrium between fluid formation and absorption is lost emerging in effusion accumulation, pleural[4] thickening, septae and adhesions formation and in some cases even trap lung can be the outcome. Vorster MJ et al (2015) communicated that residual pleural thickening is a well-recognized complication of tubercular pleural effusion (TBPE) having prevalence, varying between 5-55%[5].

It is estimated that 3-25 % of TB-patients develop pleural effusion in endemic populations. In a

series of 833 Chinese patients, 40.1% were confirmed TB on medical thoracoscopy while Chen RL et al (2017) reported a percentage of 23.3%[6,7]. In India, Prabhu VG and co-workers (2012) revealed 23.5% TB pleural effusion[8]. Diacon AH (2003) disclosed 84.2% in South Africa[9]. DePew ZS and associates (2014) divulged 0.0% tubercular pleural effusions in USA[10]. The incidence of TB pleural effusion is increasingly recognized, even in developed countries following HIV pandemic[11] Gopi A et al. (2006) exhibited that even after successful treatment with standard anti-TB drugs, pleural thickening and calcification can occur in 10–72% of patients[12]. Kumar A et al described pleural thickening as organizing phase after granuloma formation in tubercular pleural effusions[13]. Meghji J et al manifested that post treatment pleural thickening of more than 10 mm was seen in 20–46% patients[14].

A TB-pleural effusion presents usually, as an acute illness by chest pain, shortness of breath, fever and dry cough, interfering with daily activities[8,9]. About 50-100ml pleural fluid is aspirated for diagnostic purpose in routine and remaining fluid is left inside to be absorbed by medical treatment. Around 50% patients show variable degree of pleural thickening at the conclusion of treatment which appears as a homogenous opacity obscuring costo-phrenic angle. While the patient experiences chest pain & shortness of breath and remains upset for abnormal x-ray even after completing full course of treatment. Patient visits pulmonology or thoracic surgery department for the rectification of these issues. Each following physician considers such cases as pleural effusion but no fluid is found on attempted pleural aspiration. Patients are subjected to sophisticated costly procedures in search of diagnosis an ultrasound and or CT-scan usually uncovers residual pleural thickening. Literature points out that complete thoracentesis may reduce residual pleural thickening[15,16].

Since we encounter a significant number of such cases in our department daily, we conducted this research to determine the effect of complete thoracentesis on post treatment pleural thickening. And its objective is to determine the usefulness of complete thoracentesis over diagnostic aspiration in TB-pleural effusions, for precluding residual pleural thickening.

MATERIAL AND METHODS

This prospective, case-control study was conducted at Pulmonology-OPD of Gulab Devi Teaching Hospital Lahore-Pakistan. The research ensued on 01-07-2021 and continued till 30-06-2022. Ethical approval was obtained from IRB of the hospital vide no Admin/GDEC/257/19..

An interventional case was defined as a patient for which thoracentesis was done under ultrasound guidance till complete evacuation. While a control case was defined as a patient for which only 50-100ml fluid was drawn for diagnostic purposes only, while remaining fluid was left behind, in pleural space. Three hundred adult patients of both genders with unilateral pleural effusion, having volume 500ml-1000ml measured by trans-thoracic ultrasound, willing for intervention and participation in study were included via out-patient department. While patients with age < 14 years, small pleural effusion, bilateral pleural effusion, massive effusion, suspected non-TB effusion, pregnancy, Hematopoietic malignancy, Known Hepatic disease, not willing for intervention, ADA estimation and participation in study were excluded.

300 consecutive patients were divided into two groups Interventional (group-A) and Control (group-B), containing 150 patients each with approximately similar demography, by odd and even numbers. All patients were investigated with thorough history, physical examination, radiography, ultrasonography, CBC, ESR and pertinent biochemical tests. The Group-A patients underwent complete thoracentesis, but diagnostic aspiration was performed for G±±roup-B patients. Fluid aspiration was carried out under ultrasound guidance and complete evacuation was obtained under real-time visualization, using Sonovista-fx(Siemen)machine. Pleural fluid biochemistry, cytology and ADA estimation was done.

A diagnosis of tubercular etiology was made by clinical scenario, exudative lymphocytic pleural fluid combined with pleural fluid Adenosine Deaminase (ADA) level. A cut-off value of 40 IU/L or more was considered diagnostic for TB. All patients were treated with Anti-TB medicines according to DOTS (Directly observed treatment short course) protocol. Patients were followed up for 6-9 months. Chest radiography and ultrasonography were performed at day 0, 60 and 180. Pleural thickening was measured by trans-thoracic ultrasound. A pleural thickness < 5mm were considered mild, 5-10mm moderate, while > 1.0cm were labeled as gross pleural thickening.

All findings were recorded on a preformed case report form. Findings were summarized, tabulated and conclusions were drawn by statistical analysis. SPSS-24, software, was used for statistical analysis. Categorical variables were represented as

frequency; quantitative data was computed as mean with ± SD and Fisher Exact test was utilized for comparison. Odds ratio was calculated to determine the level of association between complete thoracentesis and residual pleural thickening (RPT). Sensitivity, specificity, PPV, NPV and accuracy of therapeutic thoracentesis was calculated, considering "Complete clearance" as benchmark. 95 % confidence interval was observed for defining precision. A value of $p < .05$ was considered to be statistically significant.

RESULTS

The study population included 210 (70%) male and 90 (30%) female patients. Male to female ratio was 2.3:1. The age range was 14-85 years. Mean age was 32.94 ± 17.38 years for group (A) and 33.45 ± 17.15 years for (B) respectively with a p-value of 0.19. Patients presented with general and respiratory symptoms (Table-1). Trans-thoracic ultrasonography showed 96/150 cases (64.0%) with complex septated pleural effusions and 54/150 patients (36.0%) with non-septated pleural effusions in interventional group. The control group showed 89/150 cases (59.33%) with complex septated pleural effusions & 61/150 patients (40.66) with complex non-septated pleural effusions at the initiation of the study. The p-value was 0.4762. The result was not significant at $p<0.05$. Transthoracic findings were recorded in (Table-2).

No.	Clinical presentation	Observed cases	Frequency
1.	Chest Pain.	280	93.33%
2.	Shortness of Breath	230	76.66%
3.	Fever	225	75.00%
4.	Decreased Appetite	219	73.00%
5.	Weight loss	240	80.00%
6.	Cough	168	56.00%
7.	Contact History	54	18.00%
8.	H/o Night sweats	221	73.66%

Table-1: Frequency of clinical features in 300 patients

No.	Study Groups	Pleural Thickening Cases N(freq) Day-0	Pleural Thickening Cases N(freq) Day-60	Pleural Thickening Cases N(freq) Day-180
1.	Interventional Group A (n=150)	Mild = 37(24.66%)	Mild = 54(36.0%)	Mild = 19(12.66%)
		Moderate = 94(62.66%)	Moderate = 22(14.66%)	Moderate = 12(8.0%)
		Gross = 19(12.66%)	Gross = Nil(0.0%)	Gross = Nil(0.0%)
				No Pleural Thickening (Complete Clearance)= 119 (79.33%)
2.	Control Group B (n=150)	Mild = 45(30.0%)	Mild = 37(24.66%)	Mild = 12(8.0%)
		Moderate = 87(58.0%)	Moderate = 99(66.0%)	Moderate = 25(16.66%)
		Gross = 18(12.0%)	Gross = 14(9.33%)	Gross = 111(74.0%)
				No Pleural Thickening (Complete Clearance)= 02 (1.33%)

Table-2: Ultrasonographic Findings n=300
*Mild pleural thickening:< 0.5cm, Moderate pleural thickening: 0.5-1.0cm, Gross pleural thickening:> 1.0cm, n: number.

The interventional group showed mild to moderate pleural thickening in 31 cases while complete clearance was noted in 119 cases. This group displayed no cases with gross pleural thickening. The control group demonstrated variable pleural thickening in 148 cases while complete clearance was found only in 02cases. Fisher exact test statistic value was <0.00001, significant at $p< .05$. shown in Fig-1 and Fig-2.

The Comparative analysis is shown in Table-3. Odds ratio was calculated using Table-4. Considering, sonographic clearance as positive outcome, the odds of a patient experiencing a positive outcome, with complete thoracentesis was calculated as: Odds = P(positive) / 1 – P(positive) = (119/150) / 1-(119/150) = (0.793) / (0.207) = 3.83. Similarly, the odds of a patient experiencing a positive outcome with existing treatment, was calculated as: Odds = P(positive) / 1 – P(positive) = (2/150) / 1-(2/150) = (0.013) / (0.987) = 0.013.
Odds Ratio = 3.83 / 0.013 = 294.61
Therapeutic efficacy of complete evacuation was tabulated Table-5.

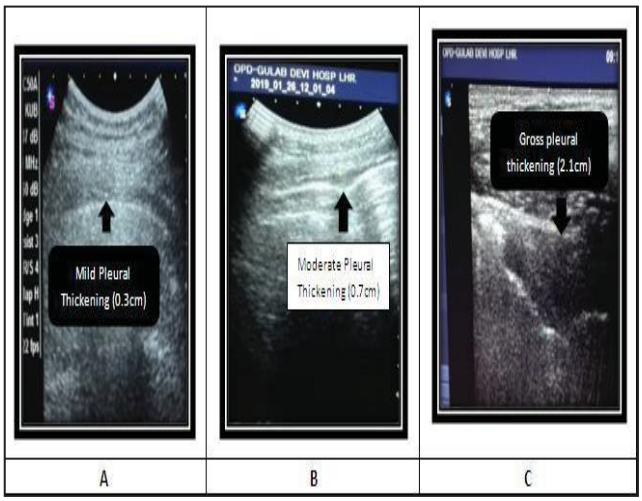

Fig-1: Sonographic grading of pleural thickening.
A:Mild Pleural Thickening.
B:Moderate Pleural Thickening.
C:Gross Pleural Thickening.

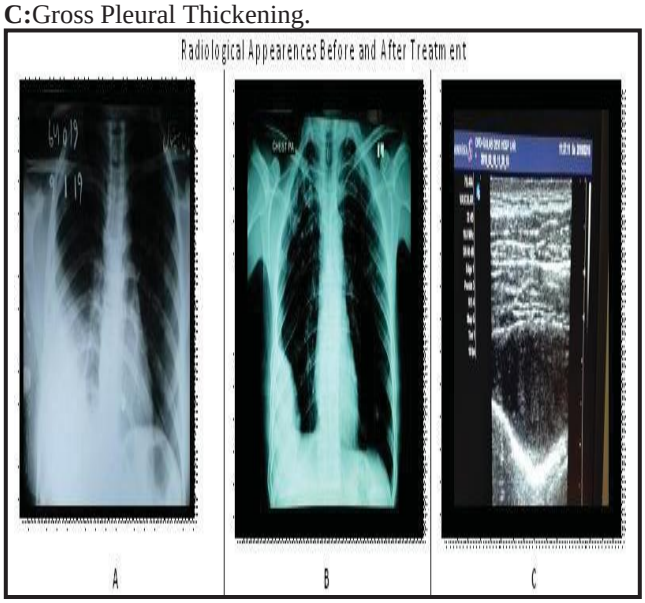

Fig-2: Radiographical Appearance Before & After Treatment.
A: CXR-Before Treatment.
B: CXR-After Treatment.
C: Sonogram- Residual pleural thickening.

Sonographic Appearence	Group A Patient	Group B Patient	Fisher exact test statistic value	P-value significant at p<.05
Mild pleural thickening	19	12	0.261	Not significant
Moderate pleural thickening	12	25	0.0546	Not significant
Gross pleural thickening	00	111	<0.00001	Highly significant
Total pleural thickening cases	31	148	<0.00001	Highly significant
Complete clearance	119	02	<0.00001	Highly significant

Table-3: Comparative analysis between groups

Therapeutic outcome	Positive outcome	Negative outcome
Effect with new Treatment (Intervention) Group-A	119	31
Effect with existing Treatment (Control) Group-B	02	148

Table-4: Odds ratio calculation for complete clearance.

Statistic	Value	95% Confidence Interval
Sensitivity	98.35%	94.16% to 99.80%
Specificity	82.68%	76.33% to 87.92%
Positive Predictive Value	79.33%	73.58% to 84.11%
Negative Predictive Value	98.67%	94.92% to 99.66%
Accuracy	89.00%	84.90% to 92.31%

Table-5: Efficacy of complete thoracentesis for complete sonographic clearance.

DISCUSSION

The aim of this study was to find ways for reducing the frequency of RPT in tubercular pleural effusions and in turn the miseries of the patients. Any patient once treated should be able to lead a normal life rather than repeated visits to pulmonology or thoracic surgery departments. People had been using corticosteroids, intra-pleural fibrinolytics and intercostal drainage by catheter for preventing RPT but results are variable[17,19]. Barbas CS et al (1991) concluded their research by commenting that approximately 50% of patients of pleural tuberculosis will develop residual pleural thickening at treatment completion but which patient is going to develop is quite uncertain[20].

In this study, patients of interventional and control groups were between 15 to 38 years of age.

A p-value of 0.19, not significant at p<.05, indicated that both groups were comparable demographically to each other at the baseline. A mean age 32.94 years for group A and 33.45 years for group B, reflected that tubercular pleural effusions are common in younger age group. This finding is in agreement with the reports of Bhuniya S. et al (2012) and Singla R. and colleagues (1995)[21,22]. Developing residual pleural thickening at a young age and having a good quality of life ahead is not possible and is of major concern .

Male to female ratio 2.3:1 indicated male predominance in TB-pleural effusions, which may be owing to socioeconomic responsibilities imposed on the male gender. Males being responsible in our setup especially for supporting the family, remain working outside and are at greater risk of TB exposure and of contracting the disease. Likewise, the disease is more common in males of lower socio-economic group where being hard pressed to earn, they go for medical consultation only when their problems interfere with the work-place activities. This delayed health seeking attitude may be responsible for more involvement of male gender in RPT. Additionally the high prevalence of cigarette smoking in male may be another factor for promoting pleural thickening[23]. This finding is incongruous with the report of Naseem Khan R et al (2019) who found a female preponderance[24]. While Kumar Rai D et al (2021) reported male gender with increased risk of RPT[25]. Because, male are more vulnerable to RPT and being the dominant earning member of the family, they should remain fit for fulfilling their responsibilities. RPT interfering with normal living can be a source of uneasiness for their family also, therefore it requires real rectification. This study demonstrated that most of the patients had symptoms of fever, chest pain, dyspnea and weight loss. These features are similar to those reported by Nasim Khan R et al (2019), Basu, A et al (2012), Valdés, L and colleagues (2010)[24,26,27].

In this study, Group-A patients, who were managed by complete aspiration, displayed immediate relief in shortness of breath, chest pain and cough just after complete thoracentesis while the patients of Group-B had a gradual relief from symptoms. This subjective improvement may possibly be due to altered nerve impulses arising from the lung or the chest wall after complete evacuation. According to Estenne M and associates (1983), the relief of dyspnea after complete evacuation results primarily from reduction in size of the thoracic cage which improves the efficiency of inspiratory muscles to work on a more advantageous portion of their length–tension curve[28]. Similarly, these patients returned to their daily routine activities immediately after complete evacuation while the control patients took far more time to rejoin their workplace because of delayed improvement. Even with regular anti-TB treatment, the incidence of RPT still ranges from 10-72%. These patients develop RPT and remain anxious for abnormal chest x-ray even after full course of treatment and consult a number of physicians and even quakes desperately, with a hope of rectification. Some of these patients are subjected to decortication but they have to face the complications of thoracotomy as well[11].

Ana Maria et al. (2011) displayed that therapeutic aspiration provides relief from dyspnea not only at rest but also on exertion and allows quick and better re-adaptation of patients to routine activities[29].

The exact mechanism of pleural thickening in tubercular pleural effusion is not clearly understood. However, circumstantial evidence from literature provides ample clues in this context. In tubercular effusion, exudate contains high levels of protein "fibrin" which is deposited on pleural surface, lymphatic vessels are clogged, thus hindering the absorption of fluid, accumulating effusion and resulting in adhesions formation leading to pleural thickening. This may be due to disordered fibrin turn-over. Fibrin formation is up-regulated while fibrin dissolution is down-regulated disrupting equilibrium. Philip-Joët F et al (1995) reported decreased level of fibrinolytic activity in TB-pleural effusion as compared to malignancy[30]. Furthermore, TGF-β and TNF-a present in pleural fluid, promote fibrin matrix formation. Hua CC et al (1999) reported that TB of pleura may enhance the release of pro-inflammatory cytokines like TNF-alpha, which may increase plasminogen activator inhibitor-1 (PAI-1) and decrease tissue Plasminogen Activator (tPA) in pleural fluid. This imbalance of PAI-1 and tPA may lead to fibrin deposition and pleural thickening[31].Chen WL (2015) and co-workers reported about the possible role of TNF-a in the pathogenesis of RPT.32 Extensive thickening may results in severe restrictive ventilatory disorder[33].

Kunter E et al (2002) reported that high levels of glucose, alpha-1 acid glycoprotein (AAG) and C-Reactive protein in pleural fluid, might be responsible for pleural thickening.[34]Hsieh CY et al (2019) disclosed that thrombin upregulates plasminogen activator inhibitor-1 (PA1-1) and Mesothelial-Mesenchymal Transition through protease-activated receptor-1 and cause pleural fibrosis in tubercular pleural effusion[35]. Gopi et al (2007) revealed that development of pleural thickening is closely related to time for diagnosis and treatment, pleural fluid protein content and timely thoracentesis.[36] It means if pleural fluid is allowed to stay for a longer time in the cavity, protein keeps on depositing on pleural surface, resulting in pleural thickening. Establishing TB-

diagnosis in pleural effusion is a time-consuming process because ultimate diagnosis is usually made on biopsy, histopathology or culture for Acid Fast Bacillus. Therefore, this malady can be controlled by finding rapid ways of diagnosis. Kwon JS and co-workers (2008) described symptom duration as predictors of RPT[37]. Therefore, early diagnosis and immediate complete aspiration can be employed for prevention of RPT. It is very logical to expect if protein-rich fluid is removed from the cavity, there is nothing behind to be deposited on pleural surface, eventually no pleural thickening can occur. Furthermore, there is no contraindication for complete thoracentesis in tubercular pleural effusions. So complete thoracentesis can be a very simple tool for preventing RPT. Doosoo Jeon (2014) communicated that the prevention of pleural fibrosis should be included in the treatment goals for tubercular pleural effusions[38]. Feller-Kopman and associates suggested that pleural space should be drained completely in order to avoid RPT[39]. Lai et al communicated that complete drainage had no beneficial effect on RPT reduction[40].But Balkissou AD and associates (2016) conveyed that RPT patients can be benefitted by appropriate management[41].

The objective of this study was to determine the usefulness of complete evacuation of pleural space for precluding residual pleural thickening. In this case-control study, an odds ratio of 294.61 (Table-IV) indicated tremendous association between complete evacuation and complete clearance. This result demonstrated that RPT can be prevented effectively by early diagnosis and complete thoracentesis. Wyseret al, and Chung CL et al reported that standard anti-TB medicines and early complete aspiration are adequate for the management of tubercular pleural effusion[42,43]. Bhuniya et al also demonstrated a lower rate of RPT with therapeutic drainage[21]. Considering "complete sonographic clearance" (no residual pleural thickening) as reference, the sensitivity 98.35% (95% CI: 94.16% to 99.80%), specificity 82.68% (95% CI: 76.33% to 87.92%) and an accuracy of 89.00% (95% CI: 84.90% to 92.31%) was observed, displaying remarkable efficacy.

The main limitation of this study is that it is a single centered study performed on limited number of patients. A short follow-up period was another limitation. We encountered some cases with longer follow up showing decreased pleural thickness three to nine months after treatment completion. A multi-centered study with larger sample size and longer follow up can explore the subject more effectively and more generalizable results can be obtained. Since, pleural thickening was estimated by trans-thoracic ultrasound which is a new opted method depending upon the expertise of the operator, can create a source of bias by inter-observer variation. The RPT cases, encountered even in interventional group, were perhaps those who reported late for the management. They spent significant time for getting treatment from local physicians and developed some pleural fibrosis before reaching the hospital. This patient-dependent factor may be confounding.

We obtained promising results by complete evacuation under ultrasound guidance. A sensitivity of 98.35% for sonographic clearance is a remarkable outcome. The frequency of RPT was very low because this procedure precluded residual pleural thickening. The results of current study are very important because by utilizing this technique, RPT and post treatment afflictions of patients can be minimized effectively. Although minimally invasive, but procedure is simple, rapid, safe and can be performed at day care clinics, even in peripheral areas of the country. Additionally, by opting for this tool, we can not only reduce the suffering of patients, but rather lessen the burden on radiology, pulmonology and thoracic surgery departments by reducing RPT.

In the light of this discussion, we recommend without any hesitation that we should not allow protein rich pleural fluid, stay in pleural space for longer time. Complete thoracentesis under ultrasound guidance and the earliest institution of anti TB medicine can be the best strategy for preventing residual pleural thickening.

CONCLUSION

Complete thoracentesis of tubercular pleural effusion under ultrasound guidance, combined with anti TB medicines, effectively precludes residual pleural thickening.

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