

Utility of pleural fluid routine and microscopy examination plus adenosine deaminase levels in the diagnosis of tuberculous pleural effusion

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Received: August 16, 2017; Accepted: September 11, 2017

ABSTRACT

Background: Tuberculous pleural effusion is the second most common site of extrapulmonary tuberculosis. Not all centers have access to advanced and invasive tests and affordability is also an issue. Hence, diagnosis is largely based on history, clinical examination, and pleural fluid analysis. **Objectives:** Our aim was to evaluate the utility of pleural fluid routine micro examination along with adenosine deaminase (ADA) levels in diagnosis of tuberculous pleural effusion. **Materials and Methods:** A retrospective analysis was done of the 100 adult patients with pleural effusion predefined criteria were adopted to label a case as tuberculous. Using MS Excel 2007 sensitivity, specificity, positive and negative likelihood ratio, accuracy, etc., were derived and various parameters in pleural fluid were also studied. **Result:** The sensitivity, specificity, positive, and negative predictive values, positive and negative likelihood ratios, accuracy, and discordance were 95.74%, 94.33%, 93.75%, 96.15%, 16.88%, 4.51%, 95%, and 5%, respectively. **Conclusion:** Pleural fluid routine micro examination along with ADA levels has an acceptable sensitivity, specificity, and accuracy for the diagnosis of tuberculous pleural effusion.


KEY WORDS: Pleural Effusion; Adenosine Deaminase; Tuberculosis

INTRODUCTION

Tuberculosis (TB) is one of the most common causes of exudative pleural effusion in India and pleural effusion is the second most common site of extrapulmonary TB after lymph node.^[1,2] A lot of newer diagnostic methods have come up in recent years to aid in the diagnosis of TB like the Xpert mycobacterium TB (MTB)/resistance to rifampicin (RIF) which is available as a cartridge-based nucleic acid amplification test (CBNAAT) and it can identify MTB DNA and RIF simultaneously. Although its specificity is very good, its sensitivity is less.^[3] Culture which is considered as gold standard takes a long time to give results.^[4] Pleural

biopsy and histopathological examination is an invasive test, requires great skill and has many complications.^[5] Hence, a rapid test which is relatively inexpensive and has good sensitivity and acceptable specificity is needed for diagnosis of tuberculous pleural effusion.

Adenosine deaminase (ADA) is an enzyme, which catalyzes the irreversible hydrolytic deamination of adenosine to inosine and ammonia as a step in metabolism of purines. ADA is present in most mammalian tissues, the activity being highest in organs containing many lymphoid cells.^[6] An increase in ADA activity is found where cell-mediated immunity is stimulated. ADA is raised in fluids with lymphocytic predominance. There are multiple causes of lymphocytic predominant pleural effusion other than TB such as malignancy and connective tissue diseases. Hence, an elevated ADA level cannot always be due to TB. Hence, lymphocytes to neutrophils ratio is important in routine and microscopy examination and an increase in this ratio increases the possibility that pleural effusion is due to TB.^[7]

Access this article online	
Website: http://www.ijmsph.com	Quick Response code
DOI: 10.5455/ijmsph.2017.0925511092017	

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Hence, we carried out this study with an objective of highlighting the importance of pleural fluid ADA plus basic pleural fluid analysis in form of routine and microscopy examination in evaluating a case of tuberculous pleural effusion. In various past studies, pleural fluid ADA was found a reliable investigation to aid in diagnosis of tuberculous pleural, peritoneal and pericardial effusion, and tuberculous meningitis.^[8,9] However, very few studies investigated the combined utility of pleural fluid ADA plus routine and microscopy examination, and so, we did this study to bridge the gap in knowledge.

MATERIALS AND METHODS

A retrospective analysis was done of the 100 adult patients aged 20 to 80 years of age who presented with pleural effusion. The presence of one or more than one of the following criteria was adopted to label a case as tuberculous: (1) bacteriological confirmation of presence of MTB (by culture or CBNAAT); (2) radiological findings consistent with TB; (3) clinical presentation consistent with TB; (4) definite clinical and radiological improvement after administration of exclusive anti-tubercular treatment. Patients who were subsequently diagnosed as having non-tuberculous pleural effusion were considered false positives and similarly patients with pleural effusion who were initially considered non-tuberculous and diagnosed as suffering from TB later in the course of treatment were included in false negatives. Patients suffering with HIV-AIDS were excluded from the study.

Pleural fluid aspiration was done by the conventional technique after confirmation of presence of fluid in pleural cavity and confirming suitable site for aspiration by ultrasound of chest. The reports of pleural fluid routine and micro examination and pleural fluid ADA levels were reviewed. Parameters studied in pleural fluid were sugar and protein levels, total cell count, percentage of lymphocytes, and neutrophils and their ratio and ADA levels in the fluid. Pleural fluid ADA level of 40 IU/ml or more was considered significant for the diagnosis of tuberculous pleural effusion.

Statistical Analysis

Analysis was done using MS excel 2007 with the help of inbuilt formulas. Mean, median, standard deviation, and confidence interval of the various pleural fluid parameters were calculated. Sensitivity, specificity, positive and negative predictive values, positive and negative likelihood ratio, accuracy, and discordance were calculated.

RESULTS

Results of analysis of various pleural fluid parameters are shown in Table 1. The analysis of the positives and negatives made at the end of study is shown in Table 2. The diagnostic

reliability of pleural fluid parameters studied is shown in Table 3.

DISCUSSION

It has been postulated that in the beginning, pleural fluid is predominantly neutrophilic and as days progress it changes to predominantly lymphocytic.^[10] However, it was observed in our study that all patients had a predominantly lymphocytic pleural effusion with mean percentage of neutrophils, lymphocytes, and their ratio as per depicted in Table 1. The reason could be that most of the patients who come to our hospital which is a tertiary care institute, have received some empirical treatment in primary or secondary health-care setting previously and we see patients late in course of disease.

Mean pleural fluid protein levels was more than 3 g/dl indicating its exudative nature but some patients had values

Table 1: Results of analysis of various pleural fluid parameters

Parameters	Mean±SD	Confidence interval (95%)
Total cells	230±107.618	200.17-259.83
Lymphocytes (%)	74.3±9.794	71.586-77.014
Neutrophils (%)	25.7±9.794	15.906-35.494
Lymphocyte/neutrophil	3.945±3.189	3.062-4.828
Protein (g/dl)	3.968±1.045	3.679-4.257
Sugar (mg/dl)	53.5±59.865	36.907-70.093
ADA levels (IU/L)	63±0.2.623	53.958-72.042

SD: Standard deviation, ADA: Adenosine deaminase

Table 2: The analysis of the positives and negatives made at the end of study

Initial diagnosis	Final diagnosis		Total
	Tuberculous	Non-tuberculous	
Tuberculous	45 (true positive)	3 (false positive)	48
Non-tuberculous	2 (false negative)	50 (true negative)	52
Total	47	53	100

Table 3: The diagnostic reliability of pleural fluid parameters

Statistical analysis	Value (%)
Sensitivity	95.74
Specificity	94.33
Positive predictive value	93.75
Negative predictive value	96.15
Positive likelihood ratio	16.88
Negative likelihood ratio	4.51
Accuracy	95
Discordance	5

lower than 3g/dl but other tests such as pleural fluid LDH and high cell count in fluid routine microscopy, indicated its exudative nature.^[11] This could be due to severe hypoproteinemia. Pleural fluid glucose level was decreased in most patients but never zero. In addition, a high level was attributed due to concomitant diabetes. Pleural fluid ADA was always above 40IU/L in our study although it is possible to have low ADA level in tuberculous effusions, especially in patients who were elderly. There is a significant negative correlation between pleural fluid ADA and age.^[12]

Elevated lymphocytes to neutrophils together with high ADA levels were the most useful parameters in diagnosing tuberculous pleural effusion. This finding was consistent with some of the previous studies.^[7] All the patients who had false positive results were subsequently diagnosed as malignant pleural effusion. Patients who were false negative for TB actually had coexisting cardiac disease depicted by electrocardiogram and 2D echocardiography and those patients were started with treatment directed toward cardiac failure. In due course of treatment, when those patients had persistent symptoms and pleural effusion were subjected to repeat pleural fluid analysis, and then, tuberculous etiology of pleural effusion was established.

Limitation of this study is that we cannot have the information about drug resistance from these tests. Revised national TB control program has advised testing for drug resistance by CBNAAT in all retreatment cases and contacts of drug-resistant cases (and all pediatric cases as well as patients with HIV-AIDS).^[13] In addition, in the future, these criteria will be extended so that all patients irrespective of history of previous anti-TB treatment will be subjected to drug-sensitivity testing because the incidence of drug-resistance TB is increasing day-by-day.

CONCLUSION

In a resource limited setting and where cost is an issue pleural fluid routine and microscopy and ADA levels have an acceptable sensitivity, specificity, and accuracy for the diagnosis of tuberculous pleural effusion as is evident from our study. Ultrasound-guided pleural fluid aspiration and pleural fluid analysis for routine and microscopy examination and ADA levels remains the first line investigation to identify the etiology of pleural effusion, and in major cases, no more tests are needed for diagnosis. Another benefit is that it can be done as a day-care procedure in selected patients. Obviously, if the reports are indeterminate patient can be subjected to further testing.

REFERENCES

1. Mehta AA, Gupta AS, Ahmed S, Rajesh V. Diagnostic utility of adenosine deaminase in exudative pleural effusions. *Lung India*. 2014;31(2):142-4.
2. Karkhanis VS, Joshi JM. Pleural effusion: Diagnosis, treatment, and management. *Open Access Emerg Med*. 2012;4:31-52.
3. Sehgal IS, Dhooria S, Aggarwal AN, Behera D, Agarwal R. Diagnostic performance of Xpert MTB/RIF in Tuberculous pleural effusion: Systematic review and meta-analysis. *J Clin Microbiol*. 2016;54(4):1133-6.
4. Ryu YJ. Diagnosis of pulmonary Tuberculosis: Recent advances and diagnostic algorithms. *Tuberc Respir Dis Seoul*. 2015;78(2):64-71.
5. Chakrabarti B, Ryland I, Sheard J, Warburton CJ, Earis JE. The role of Abrams percutaneous pleural biopsy in the investigation of exudative pleural effusions. *Chest*. 2006;129(6):1549-5.
6. Hovi T, Smyth JF, Allison AC, Williams SC. Role of adenosine deaminase in lymphocyte proliferation. *Clin Exp Immunol*. 1976;23:395-403.
7. Akturk UA, Ernam D, Akbay MO, Koçak ND, Oğur E, İrmak I. Role of the neutrophil-lymphocyte ratio in the differential diagnosis of exudative pleural effusion. *Clinics Sao Paulo*. 2016;71(10):611-6.
8. Kumari RP, Reddy BL, Vipula VA. Role of adenosine deaminase in diagnosis of exudative type of pleural effusion. *Int J Med Sci Public Health*. 2017;6(2):286-7.
9. Shah PC, Shah CP, Dighe MP, Dalal PC. Role of adenosine deaminase in diagnosis of tuberculous pleural effusion. *Int J Med Sci Public Health*. 2014;3(9):1051-5.
10. Vorster MJ, Allwood BW, Diacon AH, Koegelenberg CF. Tuberculous pleural effusions: Advances and controversies. *J Thorac Dis*. 2015;7(6):981-91.
11. Na MJ. Diagnostic tools of pleural effusion. *Tuberc Respir Dis Seoul*. 2014;76(5):199-210.
12. Tay TR, Tee A. Factors affecting pleural fluid adenosine deaminase level and the implication on the diagnosis of tuberculous pleural effusion: A retrospective cohort study. *BMC Infect Dis*. 2013;13:546.
13. Hillemann D, Rüsç-Gerdes S, Boehme C, Richter E. Rapid molecular detection of extrapulmonary tuberculosis by the automated GeneXpert MTB/RIF system. *J Clin Microbiol*. 2011;49:1202-5.

How to cite this article: Upadhyay GP, Thakker RM. Utility of pleural fluid routine and microscopy examination plus adenosine deaminase levels in the diagnosis of tuberculous pleural effusion. *Int J Med Sci Public Health* 2017;6(11):1562-1564.

Source of Support: Nil, **Conflict of Interest:** None declared.