# Pleural effusion in 100 Malaysian patients

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## Summary

In a retrospective study of 100 patients with pleural effusion the final diagnosis was tuberculosis in 49, malignancy in 43, malignancy with tuberculosis, bacterial infection, hydrothorax with cirrhosis, reaction to pneumothorax in one each, and unknown in 4. Most of the effusions analysed were exudates (94%). Pleural biopsy was diagnostic in 46% of tuberculous effusions (13/28) and 67% of malignant effusions (20/30). Tuberculosis accounted for 87% of cases in patients aged 40 years and under. In this age group, patients with exudative pleural effusion and a positive tuberculin test are likely to have tuberculosis and early therapeutic trial is justified.

*Keywords*: Pleural effusion, tuberculosis, malignancy.

## Introduction

Pleural effusion is a common diagnostic problem encountered in hospital practice, and in a proportion of cases the cause remains elusive despite investigation.[1] The incidence of different aetiologies is known to vary in different communities.[2-4] Since knowledge regarding the local pattern of causes would be a useful guide for management, a study was done to determine clinical presentation and the specific causes of pleural effusion in patients treated by the Chest Unit, Penang General Hospital.

## Materials and methods

A retrospective study was made of 100 consecutive patients with pleural effusion presenting to the Chest Unit, Penang General Hospital, during a two year period from March 1989 to February 1991. Clinical data as well as results of investigations were recorded. The presence of pleural fluid was based on clinical and radiological findings in all cases and confirmed by thoracocentesis in 87 patients.

Group differences were tested using the chi-square method.

## Results

The 100 patients included 71 males and 29 females aged 8 to 83 (mean 51.5 years).

The effusion was in the right pleural space in 47 cases and in the left pleural space in 49; the remaining 4 patients had fluid in both pleural spaces.

### Causes of pleural effusion

The commonest causes were tuberculosis and malignancy which accounted for 49% and 43% of the total respectively (Table 1). One patient had both tuberculosis and malignancy. In four patients the aetiology could not be determined; all these patients (aged 51, 63, 79 and 82 years) had haemorrhagic effusions and were suspected of having malignant disease but were lost to followup before any diagnosis could be made.

**Table 1**
**Causes of pleural effusion in 100 patients**

| Cause | | Number of patients |
|---|---|---|
| Tuberculosis | | **49** |
| Malignancy | | **43** |
| Carcinoma of bronchus (adenocarcinoma 18, squamous cell 9, small cell 2, poorly differentiated 2, unspecified cell type3) | 34 | |
| Metastatic (ovary 2, cervix 2, breast 1, liver 1, bone 1) | 7 | |
| Malignant thymoma | 1 | |
| Mesothelioma | 1 | |
| Other causes | | **4** |
| Tuberculosis with adenocarcinoma | 1 | |
| Hydrothorax with cirrhosis | 1 | |
| Bacterial infection | 1 | |
| Reactive to pneumothorax | 1 | |
| Unknown | | **4** |
| **Total** | | **100** |

**Presenting symptoms**

Cough was the most frequent presenting symptom occurring in 84% of patients. Breathlessness occurred in 81%; loss of weight, loss of appetite, fever and chest pain were noted in 73%, 61%, 50% and 46% of patients respectively. Fever was a more common symptom in patients with tuberculous effusions than in patients with other diagnoses (73% vs 30%, $p<0.01$).

**Examination of pleural fulid**

The appearance of the pleural fluid was recorded in 80 patients. Malignant effusions were more likely to be haemorrhagic than effusions caused by other conditions (48% vs 7%, $p<0.01$). The pleural fluid was straw coloured in 79% of tuberculous effusions compared to 52% of malignant effusions and also in one case of hydrothorax associated with cirrhosis and one effusion caused by bacterial infection. In this series, 7 effusions yielded cloudy fluid or frank pus: six were tuberculoous in origin and one was reactive to pneumothorax.

Analysis of pleural fluid in 70 patients showed that 66 (94%) were exudates ie., protein content of more than 3g/100ml. Of the four effusions classified as transudative one was tuberculous (diagnosis based on pleural biopsy), two were malignant (diagnosis established on bronchial biopsy and pleural biopsy respectively) and one was a hydrothorax associated with liver cirrhosis.

Microscopy of the fluid in 67 patients revealed that lymphocytes were the predominant cells in more than 50% of effusions regardless of aetiology. In patients with malignant disease cytological examination of pleural fluid was positive for malignant cells in 13 of 34 patients (38%).

Culture of pleural fluid grew *M. tuberculosis* in 5 of 37 patients with tuberculous effusion (14%). Direct smear for acid fast bacilli was done on pleural fluid from 36 patients with tuberculosis but was positive in only 3 cases (8%) all of whom had tuberculous empyema and frankly pleural fluid.

**Pleural biopsy**

Pleural biopsy using Abrams' needle was carried out in 64 patients and the results are shown in Table 2. This procedure was diagnostic in 33 of the 64 patients (52%) ie., in 13 of 28 tuberculous effusions (46%) and 20 of 30 malignant effusions (67%). It was the only test which was diagnostic in 12 patients with tuberculous effusion and 8 patients with malignant disease.

**Table 2**
**Results of pleural biopsy in 64 cases of pleural effusion**

| Final Diagnosis | No. of cases | No. of biopsies | Inflammatory | Tuberculous | BIOPSY RESULTS Malignant | Non-specific |
|---|---|---|---|---|---|---|
| Tuberculosis | 28 | 32 | 9 | 13 | 0 | 10 |
| Malignancy | 30 | 46 | 2 | 0 | 20 | 24 |
| Tuberculosis with malignancy | 1 | 2 | 2 | 0 | 0 | 0 |
| Hydrothorax with cirrhosis | 1 | 1 | 0 | 0 | 0 | 1 |
| Bacterial infection | 1 | 1 | 1 | 0 | 0 | 0 |
| Unknown | 3 | 3 | 0 | 0 | 0 | 3 |
| **Total** | **64** | **85** | **14** | **13** | **20** | **38** |

**Other methods of diagnosis**

Table 3 shows the methods of diagnosis in 49 patients with tuberculous effusion. Sputum culture for *M. tuberculosis* was positive in 8 of 38 patients with tuberculous effusions (21.1%) and sputum direct smear revealed acid fast bacilli in 8 of 46 patients (17.4%). In 22 patients the diagnosis of tuberculous effusion was based solely upon clinical and radiological response to a therapeutic trial. Radiological evidence of coexisting parenchymal disease was present in 18 patients with tuberculous effusion.

Table 4 shows the methods of diagnosis in 43 patients with malignant effusion.

**Table 3**
**Methods of diagnosis in 49 patients with tuberculous effusion***

| Method | Number of patients |
|---|---|
| Pleural biopsy | 13 |
| Pleural fluid culture | 5 |
| Pleural fluid AFB direct smear | 3 |
| Sputum culture | 8 |
| Sputum AFB direct smear | 8 |
| Lymph node biopsy | 1 |
| Response to anti-tuberculosis treatment | 22 |

**More than one investigation was positive in 8 patients (16% of cases)*

**Table 4**
**Methods of diagnosis in 43 patients with malignant effusion***

| Method | Number of patients |
|---|---|
| Pleural biopsy | 20 |
| Pleural fluid cytology | 13 |
| Bronchoscopy (biopsy/cytology) | 11 |
| Lymph node biopsy | 6 |
| Biopsy of chest wall metastasis | 2 |
| Sputum cytology | 2 |
| Mediastinoscopy and biopsy | 1 |
| Liver biopsy (post mortem) | 1 |
| Clinical evidence of metastasis | 4 |

**More than one investigation was positive in 14 patients (33% of cases)*

In the patient with carcinoma and concurrent pulmonary tuberculosis, diagnosis was made from trucut lung biopsy which showed adenocarcinoma and positive sputum culture for *M. tuberculosis.*

There were three patients with diagnosis other than tuberculosis and malignancy. The diagnosis of hydrothorax associated with cirrhosis was made in one patient, a Hepatitis B surface antigen carrier, who had transudative effusion and cirrhosis with chronic active hepatitis confirmed on liver biopsy. Another patient had parapneumonic effusion attributed to infection with *Staphylococcus aureus* which was cultured from the pleural fluid. In the third patient the effusion was thought to be reactive to pneumothorax since it developed after intercostal drainage for pneumothorax in the absence of evidence to support any other diagnosis.

### Tuberculin test

The tuberculin test was done in 88 patients. It was positive (Mantoux reading < 10mm) in a higher proportion of patients with tuberculosis than in patients with other diagnosis (62.5% vs 35.1%, $p<0.02$).

In patients aged 40 years and under the tuberculin test was a useful indicator since it was positive in 71% of patients with tuberculous effusion but in none of the patients with effusions caused by other diseases. In patients above 40 years of age the tuberculin test was positive in 54% of patients with tuberculosis and 38% of patients with other diseases (the difference is not statistically significant).

### Age and sex distribution

Tuberculous effusions occurred in all age groups from the first to the eighth decades. In patients aged 40 years and under tuberculosis was the cause in 87% of the cases.

The majority of malignant effusions occurred in patients aged above 40 years but in this age group tuberculosis still accounted for 34% of pleural effusions studied.

Both tuberculous and malignant effusions occurred more commonly in males and the sex of the patient had little relation to the diagnosis. However in patients with carcinoma of the bronchus there was a marked difference in the smoking history between male and female patients: only one of 26 male patients had never smoked whereas 8 of 9 female patients were lifelong non-smokers. In all these non-smokers with carcinoma of the bronchus, the cell type was adenocarcinoma.

## Discussion

Many systemic and local diseases result in accumulation of pleural fluid.[5,6] This study provides information on a selected group of patients with mainly pleural exudates since most patients with pleural effusion referred to the Chest Clinic had known or suspected tuberculosis or malignant disease. Exudative pleural effusion caused by connective tissue disease or infections other than tuberculosis, and pleural transudates such as those caused by congestive heart failure and hypoproteinaemia due to cirrhosis and nephrotic syndrome were few in number because patients with these conditions usually received treatment for the primary disorder and were not referred for further investigation of pleural disease.

Tuberculosis remains a public health problem in Malaysia and was the cause of the largest number of pleural effusions in the study. Malignant disease also accounted for a significant proportion of cases and this is not surprising since carcinoma of the bronchus which is the leading cause of malignant pleural effusion is a common form of cancer and the most important cause of cancer mortality in Malaysia.[7,8]

Thoracocentesis is the procedure most often done for the initial investigation of undiagnosed pleural effusion, and one of the main purposes is to determine whether the effusion is transudative or exudative. Traditionally a pleural fluid has been classified as an exudate if the protein level exceeds $3g/100ml^{-2}$ Using this criterion, the great majority of tuberculous and malignant effusions in this study were classified as exudates but one tuberculous and two malignant effusions were classified as transudative. It is known that tumour obstructing lymphatic drainage can give rise to transudative effusion[10] and the two patients with transudate and malignant disease in this study had evidence of mediastinal/paraortic node metastasis.

In 1972 Light et al [11] proposed further criteria ie., pleural fluid/serum protein ratio greater than 0.5, pleural fluid/serum LDH ratio greater than 0.6, and pleural fluid LDH, greater than two-thirds upper limit of normal for serum LDH, which have been widely accepted as classifying exudative effusions more accurately. These criteria were not used in this study but perhaps in the future, pleural fluid and serum LDH should be routinely done in patients with pleural effusion.

Even more recent criteria suggested to improve sensitivity and specificity for identifying exudates include serum-effusion albumin gradient of 1.2g/100ml or less[12] and pleural fluid/serum bilirubin ratio greater than 0.6.[13]

Pleural fluid lymphocytosis is known to occur in malignant and benign effusions, especially tuberculosis, and is not helpful in diagnosis but grossly bloody pleural fluid is suggestive of trauma, malignancy or pulmonary embolism. No patients with trauma or pulmonary embolism were included in this study and the majority of patients with haemorrhagic effusions had malignant disease.

Since Abrams described his pleural biopsy punch in1958,[14] the technique has been widely used in the investigation of patients with pleural effusion. Positive yield from pleural biopsy was 46% for patients with tuberculous effusions and 67% in patients with malignant disease; similar studies have produced figures ranging from 28% to 80% for tuberculous effusions and 40% to 69% for malignant effusions.[15-18]

For patients with tuberculous effusions the yield from pleural fluid culture for *M. tuberculosis* was only 14%; in most other series pleural fluid culture is positive for mycobacteria in fewer than 25% of cases and direct smear examination of the fluid has seldom been found helpful.[19,20]

Tuberculous effusion has been considered a manifestation of primary tuberculosis seen largely in children and young adults but in recent years it has been noted more and more as a disease affecting older individuals[19,21] Furthermore basal pleural effusion associated with pulmonary shadowing has been reported as one of the atypical radiological features found in elderly patients with pulmonary tuberculosis.[22] In this series, of 49 patients with tuberculous effusion, 24% were above the age of 60 and 49% were above the age of 40.

In patients aged 40 years and below tuberculosis was the predominant cause of pleural effusion accounting for 87% of cases. In this age group, patients with exudative pleural effusion and positive tuberculin test are likely to have tuberculosis and anti-tuberculosis treatment may be started empirically if clinical evaluation, pleural fluid analysis and pleural biopsy have failed to establish a definite diagnosis.

The tuberculin test was positive in a substantial proportion of patients with non-tuberculous effusion over the age of 40 years (38%) reflecting the high prevalence of tuberculosis infection in our Malaysian population which increases with age.

Apart from pleural biopsy, pleural fluid cytology was the most useful diagnostic investigation for malignant effusions. In this series pleural fluid cytology was positive in 38% of patients with malignant disease whereas other reports quote a positive rate of 25% to 87%.[10]

Among patients with lung cancer and pleural effusion the commonest histological cell type was adenocarcinoma. An earlier study on Malaysian lung cancer patients has shown that adenocarcinoma is the most common cell type in female patients and non-smokers,[8] and in this study the majority of female lung cancer patients with pleural effusion were non-smokers with adenocarcinoma.

In many studies the cause of pleural effusion remains unexplained after clinical evaluation, pleural biopsy and pleural fluid analysis in a small proportion of cases. In this series of 100 patients the diagnosis could not be ascertained in four patients who did not wish to have further investigations and did not return for followup of their own accord. Much has been written about pleural effusion of indeterminate cause[23,24] and for difficult cases a variety of diagnostic techniques have been employed including fibreoptic bronchoscopy, thoracoscopy and open thoracotomy.[25-27]

## Conclusion

This study has shown that tuberculosis and malignancy are common causes of pleural effusion and pleural biopsy is a useful diagnostic tool. Patients aged 40 years and under with exudative pleural effusion and a positive tuberculin test are likely to have tuberculosis and therapeutic trial is justified if pleural tap and biopsy are non-diagnostic, whereas older patients should be carefully evaluated for both tuberculosis and malignant disease.

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