Pleural effusions: role of commonly available investigations

How S H, Chin S P, Zal A R, Liam C K

ABSTRACT

Introduction: Previous studies have reported high rates of undetermined causes of pleural effusions. We aimed to find out the proportion of pleural effusions in which the aetiology is uncertain despite commonly available investigations.

Methods: A prospective study was carried out at the University of Malaya Medical Centre from May 2001 to January 2002. All patients with pleural effusion admitted to the medical wards and non-medical wards during that period were included in the study.

Results: Of 111 patients with pleural effusion, malignancy was the commonest cause of pleural effusion (34.2 percent), followed by tuberculosis (22.5 percent) and parapneumonic effusions (18.9 percent). There were only two patients (1.8 percent) with undetermined cause despite extensive investigations. Carcinoma of the lung was the commonest cause of malignant effusions and bronchoscopic biopsy gave the highest yield of histological diagnosis (66 percent), followed by pleural fluid cytology (59 percent) and pleural biopsy (50 percent). The combination of these three procedures increased the diagnostic yield to 96 percent. In tuberculous pleural effusion, pleural fluid staining for acid-fast bacilli was negative in all cases but mycobacterial culture was positive in 24 percent of cases while pleural biopsy gave a better yield of 68.8 percent. Examination of sputum and bronchoalveolar lavage specimens confirmed the diagnosis of tuberculosis in 40 percent of cases. A combination of these investigations yielded the diagnosis in 92 percent of patients with tuberculous effusion.

Conclusion: Malignancy is the commonest cause of pleural effusion, followed by tuberculosis and pneumonia, in patients treated in a teaching hospital in Malaysia. The number of undetermined causes could be minimised with a combination of readily-available and established investigations.

Keywords: bronchoscopy, malignant pleural effusion, pleural biopsy, tuberculosis

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Department of Internal Medicine
Faculty of Medicine
International Islamic University Malaysia
PO Box 141
Kuantan 27510
Malaysia

How S H, MMed
Assistant Professor

Chin S P, MRCP
Lecturer

Department of Medicine
Faculty of Medicine
University of Malaya
Kuala Lumpur 50603
Malaysia

Liam C K,FRCP
Professor

Zal A R, MMed
Lecturer

Correspondence to:
Dr How Soon Hin
Tel: (60) 9513 3710 ext 3445
Fax: (60) 9513 3615
Email: how_sh@yahoo.com

INTRODUCTION

Approximately a million patients worldwide develop pleural effusion each year[1]. This may be a complication of various illnesses. The frequency of the various causes of pleural effusion depends on the incidence of tuberculosis in the region where the study is conducted. In an area with a high incidence of tuberculosis, the commonest causes of pleural effusion include tuberculosis (25%), neoplasia (22.9%), congestive cardiac failure (17.9%) and pneumonia (14%)[2]. The incidence of tuberculosis in Malaysia is 58 per 100,000 population (*1995 Annual Report of the Tuberculosis Control Division of the Ministry of Health, Malaysia*). An earlier study by Liam et al from 1995 to 1998 conducted in this same institution showed that tuberculosis (44.1%) was the commonest cause of exudative effusions followed by malignancy (29.6%) and pneumonia (20.4%)[3].

Patients who are admitted to a hospital with a pleural effusion undergo extensive investigations to identify the underlying aetiology. The common procedures performed include chest radiography, computed tomography (CT) of the thorax, pleural fluid analysis, pleural biopsy, bronchoscopy, Mantoux tuberculin skin test, staining of sputum specimens for acid-fast bacilli (AFB) and bacteriological cultures. Several studies have reported relatively large numbers of patients with pleural effusion in whom a definite diagnosis could not be made, despite extensive investigations[4,5]. Even though thoracoscopy can be used to determine the diagnosis in this group of patients, this facility is not available in most hospitals in Malaysia. The primary objective of our study was to find out the proportion of pleural effusions in which the aetiology is uncertain despite commonly

available investigations. The secondary objective was to evaluate the roles of pleural fluid analysis, pleural biopsy and bronchoscopy in the diagnosis of the malignant and tuberculous effusions.

METHODS

A prospective study was conducted at the University of Malaya Medical Centre (UMMC), a community teaching hospital in Kuala Lumpur, Malaysia, from May 2001 to January 2002. All patients with clinical and chest radiographical evidence of pleural effusion, including those with abnormal lung parenchyma, admitted to the medical wards of the hospital or referred to the respiratory team from non-medical wards during this period, were included in the study. Patients with minimal effusion noted on CT of the thorax but not on chest radiograph and/or coagulopathy (prothrombin time greater than 2.0 by international normalised ratio, [INR]) and/or platelet count less than 20×10^9/L were excluded from the study. Informed consent was obtained from each patient before he or she was entered into the study. The study design was approved by the UMMC ethics committee. Demographical data, characteristics of the pleural effusion, clinical presentation, investigation results, and the final diagnoses were obtained.

All patients routinely underwent diagnostic thoracocentesis using a 16G needle to obtain 60 ml of pleural fluid specimens for cell count, measurement of protein, lactate dehydrogenase (LDH), cytological examination, Gram-stain, culture, Ziehl-Neelsen stain and mycobacterial culture. Serum was taken at the same time for the measurement of protein and LDH levels. The pleural fluid specimens were collected in EDTA tubes for cell count and in plain tubes for the other tests. Pleural biopsy using the Abram's needle was performed if the effusion was found to be exudative or when the diagnosis was uncertain. Other investigations that might contribute to the diagnosis were carried out. These included but were not limited to sputum direct smear for AFB, two-dimensional echocardiography for heart failure, CT of the thorax, and bronchoscopic examination for suspected lung carcinoma and pulmonary tuberculosis.

The pleural effusions were classified according to aetiology. A neoplastic pleural effusion was defined as an effusion due to an underlying malignancy. It can be a malignant or paramalignant effusion. Malignant effusions were diagnosed when pleural biopsy specimens or pleural fluid cytology specimens were conclusively positive for malignancy. Paramalignant effusions were diagnosed when pleural biopsy specimens or pleural fluid cytology specimens were negative and other known causes of the pleural effusions were excluded in patients with a histologically-proven malignancy elsewhere, for example, by percutaneous lung biopsy or transbronchial lung biopsy. Tuberculous pleural effusions were diagnosed when one or more of the following criteria were satisfied: pleural fluid or respiratory secretions were culture-positive for *Mycobacterium tuberculosis* or smear-positive for AFB; presence of epithelioid granulomas with or without caseating necrosis and/or presence of AFB on histological examination of pleural biopsy specimen; clinical and radiological response to anti-tuberculosis treatment in the absence of bacteriological and histological confirmation of tuberculosis.

Parapneumonic effusions were defined as pleural effusions associated with an acute febrile illness and cough, in which the chest radiographs revealed pulmonary infiltrates and the patient responded to antibiotic treatment. Empyema was diagnosed when pus was present or microorganisms isolated from the pleural aspirate. Transudative effusions were identified according to Light's criteria. Causes of other exudative effusions, which were not due to malignancy or infection and in which definite underlying cause could be found, included systemic lupus erythematosus (SLE), serositis and pulmonary embolism. Data were analysed using the Statistical Package for Social Sciences (SPSS) version 10.0 (Chicago, IL, USA). Two-tailed unpaired Student's t-test was used to compare the mean age of different groups and χ^2 test was used for the comparison of proportions. A p-value of <0.05 was taken as being statistically significant.

RESULTS

A total of 111 patients were studied. All patients were grouped according to the cause of the pleural effusions (Fig. 1). There were two patients who had no obvious cause for their exudative pleural effusions despite pleural fluid analysis, pleural biopsy, CT of the thorax and abdomen, and other investigations, and in whom no cause was found at the conclusion

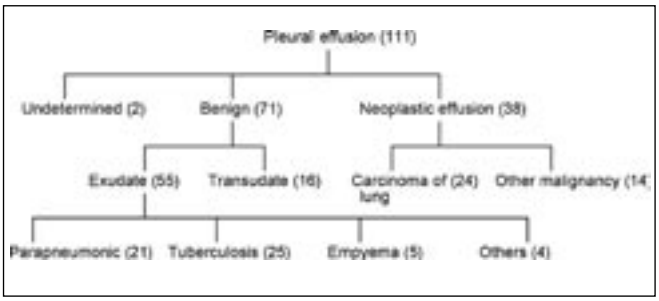

Fig. 1 Flow chart shows the causes of pleural effusions (the number of patients are shown within brackets).

Table I. Baseline cohort and characteristics of 109 patients with malignant and benign pleural effusions.

	Malignant	Benign	p-value
Male:female ratio	19:19	43:28	0.29
Age (± SD) (in years)	60 (±14)	54 (±19)	0.02
Ethnicity – Malay:Chinese:others ratio	8:27:3	17:35:19	0.08
Distribution of effusion – left:right:bilateral ratio	8:23:7	19:38:14	0.80

Table II. Causes of pleural effusion and percentage which was lymphocyte-predominant.

Cause of effusion	N	n
Tuberculosis	24	21 (87.5)
Carcinoma of lung	24	13 (54.1)
Other malignancies	14	12 (85.7)
Paramalignant effusion	16	11 (68.7)
Malignant effusion	22	14 (63.6)
Parapneumonic effusion	21	3 (14.2)
Empyema	5	1 (20.0)
Transudative effusion	14	5 (35.7)

n: No. of patients with lymphocyte-predominant effusions

N: No. of patients in whom the test was performed

Table III. Investigations that yielded a positive diagnosis in 24 patients with carcinoma of lung.

Diagnostic test	n/N (%)
Pleural fluid cytology positive	14/24 (59)
Pleural biopsy positive	7/14 (50)
Either pleural fluid cytology or pleural biopsy positive	17/24 (71)
Bronchoscopic procedures	10/15 (66)
Any one of the above investigations positive for malignancy	23/24 (96)
CT-guided percutaneous needle biopsy of lung lesion	1/24 (4)

n: No. of patients with a positive result

N: No. of patients in whom the test was performed

of the study. Of the 109 patients in whom a cause of the pleural effusion was identified, 62 patients (56%) were male. There were 25 Malays (23%), 62 Chinese (57%), and the remainder consisted of Indian and other ethnic groups. Patients with neoplastic pleural effusions were significantly older than those with non-malignant pleural effusions (p=0.02). (Table I).

Exudative pleural effusions were most commonly related to an underlying malignancy (41%) followed by tuberculosis (27%). 24 patients had primary lung carcinoma, namely: adenocarcinoma (15), squamous cell carcinoma (4), poorly- differentiated non-small cell lung cancer (3), small cell carcinoma (2), and 14 patients had other malignancies, such as lymphoma (3), breast cancer (3), endometrial carcinoma (2), uterine cervical carcinoma (2), colonic carcinoma (1), carcinoma of the tongue (1), fallopian tube carcinoma (1) and teratoma (1). Lymphocytic pleural effusion was commonly associated with malignancy and tuberculosis (Table II). 87.5% of tuberculous effusions were lymphocyte-predominant (i.e. lymphocyte constituted more than 50% of the white cell count) as compared to only 14% of patients with parapneumonic effusion and 25% of empyema ($p<0.0001$). There was no significant difference in the proportions of malignant and paramalignant effusions which were lymphocyte-predominant ($p=0.536$).

Pleural fluid cytological examination was positive for malignant cells on initial thoracocentesis in 15 (39.4%) out of the 38 patients with neoplasm. When thoracocentesis was repeated two or three times, cytological examination was positive in 18 (47.4%) of these patients. Pleural biopsy was performed in only 14 patients with carcinoma of the lung and two patients with other malignancies, and was positive in seven patients (44%). Investigations that yielded a diagnosis of carcinoma of the lung are shown in Table III.

Tuberculous pleurisy was the cause of pleural effusions in 22.5% of our patients. The criteria for diagnosing tuberculous effusions is shown in Table IV. Pleural fluid direct smear for AFB was negative in all 25 patients while pleural fluid mycobacterial culture was positive in six patients (24%). Sputum or BAL specimens of ten (40%) of the 25 patients with tuberculous effusion were direct smear positive for AFB or mycobacterial culture positive. Pleural biopsy was performed in 16 patients and revealed granulomas with or without caseating necrosis in 11 patients. Two (8%) patients who had negative results from pleural fluid, pleural biopsy and respiratory tract specimen examinations showed clinical and radiological response to anti-tuberculosis treatment. In summary, investigations were helpful in confirming tuberculosis in 23 patients (92%).

DISCUSSION

In contrast to most previous studies which showed that up to 20% of patients with pleural effusions

Table IV. Diagnostic investigations in 25 patients with tuberculous pleurisy.

Diagnostic investigation	n/N (%)
Pleural fluid AFB direct smear positive	0/25 (0)
Pleural fluid mycobacterial culture positive	6/25 (24)
Pleural biopsy showed presence of granulomas with or without caseating necrosis	11/16 (68.8)
Sputum or BAL direct smear positive with or without positive mycobacterial culture	5/25 (20)
Sputum or BAL direct smear negative but mycobacterial culture positive	5/25 (20)
Any one of the above tests positive for tuberculosis	23/25(92)
Above tests negative but clinical and radiological response to anti-tuberculosis chemotherapy	2/25 (8)

n: No. of patients with a positive result

N: No. of patients in whom the test was performed

had no definite aetiology despite extensive investigations[2,4,5], this study has shown that the number of undetermined causes could be reduced to 1.8% with a combination of readily-available and established investigations. Obtaining a definite diagnosis was important not only for proper treatment but also because one-fifth of patients with no definite diagnoses continue to have recurrent effusions[6] and was more likely to be associated with an occult malignancy[7]. Thoracoscopy is the gold standard and can confirm the diagnosis in more than 90% of cases. However, this investigation is not widely available[7]. On the other hand, the combination of sputum examination, pleural fluid cytotology, pleural biopsy and bronchoscopy detects up to 96% of malignancy due to carcinoma of the lung and 92% of tuberculosis, the two most common causes of pleural effusions in our study.

In this study, malignancy (34.2%) was the most common cause of pleural effusions as compared to the earlier studies[2,3,8], which showed a higher incidence of tuberculous effusions due to exclusion of referral cases from non-medical wards as the majority of theses patients had malignancy as a cause of the effusion. Only 14% of our patients had transudative effusions, which was relatively low compared to the incidence reported in other studies[2,9]. Transudative effusions were most frequently due to congestive cardiac failure and frequently responded to anti-failure therapy. Therefore, some of these patients were not referred to respiratory team and not included in the study.

Cytological examination of pleural fluid specimens is the most specific method for identifying malignant effusions but has a sensitivity of only 56% to 75%[3,10-13]. A previous study has shown that one sample of pleural fluid cytology has a sensitivity of 48.5% in identifying a malignant effusion and this may increase to 56.3% when diagnostic thoracocentesis is repeated two or three times[12]. In our study, the sensitivity of repeating pleural fluid cytology was 47.4%. Pleural biopsy in this study had a diagnostic yield of 44% which is consistent with that of 43% to 57% reported in other studies[3,10-13]. In our study, not all patients with suspected malignancy had repeated pleural cytology and pleural biopsy. This was to reduce the risk of complication due to invasive tests, especially when histological diagnosis was confirmed by one of these investigations.

The converse is true for tuberculosis and tuberculous pleurisy and concurs with other studies[3,5,10]. Mycobacterial culture has a higher sensitivity than direct smear for AFB because direct examination requires bacilli concentration of 10,000/ml whereas the culture only requires the presence of ten to 100 organisms per ml. The sensitivity of pleural biopsy for diagnosing tuberculous pleural effusion is higher than these two tests[3,5,10]. We found pleural biopsy to have a sensitivity of 68.8% which is within the range of 50%-74% reported by others[3,5,10]. Two of our patients had no conclusive evidence and the diagnoses were based on clinical response to anti-tuberculuous drugs. Although pleural fluid polymer chain reaction (PCR)[14] and adenosine deaminase[8] may be helpful in situations when all the above investigations are negative, these tests are not widely available.

In our study, lymphocytic effusion occurs most commonly in tuberculous effusion. On the other hand, smaller proportions of parapneumonic effusion and empyema were lymphocytic. This may help us in differentiating tuberculous effusions from parapneumonic effusions in the patients who present with fever and pleural effusion. Differential white cell counts may not be useful in other causes of pleural effusions, for example, carcinoma of lung and transudative effusions. In contrast to the findings of Ong et al[13], we did not find any difference in the frequency of effusions which were lymphocyte-predominant in malignant and paramalignant effusions. In conclusion, we found that malignancy was the commonest cause of pleural effusion followed by tuberculosis and pneumonia in patients treated in a community teaching hospital in Malaysia. The number of undetermined causes could be minimised with a combination of readily-available and established investigations.

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