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A PROSPECTIVE STUDY TO EVALUATE THE TREATMENT OUTCOME OF TUBERCULAR PLEURAL EFFUSION REGISTERED UNDER NATIONAL TUBERCULOSIS ELIMINATION PROGRAMME

Respiratory Medicine

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ABSTRACT

Background: Tuberculosis is the leading etiology of pleural effusion in developing countries. Administration of anti-tubercular therapy (ATT) cures tuberculous pleural effusion and reduces the incidence of subsequent TB, hence it is important to establish the diagnosis of tuberculous pleural effusion and initiate the proper treatment. This study aims to assess the treatment outcome of tubercular pleural effusion patients treated under NTEP. **Material & Methods:** A prospective study was done on 72 patients attending with pleural effusion at IRD, SMS Medical College, Jaipur after applying inclusion and exclusion criteria from April 2021 to March 2022. The patients included were diagnosed completely by collecting their detailed history, clinical examination, routine blood investigations, sputum examination, chest X-rays, ultrasound of thorax and pleural fluid analysis. Data from the study were collected, tabulated and analyzed statistically using SPSS version 22.0 for data processing and statistics. The following tests were used t-test, Chi-Square (x2), and Logistic regression analysis.**Results:** Our study showed that 62.5% of patients reside in rural areas and 37.5% of patients were resides in the urban area. Most patients were Hindus (86.11%) and 16.66% were Muslims. They were mostly married. On the estimation of pleural fluid protein, 66 (91.66%) patients were having pleural fluid protein values of more than 3.0 g/dl. Our study showed that 30 (41.66%) were reported as having ADA in the ranges 40-60 U/L, 22 patients having 60.1-80U/L and only 4 patients had >100U/L. In the present study, the random blood sugar observed was >200 mg/dl in 4.16% of the patients with TPE. After treatment, 1 patient died during the course of treatment, 9 loss to follow-up, 7 were abnormal in chest x-ray and 2 did not attend for X-ray in our study. **Conclusion:** The definitive diagnosis of TB pleural effusions depends on the demonstration of M tuberculosis in sputum, pleural fluid, or pleural biopsy specimens. Supportive evidence includes the demonstration of classical TB granulomas in the pleura and elevated adenosine deaminase (ADA) in pleural fluid. Clinical profile &chest X-ray showed marked improvement on NTEP regimen. Hence our study also supports better treatment outcomes on NTEP regimen in tubercular pleural effusion.

KEYWORDS

Tuberculosis, Pleural effusion, NTEP, USG, X-ray, ADA

INTRODUCTION

Tuberculosis (TB) remains a major public health problem in developing countries. Extra pulmonary tuberculosis (EPTB) is present in around 15-20% of cases. Lymph nodes and pleura are involved in most cases of EPTB.[1]

A total of 1.6 million people died from TB in 2021 (including 187 000 people with HIV). In 2021, an estimated 10.6 million people fell ill with tuberculosis (TB) worldwide. Six million men, 3.4 million women, and 1.2 million children.[2] In India, more than 40% of the adult population is infected with TB and about 1.9 million people develop TB disease every year. The prevalence is 299 and the mortality is 28 per 1,00,000 population, respectively. The HIV-infected population in India was estimated to be about 40.1 million, they are at greater risk of breaking down with TB disease.[3]

Tuberculosis is the leading etiology of pleural effusion in developing countries. Pleural effusion is an abnormal collection of fluid in the pleural space resulting from excess fluid production or decreased absorption.[4]Tubercular pleural effusion is invariably exudative with adenosine deaminase (ADA) levels >40 U/L.[5]

Tuberculous pleurisy may occur during primary infection when it tends to affect younger individuals in areas with a high prevalence of tuberculosis, or it may be recognized as a manifestation of disease reactivation, particularly affecting older patients. Pleural fluid is usually a serous exudate and pleural fluid glucose and pH values are lower in a minority of patients. Pleural fluid lymphocytosis is a typical finding, although neutrophilia may be observed early in the disease. To achieve a definitive diagnosis of tuberculous pleurisy, *Mycobacterium tuberculosis* must be isolated from the culture of pleural fluid; the presence of granulomas in pleural tissue is suggestive.[6]

Early approaches to the treatment of tuberculosis include adequate rest, good food, a good climate, and the use of a variety of agents such as cod liver oil, antimony, alkaline mineral water and gold. The national tuberculosis control programme (NTCP) was introduced by the Government of India in 1962 and its backbone was the district tuberculosis programme. It was integrated with and implemented through the general public health services.[7] Based on an appraisal of the NTCP, the revised national tuberculosis control programme (RNTCP) was introduced in India in 1993 guided by WHO and supported by World Bank.[8] The RNTCP introduced directly observed treatment-short course (DOTS) for treating cases and has been recognized as the best cost-effective approach to TB control.[9]

Administration of anti-tubercular therapy (ATT) cures tuberculous pleural effusion and reduces the incidence of subsequent TB, hence it is important to establish the diagnosis of tuberculous pleural effusion and initiate the proper treatment.[10]

The National Tuberculosis Elimination Program (NTEP**)** is the public health initiative of the Government of India that organizes its anti-Tuberculosis efforts in 2020. It functions as a flagship component of the National Health Mission (NHM) and provides technical and managerial leadership to anti-tuberculosis activities.[11] Tuberculosis (TB) is one of the major critical health problems worldwide, where drug treatment is fundamental for controlling TB promoting the cure of the patient, and breaking the chain of transmission when treatment is completely and correctly followed. This study aims to assess the treatment outcome of tubercular pleural effusion patients treated under NTEP.

MATERIAL & METHODS:

A prospective study was done on 72 patients attending with pleural effusion at IRD, SMS Medical College, Jaipur after applying inclusion and exclusion criteria from April 2021 to March 2022.

The following data were collected from patient's files and also were obtained from new cases:

a. Thorough medical history: socioeconomic data, history of contact with tuberculous cases, history of previous anti-TB treatment (new patients or had history of previous treatment either as relapse, treatment after interruption and treatment after failure[12]) and comorbidities.

b. Full clinical examination: including both general and local chest examinations.

c. Radiological scanning:

I. Plain chest X-ray (posterior-anterior and lateral views) for all patients. The lung was divided into three zones to evaluate the extent of pulmonary lesions (consolidation, cavitations, nodules, bronchiectasis, lymph nodes, and pleural effusion).[13] The radiological extent of the tuberculous lesions was classified according to the National Tuberculosis Association of USA[14] into Minimal, moderately advanced, and far advanced: lesions that were more extensive than moderate.

II. Chest Ultra-Sound

d. Laboratory investigations:

Complete blood count (CBC), Erythrocyte Sedimentation Rate (ESR), Liver function test before, one week after the start of treatment and whenever indicated, Fasting and 2 h postprandial blood glucose, HIV serology, Renal function test (Serum creatinine and blood urea), Adenosine deaminase (ADA) for pleural fluid.

e. Tuberculin Skin Test (TST).

f. Bacteriological examination:

either sputum sample for all cases of pulmonary TB, 3-morning specimens were taken (sputum induction was done for cases who didn't give sputum, they were 10 cases), Pleural fluid.

g. Classification of TB cases according to NTEP[12]:

Cases of the study were classified according to:

- Anatomical site of the disease: Pulmonary TB (involving lung parenchyma and cases with both pulmonary and extrapulmonary TB in the form of mediastinal lymphadenopathy or TB pleural effusion) and Extra-pulmonary TB (involving TB mediastinal or hilar lymphadenopathy or TB pleural effusion without parenchymal lung affection)
- Bacteriological results:

I. Smear-positive TB cases where one or more sputum smear specimens at the start of the treatment are positive for AFB.
II. Smear negative TB cases:
III. Presenting complaints consistent with TB.
IV. Radiological abnormalities are consistent with pulmonary TB.
V. Two sets of sputum smear negative for AFB separated by a course of antibiotic with no clinical or radiological improvement.
VI. The decision by a clinician to treat with a full course of anti-TB therapy.

h. Treatment[12]:

The treatment strategy adopted by NTEP is DOTS through an observer watches the patient swallowing their tablets in a way that is sensitive and supportive to the patient either in the hospital under the observation and direction of Chest Hospital staff members or at the patient's home for patients who are unable to attend to the hospital under the observation of health visitors.

Finally the outcome groups were classified either as successful or unsuccessful group[15]:

- A successful group included patients who were cured and completed their treatment.
- An unsuccessful group includes treatment failure, loss to follow-up, death, and transfer out.

Data from the study were collected, tabulated and analyzed statistically using SPSS version 22.0 for data processing and statistics. The following tests were used t-test, Chi-Square (x2), and Logistic regression analysis.

RESULTS:

In the present study, 66.66% were males and 33.33% were females, 50% of the patients were in the age group of 21-40 years. 62.5% of patients reside in rural areas and 37.5% of patients were resides in urban areas. Most patients were Hindus (86.11%) and 16.66% were Muslims. They were mostly married. Our study showed that educated patients occurred in 87.5% and 12.5% of cases were uneducated (table 1).

Our study showed that left pleural effusion was seen in 34 (47.22%), right pleural effusion in 36 (50%) cases, and bilateral pleural effusion was seen in 2 patients (2.77%) (table 2).

The hematological estimation among all the patients involved in the study. 37 (51.38%) patients were reported of having >10 g/dl of hemoglobin and 48.61% patients had <10 g/dl hemoglobin. Out of 72, 46 (63.88%) patients were reported as having >11000 (cells/cumm) of TLC, and 2.77% of patients had <4000 (cells/cumm) of TLC. The pleural fluid was analyzed for the presence of proteins and ADA. On the estimation of pleural fluid protein, 66 (91.66%) patients were having pleural fluid protein values of more than 3.0 g/dl. Our study showed that 30 (41.66%) were reported as having ADA in the ranges 40-60 U/L, 22 patients had 60.1-80U/L and only 4 patients had >100U/L (table 3).

After completion of treatment out of 72, 53 patients were analyzed with USG and the outcome observed was bilateral clear observed in 53 patients during the intensive phase and 54 patients after treatment. In the case of the remaining 19 patients, 4 patients had minimal pleural effusion on the left side, 4 patients had minimal pleural effusion on right side and 11 patients did not attend during the intensive phase. After treatment, 1 patient died during treatment, 3 patients had pleural thickening on left side, 3 patients had pleural thickening on the right side, 1 patient had left pleural space clear & right pleural thickening present and 1 did not attend for USG (table 4).

After completion of treatment out of 72, 53 patients were analyzed with chest X-ray and the outcome observed was normal appearance during the intensive phase and after treatment. In case of remaining 19 patients, 1 patient died during course of treatment, 5 were loss of follow-up from during treatment, 12 were abnormal in chest x-ray during treatment and 1 did not attend for X-ray during intensive phase. After treatment, 1 patient died during course of treatment, 9 were loss of follow-up, 7 were abnormal in chest x-ray and 2 did not attend for X-ray (table 5).

DISCUSSION:

Tuberculosis is the leading etiology of pleural effusion in developing countries. TPE is the second most common form of extrapulmonary tuberculosis and a common cause of pleural effusions in endemic tuberculosis areas.[16] Pleural fluid analysis is the most useful test in differentiating possible causes and directing further investigations. Therefore aspiration should be performed in all cases of radiological confirmed pleural effusion, except cases where the clinical context is suggestive of a transudative process.

In the present study, 66.66% were males and 33.33% were females, 50% of the patients were in the age group of 21-40 years. This can be explained by the fact that this age group is associated with a high risk of exposure and stress at work (being the period of productivity with high activity) which are the most likely to play a role in the occurrence of TB. Adolescents are more susceptible to developing TB disease than younger children because of hormonal changes and altered protein and calcium metabolism associated with adolescent growth.[17] This demographic status present in our study was similar to the study conducted by Reechaipichitkul et al on 132 patients.[18] The increased incidence of the disease in males as compared to females is possible because both tuberculosis and diabetes are more common in males. TPE predominates in men, with an overall male-to-female ratio of 2:1.[19] In an epidemiological analysis from the United States, TPE occurs significantly more often than pulmonary tuberculosis among persons >65 years old, and the mean age of patients with TPE is 49 years: about 50% were younger than 45 years and 30% were over 65 years of age.[20] In contrast, TPE affects mainly younger individuals (mean age =34 years) in higher tuberculosis burden areas, where primary infection accounts for a large percentage of patients with TPE.[19] Also there is no doubt that the disease is more likely to be detected and treated in males than females assuming that males move outdoors with a higher incidence of crowdedness and exposure together with bad hygiene. In addition, some occupations which suites males can predispose to TB e.g. silicosis. Furthermore, females in our community consider this disease as a stigma.

Our study showed that 62.5% of patients reside in rural areas and 37.5% of patients were resides in urban areas. Most patients were Hindus (86.11%) and 16.66% were Muslims. They were mostly married. AL-Helaly et al.[21] and Olfat et al.[22] found that the infection of

tuberculosis was higher among rural residents, they explained their observation by low socioeconomic level, bad housing, and dusty environment as well as poverty.

Our study showed that educated patients occurred in 87.5% and 12.5% of cases were uneducated. Morsyet al.[23] found that the prevalence of tuberculous infection was highest in the uneducated (59.7%).

Yu et al.[24] showed a relative risk for TB among smokers consuming 400 or more cigarettes per year independently of age, gender, contact, and type or place of work. This result may be due to the toxic factors present in smoking capable of reducing the host defense mechanism.[25] Santha et al.[26] found that 20% of patients in his study were found to be addicted to narcotic substances assuming that narcotic addiction may reduce immunity and consequently increase the susceptibility to pulmonary TB.

Our study compatible with Lokesh MR et al.(2016)[27] found that 30 (60%) patients were reported as having >10 g/dl of hemoglobin, 36 (72%) with total leucocyte count 4000-11000 cells/cumm and 45 (90%) with ESR >20 mm/hr. In the present study, the random blood sugar observed was >200 mg/dl in 4.16% of the patients with TPE. In a study done by Sachdeva et al and others, it was shown that a high incidence of pulmonary tuberculosis was associated with severe hyperglycemia.[28]

Many studies have investigated the usefulness of ADA in pleural fluid for the early diagnosis of TPE and confirmed that the determination of ADA levels is an easy and inexpensive method for diagnosing TPE. The recent meta-analysis involving 63 studies demonstrated that the summary receiver operating characteristic curves for the sensitivity and specificity of ADA in pleural fluid in the diagnosis of TPE were 92% and 90%, respectively. The positive likelihood ratio was 9.03, the negative likelihood ratio was 0.10, and the diagnostic odds ratio was 110.08.[29] Almost all patients with TPE have a pleural fluid ADA level above 40 U/L, which is the most widely accepted cut-off value for the diagnosis of TPE.32 The higher the level, the greater the chance of the patient having TPE while the lower the level the lesser the chance of the patient having TPE.[30]

Lokesh MR et al.(2016)[27] found 48 (96%) patients were having pleural fluid protein values of more than 2.9 g/dl and 49 (98%) patients had pleural fluid sugar of more than 60 mg/dl. 14 (43%) were reported as having ADA (elaborate the abbreviation- Adenosine deaminase) in the ranges 100-150 U/L.

After completion of treatment out of 72, 53 patients were analyzed with chest X-ray and the outcome observed was normal appearance during the intensive phase and after treatment. Khan et al.(2016)[10] found that in tubercular pleural effusion, the treatment success rate was 75 %, defaulter rate was 9.3%. Deaths were found in 7.81 % of cases. Loss of follow-up from treatment is 7.81%.

According to Halprashanth, the cure rate was 74.6% and the default rate was 14.5%. The failure rate was 9.1% and the death rate was 1.8%, as an outcome of sputum-positive pulmonary tuberculosis treated with RNTCP-DOTS.[31] In another study conducted by Reddy, the cure rate was 78.6% and the default rate was 8.6% and the death rate was 12.9%.[32] Lokesh MR et al.[27] Performed a prospective study done on 50 patients. They concluded that the cure rate of tubercular pleural effusion cases treated under DOTS is 80%. While 8% didn't complete the full treatment, 10% didn't follow up for a repeat chest X-ray, and 2% of patients expired.

Table – 1 Demographic Profile Of Patients

Demographic profile	No. of patients (N=72)	Percentage
Age groups		
10-20 yrs	13	18.05%
21-30 yrs	17	23.61%
31-40 yrs	19	26.38%
41-50 yrs	7	9.72%
51-60 yrs	5	6.94%
61-70 yrs	8	11.11%
>70 yrs	3	4.16%
Gender		
Male	48	66.66%
Female	24	33.33%
Religion		
Hindus	60	86.11%
Muslims	12	16.66%
Marital status		
Married	55	76.38%
Unmarried	17	23.61%
Residence		
Rural	45	62.5%
Urban	27	37.5%
Family type		
Nuclear	35	48.61%
Joint	37	51.38%
Employment		
Employed	42	58.33%
Unemployed	30	41.66%
Education		
Illiterate	9	12.5%
Primary level	20	27.77%
Secondary level	21	29.16%
Higher secondary level	17	23.61%
Graduate & post graduate	5	6.94%

Table 2: Distribution of patients according to X-ray findings

X-ray findings	No. of patients	Percentage
Left pleural effusion	34	47.22%
Right pleural effusion	36	50%
B/L pleural effusion	2	2.77%
Total	72	100%

Table 3: Distribution of patients according to Biochemical analysis

Hemoglobin level (g/dl)	No. of patients	Percentage
<7.0	2	2.77%
7.0-10.0	33	45.83%
10.1-12.0	24	33.33%
>12.0	13	18.05%
Random blood sugar (mg/dl)		
<100	35	48.61%
100-200	34	47.22%%
>200	3	4.16%
Total leucocyte count (cells/cumm)		
<4000	2	2.77%
4000-11000	24	33.33%
>11000	46	63.88%
Pleural fluid protein (g/dl)		
<3.0	6	8.33%
3.0-4.0	52	72.22%%
4.1-5.0	12	16.66%
>5.0	2	2.77%
Adenosine deaminase values (U/L)		
<40.0	5	6.94%
40.0-60.0	30	41.66%
60.1-80.0	22	30.55%
80.1-100	11	15.27%
>100	4	5.55%

Table 4: Distribution of patients according to USG at completion of intensive phase & after treatment

USG	Completion of intensive phase	Completion of treatment
B/L clear	53	54
Left minimal pleural effusion	4	-
Left pleural thickening present	-	3
Right minimal pleural effusion	4	-
Right pleural thickening pressure	-	3
Left pleural space clear & right pleural thickening present	-	1
nil	11	11
Death	-	1

Table 5: Distribution of patients according to X-ray findings at completion of intensive phase & after treatment

X-ray findings	Completion of intensive phase	Completion of treatment
Normal	53	53

Abnormal	12	7
Not done	1	2
Not done (loss of follow-up)	5	9
Not done (Death)	1	1

CONCLUSION:

Pleural effusion is commonly encountered in medical practice and the commonest cause is tuberculosis and malignancy. The definitive diagnosis of TB pleural effusions depends on the demonstration of M tuberculosis in sputum, pleural fluid, or pleural biopsy specimens. Supportive evidence includes the demonstration of classical TB granulomas in the pleura and elevated adenosine deaminase (ADA) in pleural fluid. Patient evaluated at the initiation of treatment, end of an intensive phase and end of treatment. Clinical profile &chest X-ray showed marked improvement on NTEP regimen. Hence our study also supports better treatment outcomes on NTEP regimen in tubercular pleural effusion.

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