ORIGINAL ARTICLE

Diagnostic Efficacy of Pleural Fluid Adenosine Deaminase Level in diagnosing TB Pleural Effusion is Excellent in a High Prevalence Area

Abdul Rasheed Qureshi[1], Hamid Mehmood[2], Muhammad Irfan[3], Ammara Waqar[4]

Author`s Affiliation

[1,3]Assistant professor, Pulmonology department, Gulab Devi Chest Hospital Lahore, Pakistan
[2] Professor of Biochemistry, Federal Medical and Dental College/ Registrar, Shaheed Zulfiqar Ali Bhutto Medical University, Islamabad
[4] P.hD scholar, University of Lahore, Lahore

Author`s Contribution

[1,3]Conception, planning of research and writing of the manuscript, Discussion
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Address of Correspondence
Prof Hamid Mehmood
drhamidmahmood373@gmail.com

ABSTRACT

Objectives: To evaluate the efficacy of Pleural Fluid ADA level in diagnosing tuberculous pleural effusions.

Place and Duration: The study was conducted at the Gulab Devi Chest Hospital Lahore from 03-01-2017 to 30-09-2017.

Methodology: 456 cases having age > 14 years and radiological evidence of pleural effusion were included. Patients having Age > 65 years, minimal inaspirable pleural effusion, negative consent for ADA estimation and with obvious radiological signs of malignancy were excluded. Detailed history, physical examination, radiological, haematological and biochemical findings were recorded. Pleural fluid analysis including ADA levels were recorded. Statistics was applied to reach the conclusion.

Results: 422/456(92.54%)cases were exudates while 34/456(7.45%) were transudate. 352 cases were diagnosed as TB pleuritis. 330(93.75%)cases showed PFADA levels 40 IU/L and above, while 22 cases showed ADA level < 40IU/L. Mean ADA level for TB peural effusion is 74.43IU/L. Using a cut off value 40 IU/L, we got a sensitivity of 93.75%, specificity 91.42 % and Positive predictive value 98.21% for tuberculosis.

Conclusion: Pleural fluid ADA level is a valuable bio-marker for TB diagnosis in an area of high prevalence. It successfully differentiates between tuberculous and non-tuberculous pleural effusion.

Keywords: Pleural Fluid–ADA level-TB/Malignancy-Discrimination.

Introduction

Tuberculosis is a global problem. Pakistan ranks 5th among the high burden countries and has an annual incidence of 497/100 000.[1-2] Pleural effusion is the most common extra-pulmonary manifestation of tuberculosis[12] encountered in daily pulmonology practice. Malignancy is also a significant contributor in addition to acute infection. [20] Differentiation between a malignant and tuberculous PE is a major issue because both present as exudative lymphocytic pleural effusion. The definitive diagnosis of TB can be established either by finding AFB in the smear of pleural fluid but its yield is less than 20%. 40-70% cases can be differentiated by histopathology of pleural biopsy. If tissue culture is added to the histopathology, yield can be increased to 90%.[3] Despite utilizing all these modalities, 10-20% cases still remain undiagnosed.[9,10] Similarly AFB negative smear, no growth on AFB culture and absence of a caseating granuloma on histopathology does not exclude tuberculosis.[4] So there is a real need of a biomarker capable of diagnosing or excluding TB precisely.

Several biomarkers have been tried in this context, the commonest is ADA (Adenosine Deaminase) which is not only easily available, also highly cost-effective and is in use since 1978.[46] When non differentiated T-lymphocytes are stimulated antigenically and mitogenically its value is increased due to CD4 blastogenesis. ADA level in pleural fluid is increased by T-lymphocytes, sensitized by

Mycobacterium Tuberculosis.[5,47] A number of studies showing high sensitivity and specificity for the diagnosis of TB pleuritis have been conducted in this decade. The ADA level shows significant efficacy for diagnosing TB in high burden population.[6,13-14,17-19,22-40] As this test is less invasive, highly cost-effective, easily available, repeatable and gives better yield as compared to biopsy and histopathology in young patients in a high prevalence area of tuberculosis. [7-8] We conducted this study to assess its efficacy for the differential diagnosis of TB and non-TB pleural effusions in our community.

Methodology

This prospective study was conducted at OPD, Gulab Devi Chest Hospital, Lahore-Pakistan. 456 cases with age > 14 years, radiological & clinical evidence of pleural effusion and willing for ADA estimation were included in the study. On the other hand, patients having Age > 65 years and <14years, minimal inspirable effusion, negative consent for ADA estimation, obvious radiological signs of malignancy & pregnancy cases were excluded. In addition to the history including history of contact & thorough physical examination, all patients were subjected to U/S chest & Abdomen, ECG / Echo, CT when suspicion of CA on US and pleural aspiration. Pleural fluids were evaluated with Z-N stain, Gram stain, C/S pyogenic, Cytology, ADA and routine biochemical estimation. Each patient was evaluated for CBC, ESR, RFTs, LFTs, Viral markers & Serum Protein. Empirical ATT was started in all patients suggesting tuberculosis both clinically and radiologically, having PF ADA level >40 IU/L & with no evidence of Pneumonia, Malignancy, CLD, CRF, CCF & Malnutrition. Similarly, 22 patients with ADA level <40 but with very high index of suspicion for TB were also put on anti-TB drugs. A short course of steroids was also given to enhance the absorption of residual fluid.[15-16] The response to treatment was noted. Patients were followed up for 6—9 months. Malignancy was diagnosed by finding cancer cells in pleural fluid cytology. Decision about pneumonia was made by acute history, significantly raised TLC, Polycytosis and predominant neutrophilic aspirate with microbial evidence on Gram staining /culture. Data of all the patients was recorded, tabulated and statistics was applied to reach the conclusion.

Results

Age group was 14-64 years. Patients aged 14-30 years constituted 74.56% of study population with median age 29 Years. Out of total 456 cases, 314 (68.85%) were male on the other hand, 142 (31.14%) cases were female. Male to Female Ratio was 2.2 :1 which shows that pleural effusion being more common in males members of the population.

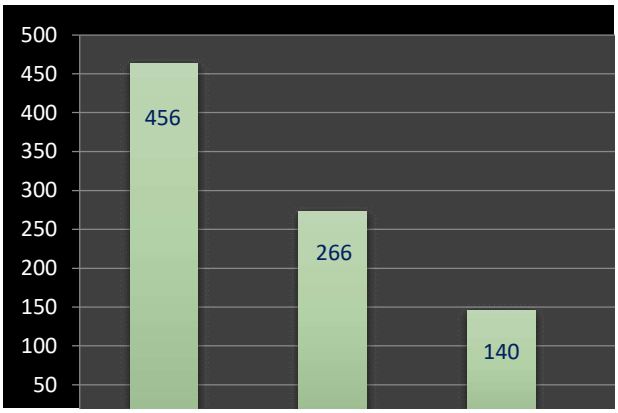

Figure 1. showing the frequency of laterality of pleural effusion (n = 456)

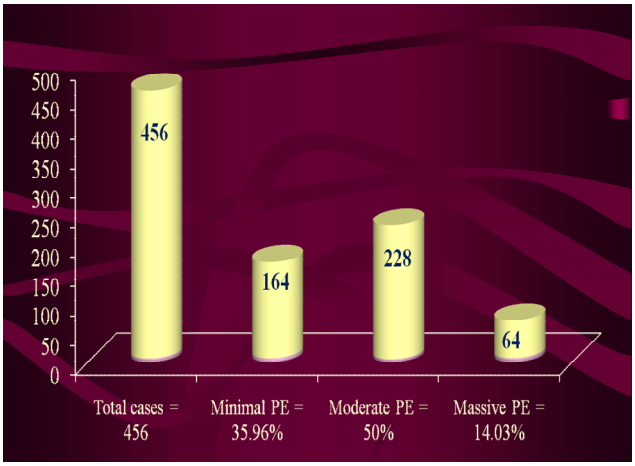

Figure 2. Showing the Quantitative Distribution of Pleural Effusion (n =456)

Table I: Showing the clinical presentation (n = 456)

Nos.	Clinical Presentation	No of cases	Percentage*
1.	Chest Pain	374	82.01%
2.	Cough	359	78.72%
3.	Fever	344	75.43%
4.	Dyspnoea	309	67.76%
5.	Weight Loss	301	66.00%
6.	Loss of Appetite	292	64.03%

Table II: Hematological Presentation in Exudative Pl. Effusions cases (n = 422)				
Total Exudates	Mean ESR mm 1st hour	Mean TLC /mm^3	Mean Hb gm%	Mean Serum Protein gm/dl
Tuberculous PE (n =352)	38.577	8,450	11.86	7.3
Parapneumonic PE (n=60)	31.6	13,750	10.9	7.34
Malignant PE (n= 10)	59	10,220	8.2	7.1

Table III: Pleural Fluid Features in exudates (n = 422)							
Total cases	Clot Formation	Mean Protein gm / dl	Mean ADA Level IU/L	ZN Stain	Gram stain / Pyogenic Culture	Cells Poly / Lymph Mean Percentage	Malignant Cells %
TB PE (n=352)	97%	7.09	74.43	-ve	00.00%	Lymph = 98.43%	0.00 %
Parapneumonic PE (n=60)	NIL	7.7	18.9	-ve	100.00%	Poly = 82.0%	0.00 %
Malignant PE (n=10)	Nil	7.05	14.7	-ve	00.00%	L = 77 .0%	100%

Quantification was done by ultrasound examination. Patients with less than 200ml fluid were regarded as minimal, 200ml—500ml mild while >500ml<1000ml as moderate and more than 1000ml were considered as massive pleural effusions.

Out of 456 aspirates, 422 /456(92.54%) pleural fluids were exudates while 34/456(7.45%) were found transudate by Light's criteria.

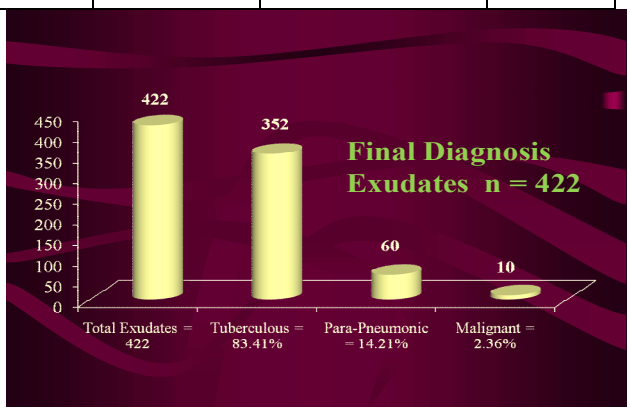

Chart-4 Showing Final diagnosis in Exudates (n= 422)

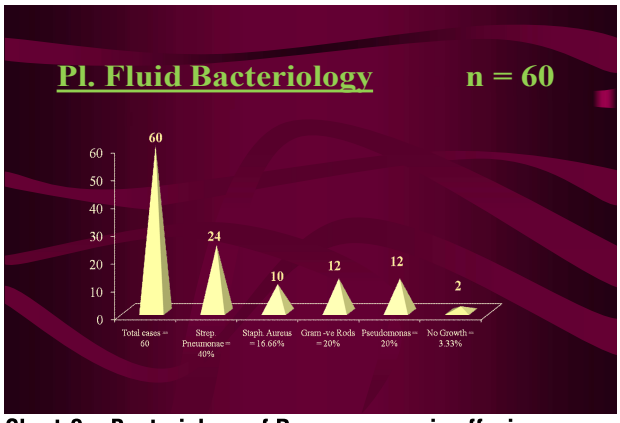

Chart-3. Bacteriology of Para-pneumonic effusions. (n = 60)

Table IV: Transudative Pleural Effusion Etiologies (n = 34)				
Diagnosis	Cases	Percentage n = 34	ADA Range IU/L	Mean ADA value
TB PE	07	20.58%	34 → 85.6	55.86
Parapneumonic	05	14.70 %	07→11	09.2
LVF	05	14.70 %	07→16	8.66
CLD	03	8.82 %	07→18	12.95
CRF	03	8.82 %	9.8→12	11.34
Hypoproteinemia	01	2.94 %	16.5	16.5
Dilated Cardiomyopathy	04	11.76%	8→12.5	10.7
Malignancy	06	17.64 %	13→22	17.7

Table-5 ADA Biostatistics for TB diagnosis in Exudates n = 422 Cut off = 40 IU/L				
cases	TB Pleuritis	Non-TB Pleuritis	Total	Predictive Value
ADA Positive	330	06	336	**Positive (98.21%)**
ADA Negative	22	64	86	**Negative (74.41%)**
Total	352	70	422	
	Sensitivity = Specificity =	**93.75% 91.42%**		

Discussion

TB is a big problem in our community and pleural effusion is not only the commonest type of extra-pulmonary tuberculosis also the commonest diagnosis of pleural effusion. Young population is usually affected but old age is not immune. When old are affected, the differential diagnosis between TB and malignancy becomes a real problem because this age favors both malignancy and reactivation tuberculosis. Evidence based diagnosis of TB in pleural effusion is very difficult because AFB negative smear and culture & absence of a caseating granuloma on histopathology does not exclude tuberculosis.[4]

In our study of 456 cases, patients aged14--30 years constituted 74.56% of the study population with median age 29 years. In one recent series from Qatar, Ibrahim WH reported the mean age of 100 patients with tuberculous pleuritis as 31.5 years.[41] Denise Duprat Neves et al reported the mean age in patients with TB pleuritis as 33.76 years.

In our study, the comparison between the ages of TB & malignant PE groups revealed a value, $P < 0.001$ which is highly significant & shows the statistically significant difference of age-based distribution of TB and Malignancy. This finding was also agreed by the current researchers[6, 11] As for as gender is concerned, no statistically significant difference of disease distribution is found between these two conditions because the P-value is more than 0.05 in our study which is similar to the observations made by Nariman A. et al.[11]

In our study, male patients were 68.85%, while female were 31.15% in comparison with the previous studies, Leesly. J. Burgess[15] - 58% males and 42 % females, L. Valdes [(6)] 56.6% males and 43.3% females.

Three common causes of exudative effusion found in our study were tuberculosis 83.41%, malignancy 2.36% and parapneumonic effusions 14.21% & TB is the most common cause. This is similar to the observations made by Maldhure et al[42] where they showed tuberculous pleural effusion as the commonest type.

Current literature states that pleural fluid ADA levle has got a high discriminative value in differentiating tuberculous from malignant pleural effusion.[43-45] Similarly, the McNemar's test of statistics, demonstrated that from a statistical view point ADA determination was more sensitive than pleural histopathological examination. Shibagaki T et al. demonstrated that tuberculous pleural effusion had a much higher ADA activity than cancer effusion and total ADA activity in tuberculous pleural effusion decreases after anti-tubercular therapy.[21]

Cut off value of ADA varies in various studies from 30 IU/L to 40 IU/L. We have used cut off value 40 IU/L to increase specificity of the test.

In our study, 330(93.75 %) TB pleural Fluid ADA levels were 40 IU/L and above, while 22 cases of TB showed PF ADA level < 40 IU/L (33 → 38). Lower marginal levels were found in TB pleural effusion associated with old age, DM, Loculated Effusion & Min. PE.

In our study, ADA level for TB pleural effusion ranged between 33—211 with mean ADA level 74.43 IU/L on the other hand for non TB pleural effusion range was between 05—32 IU/L with mean value of 18.0 IU/L. The mean value for para-pneumonic PE was 18.9 IU/L and for malignant PE it was 14.7 IU/L with $p<0.001$ which is highly significant. These figures show that there is a wide gap between the mean values of TB-PE and Malignant-PE. So this biomarker has shown an excellent discrimination value between TB and malignancy.[43] By applying a cut-off value 40 IU/L to pleural exudates, the sensitivity and specificity for diagnosing TB Pleural effusion was 93.75 % and 91.42% respectively with positive and negative predictive values of 98.21% and 74.41 % in our study.

Diagnosing 07 cases of TB and 06 cases of malignancy out of 34 transudate pleural fluids is an eye opening finding in addition to para-pneumonic and LVF etiology 05 cases each along with CLD and CRF 03 cases each, 04 cases of dilated cardiomyopathy and 01 case of hypoproteinemia was also found.

Conclusion

1. Because, ADA estimation is non invasive, rapid, cost effective & easy to perform test, we have no hesitation to conclude that " Pleural fluid ADA level is an excellent biomarker in diagnosing tuberculosis and effectively discriminating malignancy having a high sensitivity, specificity, PPV & good NPV for TB diagnosis in an area of high TB prevalence".
2. Transudative pleural effusion is a false reassurance against TB and Malignancy. So on finding a transudative pleural effusion one must go for a comprehensive work-up to make a precise diagnosis and TB along with malignancy should be included in the differential diagnosis.

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