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Evaluation Of Clinical Profile And Outcomes Of Tubercular Pleural Effusion Based On Its Biochemical And Cytological Findings.

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Abstract:
Background:
Tubercular pleural effusion (TPE) is a common manifestation of extrapulmonary tuberculosis, presenting significant diagnostic and therapeutic challenges. The purpose of this study was to evaluate the clinical profile and outcomes of patients with TPE, focusing on the biochemical and cytological characteristics of pleural fluid.
Method:
This cross-sectional study was conducted in the Department of General Medicine at a tertiary care center in Ballari. We enrolled a total of 110 patients based on predetermined inclusion and exclusion criteria. A pre-designed, semi-structured questionnaire was developed and underwent pilot testing to collect socio-demographic data for all participants. Subsequently, the clinical profile and outcomes of TPE were evaluated based on biochemical and cytological investigations.
Results:
In the present study, 110 consecutive patients with pleural effusions were enrolled from February 2020 to July 2020. Among the selected participants, 74 were males and 36 were female patients, with a mean age of 41.6±15.74 years. The symptoms such as cough were most common (70.9%), followed by fever (60%) and chest pain (41.9%). Breathlessness and sputum occurred in 23.6% and 12.7% of cases, respectively. For LN ratio and etiology, 71.8% of cases had an LN ratio >75%, with notable prevalence in E1 and E3.
Conclusion:
The present study highlighted that, the integration of routine laboratory investigations is crucial for the effective management of tubercular pleural effusion, leading to improved patient outcomes. Early diagnosis and comprehensive treatment remain essential for reducing morbidity and ensuring better recovery.

Keywords: *Tuberculosis, Pleural Effusion, Biomarker, Pleurocentesis.*

INTRODUCTION:

All over the globe, tuberculosis (TB) continues to cause significant morbidity and mortality. [1] According to recent statistics revealed by the World Health Organization (WHO), estimated 10.6 million TB cases worldwide in 2022. [2] In accordance with the Global TB report 2022, India has a high TB burden, accounting for 28% of the global TB cases. [3] While TB has the potential to affect virtually any organ, pulmonary TB is the most common manifestation, underscoring the primary respiratory nature of this infection. However, beyond the lungs, TB can manifest in other forms, notably in the lymph nodes and pleura. Among these extrapulmonary sites, tubercular pleural effusion (TPE) has emerged as a prevalent and concerning condition, following lymph node involvement. TPE not only reflects the systemic spread of Mycobacterium tuberculosis but also poses a significant diagnostic and therapeutic challenge, particularly in TB-endemic regions. [4] TPE accounts for a substantial proportion of extrapulmonary TB cases and often presents with non-specific symptoms, complicating early diagnosis and management. The traditional diagnostic methods, including radiological imaging, biochemical analysis, and cytological examination of pleural fluid, have been widely employed to identify and manage TPE. [5] However, these methods have limitations in sensitivity and specificity, leading to diagnostic delays and the potential for underdiagnosis or misdiagnosis.

The diagnosis of tubercular pleural effusion relies on a combination of clinical assessment, imaging, and laboratory investigations, especially pleural fluid analysis. Biochemical and cytological evaluation of pleural fluid, including measurements of protein, glucose, lactate dehydrogenase (LDH), and adenosine deaminase (ADA) levels, as well as cytological examination, provide critical insights into the underlying pathology. ADA levels, in particular, have been widely used as a biomarker for tuberculous pleuritis due to their high sensitivity and specificity in TB-endemic regions. Cytological findings such as lymphocyte predominance also support the diagnosis.

Evaluating the clinical profile and outcomes of tubercular pleural effusion based on its biochemical and cytological findings can provide valuable information for early diagnosis and appropriate treatment, which is essential to prevent complications such as pleural fibrosis or progression to pulmonary tuberculosis. This study aims to examine these findings comprehensively to enhance our understanding of the disease's clinical course and outcomes.

METHODOLOGY:

In a tertiary care center in Ballari, we conducted the cross-sectional study in the Department of General Medicine. This study included 110 patients according to the following selection criteria:

Inclusion criteria:

Chest X-ray showing evidence of pleural effusion

Exudative pleural effusion according to light criteria

Age more than 18 years.

Patients who have given written informed consent.

Exclusion criteria:

We excluded patients who did not consent to participate and those who underwent repeated pleurocentesis.

A pre-designed, semi-structured questionnaire was developed and subjected to pilot testing, gathering socio-demographic information for all individuals. Following the pilot study, the questionnaire was standardized and subsequently used for the main study.

All patients underwent a comprehensive clinical history and physical examination. A pleural effusion size estimate was obtained using a posterior-anterior view chest radiograph. Effusions occupying less than two-thirds of the hemithorax were categorized as not large, whereas those occupying more than two-thirds were classified as large. Informed consent for pleurocentesis and pleural biopsy was obtained from all patients.

Investigations:

A diagnostic pleurocentesis was performed on all patients. Based on the recommendations of R.W.Light's, criteria patients were positioned beside the bed and supported with a footstool, and their arms and heads rested on pillows on a bedside table. The patient was positioned with the side containing the fluid toward the foot of the bed, ensuring the back was vertical. In this position, fluid was aspirated. Thoracocentesis was performed in the mid-axillary line, one intercostal space below the area of percussion, with the exact location confirmed by chest radiograph. In cases where the effusion was too small to be detected by percussion, a chest ultrasound was utilized.

Procedure for therapeutic thoracocentesis:

The thoracocentesis site was identified and marked with the end of a retracted ballpoint pen. The area was cleaned with Povidone-iodine, followed by surgical spirit, extending 4 inches from the mark in all directions. A sterile drape with a central hole was then placed, with another sterile drape covering the bed. The skin, periosteum, and parietal pleura were anesthetized with xylocaine using a 25-gauge needle. Fluid was aspirated using a 50 ml syringe with a 22-gauge needle, with 1 ml of heparin added to prevent clotting. If fluid was not obtained, ultrasound-guided pleurocentesis was performed.

Processing of Fluid:

The pleural fluid was distributed for laboratory analysis as follows:

Biochemistry: 5 ml for protein, lactate dehydrogenase (LDH), glucose, and adenosine deaminase (in suspected tubercular or malignant effusions).

Hematology: 5 ml for white blood cell count.

Bacteriology and Tuberculosis: 10 ml for Gram stain, aerobic culture, and acid-fast stain.

Cytology: 25 ml for cytological examination.

Therapeutic thoracocentesis was performed when indicated. Patients were observed post-procedure for any evidence of pneumothorax. If clinical suspicion was high, a chest X-ray was performed, and necessary interventions were undertaken as indicated.

Needle Biopsy of Pleura

A needle biopsy of the pleura was performed after ruling out parapneumonic effusion or empyema, both clinically and based on laboratory investigations, particularly when tuberculosis (TB) or malignant effusions were suspected.

Procedure:
The biopsy procedure closely resembled pleurocentesis. After administering sufficient local anesthesia, a small incision was made at the anesthetized site using a scalpel. An Abrams needle was introduced, with the stylet placed inside the inner cannula, which was then inserted into the outer trocar. The inner cannula was rotated clockwise, effectively closing the distal notch of the outer trocar, and the needle was advanced under firm pressure. Upon reaching the pleural space, the stylet was withdrawn, leaving the inner cannula in the closed position. A syringe was attached to facilitate fluid aspiration. The inner cannula was then rotated counterclockwise to open the distal notch, allowing for pleural fluid collection. The needle was rotated, positioning the knob on the outer trocar inferiorly, and the needle was secured to the pleura. While holding the outer trocar in place, the inner cannula was rotated back to the closed position, excising a small section of the parietal pleura. A minimum of three biopsy samples were collected. The biopsy site was massaged to prevent the formation of a needle tract, and adhesive tape was applied for closure. A postprocedure chest radiograph was conducted to exclude pneumothorax.
The pleural fluid specimens were promptly transported to the biochemistry, pathology, and microbiology laboratories. The EDTA sample for white blood cell count was centrifuged at 2000 revolutions per minute, and the smear was stained with Wright stain for differential counting. Protein, glucose, and LDH were measured using an automated analyzer. In order to quantitate ADA, the fluid was centrifuged at 4°C for 20 minutes at 3000 revolutions per minute. The supernatant was stored at -70°C until it was analyzed using a Giusti colorimetric method.
Statistical analysis:
The analysis was conducted using SPSS software, version 20. An alpha level of 5% was applied, meaning any p-value less than 0.05 is considered statistically significant.

RESULTS:

In this study, 110 consecutive patients diagnosed with pleural effusion were enrolled over a six-month period from February 2020 to July 2020. Of the total participants, 74 were male and 36 were female. The average age of the patients was 41.6 ± 15.74 years, as detailed in Table 1.

Table-1: Demographic profile of study participants.

Age groups (in years)	Gender		Total
	Female	Male	
	No. (%)	No. (%)	No. (%)
<20	2 (50)	2 (50)	4 (100)
21 to 40	8 (17.0)	39 (83.0)	47 (100)
41 to 60	21 (50)	21 (50)	42 (100)
>61	5 (29.4)	12 (70.6)	17 (100)

According to Table 2, cough was most common (70.9%), followed by fever (60%) and chest pain (41.9%). Breathlessness and sputum occurred in 23.6% and 12.7% of cases, respectively.

Table-2: Frequency of symptoms* with different etiology

	Etiology							Total
	E1	E2	E3	E4	E5	E6	E7	
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
Cough	41 (77.4)	21 (75.0)	5 (50.0)	5 (71.4)	4 (66.7)	0 (0.0)	2 (50.0)	78 (70.9)
Sputum	6 (11.3)	4 (14.3)	0 (0.0)	2 (28.6)	2 (33.3)	0 (0.0)	0 (0.0)	14 (12.7)
Fever	36 (67.9)	15 (53.6)	3 (30.7)	4 (57.1)	4 (66.7)	2 (100.0)	2 (50.0)	66 (60.0)
Chest Pain	22 (41.5)	12 (42.9)	3 (30.0)	5 (71.4)	4 (66.7)	0 (0.0)	0 (0.0)	46 (41.9)
Breathlessness	13 (24.5)	5 (17.9)	6 (60.0)	0 (0.0)	2 (33.3)	0 (0.0)	0 (0.0)	26 (23.6)

Footnote: E1= Definite TB, E2= Probable TB, E3= Malignancy, E4= Parapenumonic, E5= Empyema, E6= Others, E7= Unknown
According to Table 3, straw color was predominant, seen in 81.8% of cases, particularly in E1 and E2. Hemorrhagic color was present in 10.9% of cases, mostly in E1 and E3. Pus appeared in 5.5% of cases, and anchovy color was rare at 1.8%, only in E6.

Table-3: Appearance of pleural fluid in different etiologies

Color	Etiology							Total
	E1	E2	E3	E4	E5	E6	E7	
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
Anchovy	-	-	-	-	-	2 (100)	-	2 (1.8)
Hemorrhagic	8 (15.1)	-	8 (80.0)	2 (28.6)	-	-	-	12 (10.9)
Pus	-	-	-	-	6 (100.0)	-	-	6 (5.5)
Straw	45 (84.9)	28 (100.0)	2 (20.0)	5 (71.4)	-	-	4 (100.0)	90 (81.8)
Total	53 (100.0)	28 (100.0)	10 (100.0)	7 (100.0)	6 (100.0)	2 (100.0)	4 (100.0)	110 (100)

Footnote: E1= Definite TB, E2= Probable TB, E3= Malignancy, E4= Parapenumonic, E5= Empyema, E6= Others, E7= Unknown

For LN ratio and etiology, 71.8% of cases had an LN ratio >75%, with notable prevalence in E1 and E3. In contrast, 28.2% had an LN ratio <75%, predominantly in E4 and E5, as Table 4.

Table-4: Association of lymphocyte predominant effusion with etiology

LN Ratio & Etiology	Etiology							Total
	E1	E2	E3	E4	E5	E6	E7	
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
<75%	8 (15.1)	7(25.0)	1 (10.0)	5 (71.4)	6 (100.0)	2 (100.0)	2 (50.0)	31 (28.2)
>75%	45 (84.9)	21 (75.0)	9 (90.0)	2 (28.6)	-	-	2 (50.0)	79 (71.8)
Total	53 (100.0)	28 (100.0)	10 (100.0)	7 (100.0)	6 (100.0)	2 (100.0)	4 (100.0)	110 (100.0)

E1= Definite TB, E2= Probable TB, E3= Malignancy, E4= Parapenumonic, E5= Empyema, E6= Others, E7= Unknown, LN ratio= Lymphocyte Neutrophil ratio

Table-5: Biopsy Results

Biopsy	No. (n = 42)
Granulomatous inflammation	14
Chronic non-specific inflammation	14
Malignancy	3
Inadequate	11

Among the 42 biopsies, 14 showed granulomatous inflammations, 14 showed chronic non-specific inflammations, 3 were diagnosed with malignancy, and 11 were deemed inadequate (Table 5).

Among the 42 biopsies, granulomatous inflammation was found in 93.3% of E1 cases, chronic non-specific inflammation in 66.7% of E2 cases and 100% of E7 cases, and malignancy in 100% of E3 cases, (Table 6).

Table-6: Association of Biopsy with Etiology

Biopsy	Etiology				Total (n=42)
	E1	E2	E3	E7	
Granulomatous inflammation	14 (93.3%)	0	0	0	14
Chronic non-specific Inflammation	0	12 (66.7%)	0	2 (100%)	14
Malignancy	0	0	3	0	3

E1= Definite TB, E2= Probable TB, E3= Malignancy, E4= Parapenumonic, E5= Empyema, E6= Others, E7= Unknown

DISCUSSION:

In this prospective study, which included a cohort of 110 patients diagnosed with exudative pleural effusion, the mean age of the participants was 41.6 ± 15.74 years. The key underlying causes of exudative pleural effusion identified during the study were tuberculosis, malignancy, and conditions such as parapneumonic effusions and empyema. Notably, patients with tuberculosis tended to be younger in comparison to those diagnosed with malignancy, highlighting an age-related distinction in the etiology of exudative pleural effusions.

The findings of the present study demonstrated a male predominance of 80%. This was consistent with previous research, including studies by Modi et al. (73.33%),[6] Chakraborthy A, et al., (76%),[7] Sharma SK, et al., (78%),[8] and Kate et al. (72%).[9] The higher incidence of TB in males may be attributed to factors such as increased exposure to outdoor pollutants, smoking, and migration to regions with high TB prevalence. Additionally, social

stigma may contribute to a lower hospital attendance rate among females, potentially influencing the observed gender distribution in this study.

The most prevalent symptom among TB patients was fever, observed in 82.06% of cases, followed by cough (72.46%) and chest pain (31.8%). In a broader analysis of symptoms by etiology, cough was the most frequently observed symptom, reported in 78 (70.9%) cases, followed by fever in 66 (60%) cases, chest pain in 46 (41.9%), and sputum production in 14 (12.7%). The observed findings concordance with the research conducted by Srinidhi R. et al.,[4] where cough emerged as the predominant presenting symptom, documented in 85% of cases. This trend was further corroborated by the studies of Chakraborthy A, et al.,[7] which reported a similar incidence of cough at 89%, and Reddy L, et al.,[10] who identified it in 73.3% of their patients. In contrast, Shukla et al. and Kate S, et al.,[9] reported that, fever as the most frequent presenting symptom in their respective cohorts.

In our study, chest pain was the second most common symptom, observed in 78% of cases, which is comparable to the 71.5% reported by Sharma et al.[8] Fever was noted in 68% of our patients, aligning closely with the 70% reported by Lokeswara Reddy et al.[10] Other symptoms such as weight loss and loss of appetite were also noted, reflecting the chronic nature of the disease, as similarly observed by Anushree Chakraborthy et al.[7]

When we used the pleural ADA with a lymphocyte neutrophil ratio greater than 75%, we found that there is an increase in specificity from 83% to 90% at an ADA level of 30 IU/L, which was not statistically significant. Our study, along with the one by Sharma SK et al., [8] suggests that, the ADA levels are lower in patients with TB effusions in the subcontinent. This was similar to studies done in Japan. This is probably due to the difference in ethnicity. A pleural biopsy was performed in all patients where tuberculosis or malignancy was suspected. A biopsy was diagnostic in 73.8% of those biopsies. In our study, 4 patients (26.7%) had AFB demonstrable in the biopsy, similar to the finding of Mandal S. et al., (2019).[12] The present study underscores, the importance of integrating clinical, radiological, biochemical, and cytological evaluations for comprehensive diagnosis and management of TPE. This was supported by Naik M, et al., (2019).[13] The combination of these diagnostic approaches improves accuracy, expedites diagnosis and facilitates appropriate treatment, ultimately enhancing patient outcomes.

CONCLUSION:

The evaluation of the clinical profile and outcomes of tubercular pleural effusion based on its biochemical and cytological findings highlighted, the significant role of pleural fluid analysis in diagnosing and managing the condition. Key biochemical markers such as elevated protein levels, LDH and ADA along with lymphocyte predominance in cytological findings, aid in confirming the tubercular etiology. Early diagnosis and timely initiation of anti-tubercular treatment improve patient outcomes, reducing complications like fibrosis or chronic effusions. Thus, a comprehensive approach using biochemical and cytological findings is crucial for optimizing the clinical management and prognosis of tubercular pleural effusion.

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