Adenosine Deaminase (Ada) Analysis In Pleural Fluid: A Diagnostic Tool For Tuberculous Pleurisy

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Abstract: Objective: Tuberculous pleurisy is categorised as extra-pulmonary despite an intimate anatomic relationship between pleura and the lungs. The diagnosis of tuberculous pleurisy is often difficult. A reliable, cost effective and rapid diagnostic test, which can be performed in any routine laboratory, could be of help in the diagnosis of tuberculous pleurisy. In the present study we measured the adenosine deaminase (ADA) activity in pleural fluid of tuberculous pleurisy and non tuberculous pleurisy patients. Method: ADA activity in pleural fluid was determined according to a method based on the modified Berthlot reaction, which is the formation of a colour indophenol complex from ammonia liberated from adenosine, and quantified spectrophotometrically. Results: ADA activity was studied in pleural fluid of 106 cases of suspected tuberculous pleural effusions. Culture for M.tuberculosis was positive in 43 cases, while in 63 cases culture was negative. From 49 ADA test positive samples 43 were culture positive and 6 were culture negative. The higher level of ADA in tuberculous pleurisy was statistically highly significant (p < 0.00001). The sensitivity and specificity of ADA test in pleural fluid was 100% and 90.47% respectively. Conclusion: This study demonstrated that adenosine deaminase activity in pleural fluid, a relatively inexpensive and easy procedure, can be of great value in the diagnosis of tuberculous pleurisy. This test can be performed in any routine laboratory where more sophisticated methods are not available [Malek S Natl J Integr Res Med, 2019; 10(5): 1-6]

Key Words: Adenosine deaminase, tuberculous pleurisy and pleural fluid

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Introduction: Tuberculosis has been an inevitable companion of man for generations. Evidence of existence of tuberculosis has been found in bones of prehistoric man, found in Germany. This remains date back to about 8000 BC. Typical tuberculosis changes have been found in the spines of skeletons of ancient Egyptian dating from about 2500 to 1000 BC.[1] Presently about one third of the world's population is infected with Mycobacterium tuberculosis. It is estimated that currently there are about 10 million new cases of tuberculosis every year with 3 million deaths occurring world-wide.[2]

Currently more people die of tuberculosis than from any other infectious disease. Deaths from tuberculosis comprise 25% of all avoidable deaths in developing countries. Nearly 95% of all tuberculosis cases and 98% of deaths due to tuberculosis are in developing countries and 75% of tuberculosis cases are in economically productive age group.[3] In India, out of a total population of over 1 billion, each year about 2 million develop active disease and up to half a million die.[4] It implies that every minute, a death occurs due to tuberculosis in our country. It also imposes a cost on our economy in terms of current and future output losses because of premature deaths and ill health.[5]

The routinely used tests for diagnosis of tuberculosis include sputum examination for AFB (Acid Fast Bacilli), culture, tuberculin skin test and radiological examination. Sputum is positive for AFB and only in the 'open' cases. Moreover, sputum examination may give false negative results if the number of AFB is low. Sputum culture requires proper laboratory facilities and is time consuming. Moreover, it is difficult to obtain sputum samples from many patients, particularly children. In adults, the tuberculin skin test cannot discriminate between active disease and previous exposure to M.tuberculosis. Moreover, the facility for X-ray is not available in most of the rural areas. In view of these limitations, continuous efforts have been made to develop simple and sensitive assays for diagnosis of tuberculosis.[6]

Tuberculous pleurisy usually presents as an acute illness and the duration ranges from a few days to few weeks. Most patients complain of pleuritic chest pain, non-productive cough and dyspnoea. The pleural fluid is typically clear or straw coloured, but cloudy or serosanguinous fluid may also be obtained. The pleural fluid is exudative and lymphocyte rich.[7]

The definitive diagnosis of tuberculous pleurisy depends on the detection of acid fast bacillus and

culture of Mycobacterium tuberculosis in pleural fluid. However, culture is positive with varying degree and the facility is not always available. Therefore a reliable and rapid diagnostic test, which can be performed in any standard laboratory, could be of help in diagnosis of tuberculous pleurisy. Any test which facilitates a correct and rapid diagnosis of tuberculous pleurisy should be very valuable.

Adenosine deaminase (ADA) is an enzyme that catalyzes the deamination of adenosine, forming inosine in the process.[8] The chief physiological function of ADA is related to lymphocytic proliferation and differentiation.[9] As a marker of cellular immunity, activity is found to be elevated in those diseases in which there is a cell-mediated immune response.[10] The present study was conducted to confirm the usefulness of adenosine deaminase assay for diagnosis of tuberculous pleurisy.

Material And Methods: This study was carried out on 106 patients suffering from pleural effusion who attended OPD or were admitted in Sir Takhatsinhji Hospital and Govt. Medical College, Bhavnagar. This study was approved by the Ethical Review Committee.

All 106 patients were clinically suspected as cases of extra-pulmonary tuberculosis. Detail clinical histories were taken in all cases. After obtaining pleural fluid we performed three tests in each case, viz. ADA test, culture and Z-N stain.

Adenosine deaminase (ADA) activity assay: ADA activity was assayed on the same day of the collection of pleural fluids samples. The ADA activity was measured by the spectrophotometric method described by Guisti and Galanti.[11] ADA activity was expressed as international unit (IU/L). For this ADA activity assay ADA – MTB Kit was used developed by Tulip Diagnostic Lab., India.

Result: Out of 106 samples of clinically suspected extra-pulmonary tuberculosis (pleurisy), the positivity in various tests are shown in table 1.

Among all these tests, ADA showing highest positivity (46.22%) followed by culture (40.56%) and Z-N staining showing lowest positivity (4.71%). The comparison of ADA test with Z-N staining is shown in table 2.

Table 1: Relative efficiency of various tests in pleural effusion

Sr. No.	Test	Positive out of 106 samples	Percentage of positivity
1	ADA test	49	46.22%
2	Z-N Staining	05	4.71%
3	Culture	43	40.56%

Table 2: Comparison of ADA test with Z-N stain

	Positivity in ADA test	Percentage
AFB (+)	5/5	100%
AFB (-)	39/101	38.61%

Out of 12 Z-N stain positive smears 10 were also positive in ADA test (100%). Even in Z-N stain negative 94 cases 39 were positive in ADA test (38.61%).

Now, culture of M.tuberculosis is considered as a 'gold standard' for the diagnosis purpose. We take culture positive cases as diseases and culture negative cases as non-disease. Table 3 shows comparison of ADA test with culture.

Table 3: ADA test positivity in reference to culture.

	CULTURE		
ADA test	Positive	Negative	total
Positive	43	6	49
Negative	0	57	57
Total	43	63	106

Total of 106 pleural fluid samples were tested for ADA test, out of which 49 turned out to be positive and remaining 57 were negative. Culture for M.tuberculosis was positive in 43 cases, while in 63 cases culture was negative. From 49 ADA test positive samples 43 were culture positive and 6 were culture negative.

From table – 3 sensitivity of ADA test is 100% and specificity is 90.47%. Positive predictive value of the ADA test is 87.75% and negative predictive value is 100%. While applying chi-square test $p<0.00001$, which is highly significant.

Table 4: shows distribution of pleural effusion cases according to sex.

Sex	Frequency	Percentage
Female	32	30.2%
Male	74	69.8%

Table 5: shows distribution of pleural effusion cases according to age.

Age	Frequency	Percentage
1 to 15	13	12.3%
16 to 30	26	24.5%
31 to 45	41	38.7%
46 to 60	19	17.9%
>61	7	6.6%

Discussion: Identifying tuberculosis in pleural fluid is still a common clinical problem with multiple pitfalls. The AIDS epidemic has reminded us of the importance of identifying tuberculosis and treating it. Since 1978, when adenosine deaminase activity (ADA) was found to be high in tuberculous pleural exudates by Piras and colleagues[12], ADA has been used in the diagnosis of tuberculous effusion. ADA analysis is a simple and inexpensive colorimetric test that can be performed on body fluids.

We studied 106 cases of pleural effusion and in all cases we done three tests viz. ADA test, Z-N stain and culture on L-J medium. Direct examination of pleural fluid by Zeihl – Neelsen staining requires bacillary density of 10,000/ml.[13] In our study out of 106 samples of pleural fluid only 5 were positive for AFB by Z-N staining, which shows only 4.71% positivity of Z-N stain. Many previous studies shows that detection of AFB from pleural fluid in <10% pleural effusion cases.[14,15,16,17,18,19] We also got the similar kind of result in Z-N stain.

We found that in our study culture from pleural fluid were positive in about 40.56% of cases. Culture requires a minimum 10 to 100 viable bacilli with a yield ranging from 12-70%.[13,14,20,21,22] While some studies also shows that diagnostic yields of culture is of <30%.[16,17,18,19] Allan et al[23] shows that culture from pleural fluid was positive in 58% of all cases of pleural effusion. The vast differences of culture yields may be due to patient's conditions during the study. In studies with higher number of HIV positive or immuno-compromised patients culture yields comes at higher percentages. Similarly when there is less number of HIV positive or immuno-compromised patients in the study culture yields comes at lower percentages.

Now, culture is the 'gold standard' for the diagnosis of tuberculosis. In our study we found that out of 106 cases of pleural effusion 43 were culture positive. We consider cut off value of ADA test was 40 IU/L i.e. if the result is < 40 IU/L the ADA test negative and if the result is > 40 IU/L the ADA test positive.

Now, if we consider the culture positive as cases of tuberculosis and culture negative as cases of non-tuberculosis the sensitivity and the specificity of ADA test was about 100% and 90.47% respectively. Sam way, positive predictive value and negative predictive value of ADA test were about 87.75% and 100% respectively. We compare our ADA tests results with the few previous similar kind of studies and the results of those studies are given in following table 6.

Table 6 : Summary of literature reviewed related to role of ADA test in the diagnosis of tuberculous pleural effusions

Sr. No.	Study	No. of patients	Sensitivity (%)	Specificity (%)
1	Piras et al[12]	54	100	100
2	Ocana et al[24]	182	100	97
3	Segura et al[25]	600	100	92
4	Valdes et al[26]	405	100	95
5	De Olivera et al[27]	276	91	88
6	Burger et al[28]	462	90	89
7	Valdes et al[29]	350	100	91
8	Villena et al[30]	228	90	85
10	Perez-Rodriguez et al[31]	140	88	86
11	Villegas et al[32]	132	80	81
12	Reechaipichitkut et al[33]	45	68	72
13	Lima et al[34]	51	95	89
14	Diacon et al[35]	62	91	89
15	Tahhan et al[36]	202	95	96
16	Blake et al[37]	368	93	81
17	Martiz et al[38]	90	100	76
18	Pettrsson et al[39]	74	100	97
19	Ocana et al[40]	86	100	87
20	Strankinga et al[41]	138	100	100
21	Fontan-Bueso et al[42]	73	100	100
22	Fontes Baganha et al[43]	218	98	96
23	Jose et al[44]	50	100	100
24	Mathur et al[45]	53	100	94
25	Gupta et al[46]	75	83	67
26	Present Study	106	100	90

From above table, we find that several studies like Piras et al[12], Ocana et al[24], Segura et al[25], Valdes et al[26], Gupta et al[46] etc. shows very high

sensitivity and specificity of ADA test in pleural fluid. Similar kinds of results also obtain in our study.

Some studies shows even 100% sensitivity and specificity like Fontan-Bueso et al[42], Fontes Baganha et al[43] and Mathur et al[45]. While some studies also shows very low sensitivity and specificity like Lima et al[34] and Sharma et al[47]

The discrepancies in the results among the reported studies can be attributed to the use of different methods of ADA analysis, with the most frequent being the calorimetric assay by Guisti and Galanti.[11] We used the same method.

The other reason for these types of discrepancies is the prevalence of disease. When the prevalence of disease is low (*i.e*. < 1%), as in developed countries, the positive predictive value may be as low as 15%, although the negative predictive value increases.[48] In contrast, in areas of high prevalence, ADA measurement is an inexpensive, minimally invasive, rapid, and readily accessible test that has gained popularity because the sensitivity and specificity reach 95% and 90%, respectively.[49]

However, elevated ADA in lymphocyte rich pleural effusions has been reported in other diseases, such as rheumatoid arthritis, bronchoalveolar carcinoma, mesothelioma, mycoplasma and chlamydia pneumonia, psittacosis, paragonimiasis, infectious mononucleosis, brucellosis, Mediterranean fever, histoplasmosis, coccidioidomycosis,[48] and in most patients with empyema.[49]

The levels of ADA in HIV/AIDS and postrenal transplant patients are comparable to immunocompetent individuals[50,51].

Tuberculous pleurisy was described in the literature of the mid 20th century as a sequel to recent infection occurring almost exclusively in children and young adults. As early as 1973, Berger and Mejia's series[15] suggested that average age of patients with tuberculous pleurisy was increasing. This observation was repeated 14 years later when Epstein et al[16] described 26 patients with tuberculous pleurisy with a mean age of 56. Allan et al[23] also demonstrated that mean age of patients with tuberculous pleurisy has increased. In our study we also found that incidence of pleural effusion is higher among 31-45 years (38.7%) of age.

Conclusion: In conclusion, ADA test for the diagnosis of tuberculous pleurisy is simple, inexpensive, rapid, highly sensitive and specific test in comparison to the conventional methods also ADA test can be use efficiently where bacteriological prrof is difficult to obtain. Due to high specificity of ADA test, it can be used to rule out tuberculosis from confusing clinical picture.

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