Original Article

Frequency of Tuberculosis and Malignancy in Transudative-pleural effusions: A rare but real finding

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Abstract

Objectives: To determine the frequency of tuberculosis and malignancy in transudative pleural effusions.

Material and Method: The study was conducted in Pulmonology-OPD, Gulab Devi Teaching Hospital Lahore from Oct. 2017 to Feb. 2019. One hundred and twenty-eight consecutive patients with transudative pleural effusions and 14-69 years age, willing for invasive investigations & ADA estimation were included, while those not willing for further investigations, participation in the study, and exudative effusions were excluded. The clinical features, pleural fluid analysis findings, ADA (Adenosine deaminase) estimation results, hematology, echocardiography, bronchoscopy, Lymph node biopsy, CT-thorax, ultrasound chest & abdomen results were recorded on a preformed proforma. Findings were summarized, tabulated, and analyzed statistically using SPSS-16 software.

Results: Out of 1370 cases of pleural effusion, 128 cases (9.34%) with pleural transudate were isolated. In all patients, pleural fluid protein/serum protein level was < 0.5. The age ranged 14-69 years with a mean of 39 years $\pm$ 11.3. Fifty-two cases (40.62%) had right-sided, 38 cases (29.68%) left-sided while 38 cases (29.68%) had bilateral pleural effusions. Seventy-six aspirates (59.37%) were yellow, 20 (15.62%) reddish, 18 (14.06%) straw-colored and 14 fluids (10.93%) were watery in color. Out of 128 transudative effusions, malignant etiology was found in 23 cases (17.96%), tubercular in 17 cases (13.28%) and 19 cases (14.84%) of Para-pneumonic origin were detected.

Conclusion: Tuberculosis and malignancy can be the possible etiology of transudative effusion.

Keywords: Pleural transudate, Malignancy, Systemic disorders, TB.

Introduction

A pleural effusion is always due to underlying disease and can be exudative or transudative, depending upon the pleural fluid protein and serum protein content. Classification into exudate or transudate is usually done according to the Light's criteria. Transudative pleural effusions develop when the hydrostatic and oncotic pressures across the pleural membrane are disturbed & dynamic equilibrium between the fluid formation and absorption is lost. There is no change in the pleural membrane, the endothelium is usually intact and cells & protein content of effusion is low.[1-4] About 5-25% of total pleural effusions are usually transudative in nature.[5] According to conventional teaching, this effusion is considered mainly due to cardiac, hepatic, renal, and systemic disorders.[6-7] But tuberculosis and malignancy can also be infrequent etiology.[8] Malignant cells have been detected in a significant number of transudates, representing advanced malignant processes with high morbidity and mortality, precluding the possibility of treatment with a curative approach. Metastatic adenocarcinoma is the commonest histological finding, while the primary tumor is not identified in approximately 10% of patients of malignant pleural effusions.[9-10]

Similarly, cases with tubercular etiology have also been reported in transudates and pleural fluid estimation of ADA (Adenosine deaminase) level is found a good diagnostic tool for TB diagnosis.[11-12] Because of this association of malignancy and TB (Tuberculosis) with transudative PE, pleural fluid cytology and Adenosine deaminase (ADA) estimation should be employed for all transudative pleural effusions.[11,13] We designed this study to identify and compute the proportion of TB and malignancy associated with transudative pleural effusions.

Materials and Methods

Objectives: To determine the frequency of tubercular and malignant etiology in transudative pleural effusions & also to evaluate the need for performing cytology and ADA estimation in pleural transudates.

Study Design: Prospective study.

Patients and Methods: This study was conducted at the out-patient department of Respiratory Medicine, Gulab Devi Chest Hospital Lahore a 1500 bedded tertiary care hospital, from October 2017 to February 2019.

Inclusion criteria: A total of 128 consecutive adult patients, with 14-69 years of age, no obvious evidence of TB or malignancy, no history of diuretic therapy, with transudative pleural effusion, willing for invasive investigations, and participation in the study, were included.

Exclusion criteria: Patients below 14 years, exudates, incomplete data, on diuretic therapy, not willing for ADA estimation, invasive investigation or participation in the study and known cases, or having radiological suspicion of tubercular or malignant etiology were excluded.

Method: The study was approved ethically by the IRB of the hospital vide No. Admin/GDEC/18.491 and conducted over a period of 17-months. Detailed clinical history including cigarette smoking and contact with a TB-patient were recorded. A thorough physical examination was performed. Chest x-ray-PA and Lateral views, ultrasound abdomen, pelvis, and chest were done which was followed by ultrasound-guided pleural aspiration, and the fluid sample was sent for biochemistry including ADA & LDH estimation, cytology, and bacteriology. CBC with ESR, Serum Protein, serum LDH, LFTs, RFTs, thyroid function tests, and viral markers for hepatitis was performed in pertinent cases. Sputum was evaluated by Gram stain, Z-N stain & cytology. Light's Criteria was applied for differentiating transudate from exudate.

A transudative pleural effusion was defined by meeting at least one of the following criteria: 1. Pleural fluid protein/serum protein level < 0.5., 2. Pleural fluid LDH level < 2/3 of the upper limits of the normal serum value. 3. Pleural fluid LDH/serum LDH value < 0.6.

ECG, Echocardiography, CT-thorax, Bronchoscopy & biopsy along with BAL (Broncho-alveolar lavage) cytology were employed for precise diagnosis, in pertinent cases. Lymph node biopsy and histopathology were carried out in the required cases. Pleural fluid culture & sensitivity was utilized to isolate pyogenic etiology. Pleural fluid ADA level, 40 IU/L and above was considered as the cut-off for TB-diagnosis. Tubercular patients were put on anti-TB therapy via standard DOTS regimen and were followed for six months. The response to treatment was noted. Fluid immuno-staining and cytopathology diagnosed malignant etiology.

All clinical findings were recorded in the pre-formed proforma. Data was summarized; organized, tabulated, and SPSS-16 software was used for statistical analysis to reach the conclusion. Descriptive

statistics including mean with ± SD were calculated. Categorical data were presented as a percentage.

Results

Out of 1370 cases of pleural effusion, 128 cases (9.34%) with pleural transudate were isolated. In all patients, pleural fluid protein/serum protein level was < 0.5. The age ranged 14-69 years with a mean of 39 years ± 11.3. Eighty-six patients (67.18%) were male while 42 patients (32.81%) were female. The male to female ratio was 2:1. Majority of the patients presented with respiratory complaints (Table 1). Cigarette smoking (73.43%), history of contact with a TB-patient (10.15%), and Diabetes Mellitus (30.46%) were major risk factors.

Table 1: Clinical presentation in 128 patients

Nos.	Clinical features	Observed cases	Percentage (%)
1.	Chest pain.	115	**89.84**
2.	Cough	102	**79.68**
3.	Fever	97	**75.78**
4.	Shortness of breath	93	**72.65**
5.	Weight loss	70	**54.68**
6.	Loss of Appetite	62	**48.43**

Fifty-two cases (40.62%) had right-sided, 38 cases (29.68%) left-sided while 38 cases (29.68%) had bilateral pleural effusions. Seventy-six aspirates (59.37%) were yellow, 20 (15.62%) reddish, 18 (14.06%) straw-colored and 14 fluids (10.93%) were watery in color. Cytology and bacteriology of 128 pleural fluids are tabulated (Table 2). BAL analysis revealed malignant cells in 03 cases while 01 case was diagnosed as TB on Gene-Xpert. Out of 04, two lymph node biopsies showed lymphoma and two caseation granuloma.

Table 2: Pleural Fluid Cytology and Bacteriology n=128

Pleural Fluid Cytology in 128 patients			
Nos.	**Microscopic Appearance**	**Observed cases**	**Percentage**
1.	Lymphocytic	102	79.68 %
2.	Neutrophillic	26	20.31 %
3.	Malignant cytology	18	14.06 %
Pleural Fluid Bacteriology in 19 patients			
1.	Streptococcus Pneumonie	06	31.57 %
2.	Staphylococcus Aureus	05	26.31 %
3.	Gram –ve Rods	03	15.78 %
4.	Pseudomonas	03	15.78 %
5.	No-growth	02	10.52 %

*n= total pyogenic transudates.

Out of 128 transudates, 105 patients (82.03%) were diagnosed with non-malignant while 23 cases (17.96 %) with malignant pathologies (Table 3 & Figure 1).

Table 3: Frequency of non-malignant pathologies with ADA values n=105

No	Diagnosis	Observed Cases	Percentage of (n)*	ADA Range IU/L	Mean ADA value IU/L
1.	**TB PE**	17	16.19 %	34-85.6	55.86
2.	**Para-pneumonic**	19	18.09 %	07-11	09.2
3.	**Cardiogenic cause**	35	33.33 %	07-16	8.66
4.	**CLD**	13	12.38 %	07-18	12.95
5.	**CRF**	10	9.52 %	9.8-12	11.34
6.	**Hypo-proteinemia**	03	2.85 %	14-19	16.5
7.	**Non Specific**	04	3.80 %	12-15.5	13.7
8.	**SLE**	03	2.85 %	17-18	17.4
9.	**Rheumatoid Arthritis**	01	0.95 %	14.0	14.0

*** Percentage is calculated for 105 non-malignant transudates.**

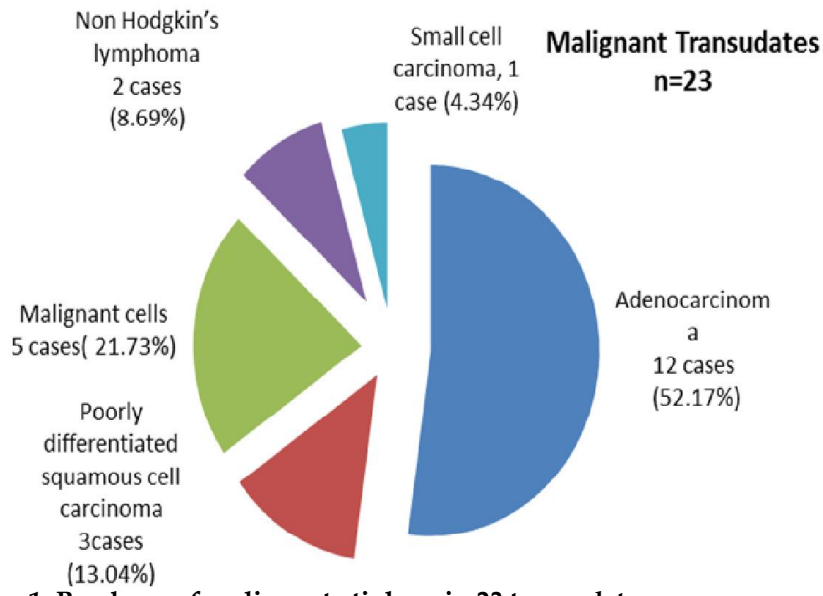

Figure 1: Break-up of malignant etiology in 23 transudates

Discussion

While investigating an undiagnosed pleural effusion, biochemistry is utilized for deciding exudative or transudative nature & transudate fluids are investigated by keeping a focus on systemic causes without including tuberculosis and malignancy in the list of differential diagnosis because of their documented exudative nature.[14-15]

This study last for a 17-month period during which 1370 pleural effusions were investigated and 128 cases (9.34%) of pleural transudates were isolated, which included 35 cases (27.34%) cardiac, 23 cases (17.96%) malignant, and 19 cases (14.84%) of Para-pneumonic origin while 17 cases (13.28%) with tubercular etiology were also obtained.

The study population had a mean age of 39 years $\pm$ 11.3 and two of third patients were men. This age along with (73.43%) cigarette smoking and (30.46%) diabetes mellitus favor cardiac and renal etiology. We had 35/128 cases with cardiogenic and 10/128 cases with renal etiologies in our study. As smoking is more common in men, we had 67.18% of patients with the male gender. Smoking is started early in childhood in males than in females, they consume more pack-year and are more vulnerable to the risk of smoking as compared to females. We had 73.43% of patients with smoking, which is itself an established risk factor for cardiac and malignant disorders.[16-17]

Ferreiro L et al reported the prevalence of malignant transudative pleural effusion as 10% (18), Ashchi M et al reported as 4.6% among 171 malignant pleural transudates.[19] Yuri Moltyaner et al displayed 8% malignancy[20] while our series exhibited a prevalence of 17.96% malignancy, in 128 transudates.

The possible explanation for malignant transudate formation is that initially fluid is accumulated due to lymphatic-obstruction; low protein level-ultra-filtrate is formed without pleural seeding with malignant foci. Confounding co-morbidities like heart failure may also be responsible for transudate formation. Similarly, any tumor or lymph node causing bronchial obstruction and atelectasis can result in transudate formation.[21] Commonly the tumor of lung, breast, and lymphoma invading mediastinal lymph nodes cause lymphatic obstruction, resulting in transudate formation.[22-23]

Bayhan Gl and colleagues concluded their study by commenting that pleural TB can present in the form of transudates.[24] Doerr CH and co-workers reported 27% of patients with benign tumors, tuberculosis, and heart failure, for transudative effusions.[25] Agrawal V reported 14.28% tubercular transudates.[26] A Spanish study of 3077 cases during 19 years, revealed 9.0% etiology due to tuberculosis.[27] We found 13.28% tubercular etiology in 128 transudates (19 months period) which is fairly comparable with these studies.

In this study, 13/17 cases (76.47%) diagnosed as tuberculosis had a history of contact with a TB patient in their family, which created a high index of suspicion about tubercular etiology. Tuberculosis was diagnosed by pleural fluid ADA level in all cases except three with border-line values, two were diagnosed by lymph node biopsy and one case was detected by BAL Gene-

Xpert. As tuberculosis is endemic in our region, all exudative lymphocytic pleural effusions are considered as tubercular, until proven otherwise.[28] But transudative effusions are dealt with differently. On finding a transudative pleural effusion, the diagnostic plan is oriented toward systemic causes while TB & malignancy are over-looked, that is why transudates with TB and malignant pathologies remain undetected. It is very much pertinent to make this note that tuberculosis is a curable disease if diagnosed timely, if it is missed, it can be a risk for the patient and the community as well. As pleural fluid ADA estimation is a useful biomarker for TB diagnosis in endemic areas, it should be frankly utilized for the workup of all TB-suspect transudates.[29]

Similarly, malignant pleural effusions are almost always categorized as exudates. The presence of malignant cells in transudative effusion indicates a mitotic lesion with high-grade morbidity & mortality with a brief expected life span (only 4–9 months), that is why a timely diagnosis of such patients is valuable for the patient as well as for the treating physician. It can only be achieved by having a high index of suspicion. \Although, British Thoracic Society does not recommend thoracentesis for bilateral pleural effusions, suspected to be transudate, if sampled, BTS suggests cytology for all.[30] Porcel J.M. and associates analyzed 840 malignant effusions and found that cytology was 59% accurate in detecting malignancy.[31-32] In our study, 18/23 cases (78.26%) of malignancy were diagnosed by pleural fluid cytology, 03 cases (13.04%) by BAL cytology, and 02/23 cases were diagnosed by lymph node biopsy. Moltyaner Y et al. suggested that every transudate should be investigated by cytology to maximize the diagnostic yield.[20] The traditional teaching suggests performing cytology on a transudative pleural effusion in search of a malignant cause, might not be cost-effective. In the current era of cost-effective medicine, it is mandatory to ensure that we should not sacrifice the quality of care for cost. Therefore, pleural fluid cytology seems to be essential in all transudative effusions to avoid the chances of missing malignant pathologies. Additionally, ADA estimation can be very much helpful in differentiating between malignant and tubercular transudates.

19/128 cases (14.84%) of transudate with pyogenic etiology is an eye-opening figure. Bacteriologic work-up (Table-II) reflecting the internal story, thus necessitates the need for culture and sensitivity examination for all pleural transudate. It is, therefore, suggested that in the absence of any obvious systemic etiology, all transudative pleural effusions must be subjected to fluid cytology, bacteriology & ADA estimation.

The main limitation of this study is that it is a single-center study performed on limited sample size (n=128). By further elongation of the study or a study with larger sample size and preferably, a multi-center study can further explore the subject and strengthen the study.

Our results can find very useful applications in populations with a high prevalence of tuberculosis and increasing malignant disorders due to heavy smoking, industrialization, environmental and occupational pollution, for diagnostic as well as disease control objectives.

In the light of this discussion, we have no hesitation in commenting that a transudative pleural effusion is just a false re-assurance against malignancy and tuberculosis. Therefore, all pleural transudates must be investigated from the perspective of tuberculosis and malignancy in addition to infective & systemic disorders.

Conclusion

- Tuberculosis and malignancy can be the possible etiology of transudative pleural effusions.
- Pleural fluid cytology and ADA estimation & pyogenic culture and sensitivity should be included in the diagnostic algorithm of transudative pleural effusions.
- The history of contact with a TB patient must be dug out to create a high index of suspicion about tuberculosis.

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