STUDY OF THE CLINNICAL CHARACTERISTICS AND OUTCOMES OF EXUDATIVE PLEURAL EFFUSION: IMPROVING CLINICAL DECISION MAKING IN RESOURCE LIMITED SETTING

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ABSTRACT

Introduction: In the background of resource limited setting like Nepal, we set out to identify if specific clinical characteristics and basic lab parameters would guide differentiation of Tuberculous from other causes of exudative pleural effusion.

Methodology: Retrospective study of 109 consecutive patients with exudative pleural effusion.

Results: Compared to Tubercular pleural effusions (41.3%), increased age, increased duration of symptom and increased pack years statistically favoured a diagnosis of Malignant pleural effusion(21.1%), whereas presence of fever, cough and increased pleural ADA levels favoured Tubercular pleural effusions. With regards to Parapneumonic effusions (26.6%), a shorter duration of symptom, smaller effusions, higher pleural Neutrophils, lower pleural lymphocyte neutrophil ratio and lower ADA favoured the diagnosis as compared to Tubercular pleural effusions.

Conclusions: The appreciation of important clinical and pleural biochemical differences between Tubercular and other major causes of exudative pleural effusions aids in improved clinical decision making with minimal resources in resource limited settings like ours.

Key words: *Exudative Pleural Effusion, Tuberculosis, Clinical Decision Making*

INTRODUCTION

Pleural effusion is a common presentation in the patients presenting to the Pulmonologists. The etiology of Pleural Effusion depends on geographic region, patient characteristics, and the availability of diagnostic facilities in that region. Pleural effusions can be transudative or exudative.[1, 2] In cases with transudative pleural effusion the diagnosis is usually made without much difficulties but exudative pleural effusion requires careful differential diagnosis that includes parapneumonic effusion, tuberculosis, and metastatic cancers which are found to be the cases in large number of patients.[3-5] Tuberculosis is the most common cause of exudative pleural effusion in many areas of the world.[6,7] In Nepal, Tuberculosis (TB) is a major public health problem. About 45 percent of the total population is infected with TB, of which 60 percent are adult. Every year, 45, 000 people develop active TB, out of them 20,580 have infectious pulmonary disease. These 20,000 are able to spread the disease to others[8]. Although pulmonary disease is the most common form of TB, extra-pulmonary TB affecting mainly the lymph nodes and pleura serves as the initial presentation in about 25% of adults. Pleural TB accounts for 4% of all TB cases in the United States[9]; in Spain, however, this percentage is greater than 10%.[10] TB is one of the most common causes of pleural effusion in some geographical areas.[11] But in the developed world like United States, the leading etiologies of pleural effusion in adults who undergo thoracentesis are CHF, pneumonia, malignancy, pulmonary embolus, viral disease, coronary artery bypass surgery, and cirrhosis with ascites.[12] Thus it

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becomes very important to understand the clinical characteristics of the causes of Pleural effusion as the treatment, social and economic implications of the diagnosis being Tuberculous or Non-tuberculous are tremendous.

METHODOLOGY

We conducted a retrospective review of the medical records and chest radiographs of consecutive cases of exudative pleural effusions referred to the Respiratory and Internal Medicine services of the B P Koirala Institute of Health Sciences, Nepal during a 15 month period from April 2013 till July 2014. The hospital serves as a referral hospital for the whole of Eastern Nepal. Effusions were classified as exudates when they satisfied Light's criteria[13] or if frank pus was present.

In the cases with exudative pleural effusion, the relevant data were scanned and included in the study only if the patient chart was viewed as Complete. Complete chart was defined as having detailed epidemiological data, a complete medical history and clinical examination, investigations including Pleural fluid analysis for TC/DC/sugar/ protein/light's criteria, ADA and malignant cytology if diagnosis was inconclusive by routine analysis, other special tests of pleural fluid as required, like, Amylase etc. Only the initial fluid examination was recorded. Once the above parameters were present, the Digital Radiographic Library was explored. The X-Ray was reviewed by a Pulmonology trainee. The size of the effusion was estimated on the initial upright inspiratory posteroanterior chest film. Effusions were classified as; large effusion if effusion covered greater than 50 percent of the hemithorax, medium if 25 to 50 percent was covered, and small effusion if effusion covered less than 25 percent of the hemithorax. The patient's with the following features were classified as Tuberculous pleural effusion.

1. Positive mycobacterial culture in pleural fluid or pleural biopsy tissue samples.
2. Granulomatous inflammation in pleural biopsy tissue samples.
3. Positive AFB stain or mycobacterial culture of sputum sample.
4. Clinically suspected tuberculous pleurisy and pleural effusion that were resolved with anti-TB treatment. Here, 'clinical suspicion' means that these patients had no systemic diseases, and were excluded from malignancy and other pleural diseases. Moreover, there were suggestive clues of TB from contact history, radiographical findings or clinical presentation.
5. ADA level of more than 60 with response to anti-TB treatment during hospital stay will also be taken as TB.

All other cases of exudative pleural effusion with complete medical charts were classified as Non-Tuberculous effusion. These were diagnosed in accordance to the following criteria:

Parapneumonic effusion: Pleural effusion in association with pneumonia, lung abscess, or bronchiectasis.

Empyema: Presence of purulent fluid or positive culture of parapneumonic effusion.

Neoplasia: Neoplastic tissue in the pleural cavity (biopsy and/or cytology) or CT suspicion of malignancy if biopsy and cytology were inaccessible or inconclusive.

Other diagnosis made such as, cirrhosis of the liver, pancreatitis, systemic lupus erythematosus, rheumatoid arthritis, were as per the pre-established criteria.[14]

Statistical analysis

Data with parametric distribution have been expressed in mean ± SD and Independent t-test was used for the comparison of variables. Data with non parametric distribution have been expressed as median (25th percentile and 75th percentile) and Mann Whitney test was used for the comparison of variables. The chi-squared analysis was used for comparison of proportions. All statistical test values were two-sided, and a P value of <0.05 was considered to be statistically significant. Analysis was carried out using SPSS 17 software.

RESULTS

Among 109 patients, 58.7% (64) of the patients were male and the mean age was 47.97(±19.69) years. The mean age in patients with Tuberculous pleural effusion (TPE) was 42.3(±18.9) years and that in Malignant pleural effusion (MPE) was 65.5(±13.6) years. The etiological distribution of the pleural effusions with the number of patients in each etiological group and the mean age of the group are shown in Table 1. 41.3%(45) of the cases were Tuberculous in origin and there was 1

case of Hepatitis A associated pleural effusion. The majority of parapneumonic effusions (82.4%) were small in size whereas 39.1% of MPE were large; the majority of TPE were Medium in size (57.8%).

Table 1. Causes, gender and age at diagnosis of pleural effusion

	n	%	Males/ Females	Age, yrs*
Tubercular Pleural Effusion				
Tuberculosis	45	41.3	27/18	42.3±18.9
Non Tubercular Effusion				
Malignant Pleural Effusion	23	21.1	12/11	65.5±13.6
U&C Parapneumonic Effusion	17	15.6	9/8	44.1±17.7
Empyema	12	11.0	11/1	40.25±17.0
Hydropneumothorax	5	4.5	3/2	53±20.7
RA	1	0.9	0/1	81±0
SLE	2	1.8	1/1	41±2.8
Metastatic Pleural Effusion	3	2.8	0/3	48±6.2
Others#	1	0.9	1/0	16±0

*Mean ± SD, # Hepatitis **A** associated pleural effusion

The diagnosis of TB was on the basis of high ADA in 68.9% of the cases (Table 2). The ADA was less than 60 in 10 of TPE and in 4 cases ADA were not done. Comparatively, ADA of more than 60 was present in 5(21.7%) of MPE cases and in 5 (41.7%) of the cases with Empyema.

Table 2. Criteria for diagnosis of Tuberculous pleural effusion

Criteria	*n*	%
High ADA (>60)	31	68.9
Clinical Suspicion	7	15.6
Sputum AFB positive	5	11.1
Gene Xpert positive	2	4.4

On comparing the clinical and demographic characteristics, the subset of patients with MPE compared to TPE (Table 3) had a greater mean age (65±13 years vs 42±18 years), longer duration of symptoms (median duration 60 days vs 30 days), and they had a longer Smoking history in terms of the Pack years (median duration 30 years to 5 years). The subset with TPE had fever predominantly whereas chest pain was more common in the MPE subset.

On comparing the subset of patients with Para-pneumonic effusion (PPE) to TPE (Table 3), the duration of symptom was longer in the Tuberculous group (median duration 8 days to 30 days) whereas the duration of hospitalization (median duration 10 days to 6 days) was longer in the PPE subset, also the size of the effusions where Small in this group compared to the TPE group.

Table 3. Comparison of clinical, demographic and outcome characteristics of patients with tuberculous vs. non-tuberculous pleural effusion

Characteristics	Tubercular pleural effusion (n=45)	Malignant pleural effusion (n=23) *p*		Para-pneumonic effusion (n=29) *p*	
Age *(mean (sd))*	42(18)	65(13)	.000	42(17)	.950
Male *(n (%))*	27(60)	12(52)	.537	20(69)	.434
Duration of Symptom *Median (Interquartile Range)*	30(15-75)	60 (30-120)	.049	8(4-14)	.000
Duration of Hospitalization *Median (Interquartile Range)*	6(4-9)	7(6-8)	.172	10 (7-14.5)	.001
Shortness of breath *(n (%))*	33(73)	19(82)	.394	23(79)	.559
Fever *(n (%))*	33(73)	8(34)	.002	21(72)	.931
Cough *(n (%))*	33(73)	15(65)	.487	18(62)	.307
Sputum *(n (%))*	7(16)	0(0)	.046	1(4)	.102
Chest Pain *(n (%))*	17(37.8)	15(65)	.032	10(34)	.774
Right sided effusion *(n (%))*	23(51)	17(73.9)	.071	19(65)	.222
Large effusion *(n (%))*	11(24)	9(39)	.209	1(3)	.017
Smoking *(n (%))*	5(11)	19(82)	.000	11(37)	.006
Pack years *Median (Interquartile Range)*	5(3-7.5)	30 (15-40)	.001	13(5)	.008
Thoracostomy *(n (%))*	13(29)	3(13)	.145	13(44)	.161
Improved *(n (%))*	45(100)	0(0)	.000	28(96)	.210

On comparing the pleural fluid characteristics, there was no significant difference in the Pleural fluid TLC, pleural lymphocyte neutrophil ratio, pleural fluid LDH, the LDH ratio and even the pleural fluid protein in the TPE and the MPE group. The pleural fluid ADA was significantly more in the Tubercular group (median value 90U/l vs 40U/l) (Table 4). Interestingly, 17(37.8%) of the patients with TPE had pleural fluid protein more than 5 in comparison to 1(4.3%) of MPE and this difference was statistically significant. MPE was diagnosed in these cases on the basis of positive CECT Chest findings in all 23 cases and positive Malignant Cytology results in 9 (39.1%) of the cases.

On comparing the subset of patients with PPE to TPE (Table 4), the patients with PPE showed an increased percentage of pleural neutrophils (median value 85% vs 30%), a decreased percentage of pleural lymphocytes and consequently a lower pleural lymphocyte to neutrophil ratio (median value 0.17 vs 2.33). Pleural fluid ADA levels were significantly higher in the Tubercular group of the patients (median value 90U/l to 31U/l). Out of the PPE cases, 12 had empyema and in total 13 patients required thoracostomy.

In the group with TPE, 11(24.4%) had Large effusions and Steroids had to be added to 9 of these cases.

Table 4. Comparison of Pleural fluid analysis of patients with tubercular and non-tubercular effusion

Character-istics	Tubercular pleural effusion (n=45)	Malignant pleural effusion (n=23)		Para-pneumonic effusion (n=29)	
	Median (Interquar-tile Range)	*Median (Interquar-tile Range)*	*p*	*Median (Interquar-tile Range)*	*p*
Pleural fluid TLC per mm3	330 (55-630)	300 (140-800)	.645	25 (10-720)	.252
Pleural neu-trophils, %	30 (20-70)	60 (20-80)	.297	85 (67.5-90)	.000
Pleural lym-phocytes, %	70 (30-80)	40 (20-80)	.297	15 (10-32.5)	.000
Pleural lymphocyte neutrophil ratio	2.33 (.42-4.00)	.67 (.25-2.34)	.096	.17 (.11-.47)	.000
Pleural glucose, mg/dL	68 (51.5-101)	86 (54-106)	.693	21 (11.5-115.5)	.141
P/S protein ratio	.66 (.14)*	.64 (.12)*	.694	.63 (.23)*	.549
Pleural Protein more than 5g/dl	17 (37.8%)#	1 (4.3%)#	.003	6 (20.7%)#	.121
Pleural LDH, U/L	520 (341-693)	506.50 (312-583)	.702	420 (341-738)	.838
P/S LDH ratio	1.03 (.85-1.68)	1.30 (.85-1.84)	.466	1.26 (1.03-1.92)	.050
Pleural ADA, U/L	90 (61-113)	40 (20-52)	.000	31 (24.5-127)	.011

*Mean ± SD, #total number(percentage of total)

DISCUSSION

In a developing country like Nepal, even the tertiary care hospitals have at best ordinary facilities. Though the scenario is gradually changing with Nepal developing its own specialists and thus the scope of investigations and diagnosis gradually increasing day by day, it is still limited by cost factors and lack of Universal health coverage that is the case in the West. In this background, we tried to focus if differences in clinical and basic lab parameters to differentiate TPE from NTPE would improve clinical decision making.

With regards to the cut off level for ADA, Some large series suggest that a value >45 to 60 U/L is 100 percent sensitive and up to 97 percent specific for TPE.[15-19] Pleural effusions with an ADA level <40 U/L are rarely caused by TB.[20] Since this study was conducted in a resource limited setting, we wanted to increase the Specificity of the diagnosis of TPE and thus used ADA value of more than 60U/l as cut off.

As expected, TPE was the commonest cause of exudative pleural effusion (41.3%) over all age groups. When looking at patients less than 40 years of age, the percentage of TPE rose to 63% (29/46), a pattern observed in countries with high incidence of TB.[15,21,22] Fever, cough and shortness of breath were the most common symptoms occurring in 73% of the cases in agreement with other studies.[23] TPEs are typically unilateral (95%).[24] In one series of 254 patients with TB pleurisy, the effusions occupied between one-third and two-thirds of the hemithorax in 46%.[15] In our study as well, TPE was unilateral in 97.8% of the cases and there was no site predilection, and Medium sized effusion were the most common (57.8%). The pleural fluid in TPE was predominantly lymphocytic in 62.2% of the cases and in 66.7% of the cases the pleural lymphocyte neutrophil ratio was more than 0.75. The use of the ratio is particularly important as Burgess et al.[25] have shown that Specificity is increased when the lymphocyte to neutrophil ratio is greater than 0.75 and the ADA is greater than 50 U/L. Different studies have shown that the pleural fluid protein in TPE is invariably >3.0 g/dL (30 g/L), and >5.0 g/dL (50 g/L) in 50 to 77 percent of cases.[26,27] In our study, the pleural fluid protein was >5g/dl in 37.8%(17/45) of the cases whereas a level of >3g/dl was present in 88.9%(40/45) of the cases . We relied heavily on pleural fluid ADA for the diagnosis of TPE and it was >60U/l in 68.9%(31/45). The diagnosis was based on clinical suspicion in only 7 of the cases, positive sputum microscopy in 5 of the cases and positive gene xpert on sputum in 2 of the cases.

Malignancy was the second most common cause of exudative pleural effusions in our study and the most frequent cause among patients older than 60 years. Others have also made the same observation.[11] There were 23 cases (21.1%) of MPE as a result of Bronchogenic Carcinoma, whereas 3 more cases were a result of Metastatic Pleural Effusion. The differential diagnosis between TPE and MPE is a very important clinical problem. Compared to TPE, these patients were older in Age (mean age 65±13 years) and had symptoms for longer duration of time (median duration 60 days). Fever understandably was more common in TPE than MPE, whereas chest pain was more common in the MPE group which could be due to increased number of larger size effusions as well as parietal and chest wall extension of the tumour. History of Smoking was present in 82% of the cases with MPE whereas only 11% of TPE were smokers. The Median pack years for the MPE group was 30 pack years. These clinic-demographic pictures do point to some distinction in the presentation of MPE compared to TPE. Distinction of MPE and TPE is also difficult by pleural fluid analysis. There was no significant difference in the Total Leukocyte count, pleural lymphocyte percentage, pleural glucose levels or the pleural LDH. However, interestingly, though the pleural to serum protein ratio was similar in both the groups, pleural fluid protein was >5g/dl in 17(37.8%) of the patients with TPE in comparison to 1(4.3%) of MPE and this difference was significant.

Measurement of adenosine deaminase (ADA) may be helpful with a differential diagnosis of malignant versus tuberculous pleurisy when an exudative effusion is lymphocytic, but initial cytology and smear and culture for tuberculosis are negative.[16,17,28] Specificity is increased when the lymphocyte to neutrophil ratio is greater than 0.75 and the ADA is greater than 50 U/L.[25] False negatives and positive ADA results do occur, so ADA results need to be considered in the context of other features of the patient's clinical presentation.

In our study, the ADA values in TPE and MPE were discriminatory. The median ADA in TPE was 90U/l whereas it was 40U/l in the MPE subset. However, 5/23(21.7%) of the patient with MPE also had values more than 60U/l, interestingly in all 5 of these cases the pleural fluid protein was <5g/dl, which is a very interesting observation and will be interesting to see if it is replicated in our future studies. Pleural fluid lymphocyte neutrophil ratio though higher in the TPE group was not statistically significant, however there was a trend towards a difference as the p-value was .096.

Parapneumonic effusions together with empyema thoracis accounted for 26.6% of all our cases. It is estimated that about 40% of patients with pneumonia develop a concomitant pleural effusion[30] although some studies show the incidence of this complication of pneumonia to be less than 20%.[31] Compared to TPE, duration of symptoms at presentation was shorter (median duration 8 days in PPE to 30 days in TPE) which is expected as PPE has more acute presentation whereas TPE is acute or sub-acute in onset. However, these patients were hospitalized longer (median duration 10 days to 6 for TPE), and thoracostomy had to be performed in 44% of these cases. The complicated nature, the need to complete antibiotic course and the complications related to thoracostomy might have led to the longer duration of stay. The size of the effusion was large in only 1 case and majority of them were small (65.5%) and medium in size (31%).

There were quite a few discriminating factors in the pleural fluid analysis. The pleural neutrophils were more in the PPE subset and the pleural lymphocytes less, consequently, the pleural lymphocyte neutrophil ratio was 0.17 in the PPE group and 2.33 in the TPE group.

Pleural fluid glucose was lower in the PPE group however the difference was not statistically significant. Pleural ADA was again discriminatory, with median values of 31U/l in the PPE subset compared to 90U/l in the TPE subset.

CONCLUSION

Thus, using the clinical characteristics and basic lab investigations, features such as increased age, increased duration of symptom, lack of fever, positive Smoking history, lower ADA levels and a lower pleural protein of <5g/dl pointed more towards MPE than TPE. Similarly, decreased duration of symptoms, smaller size of effusion, a higher pleural neutrophil percentage, a lower pleural lymphocyte percentage, a lower pleural lymphocyte to neutrophil ratio and a lower ADA were more in favour of PPE than TPE. The appreciation of these characteristic can aid in the differentiation

of Tuberculous from Non-tuberculous causes of exudative pleural effusion and thus improve the clinical decision making in resource limited setting.

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