

DIAGNOSTIC ROLE OF ADENOSINE DEAMINASE LEVEL IN EXUDATIVE LYMPHOCYTIC PLEURAL EFFUSIONS

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ABSTRACT

Background: Exudative lymphocytic pleural effusion is common problem and tissue diagnosis is gold standard for the diagnosis but it is invasive procedure with complications. Raised ADA levels are observed in tuberculous effusion but definite cut off levels is lacking for our population.

AIMS AND OBJECTIVES: To determine the diagnostic accuracy of pleural fluid ADA while comparing with closed pleural biopsy.

STUDY DESIGN: It was a Cross-sectional (validation) study conducted in Pulmonology Department, SIMS/ Services Hospital Lahore, from December 15, 2013 to October 22, 2015.

Materials & Methods: it is a prospective, non-randomized study performed in pulmonology Department, Services Hospital Lahore. 108 patients with lymphocytic exudative pleural Effusion were enrolled in the study. ADA levels were measured using commercially available ADA kit DIAZYME (Diazyme laboratories Poway, CA 92064, USA) on pleural fluid obtained by thoracocentesis and pleural biopsy specimen was taken by close pleural biopsy from each enrolled patient after informed consent.

Results: Out of 108 patients 75 (69.4%) were males and 33 (30.6%) were females. Mean age was 45.21 +17.85 SD years. 69 (63.8%) cases were diagnosed as having Tuberculosis by pleural biopsy and/or AFB culture, 36 (33.33%) cases were diagnosed as malignant and 3 (2.7%) cases were inconclusive. In biopsy proven tuberculous pleural effusion (n=69), ADA level ranged from 30-128 IU/L with mean pleural fluid ADA level of 55.93 +14.12 IU/L and 68 patients had >40 IU/L. In non TB pleural effusion (NTPE) (n=39), ADA level ranged from 10-45 IU/L with mean pleural fluid ADA level of 21.35+ 12.65 IU/L. Only three patients had raised ADA levels >40. Taking pleural biopsy as gold standard and taking ADA level > 40 IU/L as cut off value, the sensitivity and specificity of pleural fluid ADA level in the diagnosis of TPE were 95.77% and 92.31%, respectively. Positive predictive value was 91.89%, negative predictive value was 97.29% and overall Diagnostic accuracy was 96.29%.

Conclusion: ADA level in pleural fluid can be used as a diagnostic test in the workup for tuberculosis pleural effusion with sensitivity and specificity comparable to histopathology and/or culture for acid fast bacilli in pleural biopsy specimen.

Keywords: Tuberculous Pleural Effusion; Non Tuberculous Pleural Effusion; Adenosine Deaminase

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INTRODUCTION

Tuberculosis is a leading cause of mortality and morbidity among the infectious diseases. Despite all the advancing knowledge about tuberculosis since hundred years ago, it still remains the major health problem in developing countries like Pakistan and now emerged as important health issue in developed countries due to AIDS. Developing countries bear the major burden of overall mortality due to tuberculosis (98%). Majority of affected population (75%) by tuberculosis is the economically productive age groups (15-45 years). Late diagnosis, inadequate treatment facilities, resistant strains and poverty are main reasons for the failure of eradication of tuberculosis.

Tuberculosis can involve any organ of the body with pulmonary on the top. Second most common site among the extra-pulmonary involvement is pleural tuberculosis that manifests as lymphocytic exudative effusion.¹ Lymphocytic effusion have several differential diagnosis including tuberculosis, malignancy, partially treated para-pneumonic, connective tissue disease, pulmonary embolism and transudate effusion after diuresis. The definitive diagnosis of tuberculosis pleural effusion is established either by isolation of Acid fast bacilli in pleural fluid or caseous necrosis in granuloma on histopathology.² The yield of Pleural fluid AFB smear is low (25%) that increased to 70-80% for closed pleural biopsy and 90% for combined (biopsy and pleural fluid analysis). Pleural biopsy by VATS along with pleural fluid AFB smear, Culture have 98-99% sensitivity and 100% specificity.³ Invasive nature of pleural biopsy along with multiple complications made is less preferred and patient want to avoid it.

Adenosine deaminase (ADA), a catalyst during deamination of adenosine to inosine and ammonia mostly in the cytoplasm of the cell.⁴ Though present in all cells of human body, its levels are 10 times higher in the T-lymphocytes that make it useful during diagnosis of cell mediated immune responses as in the case of tuberculosis. Multiple studies confirm the higher levels of ADA in the chronic infections like tuberculosis and in empyema.⁵ Definite cut off point for diagnosis of tuberculosis is still undetermined.

We designed this study to find out the diagnostic yield of pleural fluid ADA level in comparison with the gold standard pleural biopsy specimen histopathology and culture patients from Punjab with higher incidence of tuberculosis (345/100,000) that carrying 25% of the

total disease burden of Eastern Mediterranean Region and 56% of the total disease burden of Pakistan.

AIMS AND OBJECTIVES

To determine the diagnostic accuracy of pleural fluid ADA while comparing with closed pleural biopsy.

STUDY DESIGN

It was a Cross-sectional (validation) study conducted in Pulmonology Department, SIMS/ Services Hospital Lahore, from December 15, 2013 to October 22, 2015.

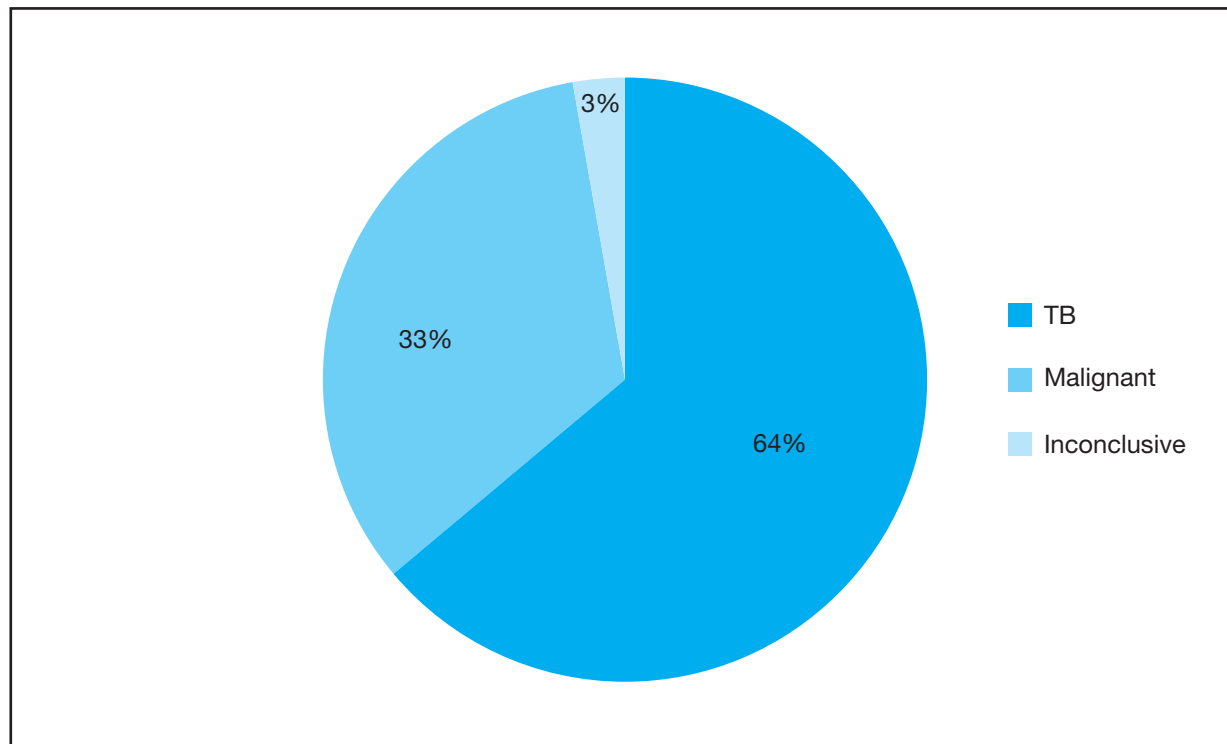
MATERIALS & METHODS

Patients of ages 15-70 years were enrolled in the study with exudative lymphocytic pleural effusion. Patients with age <15 years, visible pus in pleural fluid, known pulmonary or pleural malignancies and failure to obtain consent for biopsy were excluded from the study. Pleural biopsy of all patients was done and pleural fluid was analysed for cytology, microbiology (AFB, Bacterial smear + Culture/sensitivity) and ADA levels. ADA levels were measured using commercially available ADA kit DIAZYME (Diazyme laboratories Poway, CA 92064, USA) on pleural fluid obtained by thoracentesis and pleural biopsy specimen was taken by close pleural biopsy from each enrolled patient after informed consent. Level of ADA and histopathological diagnosis was noted and analysed by SPSS 16.0

RESULTS

Out of 108 patients 75 (69.4%) were males and 33 (30.6%) were females. Mean age was 45.21 ± 17.85 SD years. 69 (63.8%) cases were diagnosed as having Tuberculosis by pleural biopsy and/or AFB culture, 36 (33.33%) cases were diagnosed as malignant and 3 (2.7%) cases were inconclusive. In biopsy proven tuberculous pleural effusion (n=69), ADA level ranged from 30-128 IU/L with mean pleural fluid ADA level of 55.93 ± 14.12 IU/L and 68 patients had >40 IU/L. In non TB pleural effusion (NTPE) (n=39), ADA level ranged from 10-45 IU/L with mean pleural fluid ADA level of 21.35 ± 12.65 IU/L. Only three patients had raised ADA levels >40. Taking pleural biopsy as gold standard and taking ADA level > 40 IU/L as cut off value, the sensitivity and specificity of pleural fluid ADA level in the diagnosis of TPE were 95.77% and 92.31%, respectively. Positive predictive value was 91.89%, negative predictive value was 97.29% and overall Diagnostic accuracy was 96.29%.

Figure: Distribution of diagnosis on Pleural Biopsy



DISCUSSION

Lymphocytic pleural effusion have broad differential diagnosis including tuberculosis on top followed by malignancy, para-pneumonic and in patients of fluid overload on diuretic therapy. Most of the times clinical presentation help to narrow down the differential but Tuberculosis and malignancy remains undecided. Adenosine deaminase levels can replace the histopathology if higher enough in the pleural fluid. We found that that ADA levels of 40 IU/L or higher in pleural fluid is highly suggestive of tuberculosis. Levels of ADA are higher in empyema and few malignancies too. We excluded patients with visible pus and already known pulmonary or pleural malignancies to avoid confounding variable. This may be the reason that our study showed good predictive values and diagnostic accuracy as compared to study

performed by Ziaullah and colleagues.⁶ Yield of pleural fluid ADA is more sensitive and specific than the pleural fluid DNA analysis as shown by Zhou and colleagues but combined analysis not only increased the sensitivity but also improved the specificity.⁷

Good Predictive values of higher ADA levels in pleural fluids have been reported by many authors in areas of TB prevalence.⁸ A recent study performed in Europe low to medium TB prevalent area also have statistically significant diagnostic yield.⁹ Another study performed by Barrios and colleagues showed that lower cut off value >25 IU/L also had >80 % sensitivity and 90% specificity.¹⁰ For unexplained reason lower cut of value had <50 % diagnostic yield. Another interesting study was performed by Lee and colleagues in patients with non-lymphocytic pleural effusion but raised ADA level (>40 IU/L) combined with

Table 1: Comparison of ADA with histopathology

ADA >40 IU	Histopathology(Gold standard)		Total
	Positive	Negative	
Positive	68(TP)	03(FP)	71
Negative	01(FN)	36(TN)	37
	69	39	108

Table 2: Sensitivity, Specificity and Diagnostic Accuracy of ADA levels for Tuberculosis Pleural Effusion

Sensitivity	=	$\frac{\text{True Positive}}{\text{True Positive} + \text{False Negative}} \times 100$
		$\frac{68}{68 + 3} \times 100 = 95.77 \%$
Specificity	=	$\frac{\text{True Negative}}{\text{True Negative} + \text{False Positive}} \times 100$
		$\frac{36}{36 + 03} \times 100 = 92.31 \%$
Diagnostic Accuracy	=	$\frac{\text{True Positive} + \text{True Negative}}{\text{True Positive} + \text{True Negative} + \text{False Positive} + \text{False Negative}} \times 100$
		$\frac{68 + 36}{68 + 36 + 03 + 01} \times 100 = 96.29 \%$

CT Scan findings. He found that non-loculated pleural effusion with ADA >58 and pleural nodularity had sensitivity of 88 %, specificity of 93 % and positive predictive value of 91 % for diagnosis of pleural Tb.¹¹

Overall diagnostic yield of ADA >40 is statistically significant and many studies both TB prevalent and TB low prevalent countries. In appropriate clinical settings it can replace pleural biopsy.

Table 3: Positive and Negative Predictive Values for ADA levels for Tuberculosis Pleural Effusion

Positive Predictive Value	=	$\frac{\text{True Positive}}{\text{True Positive} + \text{False Positive}} \times 100 =$
		$\frac{68}{68 + 03} \times 100 = 91.89 \%$
Negative Predictive Value	=	$\frac{\text{True Negative}}{\text{True Negative} + \text{False Negative}} \times 100$
		$\frac{36}{36 + 01} \times 100 = 97.29 \%$

CONCLUSIONS

Higher ADA levels in lymphocytic exudative pleural effusion have good diagnostic yield for pleural TB and can replace pleural biopsy in appropriate clinical settings.

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