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A STUDY OF TUBERCULOUS PLEURAL EFFUSION IN PROVINCE 2, SOUTHERN NEPAL

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ABSTRACT

Introduction: *Tuberculosis (TB) is a major public health problem in developing countries. Tuberculous pleural effusion is the second most common form of extrapulmonary tuberculosis (TB) (after lymphatic involvement) and is the most common cause of pleural effusion in areas where TB is endemic. The aim of this study is to depict the pattern of the Tuberculous Pleural Effusion (TPE) with its clinical presentation and diagnosis along with the different laboratory parameters of the TB patients at a tertiary care center of the Southern Nepal.*

Methods: *A prospective hospital based cross-sectional study enrolling 107 subjects diagnosed as TBPE presenting to the Department of Internal Medicine, National Medical College was carried out from 15th March, 2023 to 14th October, 2023 (7 months). The different data collected were put in Excel Sheet and analyzed using SPSS version 26. The formal written and verbal consent was taken from the participants and ethical clearance was taken from Institutional Review Committee (IRC), National Medical College, Birgunj (Ref. F-NMC/633/079-080).*

Results: *A total of 107 subjects diagnosed with TBPE showed 67.3 % (n=72) male and 32.7% (n=35) female participants. Majority of the participants (88.8%) presented with fever, and approximately 59% of the participants had chest pain. Almost 65% of them had dyspnea and 77% presented with frank cough. Majority of the participants had right sided effusion. Pleural fluid examination showed increased total leukocyte count (mean 3191 cells/cu mm) and with lymphocytic predominance and increased protein content (5.07±0.91 g/dL). Pleural fluid Adenosine Deaminase (ADA)was found to be elevated (86.5±26.4 U/L).*

Conclusions: *The common presentation of the Tuberculous pleural effusion is deranged laboratory parameters of pleural fluid with increased fluid total leukocyte count having lymphocytic predominance and increased protein content along with high ADA levels.*

Keywords: *Adenosine Deaminase, Pleural Effusion, Total Leukocyte count, Tuberculosis*

INTRODUCTION

Tuberculosis (TB) is a major public health problem particularly in developing countries. Although the majority of TB patients have pulmonary TB, extrapulmonary TB affecting mainly the lymph nodes and pleura serves as the initial presentation in about 25% of adults.[1]

Tuberculous pleural effusion is regarded as the second most common form of extra pulmonary tuberculosis (TB) (after lymphatic involvement) and is the most common cause of pleural effusion in TB endemic areas.[2] Tuberculous pleural effusions are often unilateral in presentation, small to moderate in size, and self-limiting.[3] In patients without human immunodeficiency virus (HIV) infection, right sided tuberculous pleural effusions occur slightly more frequently than the left (55 versus 45 percent) and occupy less than two-thirds of the hemithorax in 82 percent of cases. [4,5]

TB effusions (TPE) typically presents as acute to subacute illnesses with unilateral pleuritic chest pain, cough, fever, night sweats, dyspnea, and weight loss.[6] The diagnosis of TBPE becomes challenging due to its paucibacillary nature and low sensitivity of conventional microbiological diagnostic tests, including microscopic examination of the pleural fluid for acid-fast bacilli and mycobacterial culture.[7] This can be supported by the fact that smear microscopy of pleural fluid detects acid-fast bacilli (AFB) in <10% of TPE cases.[8] Mycobacteria growth indicator tube culture for Mycobacteria from pleural fluid also has low sensitivity (24%–58%). It is also bounded by prolonged time in gaining results: in the case of solid culture media, it extends to 2 weeks more.[9]

Tuberculous pleuritis more often presents as an acute illness. Upon presentation symptoms in one series had been present for less than 1 week in 25/71 patients (35%) and had been present for less than a month 50/71 patients (71%).[10] The most frequent symptomatic presentation is cough (~70%), which is usually nonproductive and chest pain (~70%), which is usually pleuritic in nature.[11] If both cough and pleuritic painare present, the pain usually

precedes the cough. Most patients are febrile but certain individuals with TBPE(15%) will be afebrile.[12] Patients with tuberculous pleural effusions may be dyspneic in case if effusion is large. On occasions the onset of tuberculous pleuritis is less acute with mild chest pain, at most a low-grade fever, a non-productive cough, weight loss and easy fatigability. Patients with tuberculous pleuritis tend to be younger than patients with parenchymal TB. In one recent series from Qatar, the mean age of 100 patients with tuberculous pleuritis was found to be 31.5 years.[13] However, in industrialized countries, the mean age of tuberculous pleuritis patients tends to be older because it is reactivation TB.[14] In a recent study from the United States of America carried out in 14,000 patients, the mean age was reported to the Communicable Disease Center between 1993 and 2003 as 49.9 years.[15] The pleural effusions secondary to tuberculous pleuritis are usually unilateral and can be of any size. TB was the third leading cause of large or massive pleural effusion (12%) after malignancy (55%) and pneumonia (22%).[16] However, if chest CT scans are performed,more than 80% may have parenchymal abnormalities. The parenchymal disease is almost always on the side of the pleural effusion and is invariably active. On rare occasions, pleural TB can present with pleural-based nodules and thickening. The pleural fluid with tuberculous pleuritis is invariablyan exudate. Indeed, the pleural fluid protein level frequently exceeds 5 g/dL and this finding suggest stuberculous pleuritis.[11] Most patients with tuberculous pleuritis have more than 50% small lymphocytes in their pleural fluid and many have more than 90%.[12,4] Testing for pleural fluid ADA levels is an easy and inexpensive method for establishing the diagnosis of TB pleuritis.[11] ADA, a predominant T-lymphocyte enzyme, catalyzes the conversion of adenosine and deoxyadenosine to inosine and deoxy inosine, respectively. A recent meta-analysis of 63 studies including 2796 patients with tuberculous pleuritis and 5297 with non-tuberculous effusion reported that the sensitivity and specificity of ADA in the diagnosis of pleural TB 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.[17]

The optimum pleural fluid cutoffs for ADA to identify TPE have beena subject of controversy in the past. A comprehensive meta-analysis showed that pleural fluid ADA levels greater than 70 U/L are highly suggestive of TBPE, and low ADA levels below 40 U/L should prompt investigation of a non-tubercular diagnosis. Based on this meta-analysis,a cut off of 40 U/L has a sensitivity of 0.93 (0.90–0.95) and a specificity of 0.90 (0.87–0.92) with an NPV of 0.93 (range: 0.98 at a 20% prevalence to 0.93 at a 60% prevalence setting).[18]

TB is one of the top ten leading causes of death in Nepal. Almost half of Nepal's population are supposed to be infected with TB. Every year (estimated) about 69000 Nepalese develop new TB. Every year about 17000 people died due to TB in Nepal in FY 2078/79 as per National tuberculosis program., TB FACT SHEET FY 2078/79.[8] The natural history of tuberculous pleural effusion without treatment usually resolves spontaneously, but the patient frequently develops active TB at later date which will definitely hinder the national strategic plan to end tuberculosis. Thus, it becomes a important to diagnose these cases using the clinical presentation and using laboratory as well as radilogical findings in the early detection of the cases of common TBPE.

MATERIALS AND METHODS

A prospective hospital based cross-sectional study was conducted in Department of Internal Medicine, National Medical College and Teaching hospital, Birgunj, Nepal from 15th March, 2023 to 14th October, 2023 (7 months) among 107 tuberculosis patients with pleural effusion from the nearby areas of the southern Nepal. Non-probability, purposive sampling technique was used. Following were the criteria for participants selection:

Inclusion criteria

All patients presenting with acute or sub-acute febrile pleural effusion visiting the Emergency Department or outpatient or admitted in Medicine Ward of the Institution who provided written consent for the study.

Exclusion criteria

Other established diagnosis for pleural effusion

Patient already on anti-tuberculous therapy

A proforma Questionnaire Method was filled to elicit requisite data. The samples blood and pleural fluid were sent for the test parameters to be done in Central Laboratory, National Medical College for analysis. More relevant data were obtained from results of tests done. The chest X-ray was also done in the Department of Radiology. All data were processed, analyzed, and disseminated by MS office, Excel and statistical package for social sciences (SPSS) version 26. The formal written and verbal consent was taken from the participants and ethical clearance was taken from Institutional Review Committee (IRC), National Medical College, Birgunj (Ref. F-NMC/633/079-080).

RESULTS

A total of 107 subjects diagnosed as Tuberculous pleural effusion participated in this study. The average age of the subjects was 55.7±18.4 years. The oldest participant was

90 years old and the youngest one was of 14 years.

The gender distribution of the participants showed that more were the male (n=72) as shown in the figure 1.

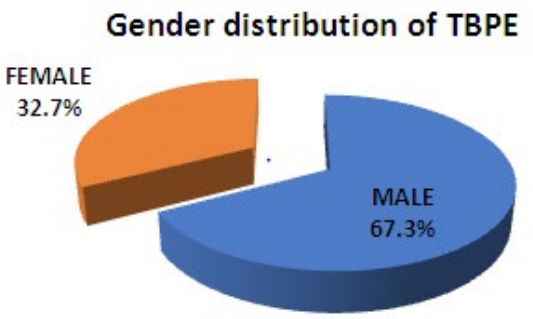

Figure 1: Gender distribution of the participants.

Majority of the participants (88.8%) presented with fever, and 11.2% of the subjects were afebrile. Approximately 59% of the participants had chest pain. Almost 65% of them had dyspnea and 77% presented with frank cough as shown in the table 1.

Table 1: Presentation and variables of the subjects

Characteristics	Categories	Frequencies (n)	Percentage (%)
Gender	Male	72	67.3
	Female	35	32.7
Fever	Yes	95	88.8
	No	12	11.2
Cough	Yes	83	77.6
	No	24	22.4
Chest Pain	Yes	63	58.9
	No	44	41.1
Dyspnea	Yes	70	65.4
	No	37	34.6
Site of effusion	Right	65	60.7
	Left	38	35.5
	Bilateral	4	3.7
Massive effusion	Yes	9	8.4
	No	98	91.6

About 17% (n=18) participants presented with multi comorbid conditions and 37% had single morbid conditions. More than 45% of the participants had no morbidity.

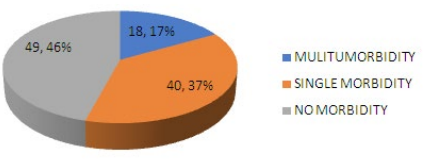

Figure 2: Participants with the morbidity

The participants with the right sided pleural effusion were seen in 65 subjects (60.7%) followed by 35.5% (n=38) of subjects with left sided TPE and only 3.7% of the participants had bilateral TPE. The massive pleural effusion was only seen in 8.4% (n=9) of the participants as shown in Table 1.

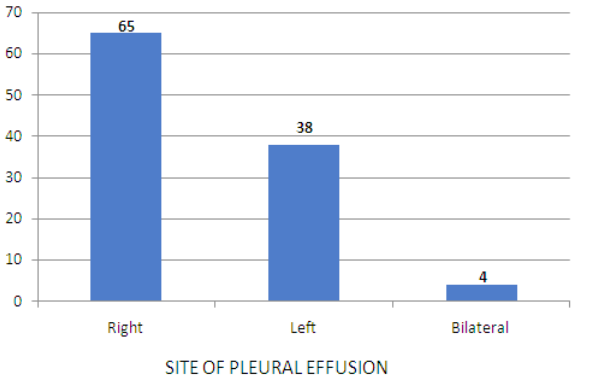

Figure 3: Participants with lung side involvement

The laboratory parameters showed that the mean hemoglobin concentration of the participants was 11.33±2.02 gm%. The whole blood TLC was found to be 8750 cells/cu mm with highest count of 17600 cells/cu mm. The average serum creatinine was found to be 1.02±0.51 mg/dL. The pleural fluid analysis showed the mean TLC of 3191 cell/cu mm with the highest count of 45000 cells/cu mm. The differential count showed the lymphocytic predominance of average 76.1% of the total. The protein content was high as shown in the table 2 and fluid ADA levels were also elevated with the average ADA of 86.5±26.4 U/L.

Table 2: Different laboratory parameters of the subjects

Parameters	N	Minimum	Maximum	Mean	Std. Deviation
HEMOGLOBIN (gm%)	107	5.91	17.00	11.3332	2.02891
BLOOD TLC (cells/cumm)	107	3200	17600	8750.47	3149.914
CREATININE (mg/dL)	107	0.60	4.89	1.0218	0.51731
FLUID TLC(cells/cumm)	107	120	45000	3191.63	5267.658
FLUID LYMPHO %	107	5	95	76.11	17.983
FLUID PROTEIN (g/dL)	107	3.00	7.50	5.0739	0.90872
FLUID ADA (U/L)	107	23.00	172.00	86.5041	26.38267

DISCUSSION

A prospective hospital based cross-sectional study enrolling 107 subjects diagnosed as TBPE presenting to the Department of Internal Medicine, National Medical College Teaching Hospital showed 67.3 % (n=72) male and 32.7% (n=35) female participants. Majority of the participants (88.8%) presented with fever, and

approximately 59% of the participants had chest pain. Almost 65% of them had dyspnea and 77% presented with frank cough. Majority of the participants had right sided effusion. Pleural fluid examination showed increased total leukocyte count (mean 3191 cells/cu mm) and with lymphocytic predominance and increased protein content (5.07±0.91 g/dL). Pleural fluid Adenosine Deaminase (ADA) was found to be elevated (86.5±26.4 U/L).

A study done in 2007 by Gopi et al in India showed that tuberculous pleural effusions are usually unilateral, small to moderate in size, and self-limiting.[3] The results are similar to our study. This is again supported by the findings of another study by Valdes et al in 1998[4], and Frye et al in 1997[5]. The results showed that in patients without human immunodeficiency virus (HIV) infection, tuberculous pleural effusions occur slightly more frequently on the right side than the left (55 versus 45 percent and occupy less than two-thirds of the hemithorax in 82 percent of cases.

TB effusions can be typically characterized by acute to subacute illnesses with unilateral pleuritic chest pain, cough, fever, night sweats, dyspnea, and weight loss. The findings of the TPE patients were similar in our study.[6]

A study by Berger et al showed that if both cough and pleuritic painare present, the pain usually precedes the cough. Most patients are febrile but approximately 15% willbe afebrile.[12] The results of our study are also comparable to this. Patients with tuberculous pleural effusionsmay be dyspneic if the effusion is large. On occasions the onset of tuberculous pleuritis is lessacute with mild chest pain, at most a low-gradefever, a non-productive cough, weight loss and easy fatigability. Patients with tuberculous pleuritis tend to beyounger than patients with parenchymal TB. In onerecent series from Qatar, the mean age of 100 patients with tuberculous pleuritis was 31.5 years.[13] However, to the contrary the mean age of our participants was 55.7 years.

Liang et al. in 2008 in a meta-analysis of 63 studies including 2796 patients with tuberculous pleuritis and 5297 with non-tuberculous effusion reported that the sensitivity and specificity of ADA in the diagnosis of pleural TB 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.[17] The level of the pleural fluid ADA in our study also showed higher value in majority of the TPE cases.

Another study by Aggrawal et al. in 2019 states that the optimum pleural fluid cutoffs for ADA to identify TPE have been a subject of controversy in the past. A comprehensive meta-analysis showed that pleural fluid ADA levels greater than 70 U/L are highly suggestive of TBPE, and low ADA levels below 40 U/L should prompt investigation of a non-tubercular diagnosis. Based on this meta-analysis,a cut off of 40 U/L has a sensitivity of 0.93 (0.90–0.95) and a specificity of 0.90 (0.87–0.92) with an NPV of 0.93 (range: 0.98 at a 20% prevalenceto 0.93 at a 60% prevalence setting)[18] The mean fluid ADA was found to be 86.5 U/L fo r the cases of TPE that is in accordance with the conclusion of the above study results.

If the fluid ADA is above 70 U/L and the pleural fluid has a lymphocyte-to-neutrophil ratio greater than 0.75, the diagnosis of tuberculous pleuritis is virtually established. If the pleural fluid ADA is between 40 and 70 U/L and the patient has a lymphocyte-to-neutrophil ratio of more than 0.75, one can make a presumptive diagnosis of tuberculous pleuritis. In this situation, if the patient's clinical picture is not typical for tuberculous pleuritis, consideration can be given to performing a needle biopsy of the pleura or thoracoscopy. If the patient's pleural fluid ADA level is below 40 U/L, the diagnosis of TB is unlikely.[19] This also supports the higher value of fluid ADA of the study participants.

CONCLUSION

The study carried out in the tuberculous pleural effusion cases have the typical common clinical signs and symptoms with the higher fluid ADA values and increased fluid total leukocyte count with lymphocytic predominance that is the basis for the diagnosis of the TPE. The principal purpose of the present study helped in determining, interpreting and analyzing the diagnosis of tuberculous pleural effusion.

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