ETIOLOGY OF PLEURAL EFFUSION-DIAGNOSTIC OUTCOME

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SUMMARY

Pleural effusion is a common clinical and diagnostic problem. We conducted a prospective study on patients with exudative pleural effusion, who presented to chest unit. Exudative pleural fluid was analysed for protein, amylase, LDH, sugar and cell cytology. We recruited 150 patient aged 18-80 years of either sex. All of them had pleural biopsy and pleural aspiration. On basis of pleural fluid protein analysis 147(98%) turned out to be exudative while only 3 patient (2%) gave transudative results. In all the patients pleural fluid LDH/serum LDH ratio was above 0.6%. In 120 patients (80%) pleural fluid revealed predominantly lymphocytes and 30 patients (20%) showed neutrophils predominantly. In 67 patients (45%) histological examination of pleural biopsy revealed tuberculosis, 36 patients (24%) had metastatic carcinoma and 47 patients (31%) showed chronic non-specific pleuritis. We found that pleural biopsy is the most sensitive and specific way to diagnose the cause for pleural effusion. There are no differentiating features on the basis of chemical analysis among various causes of exudative pleural effusion. Age greater than 50 and haemorrhagic pleural effusion (P<0.001) was in favour of malignant pleural effusion, while positive mantoux test (P<0.001) was in favour of tuberculous pleural effusion.

INTRODUCTION

Exudative pleural effusion is a common clinical and diagnostic problem. It is sometimes impossible to diagnose the underlying aetiology, clinically, radiologically or by pleural fluid analysis. These cases usually require pleural biopsy for definitive diagnosis.

We conducted this prospective study on 150 patients, with an aim to prove that closed needle pleural biopsy is the best diagnostic tool for determining the etiology of exudative pleural effusion specially in areas where tuberculous pleural effusion is more prevalent.

MATERIAL AND METHODS

This prospective study was conducted in Postgraduate Medical Institute, Lady Reading Hospital, Peshawar in collaboration with PMRC, Peshawar from 1991-1995. The inclusion criteria was, patients of either sex, age 16-80 years, with exudative pleural effusion, fit to undergo pleural aspiration and biopsy and no history of prior treatment or procedure for this disease.

All the patients were admitted to chest ward. Pleural fluid was analysed grossly and for proteins, sugar, LDH, ANF, RA factor, amylase and cytology. Blood was taken for Hb, TLC, DLC urea, sugar, serum ANF, RA
TABLE I
HISTOPATHOLOGICAL RESULTS

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of case</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tuberculosis</td>
<td>67</td>
<td>45%</td>
</tr>
<tr>
<td>Malignancy</td>
<td>36</td>
<td>24%</td>
</tr>
<tr>
<td>Nonspecific</td>
<td>47</td>
<td>31%</td>
</tr>
<tr>
<td><strong>Total:</strong></td>
<td><strong>150</strong></td>
<td><strong>100%</strong></td>
</tr>
</tbody>
</table>

factor, LDH, and amylase. Closed pleural biopsy was performed using Abram’s needle for histopathology. Patients were re-biopsied in case of failed biopsy on first attempt. The biopsy site was selected on basis of area of maximum dullness to percussion, and fluid level on chest X-Ray films. A minimum of four biopsy specimens in one setting from one site were obtained, preserved in 10% formalaldehyde solution and sent for histological examination. Echocardiography was performed on all patients.

RESULTS

This prospective study included 150 patients, 101(67.33%) males, 49(32.66%) females, with the male to female ratio of approximately 2:1, and the age range of 16-80 years with the mean age of 47 years. Based on histopathology of pleural biopsy (Table I), in this paper, we have arranged the results under following headings.

I. Chronic granulomatous lesion compatible with tuberculosis. (TB group).

II. Metastatic adenocarcinoma or mesothelioma (Malignant group).

III. Chronic nonspecific inflammation (Nonspecific group).

IV. Comparison between TB and malignant group. (Table-II)

I. TB Group:

TB group included 67(45%) patients, 52(78%) males, 15(22%) female with male to female ratio of around 3.4:1, and mean age of 38 years.

Only 8 (12%) were smokers and mantoux was positive in 33(49%). Associated pericardial effusion was present in 12(18%). Pleural fluid analysis showed haemorrhagic pleural effusion in 4(6%), pleural fluid protein more than 3 g% in 66(99%), pleural fluid to serum LDH ratio more than 0.6 in all (100%), predominantly lymphocytic pleural effusion in 54 (81%) and predominantly neutrophilic pleural effusion in 13(19%). The pleural fluid analysis was non-diagnostic and diagnosis was confirmed by histopathology of pleural biopsy.

II. Malignant group:

Malignant group included 36(24%) patients, 19(53%) males and 17(47%) females with male to female ratio of approximately 1:1, and mean age of 55 years.

Only 8(22%) were smokers and mantoux was positive in 7(19%). Associated pericardial effusion was present in 13(36%). Pleural fluid analysis showed haemorrhagic pleural effusion in 18 (50%), Exudative criteria was met by pleural fluid protein and pleural fluid to serum LDH ratio in all (100%), predominantly lymphocytic pleural effusion was present in 26(72%), predominantly neutrophilic pleural effusion was present in 10(28%), and malignant cells were positive in 12(33.3%) patients. Pleural fluid analysis was diagnostic in 33.3% only, in the remaining patients diagnosis was confirmed by histopathology of pleural biopsy.

III. Non specific group:

This group included 47(31%) patients, 30(64%) males, 17(36%) females, with male to female ratio of 1.8:1, and mean age of 50. Only 13(28%) were smoker and mantoux was positive in 22(47%). Associated pericardial effusion was present in
TABLE II A
TB VS MALIGNANCY DATA COMPARISON

<table>
<thead>
<tr>
<th></th>
<th>TB</th>
<th>Malignancy</th>
<th>Value of P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age</td>
<td>36</td>
<td>55</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Male</td>
<td>52(78%)</td>
<td>19(53%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Female</td>
<td>15(22%)</td>
<td>17(47%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Smoker</td>
<td>8(12%)</td>
<td>8(22%)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Positive montoux</td>
<td>33(49%)</td>
<td>7(19%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Pericardial effusion</td>
<td>12(18%)</td>
<td>13(36%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>ESR</td>
<td>47</td>
<td>45</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

15(32%). Pleural fluid analysis showed haemorrhagic pleural effusion in 15(32%), pleural fluid protein more than 3g/dl in 46(99%), pleural fluid/serum LDH ratio of more than 0.6 in all (100%), predominantly lymphocytic pleural effusion in 40(85%) and predominantly neutrophilic pleural effusion in 7(15%). These patient neither fitted in TB group nor in malignant group and were treated as tuberculous pleural effusion.

IV. TB vs malignant pleural effusion (Table II).

Smoking status, ESR, and pleural fluid analysis were not helpful in differentiating malignant from tuberculous pleural effusion, (P<0.05). Advance age, female, sex haemorrhagic pleural effusion, negative montoux and associated pericardial effusion were in favour of malignancy (P<0.05).

Serum and fluid ANF, serum and fluid RA factor, serum and fluid Amylase, and pleural fluid AFB were negative in all cases. Malignant cell were positive in only 12 out of 36 (33.3%) biopsy proven malignant cases.

In our study the overall diagnostic yield of pleural biopsy was 68.8%. Pleural biopsy was performed in presence of pleural fluid from site of maximum dullness, with four or more biopsies from one site in one sitting. Our success rate of obtaining adequate pleural tissue was 80% on first attempt. The remaining 20% were re-biopsied. Complication were few and included local site pain (13.3%), subcutaneous fluid accumulation (3.3%) and tumor seeding following pleural biopsy in mesothelioma (2%).

DISCUSSION

Pleural effusions results from wide variety of causes which are broadly divided into exudates and transudates. Exudates have at least one and transudates have none of the following.

1. Pleural fluid/serum total protein ratio >0.5
2. Pleural fluid/serum LDH ratio >0.6

This discussion is limited to exudative effusion only. The two common causes of exudative effusion in our country are TB and malignancy, which are difficult to differentiate clinically, and on pleural fluid analysis, and often require pleural biopsy.

Collin TR and Sohn SA reported that thoracentesis is diagnostic in approximately 75% of patients and useful in the
TABLE – II B
T.B VS MALIGNANCY. PLEURAL FLUID ANALYSIS

<table>
<thead>
<tr>
<th></th>
<th>TB</th>
<th>Malignancy</th>
<th>Value of P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemorrhagic eff.</td>
<td>4(6%)</td>
<td>18(50%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Protein &gt;3g%</td>
<td>66(99%)</td>
<td>36(100%)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Fluid/Serum LDH ratio &gt;0.6</td>
<td>67(100%)</td>
<td>36(100%)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Pred. lymphocytosis</td>
<td>54(81%)</td>
<td>26(72%)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Pred. Neutrophils</td>
<td>13(19%)</td>
<td>10(28%)</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

management of additional 15-20%. In a prospective study of 125 patients thoracocentesis provided definitive diagnosis in 18% and a presumptive diagnosis in 55% (pleural fluid analysis compatible with single diagnosis). In the remaining 25% the pleural fluid findings were not helpful as they were compatible with two or more clinical possibilities. Light RW et al mentioned that when exudative criteria are met by LDH alone, the diagnosis of malignancy or parapneumonic effusions should be considered and that fluid leukocyte count is virtually never diagnostic. Pleural fluid lymphocytosis can be due to tuberculous pleural effusion, carcinomatous pleural effusion, lymphoma, sarcoidosis and chronic Rheumatoid pleurisy. Most authorities consider exudative lymphocytic effusion an indication for pleural biopsy.

In our prospective study of 150 patients thoracocentesis provided presumptive or definitive diagnosis in only 12 out of 150 (8%) patients (malignant cell positive). In remaining 92% pleural fluid findings were comparable in all the three major histopathologic group (granulomatous, malignant, nonspecific) found on pleural biopsy. Exudative criteria by LDH alone was a feature of granulomatus (2 patients) and not of malignant effusion (none). We also found that total and differential leukocyte count of pleural fluid is virtually never diagnostic.

Surprisingly our pleural fluid cytology for malignant cells had a diagnostic yield of only 33.3% compared to 50-90% claimed by others. Probable reasons for this variability in positivity may be

i. Paramalignant effusion

ii. Variance of tumour type (high with adenocarcinoma, low with Hodgkin’s)

iii. Number of specimens submitted (yield tend to increase with additional specimen due to exfoliation of fresh cells).

iv. Most serous fluids have a tendency to clot making cytological examination impossible. Therefore pleural fluid should be placed in sterile container with 200 units of heparin.

v. Cytological examination should be done as early as possible, because cells tends to deteriorate within 24 hours specially in bloody pleural effusion.

vi. Interest and expertise of cytopathologist.

The flaw in our study was that a single specimen was submitted without anticoagulant, and was examined by inexperienced cytopathologist after a delay of more than 24 hours. This might have contributed to unexpectedly low yield in
our study. As experienced cytopathologist are scarcely available in our country, we recommend that pleural biopsy should be the investigation of choice for diagnosis of exudative lymphocytic pleural effusion.

Since the introduction of Cope and Abram’s pleural biopsy needles in late 1950’s, pleural biopsy has been the subject of many studies. Routine pleural biopsy has become an accepted diagnostic tool and many different and improved pleural biopsy needles are introduced. It was Abram’s needle which attained world wide popularity, although recently trucut needle biopsy has been shown to be as effective and reliable as Abram’s needle.

The main indication for pleural biopsy is undiagnosed pleural effusion, and the major objective is diagnosis or exclusion of tuberculosis and malignancy. A review of 1893 pleural biopsies has shown the diagnostic yield of 57% for malignancy and 73-75% for tuberculosis.

The majority of investigators have emphasised that pleural biopsy should be performed in presence of pleural effusion but Nider and associates have demonstrated the safety and feasibility of this procedure in absence of pleural fluid. Conto and associates in their thoracoscopic analysis recommend that biopsy taken from the lowest pleural margin has the maximum diagnostic yield, and it is suggested that 4 or more biopsies in one sitting from one site will improve the diagnostic yield. A repeat pleural biopsy soon after the initial negative biopsy is shown to be of little diagnostic value although suggested by some investigators.

In our study we used Abram pleural biopsy needle, performed the procedure in presence of pleural fluid, and took 4 or more biopsies from one site in one sitting. Pleural tissue was obtained in 80% on first attempt and repeat biopsy was conclusive in all the remaining 20% patient.

The overall diagnostic yield of pleural biopsy was 68.8% for granuloma and malignancy. In the remaining the result was chronic nonspecific inflammation.

Tubercle bacilli have been notoriously difficult to culture from pleural fluid, with a positive culture in only 31.5%. The diagnosis of tuberculous pleural effusion is most often established by histological examination, and its diagnostic yield can be reinforced by culturing the pleural biopsy specimen. In this study we established the diagnosis by histological examination only.

The common complication of pleural biopsy include site pain, pneumothorax, vasovagal reaction and site haematoma, other less common complication are transient fever, subcutaneous emphysema, tumor seeding and air embolism. Tumour seeing following pleural biopsy appear to be more common following pleural biopsy in mesothelioma.

In this study apart from site pain (13.3%) subcutaneous fluid accumulation (3.3%) and tumor seeding following biopsy in mesothelioma (2%) complications were few.

**CONCLUSION**

 Clinically old age, negative montoux, and haemorrhagic pleural effusions are in favour of malignancy. Pleural fluid analysis has a low diagnostic yield and cannot differentiate between malignant and tuberculous pleural effusion in most cases. Pleural biopsy has a high diagnostic yield, safe, simple, and clearly differentiate between malignancy and tuberculosis. Therefore we recommend that pleural biopsy should be the investigation of choice in exudative lymphocytic pleural effusions.
REFERENCES


