Original Article

Validity of tuberculous pleuritis diagnosed in a resource-constrained setting in Dindigul district of Tamil Nadu

Baranidharan Chennaiyan[1], Arun N. Bhatt[2], Roopa Kancherla[3], Cijoy K. Kuriakose[4], Anand Vimal Dev[5], George A. Philip[5]

[1]Department of General Medicine, Sri Lakshmi Narayana Institute of Medical Sciences, Puducherry, [2]Department of Community Medicine, MOSC Medical College, Ernakulam, Kerala, [3]Department of Pulmonary Medicine, PSG Hospital, Coimbatore, [4]Department of Medicine, Christian Medical College, Vellore, [5]Department of Medicine, Christian Fellowship Hospital, Oddanchatram, Dindigul, Tamil Nadu, India

Abstract

Context: Majority of the Indians live in rural areas where resource constrained settings depend on cheaper and less invasive tests to diagnose extrapulmonary tuberculosis (TB). The decline in prevalence of TB in the country could affect the validity of the diagnosis. The aim was to measure validity of the pleural fluid study of proteins, lactate dehydrogenase (LDH), and cell counts in diagnosis of tuberculous pleuritis. **Materials and Methods:** This was a cross-sectional study conducted in a 300 bedded secondary care hospital in rural Tamil Nadu. Exhaustive sampling was performed during April 2013 to March 2014. Pleural fluid study of 54 patients with exudative pleural effusion was conducted. Diagnosis was established by closed needle pleural biopsy. Receiver operator curves were plotted and area under curve (AUC) was calculated for various parameters. Sensitivity, specificity, and predictive values were calculated for different cut-off values of the parameter with significant AUC. **Results:** Prevalence of tuberculous pleural effusion was 56% (95% confidence interval [95% CI] - 42.5–69.5%). Lymphocyte predominance in pleural fluid was the only valid test, and cut-off >80% had sensitivity of 70.0% (95% CI - 53.3–86.7%) and specificity of 70.8% (95% CI - 52.2–89.4%). Pleural fluid pH, protein or its ratio with serum protein, sugar, total leukocyte count, LDH or its ratio with serum LDH; erythrocyte sedimentation rate were not valid screening tests. **Conclusions:** Lymphocyte predominance > 80% can be used as a marker of tuberculous pleuritis. Since the prevalence of tuberculous pleuritis in India has come down considerably, newer tests need to be included to make a valid diagnosis.

Keywords: Extrapulmonary tuberculosis, pleural tuberculosis, tuberculosis, tuberculous pleuritis

Introduction

In India, one-fifth of new tuberculosis (TB) cases notified in 2014 were extrapulmonary.[1] Pleural effusion is the second common form, constituting about 28% of extrapulmonary TB (EPTB).[2,3] In 12th 5 years plan, new objective of early detection and treatment of at least 90% of all types of TB cases including EPTB was stated for Revised National Tuberculosis Control Program.[4] EPTB is known to be associated with delayed diagnosis.[5] Invasive or costly investigations are often required to diagnose EPTB.[6] In a rural area, healthcare settings are not well-equipped to diagnose EPTB. In India, 68.8% population live in rural area.[7]

In resource-constrained settings, pleural fluid study of protein and lymphocyte counts were suggested by World Health

Address for correspondence: Dr. Arun N. Bhatt, Department of Community Medicine, MOSC Medical College, Kolenchery, Eranakulam, Kerala, India.
E-mail: arunbhatt1984@yahoo.co.in

Access this article online

Quick Response Code:

Website: www.jfmpc.com

DOI: 10.4103/2249-4863.197322

How to cite this article: Chennaiyan B, Bhatt AN, Kancherla R, Kuriakose CK, Dev AV, Philip GA. Validity of tuberculous pleuritis diagnosed in a resource-constrained setting in Dindigul district of Tamil Nadu. J Family Med Prim Care 2016;5:615-8.

Organization (WHO) to diagnose pleural TB.[8] In our institution, we had been using pleural fluid cell counts and simple pleural fluid biochemical tests to diagnose tuberculous pleuritis. In the context of falling prevalence of TB in India, the validity of using these tests were questionable in diagnosing tuberculous pleuritis.[1] Adenosine deaminase (ADA) assay or pleural biopsy were not available in our setting. Hence, this study was undertaken to measure validity of the pleural fluid study of protein, lactate dehydrogenase (LDH), and cell counts for diagnosing tuberculous pleuritis which had been in use in our hospital.

Materials and Methods

Study design

The study design was cross-sectional.

Study setting

The study was carried out in Internal Medicine Department of a 300 bedded secondary care level hospital in Dindigul district of Tamil Nadu. For 1 year, we had service of a pulmonologist in our hospital when this study was conducted. Since our institution did not have facilities for histopathological examination, special arrangements were made for the purpose of the study to transport the biopsy specimen to a tertiary care teaching hospital nearly 400 km away.

Study participants

The study period was April 2013 to March 2014. Patients presenting with evidence of pleural effusion on chest X-ray and were exudative by Light's criteria were included in the study.

Sample size and sampling technique

We expected sensitivity of 93.5% for differential lymphocyte count cut-off more than 80%.[9] We expected prevalence of TB among exudative pleural effusion to be 43.8%.[10] For alpha error of 5% and precision of 10%, we needed sample size of 53. With exhaustive sampling done during the study period, we obtained a sample size of 54.

Study tools

A semi-structured performa was used to collect information regarding symptoms and co-morbidities from the patient interview as well as from hospital records. Cell counts and biochemical parameters of pleural fluid were studied. Diagnosis was established by pleural biopsy.

Pleural biopsies were performed by pulmonologist by closed needle technique. Pleural biopsy was conducted under strict aseptic conditions. The affected side of the chest was cleaned thoroughly with antiseptics and draped. Under local anesthesia, a 23-gauge needle was passed and pleural fluid aspirated to confirm the site for incision. Just above the upper border of the rib in the selected site, a 0.5 cm incision was made. Through this incision, Tru-Cut needle was introduced, and multiple biopsies were taken by multiple passes. The pleural tissue obtained was put into a formalin bottle. Biopsy specimens were sent for histopathological examination to Pathology Department of a tertiary care center.

Analysis

Data entry was carried out using EpiData software, version 3.1 (The Epidata Association, Odense, Denmark) and analysis was performed using SPSS software, version 20 (IBM corporation, New York). Mean and standards deviation (SD) were calculated for continuous variables. Proportions were calculated for categorical variables. Histopathology of pleural biopsy was considered gold standard. Receiver operator curve (ROC) was plotted for various laboratory parameters. Sensitivity, specificity, and predictive values for various cut-offs of parameter with a significant area under curve were calculated.

Ethical aspects

The study was approved by Ethical Committee of the Institution. Participants were explained possible complications of pleural biopsy procedure in detail, and an information sheet also was provided. They were informed that institution would bear the expense for the management of complication if any. Voluntary written informed consent was given by the study participants. Privacy was ensured for an interview. Confidentiality of the information is maintained.

Results

Characteristics of the study participants

There were 54 study participants. All of them had unilateral and exudative pleural effusion. Males comprised 35 (65%) of the study participants and females the rest. Mean age was 47.7 years (SD = 16.4), and 31 (57%) were above 60 years. Fourteen (25.9%) participants were tobacco smokers, 5 (9.3%) were diabetic, and 6 (11.1%) were hypertensive. None of them had cardiac failure or renal failure. Majority had one or the other of the following symptoms such as a cough, breathlessness, loss of appetite, loss of weight, or fever.

Laboratory parameters

Among hematological parameters, 42 (77.7%) had anemia, all had raised erythrocyte sedimentation rate (ESR), 18 (33.3%) had leukocytosis, 32 (59.2%) had neutrophilia, 3 (5.5%) had band forms, 34 (62.9%) had lymphocytopenia, none had lymphocytosis, 4 (7.4%) had eosinophilia and 10 (18.5%) had monocytosis. In pleural fluid study, mean LDH was 898.2 (SD = 551.2), mean total protein was 4.7 g/dl (SD = 0.9), and mean pH was 7.5 (SD = 0.4). Forty-two (77.7%) had lymphocyte dominance more than 50% in pleural fluid.

Validity of laboratory parameters

The diagnosis was established by pleural biopsy. Among the study participants, 30 (56%, 95% confidence interval [95% CI] - 42.5–69.5%) had tuberculous pleuritis, 7 (13%) had malignancy and 17 (31%) had other inflammatory conditions.

ROCs were plotted to explore valid laboratory parameters to diagnose tuberculous pleural effusion. The parameters studied were pleural fluid pH, protein, LDH, sugar, total leukocyte count, lymphocyte predominance, ratio of LDH in pleural fluid to serum, ratio of protein in pleural fluid to serum and ESR. Among these parameters shown in Table 1, only the pleural fluid differential lymphocyte count had a diagnostic value with an accuracy of 80.1% (95% CI - 67.8–92.4%, $P < 0.001$).

WHO criteria for diagnosing pleural effusion in resource-constrained settings (pleural fluid protein >3 g/dl and lymphocytes >50%) was 90% sensitive but specificity was 45.8%. Table 2 shows sensitivity, specificity, and predictive value of different cut-offs of lymphocyte predominance. With pleural fluid lymphocyte count > 50% as cut-off for TB, sensitivity was 93.3% (95% CI - 83.9–100%) and specificity was 41.7% (95% CI - 21.6–61.8%); with pleural fluid lymphocyte count >80%, sensitivity was 70.0% (95% CI - 53.3–86.7%), specificity was 70.8% (95% CI - 52.2–89.4%), positive predictive value was 75% (95% CI - 58.6–91.4%), and negative predictive value was 65.4% (95% CI - 46.7–84.1%), respectively [Table 2]. We had explored combinations of laboratory parameters for better sensitivity and specificity but, none emerged.

Discussion

Differentiating the pleural effusion as exudative or transudative using the Light's criteria was the first step toward diagnosis. The 54 samples identified as exudative may include some transudates as we know the specificity of Light's criteria can be as low as 71%.[11] The gold standard for diagnosis of tuberculous pleuritis is the demonstration of *Mycobacterium tuberculosis* in pleural fluid or biopsy specimen or demonstration of caseating granuloma in the biopsy specimen.[12] Tuberculous pleuritis was diagnosed in 30 (56%) samples, by closed needle biopsy. However, the sensitivity of closed biopsy is lower than biopsy taken by diagnostic thoracoscopy.[12]

Among the biochemical parameters and cell counts of pleural fluids, only pleural fluid differential lymphocyte count had a diagnostic value for tuberculous pleuritis. The WHO criteria of lymphocytes >50% and protein >3 g/dl in pleural fluid had high sensitivity (90%), but specificity was poor (45.8%). Pleural fluid lymphocytes >80% as a cut-off, sensitivity was 70.0%, and specificity was 70.8%. However, these estimates were not very precise. According to Pettersson and Riska, lymphocyte predominance >80% was characteristic of tuberculous pleuritis but also of malignant pleural effusion.[9]

The criteria recommended by WHO for diagnosing tuberculous pleuritis in resource-constrained setting was based on studies done in settings where 95% of the pleural effusions were tuberculous.[8] It is known that, in India, prevalence of TB had halved by 2013 compared to 1990.[1] In our study, only 56% (95% CI - 42.5–69.5%) of the pleural effusion were tuberculous. Similarly, in a tertiary care setting in Tamil Nadu, only 43.8% (95% CI - 29.5–58.1%) were tuberculous.[10] With low prevalence, false positive rates increase.

In this context, newer markers need to be considered for the diagnosis of tuberculous pleuritis. Burgess *et al.* had recommended to combine pleural fluid lymphocyte-neutrophil ratio and ADA, which would give sensitivity of 88% and specificity of 95% for tuberculous pleuritis diagnosis.[13] A meta-analysis estimate of sensitivity and specificity of ADA levels in pleural fluid were 92% and 90%, respectively.[14] Polymerase chain reaction for mycobacterial DNA had poor sensitivity.[15] Interferon-gamma, interleukin 12 (IL-12), IL-18 were identified as markers of tuberculous pleuritis.[16] Interferon-gamma is highly efficient marker of tuberculous pleuritis but costly.[15] Detection of free and immune complexed mycobacterial antigens ES-31 and EST-6 were suggested as an adjunct test to diagnose tuberculous pleuritis.[17]

Table 1: Area under the receiver operating curve of laboratory parameters for diagnosis of tuberculous pleuritis (*n*=54)

Laboratory parameters	AUC* with 95% CI	*P*
PF† pH	0.541 (0.383–0.699)	0.608
PF protein	0.603 (0.451–0.755)	0.198
PF LDH	0.535 (0.373–0.696)	0.663
PF sugar	0.559 (0.396–0.722)	0.459
PF total leukocyte count	0.431 (0.269–0.592)	0.384
PF differential count of lymphocytes	0.801 (0.678–0.924)	<0.001
Ratio of PF protein to serum protein	0.550 (0.395–0.705)	0.531
Ratio of PF LDH to serum LDH	0.492 (0.335–0.648)	0.917
ESR	0.542 (0.388–0.697)	0.614

*AUC: Area under curve; †PF: Pleural fluid. LDH: Lactate dehydrogenase; CI: Confidence interval; ESR: Erythrocyte sedimentation rate

Table 2: Sensitivity, specificity and predictive values of lymphocyte predominance in pleural fluid for tuberculous pleuritis (*n*=54)

Differential lymphocyte count (%)	With 95% CI (%)			
	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Above 50	93.3 (83.9–100)	41.7 (21.6–61.8)	66.7 (52.2–81.2)	83.3 (61.8–100)
Above 60	86.7 (74.3–99.1)	45.8 (25.5–66.1)	66.7 (51.6–81.8)	73.3 (50.5–96.1)
Above 70	80.0 (65.4–94.6)	66.7 (47.5–85.9)	75.0 (59.7–90.3)	72.7 (53.7–91.7)
Above 80	70.0 (53.3–86.7)	70.8 (52.2–89.4)	75.0 (58.6–91.4)	65.4 (46.7–84.1)
Above 90	60.0 (42.1–77.9)	91.7 (80.4–100)	90.0 (76.6–100)	64.7 (48.3–81.1)

CI: Confidence interval

Conclusions

Pleural fluid protein is not a valid test to diagnose TB. Lymphocyte predominance >80% in pleural fluid is a valid marker but, because of low prevalence of TB among pleural effusion, predictive values are compromised. Newer tests need to be included in pleural fluid studies with due to consideration of cost and logistics to improve validity of the diagnosis of tuberculous pleuritis in resource-constrained settings.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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