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TUBERCULOUS PLEURALEFFUSION –DIAGNOSTIC DILEMMA

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ABSTRACT: INTRODUCTION: Tuberculous PE is the second most common extrapulmonary manifestation of active Mycobacterium tuberculosis (MTB) infection after lymph node. The laboratory tests on pleural fluid which help in etiological diagnosis of tuberculous PE include cell count (total and differential count), cytology, biochemical tests (protein, lactate dehydrogenase [LDH], adenosine deaminase [ADA]), microbiological tests (Ziehl–Neelsen [ZN] stain), and culture (for aerobic bacteria, fungi, and Mycobacteria).

AIM: To determine the cytological, biochemical, and microbiological aspects of Tuberculous pleural effusion.

MATERIALS AND METHODS: Patients oftubercular PE diagnosed with the help of clinical features, ADA and/or cytology were included in the study. Pleural aspiration was done and the fluid collected wassent for investigations. A structured standard pro forma was prepared and used for recording pleural fluid findings, which included pH, sugar, proteins, LDH,ADA, TLC,DLC,culture, CBNAAT and Serum IFN γ.

RESULTS: 98% of the effusions were exudates.45 cases (90%) had cytology positive for TBwith more than 50% lymphocytes in the smears.All smears showed paucity of mesothelial cells. 49 cases (98%) had a positive ADA ie, >40 IU/L.44 cases (88%) had both cytology and ADA positive.40 (80%) cases had a raised serum INF γ. Only 10 (20%) patients had AFB positive sputum smears whereas cultures were positive in all the 50 patients.10 cases(20%) showed CBNAAT positivity.

CONCLUSION: Tuberculous PE areexudative in nature. They are lymphocyte predominant withpaucity of mesothelilal cells (<5%). LDH/ADA ratio of <16.2 is most helpful in diagnosing TB. ADA is almost always elevated, though not diagnostic. Raised serum - IFN indicatesextrapulmonary , severe disease. CBNAAT & IFN are supportive but have their own limitations.

KEYWORDS: Tuberculosis, Pleural effusion, ADA, LDH, CBNAAT.

INTRODUCTION

The normal pleuralspace contains a relatively small amount of fluid, 0.1–0.2 ml/kg of body weight on each side.[1] The pathogenesis of tuberculous pleural effusion (PE) is thought to be related to the rupture of a subpleuralcaseous focus in the lung into the pleural space.[2] Tuberculous PE is the second most common extrapulmonary manifestation of active Mycobacterium tuberculosis (MTB) infection after lymph node TB.[3,4]

Pleural biopsy for culture of MTB and histopathological detection of caseating granulomas are regarded as the gold standard for the diagnosis of tuberculous PE. Pleural biopsy is performed because the chances of obtaining a diagnosis are much greater than examination of pleural fluid alone, but it is more invasive, requires greater expertise, and is subject to sampling errors.[5]

The laboratory tests on pleural fluid which help in etiological diagnosis of tuberculous PE include cell count (total and differential count), cytology, biochemical tests (protein, lactate dehydrogenase [LDH], adenosine deaminase [ADA]), microbiological tests (Ziehl–Neelsen [ZN] stain), and culture (for aerobic bacteria, fungi, and Mycobacteria).

Pleural fluid ADA levels are very useful in diagnosing pleural TB. It was first proposed as a diagnostic test in 1978[6] and since then, it is frequently used in diagnosis of tubercular effusions. However, ADA is also raised in other conditions such as empyema and rheumatoid arthritis,[7] hence, making the diagnosis of tubercular effusion on ADA alone is difficult.

Diagnosis of tuberculous PE is typically made based on a compatible clinical presentation and the presence of suggestive pleural fluid characteristics. The aim of our study is to determine the cytological, biochemical, and microbiological aspects of Tuberculous pleural effusion.

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MATERIALS AND METHODS

This was an institutional based, descriptive cross-sectional study conducted in the Department of Pathology, Maharaja's Institute Of Medical Sciences (MIMS), Vizianagaram, Andhra Pradesh. Ethical approval was sought from the ethical review committee of MIMS. The study was conducted for a period of 2 years from July 2017 to June 2019.

Patients oftubercular PE diagnosed with the help of clinical features, ADA and/or cytology were included in the study. Pleural aspiration was done and the fluid collected wassent for routine biochemical analysis which included pH, sugars, proteins, LDH and ADA.A cutoff of 40 IU/L for ADA was taken in diagnosing tubercular effusion.Total Leucocyte Count (TLC), DifferentialLeucocyte Count (DLC), cytological examination,culture and CBNAAT were also done along with analysis fortransudate vs exudate. Patients in whom either ADA or cytology was suggestive of tubercular effusion were selected to evaluate for serum IFN-γ levels.

A structured standard pro forma was prepared and used for recording pleural fluid findings, which included pH, sugar, proteins, LDH,ADA, TLC,DLC,culture, CBNAAT and Serum IFN-γ.

The study included a total of 50 patients.

INCLUSION CRITERIA

- Diagnosed tubercular effusion by clinical features, ADA and/or cytology.
- Age 18 years and above
- Immunocompetent
- New cases
- CBNAAT / Culture positive / AFB positive
- Clinical & radiologically suspected tuberculous pleural effusion

EXCLUSION CRITERIA

- Patient unwilling to consent were excluded
- Immunocompromised
- Old cases
- Non-tuberculous lymphocytic effusions
- Not responding to ATT

STATISTICAL ANALYSIS

Analysis was done using MS excel 2007 with the help of inbuilt formulas. Mean, median and standard deviation of various pleural fluid parameters were calculated.Analyzed data is represented in percentages and proportions.

RESULTS

98% of the effusions appear to be exudates as per Lights criteria.45 cases (90%) had cytology positive for TB with more than 50% lymphocytes in the smears.TLC was in the range of 96±11.2 cells/cummwith the percentage of lymphocytes within 67±4.8%. All smears showed paucity of mesothelial cells with the percentage of mesothelial cells within 6.6±1.2%. Background of sediment was granular in 92% of the cases.

49 cases (98%) had a positive ADA ie, >40 IU/L which was taken as cutoff for diagnosing TB. 44 cases (88%) had both cytology and ADA positive.LDH/ADA ratio was in the range of 9.2±2.2. All cases in study have a ratio less than 16.2 (100%).

Out of the 45 (90%) cases which were cytologically tubercular, 35 (70%) cases had a raised serum INF-γ too. In the five cases where cytology was not tubercular, serum IFN-γ was positive or raised. Hence, such cases should be evaluated further and only cytology should not be considered for diagnosing TB.

Only 10 (20%) patients had AFB positive sputum smears whereas cultures were positive in all the 50 patients.

Similarly, only 10 cases(20%) showed CBNAAT positivity.

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DISCUSSON

LYMPHOCYTOSIS

In the study done by Valdés et al.on 254 patients with tuberculous pleuritis, 93.3% of the cases had >50% lymphocytes in the pleural fluid with only 17 cases having fewer than 50% lymphocytes.[8] In another series study done by Bielsa et al. on 214 patients, 94.8% of the cases had >50% lymphocytes.[9]Ruan et al. did a study on 382 patients in Taiwan with tuberculous pleuritis and found that the median lymphocyte percentage of total cells in pleural fluids was 84% and they found 95.5% of the cases had >50% lymphocytes .[10]In our study lymphocytosis was seen in 90% of the cases.

MESOTHELIAL CELLS

It has been confirmed by four different studies that pleural fluid from patients with TB rarely contains more than 5% mesothelial cells including the study done by Valdés L et al.[11-14] This feature was consistent with our study.

ADA

It should be noted that different authors have used different cut-off levels for ADA, ranging between 30 U/L and 70 U/L. A study by Porcelet al.[15] from 2010 analyzed pleural fluid ADA levels in different scenarios, one being pleural fluid with high lymphocyte counts, which should be suspected of TB. From these samples, an ADA level above 35 U/L had a sensitivity of 93%, a specificity of 90%, for identifying TB effusion.[11] Based on these results, the authors concluded that a cut-off level of 35 U/L is sufficient, assuming that the prevalence of the disease is high. However, due to its maintained high negative predictive value, an ADA level of less than 35 U/L confidently excludes TB.[15] In summary, measurement of pleural fluid ADA levels is useful in the diagnosis of TB pleurisy. In patients with lymphocytic pleural effusion, pleural fluid levels of greater than 40 U/L are suggestive of a diagnosis of TB pleuritis, especially in areas with a high prevalence of tuberculosis.Graciaet al reported that the sensitivity and specificity of ADA in the diagnosis of pleural TB were 89% and 92.7%, respectively.[16] In our study 49 cases (98%) had an ADA level greater than 40 IU/L.

IFN

In the study by Greco et al , the pooled overall sensitivity and specificity from the meta-analysis were 93% for ADA and 96% for □-interferon.[17] They found that IFN-γ is consistently raised in both pulmonary and extrapulmonary patients and levels of serum IFN-γ depend on the severity of disease.

A large study from 2003 by Villena et al measured pleural fluid □-interferon levels in 595 patients, including 82 with TB, and reported that a cut-off level of 3.7 IU/mL yielded a sensitivity of 0.98 and a specificity of 0.98.[18]

The study done by Hasan Z et al on 80 patients reported a raised IFN-γ in patients with pulmonary TB.[19]

ADA and IFN-γ measurements are simple and have the advantage of being a rapid and direct means of detectingM. tuberculosis in pleural fluid.

SMEAR FOR AFB

Pleural fluid smears for mycobacteria in immunocompetent patients are not routinely indicated, because they are almost always negative, unless the patient has a TB empyema.[20,21]

CULTURE

Cultures of pleural fluid should be taken, but in most series, the cultures are positive in less than 40% of immunocompetent patient.[22,23] In present study, 10 cases (20%) gave positive cultures.For mycobacterial cultures, the use of the BACTEC system (liquid cultures) with bedside inoculation provides higher yields and faster results than Lowenstein-Jensen medium (solid cultures).

PCR

These tests amplify *M. tuberculosis*-specific nucleic acid sequences with a nucleic acid. The low sensitivity of the NAAT tests might be due to the presence of inhibitors in the pleural fluid or to intracellular sequestration of the mycobacteria.

Porcel et al reported NAAT positivity in 15% of cases.[15]Our study showed 20% positivity.

PCR was a more demandingand expensive method earlier but now it is available free of cost in government set up.

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CONCLUSION

In various studies, it has been concluded that tuberculous PE areexudative in nature. They are lymphocyte predominant withpaucity of mesothelilal cells (<5%) and granular background. LDH/ADA ratio of <16.2 is most helpful in diagnosing TB. ADA is almost always elevated, though not diagnostic. Raised serum - IFN indicatesextrapulmonary , severe disease. Pleural fluid IFN is superior to serum IFN. CBNAAT & IFN are supportive but have their own limitations.

LIMITATIONS

Due to small sample size this study couldn't elaborate the significance of the cytological, biochemical, and microbiological aspects of tuberculous pleural effusion. Hence a large sample with bigger time frame is needed to determine the involvement of these aspects.

REFERENCES

[1] Sahn SA. State of the art. The pleura. Am Rev Respir Dis 1988;138:184-234
[2] Berger HW, Mejia E. Tuberculous pleurisy. Chest 1973;63:88-92.
[3] Vidal R, de Gracia J, Ruiz J, Fite E, Monsó E, Martín N, et al. Controlled study of 637 patients with tuberculosis. Diagnosis and therapeutic results with 9-and 6-month regimens. Med Clin (Barc) 1986;87:368-70.
[4] Valdés L, Pose A, San José E, Martínez Vázquez JM. Tuberculous pleural effusions. Eur J Intern Med 2003;14:77-88.
[5] Villegas MV, Labrada LA, Saravia NG. Evaluation of polymerase chain reaction, adenosine deaminase, and interferon-gamma in pleural fluid for the differential diagnosis of pleural tuberculosis. Chest 2000;118:1355-64
[6] Piras MA, Gakis C, Budroni M, Andreoni G. Adenosine deaminase activity in pleural effusions: An aid to differential diagnosis. Br Med J 1978;2:1751-2.
[7] Ocaña I, Ribera E, Martinez-Vázquez JM, Ruiz I, Bejarano E, Pigrau C, et al. Adenosine deaminase activity in rheumatoid pleural effusion. Ann Rheum Dis 1988;47:394-7
[8] Valdés L, Alvarez D, San José E, Penela P, Valle JM, García-Pazos JM, et al. Tuberculous pleurisy: A study of 254 patients. Arch Intern Med 1998;158:2017-21
[9] Bielsa S, Palma R, Pardina M, Esquerda A, Light RW, Porcel JM, et al. Comparison of polymorphonuclear- and lymphocyte-rich tuberculous pleural effusions. Int J Tuberc Lung Dis 2013;17:85-9.
[10] Ruan SY, Chuang YC, Wang JY, Lin JW, Chien JY, Huang CT, et al. Revisiting tuberculous pleurisy: Pleural fluid characteristics and diagnostic yield of mycobacterial culture in an endemic area. Thorax 2012;67:822-7
[11] Yam LT. Diagnostic significance of lymphocytes in pleural effusions. Ann Intern Med 1967;66:972-82.
[12] Light RW, Erozan YS, Ball WC. Cells in pleural fluid: their value in differential diagnosis. Arch Intern Med 1973;132:2854-60.
[13] Spriggs AI, Boddington MM. The Cytology of Effusions. 2nd edn. Grune& Stratton, New York, 1968.
[14] Hurwitz S, Leiman G, Shapiro C. Mesothelial cells in pleural fluid: TB or not TB? S Afr Med J 1980;57:937-9.
[15] Porcel JM, Esquerda A, Bielsa S. Diagnostic performance of adenosine deaminase activity in plueral fluid: a single-center experience with over 2100 consecutive patients. Eur J Intern Med 2010;21:419-23.
[16] . Garcia-Zamalloa A, Taboada-Gomez J. Diagnostic accuracy of adenosine deaminase and lymphocyte proportion in pleural fluid for tuberculous pleurisy in different prevalence scenarios. PLoS One 2012;7:e38729.
[17] Greco S, Girardi E, Masciangelo R, et al. Adenosine deaminase and interferon gamma measurements for the diagnosis of tuberculous pleurisy: a meta-analysis. Int J Tuberc Lung Dis 2003;7:777-86.
[18] Villena V, López-Encuntra A. Pozo F, et al. Interferon gamma levels in pleural fluid for the diagnosis of tuberculosis. Am J Med. 2003;115(5):365-370.
[19] Hasan Z, Jamil B, Khan J, Ali R, Khan MA, Nasir N, et al. Relationship between circulating levels of IFN-gamma, IL-10, CXCL9 and CCL2 in pulmonary and extrapulmonary tuberculosis is dependent on disease severity. Scand J Immunol 2009;69:259-67.
[20] Valdes L, Alvarez D, San Jose E, et al. Tuberculous pleurisy: a study of 254 patients. Arch Intern Med 1998;158:2017-21.
[21] Escudero BC, Garcia CM, Cuesta CB, et al. Cytologic and bacteriologic analysis of fluid and pleural biopsy specimens with Cope's needle. Study of 414 patients. Arch Intern Med 1990;150:1190-4.

ISSN- 2394-5125VOL 7, ISSUE 15, 2020

[22] Yone EW, Kenge AP, Moifo B, et al. Prevalence and determinants of extrapulmonary TB involvement in patients with pulmonary tuberculosis in a Sub-Saharan African country: a cross-sectional study. Scand J Infect Dis 2013;45:104-11

[23] Ozvaran MK, Baran R, Tor M, et al. Extrapulmonary tuberculosis in non-human immunodeficiency virus-infected adults in an endemic region. Ann Thor Med 2007;3:118-21.