Original research article

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DIAGNOSTIC VALUE OF ADENOSINE DEAMINASE (ADA) IN TUBERCULAR PLEURAL EFFUSION

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ABSTRACT:

Background: Tubercular pleurisy is a complication often seen to be associated with pleural effusion, however, its diagnosis is cumbersome and confirmation is prolonged. Adenosine deaminase has been shown to be useful in early diagnosis of tubercular pleurisy. This study is planned to evaluate the diagnostic value of adenosine deaminase in tuberculous pleural effusion in terms of its sensitivity, specificity, positive predictive value, negative predictive value and overall diagnostic accuracy. **Material and Methods**: A cross sectional study of patients presenting with pleural effusion were enrolled in the study and underwent thorough clinical examination, radiological, hematological and biochemical investigations. Pleural Fluid adenosine deaminase (ADA) levels were also assessed. Final diagnosis was made on the basis of a criteria developed combining clinical, radiological and biochemical assessment as well as on the basis of response to ATT. **Results:** Mean Pleural fluid ADA levels were found to be significantly higher (94.5±41 .8 U/I) in tubercular cases as compared to non-tubercular cases (57.9±17.7 U/I). The proposed cut-off value of ADA at 65 U/I was 83.3% sensitive, 72.2% specific, had a positive predictive value of 80% and a negative predictive value of 76.5%. The accuracy of the criteria was 78.6%.**Conclusions:**The findings in present study suggested a useful role of pleural fluid ADA in the diagnosis of tubercular pleurisy which needs further improvisation with the help of evolution of a universally acceptable cut-off value in association with some other clinical or laboratory parameter.

Keywords : ADA, pleural effusion, tubercular pleurisy.

INTRODUCTION:

Fluid accumulation in the pleural space is known as pleural effusion, Indicates disease. It is an abnormal collection of fluid in the pleural space resulting from excess fluid production or decreased absorption[1]. The accumulation is associated with many medical conditions that predispose to fluid accumulation via many different mechanisms. [2]. Tuberculosis (TB) is a major public health problem in developing countries. Although the majority of patients with TB have pulmonary TB, extrapulmonary TB affecting mainly the lymph nodes and pleura serves as the initial presentation in about 25% of adults[3]. TB is the leading cause of pleural

effusions in some countries. **(4)** From a clinician point of view, management of a case of pleural effusion depends upon the correct diagnosis of etiology of pleural effusion. A pleural effusion as an isolated manifestation of TB has been likened to a primary chance as a manifestation d syphilis. Both are self-limited and of little immediate concern, but both may bad to serious disease many years later. Tuberculous pleuritis is thought to represent primarily a hypersensitivity reaction to tuberculous protein and the bacillary burden in the pleural space is low (Light, 2010).

Clinical diagnosis of a pleural effusion begins with obtaining the patient's clinical history and physical examination and is aided by chest radiography & laboratory investigation which categorized pleural fluid into transudate and exudates. In the meantime microbiological examination of centrifuged fluid and culture if reveals bacteria, fungi or tubercle bacilli will further to direct the possible etiological diagnosis . If necessary, the process continues with further investigative studies, such as computed tomography (CT) of the thorax, pleural biopsy, thoracoscopy, and, occasionally, bronchoscopy[5] The specific diagnosis of tubercular pleural effusion requires demonstration of Acid Fast bacilli in pleural fluid and histological evidence of tubercular granuloma in pleural biopsy, but this is facility intensive and time consuming. On the top of it patient noncompliance makes the standard diagnostic procedures impractical in our health service setup.

In search of some other diagnostic tool ADA may be helpful. Study of ADA in different diseases associated with exudative pleural effusion may give assist to the clinician in diagnosis of Tuberculous Pleural effusion with more confidently. Study of ADA in different diseases associated with exudative pleural effusion may assist the clinician in diagnosis of Tuberculous Pleural effusion more confidently. The cut off value of ADA in Tuberculous Pleural effusion shall be a good tool for the region of Nepal and may be applicable in Nepal as a whole.

MATERIAL AND METHODS

This Cross-sectional hospital based descriptive study on 50 patients of tuberculous pleural effusion at Nepalgunj Medical College Teaching Hospital Nepalgunj and Kohalpur, Nepal in the department of Intemal Medicine during OCT.201 I to OCT 2012. The study included all in patient of both sex 15 year or older and Patients with exudative pleural effusions fulfilling the Light's criteria while excluded those had previously diagnosed pleural effusion and already on some treatment with treatment response and who refused to enroll in study.

Thorough clinical history was taken and physical examination was done in each patient. A chest x-ray was obtained and sputum examination, when present, was done for AFB smear and for cytological examination. Pleural fluid was aspirated and samples were sent for ADA, biochemistry, cytology and Microbiological studies. Bronchoscopy and CT/MRI thorax were done when it was thought to be indicated.

RESULTS

Age of patients ranged from 16 to 71 years with a mean age of 36.14 ±13.83 years. Male to female ratio of the study population was 2.57:1 Occupation wise, agriculturists had the maximum proportion of patients (n=19; 38%)

followed by students (n: 11; 22%) and businessmen (n; 10; 20%). Those in service (n: 5; 10%), leading a retired life (n: 4; 8%) and housewives (n=1; 2%) were some of the less common occupational groups. Majority of patients were Hindus (n: 39; 78%). Lower and lower-middle socioeconomic strata were predominant (n=31; 62% and n=11; 22%) respectively.

On the basis of presenting complains, Right side was the predominant side in majority (n=33; 66%) patients and Chest pain (n: 40; 80%) was the most common presenting complaint followed by cough (n=38; 76%), breathlessness and fever (n=37; 74%) and constitutional involvement (n: 30; 60%). There were 2 (4%) cases with hemoptysis. Past history & risk factors exposure were figured out in figure 1.

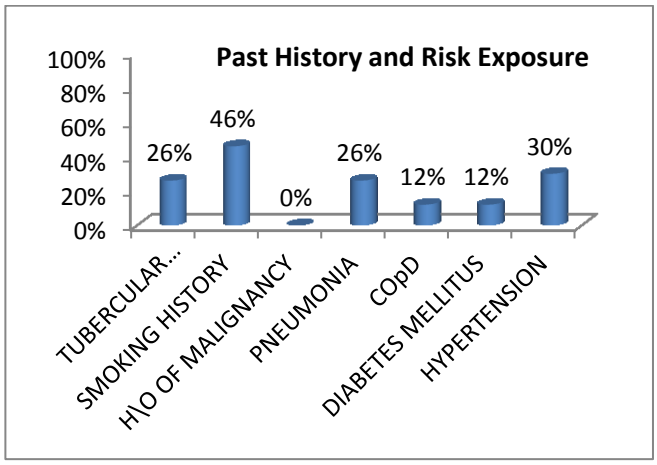

Figure 1: Past history and risk factors exposure

In investigation report showed, Haemoglobin levels ranged from 8.0 to 16.0 gm/dl with a mean value of 12.66±1.75 gm/dl, TLC ranged from 4000 to 18000 /cumm with a mean value of 9059±3207.42/cumm, Lymphocyte count ranged from 25 to 55 with a mean value of 39.12±7.19%, Neutrophil count ranged from 43 to 72 with a mean value of 60.60±7.17% and Monocytes were found to be present in 5 cases only. ESR values ranged from 23 to 70 with a mean value of 46.14±13.89. More than three fourth (n=34; 68%) had PPD >6 mm, thus showing a positive Mantoux test. Mean PPD of patients was 8.38±3.55 (range 2 to 1 5) mm.

S. blood sugar levels ranged from 80 to 210 mg/dl with a mean value of l07.32±27.42 mg/dl, S. protein levels ranged from 4.8 to 8.6 g/dl and had a mean value of 7.01±0.81. S. LDH levels ranged from 210 to 1200 U/I with a mean value of 523.24±206.60 U/I. Only 3 (6%) cases were AFB positive. None of the cases were Gram positive, showed fungal strains or malignant cells in their sputum.

Based on the diagnostic criteria used in the present study, a total of 24 (57.1%) cases were diagnosed as positive for tubercular pleurisy. Determination of positivity could be established through pleural biopsy in 3/24 (12.5%), pleural fluid culture and clinical features in combination with age and pleural fluid lymphocyte count in 5/24 (20.8%) cases each, clinical features in combination with age and Montoux test positivity in 6/24 (25%) cases, Xray/X-ray + Sputum positivity and sputum positivity in 2/24 (8.3%) cases each and clinical features in combination with Montoux test positivity and pleural fluid lymphocyte criteria in 1 (4.2%) case respectively.

Table 1: Association of presenting complain between positive & Negative cases (N=42)

SN	Variable	Positive (n=24)		Negative (n=18)		Significance of difference
		No.	%	No.	%	
1	SIDE OF INVOLVEMENT					
	Left	10	41.7	4	22.2	χ2=1.75, p=0.186
	Right	14	58.3	14	77.8	
2	Fever	20	83.3	9	50.0	χ2=5.35, p=0.021
3	Cough	17	70.8	13	72.2	χ2=0.01, p=0.92
4	Hemoptysis	2	8.3	0	0.0	χ2=1.57, p=0.20
5	Breathlessness	17	70.8	13	72.2	χ2=0.01, p=0.92
6	Chest Pain	19	79.2	16	88.9	χ2=0.70, p=0.40
7	Abdomen pain	-	-	-	-	-
8	CNS involvement	-	-	-	-	-
9	Constitution	13	54.2	9	50.0	χ2=0.07, p=0.79

No significant association between presenting complaints and final diagnosis could be seen except for fever which was found to be present in significantly higher proportion of patients with positive diagnosis (83.3%) as compared to those with negative diagnosis (50%) (P: 0.021). (table 1)

Mean leucocyte count, lymphocyte count, sugar, protein and ADA levels of positive group were higher as compared to negative group while mean neutrophil and LDH count of negative cases was higher as compared to positive cases, however, the difference between two groups was significant statistically only for ADA (p=0.001). (Table 2)

As significant differences in ADA levels were observed between subjects having tubercular pleurisy and those not having the same, hence a receiver-operator curve (ROC) analysis was performed to find out an appropriate cut-off value with a reasonable predictive accuracy. Figure 2 shows the outcome of receiver operator curve analysis:

Table 2: Association between pleural fluid examination in positive & Negative Cases (N=42)

Variable	Positive (n=24)		Negative (n=18)		Significance of difference	
	Mean	SD	Mean	SD	"t"	"p"
Turbid/Hemorrhagic colour	0		0		-	
>10 RBC/HPF	1 (4.2%)		0 (0%)		$\chi 2=0.768$, p=0.381	
leucocyte count	10.1	8.4	9.6	8.3	0.207	0.837
Lymphocyte count	82.1	10.8	78.4	10.9	1.095	0.280
Neurophil count	18.1	10.6	21.8	11.0	1.087	0.284
Sugar	57.7	27.1	55.4	13.5	0.327	0.746
Protein	5.1	1.1	4.7	0.5	1.425	0.162
LDH	3.55	1.58	3.76	1.86	0.390	0.699
ADA	94.5	41.8	57.9	17.7	3.487	0.001

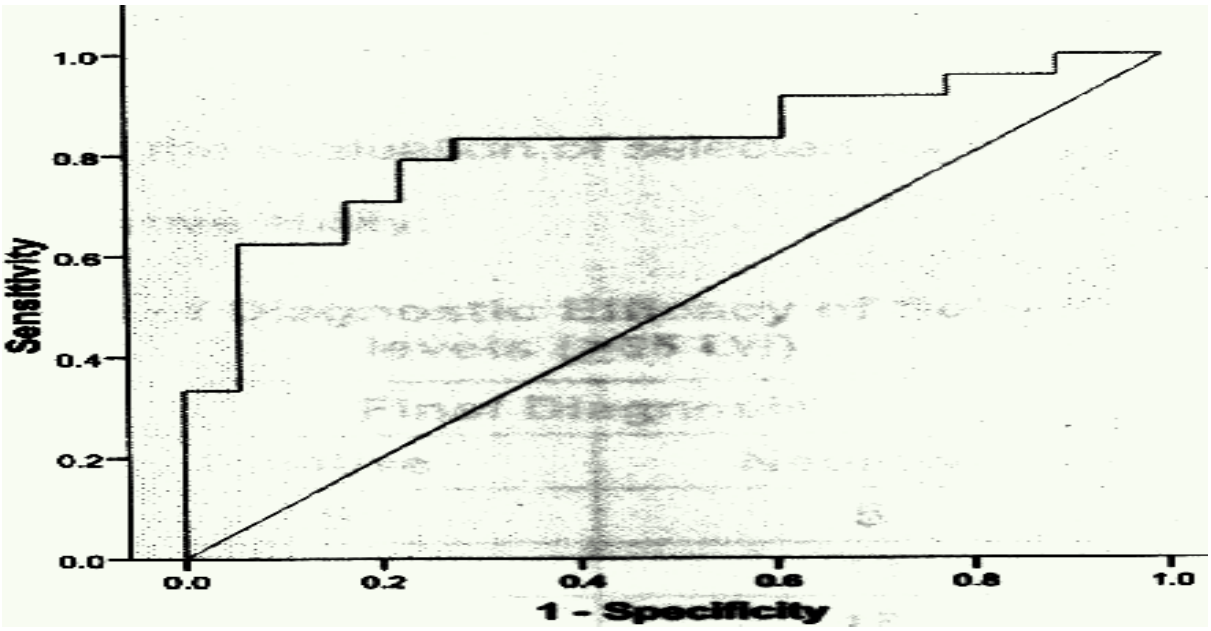

Figure 2: Outcome of receiver operator curve analysis

Table 3: Area Under the Curve I Test Result Variable S : PF Adenosine Deaminase

Area	Std. error (a)	Asymptomatic sig. (b)	Asymptomatic 95% CI	
			Lower	Upper
0.819	0.066	0.000	0.690	0.949

Table 4: Evaluation of Diagnostic Efficacy of Selected Regressed ADA levels (265 U/I)

ADA level (U/l)	Final Diagnosis		Total	
	Positive	Negative		
>65 U/l	20	5	25	
≤65 U/l	4	13	17	
Total	24	18	42	
Sensitivity	Specificity	PPN	NPN	Accuracy
83.3	72.2	80.0	76.80.05	78.6

Selected regressed cut-off value in best trade off scenario: >64.85 On the basis of receiver-operator curve analysis, the area under curve was found to be 0.819 which indicated a good discriminant ability of ADA for prediction of tubercular pleurisy. The regression cut-off value in best trade off scenario was Z=64.85 which had a predicted sensitivity of 83.3% and specificity of 72.2%.

The new cut-off value of ADA could detect 20 out of 24 cases finally diagnosed as the cases of tubercular pleurisy, thus showing its sensitivity to be 83.3%, however, it could successfully rule out the diagnosis of tubercular pleurisy in 13 out of 18 cases finally diagnosed as negative for tubercular pleurisy, thus showing its specificity to be 72.2%. With respect to positive predictive value, a total of 20 out of 25 cases having ADA levels >64.85 U/I were found to be true positive, thus showing the positive predictive value to be 80%. Similarly with respect to negative predictive value out of 17 cases having ADA level <64.85 U/1, 13 were found to be true negative, thus showing the negative predictive value to be 76.5%. Out of 42 cases in whom final diagnosis could be established, 33 (78.6%) had an agreement between final diagnosis and ADA criteria, thus showing the accuracy of the criteria to be 78.6%.

DISCUSSION:

The pleural effusion results from the combination of the increased pleural fluid formation and the decreased pleural fluid removal thus setting a chain of reactions leading to numerous biochemical changes (Light, 2007)'. Since 1978, when ADA activity was found to be high in tuberculous pleural exudates[6], ADA has been used in the diagnosis of tuberculous pleural effusions.

The age of patients ranged from 16 to 71 years, with a mean age of 36.14±13.83 years. 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 31.5 year[7], the age span of the patients presenting with features suggestive of pleuritis has been reported to be ranging from 16-89 years[8.] Thus, the age of patients in present study thus matched with the range of age reported to be susceptible to tubercular pleurisy in previous series.

In present study pleural effusion reported more males than females. In a series from Western countries, Valdes (1996)[9] reported 220 out of 350 patients with pleural effusions to be males, thus showing a male to female ratio of 1 .69:1. Although, health services utilization pattern in countries like Nepal is generally gender biased yet the prevalence of higher proportion of males in present series is in accordance with the gender ratio reported in various series.[10 &11]

The socio-economic status of the patients too reflected the general profile of the patients availing our services, mainly dominated by lower and lower-middle class. In present study, Patients with pleural effusions usually have dyspnea, cough, and occasional sharp non-radiating chest pain that are often pleuritic effusion. Fever occurs in tuberculosis, empyema, and pneumonia. Weight loss and constitutional problems can be associated with a malignant neoplasm and tuberculosis.[12]

Thus, the clinical features of the patients in present study were suggestive of a high probability of tuberculous pleuritis. Tubercular exposure and smoking history are known risk factors of tuberculosis while pneumonia has been reported to be a more common reason for pleural effusion apart from tuberculosis.[13]

Mantoux test was positive in 34 (68%) of patients. However, both the sensitivity as well as specificity of Mantoux test are poor who reported its sensitivity and specificity to be 77% and 74% for extrapulmonary tuberculosis using a cut-off level of PPD>10 mm.[14] The rate of false negative reactions to PPD has been given as high 30% of cases but even figures up to < 41% have been reported.[15 & 16] So in order to increase the sensitivity of the test we attempted to reduce the cut-off limit to >6 mm, however, there was a burden of losing specificity, resulting in a high prevalence (68%) of positive results.

In present study, sputum AFB and culture positive results were obtained in 2% and 10% patients only cases of extrapulmonary tuberculosis sputum positivity does not yield good results and as such evaluation through conventional methods of detection of tuberculosis is difficult and challenging[17-18] and in such cases pleural biopsy is the only way out. However, obtaining specimen from pleura is a difficult task most often bound through ethical reasons and patient's willingness to volunteer for the specimen.

Based on the diagnostic criteria used in the present study, determination of positivity could be established through pleural biopsy, pleural fluid culture and clinical features in various combinations. The prevalence of tubercular pleurisy in patients with pleural effusion varies depending on the criteria of diagnosis and general prevalence of tuberculosis in that population.[13& 19.]

On pleural fluid examination, except for ADA levels none of the variables showed a significant difference. We carried out a receiver operator curve analysis which provided a cutoff value of ADA≥64.85 (~65 for practical purposes). Using these criteria, analysis showed its sensitivity to be 83.3%, specificity to be 72.2%., positive predictive value to be 80% and negative predictive value to be 76.5%. Out of 42 cases in which final diagnosis could be established, 78.6% had an agreement between final diagnosis and ADA criteria, thus showing the accuracy of the criteria to be 78.6%. The sensitivity and specificity in present study is close to that reported by Maldhure ef al. (1994)[21]. The sensitivity and specificity of ADA in diagnosis of tubercular pleurisy has been reported to be varying with extreme sensitivities ranging from 47.1% to 100% and specificities from 50% to 100% using different cut-off levels and under different study designs.[20].

Despite achieving a reasonable accuracy, the present study lacked the efficiency of ADA which has been reported to be as high as 92% sensitive and 90% specific.[22] One of the reasons for this could be high prevalence of clinically positive cases and absence of a fool proof diagnostic criteria in the absence of biopsy in all the cases. Moreover, most of the studies evaluating the efficiency of ADA have been done in a case-control design where the ratio of cases and controls was matched while ours was a cross-sectional design where the ratio of cases and controls was dependent on the prevalence of disease. Apart from that a huge loss to follow up was one of the other limiting factors.

Thus, the present study found pleural fluid ADA levels to be a useful marker for identification of tubercular pleurisy among cases presenting with pleural effusion. Further studies in a larger sample size are recommended to substantiate and improve upon the findings of present study keeping in view the limitations of present study.

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