Determining the optimal number of specimens to obtain with needle biopsy of the pleura

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Abstract The aim of this study was to define the number of pleural biopsy samples necessary for optimum diagnostic performance and determine to what extent they are complementary. Eighty-four closed pleural biopsies were performed in our department between June 1996 and January 1998 on 55 males and 29 females with an average age of $64.4 \pm 16.7$ years. The study of the pleural fluid included: pH, biochemical testing of pleura/serum (proteins, lactate dehydrogenase, glucose, cholesterol, triglycerides, albumin and adenosine deaminase), haemogram, cytology and microbiological testing (Gram-staining, aerobes, anaerobes and mycobacteriae cultures). The biopsies were performed using a Cope needle, with a total of five biopsies for each patient: four for pathological examination (taken numerically in the order in which they were performed: D1, D2, D3 and D4) and one for microbiological testing. In those cases in which the diagnosis was uncertain or effusion persisted, a thoracoscopy or thoracotomy was performed. There were no significant differences in the diagnostic yield of each individual sample (D1, D2, D3 and D4), but there were differences in the sum of the samples, depending on the number of biopsies performed. This was true for total group and the group with carcinomas, but not for the group with tuberculosis. The increase in diagnostic yield with the number of biopsies was more remarkable in the carcinoma cases, where it increased by 35% when four biopsies were performed (54% with one biopsy versus 89% with four biopsies, $P<0.002$). In conclusion, the diagnostic yield increased with the number of biopsy samples in the total group and the group with tuberculosis, but not in the group with tuberculous effusions. The best diagnostic performance for malignant pathology was obtained with four samples. In pleural tuberculosis, the diagnostic yield did not increase with more biopsy samples. One high quality sample should be enough to obtain a diagnosis.

Keywords pleural biopsy; carcinoma; tuberculosis; diagnostic performance; pleural effusion.

INTRODUCTION

The diagnostic yields of pleural fluid analysis and pleural biopsy are complementary. In general, the biopsy is more useful than the fluid analysis with pleural tuberculosis (1), while the opposite is true with malignant pleural disease (2). With needle biopsy of the pleura, some authors have also stated that the increase in diagnostic yield is proportional to the number of pleural samples obtained (3). However, no systematic analysis has been performed to assess the diagnostic yield from the individual samples, to assess whether or not the yield from different samples is complementary, and to assess whether the optimum number of biopsies differs in tuberculous pleuritis and malignant pleural effusions.

The purpose of the present study was to systematically analyse the yield when obtaining one, two, three or four specimens with needle biopsy of the pleura. We hypothesized that the additional specimens would be more useful with pleural malignancy than with pleural tuberculosis because pleural involvement is more patchy with pleural malignancy.

MATERIAL AND METHODS

In this prospective study between June 1996 and January 1998, closed needle biopsy of the pleura was performed in 84 cases in the Pleural Unit of our department. During the same time period, 274 thoracentesis were performed. In all cases, a minimum of 10 ml of pleural fluid were recovered for analysis. Of the patients that underwent closed pleural biopsy, 55 (65%) were male and the average age of the patients was $64.4 \pm 16.7$ years.

The reasons for performing closed pleural biopsy were: suspected malignant pleural effusions, suspected granulomatous diseases (tuberculosis, connective disorders and others) and unexplained exudate. At our
facility, closed pleural biopsy is performed immediately, at the same time as the first diagnostic thoracentesis, when there is clinical suspicion of malignancy or tuberculous pleural effusion, given its low rate of complications and the speed with which a diagnosis can be obtained. When the diagnosis was uncertain after thoracentesis or closed pleural biopsy and the effusion persisted, we referred the patient for thoracoscopy and/or thoracotomy. The routine study of the pleural fluid includes: pH, biochemical testing of pleura/serum (proteins, LDH, glucose, cholesterol, triglycerides, albumin and ADA), haemogram, cytology and microbiological testing (Gram, Ziehl, aerobic and anaerobic cultures, and a mycobacterial culture).

The biopsies were performed using a Cope needle (4), with five pleural samples per patient: four for histological analyses numbered in the order in which they were taken (D1, D2, D3, D4) and one for microbiological analyses. The same needle was used for each patient and different areas of the pleura (12, 3, 6, 9 and 12 o’clock) were sampled. The diameter of the histological samples ranged from 1 to 3 mm. During the analyses, morphology and immunohistochemistry were evaluated to determine the type of malignancy and the Ziehl–Neelsen method was used for mycobacterial analyses. In all cases the pathologist read each slide independently without knowing the results of the other slides in the same patient.

Statistical comparisons of continuous data were done with the Mann–Whitney test and comparisons of categorical data were done with Fischer’s exact test. We accepted a $P < 0.05$ as statistically significant.

**RESULTS**

The final diagnoses in the 84 patients who underwent needle biopsy of the pleura were as follows: 35 pleural carcinoma (21 lung cancer, seven breast cancer, five unknown, one colon carcinoma, one melanoma) 16 tuberculosis and 33 other diagnosis [12 parapneumonic, nine paramalignant, four idiopathic, two congestive heart failure, one lymphoma, one chronic lymphoid leukaemia (LLC), one mesothelioma, one chylothorax, one traumatic and one rheumatoid arthritis] (Table 1). There were two pneumothoraces related to the procedure, but none of them required chest drainage. Five thoracoscopies were performed before a final diagnosis could be made.

For the 35 patients with carcinoma involving the pleura, the cytology was positive in 28 cases (80%) and the first biopsy sample (D1) was positive in 19 (54%). The yield of the cytology combined with the pleural biopsy was 91-4%. The histologic type more frequently found was adenocarcinoma 22/35 (62-8%).

For the 16 patients with tuberculous pleural effusions, the pleural fluid acid-fast bacilli (AFB) stain was positive in one (6-25%), while the pleural fluid culture was positive in five (31-2%). In the pleural tissues the AFB-stain was positive in six (37-5%) while culture was positive in nine (56-2%). Granulomas were present in D1 in 13 patients (81%). Fifteen patients (93-7%) had either positive smears of cultures or granulomas on D1. When the ADA levels in pleural fluid were analysed and a cut-off level of 40 IU was used to diagnose tuberculosis, 14 of the 16 patients (87%) with tuberculous pleuritis had a positive test. There were, however, two false-positives (3%); one patient had an empyema while the other had a lymphoma.

When the individual pleural biopsy samples were analysed, in the cases overall, each biopsy provided a definite diagnosis in about 40% (Table 2). The cases diagnosed with pleural biopsy included a lymphoma, a LLC, a mesothelioma and a rheumatoid arthritis. However, with each successive biopsy the yield increased when the results of the biopsies where combined and with all four biopsies considered together, the diagnostic yield was 58% (Tables 2 and 3). With malignancy, each of the biopsies was positive in about 55% of cases, and when all four biopsies were considered together, the diagnosis...
was established in 89%. Somewhat different results where obtained when the 16 patients with tuberculosis were considered. The diagnostic yield with each of the biopsies was more varied, ranging from 43 to 81%. Biopsies D2, D3 and D4 added very little to biopsy D1 (only one additional patient was diagnosed), but this was due in large part to the high diagnostic yield with D1.

Table 4 shows the statistical significance of the increase in diagnostic yield with the number of pleural biopsy samples. Statistical significance is obtained in the diagnostic yield with increasing number of samples in the group overall and in the group with carcinoma, but not in the group with tuberculous pleurisy.

### DISCUSSION

It is often difficult to establish the cause of a pleural effusion. Closed pleural biopsy using a needle is a simple procedure with a low morbidity and mortality rate. In most cases, it is possible to obtain an adequate pleural sample for testing. The pleural biopsy is complementary to study of the pleural fluid in establishing a diagnosis (5), particularly when effusion is caused by tuberculosis (6). In addition, the chances of obtaining a diagnosis are increased when the biopsy is repeated (7,8). In addition to standard pathology the sample of parietal pleura may be tested by other methods such as microbiology and immunohistochemistry which increase its diagnostic yield (79).

Closed pleural biopsy has proven useful in pleural tuberculosis, with a diagnostic yield of 60–95%. In cases involving malignant pleural effusion, it ranges from 5 to 7% for mesotheliomas and 40 to 87% for other neoplasias (10–12). When a patient has a malignant pleural effusion, cytology in general is more useful than needle biopsy of the pleura. This is illustrated in the study of Prakash and Reiman (2), who studied 281 patients with malignant disease and reported that the cytology was positive in 58% while the pleural biopsy was positive in 43%. The pleural biopsy was positive in only 20 of the 119 patients with malignant disease and non-diagnostic cytology and thereby increased the overall yield by 7%. It should be noted that the yield with cytology depends on the histologic type. The yield is higher for adenocarcinomas (60%), than it is with small cell carcinoma (19%), or squamous cell carcinoma (6%) (13). The diagnostic yield with the combination of cytology and pleural biopsy in the present study (9%) is comparable to that reported by Bueno et al. (9) (79), Prakash and Remain (2) (65%) and Salyer et al. (14) (90%).

The false-negative results obtained in patients with malignant pleural effusions are usually due to the fact that the samples were taken from areas is not involved by the tumour (13,15) or that there are other explanations for the pleural effusion such as lymphatic obstructions, obstructive pneumonia, hypoproteinemia, respiratory infections or heart failure. Computer tomography (CT) scan-guided biopsies can increase the diagnostic yield in pleural malignancy if nodules are present (16). After a thoracentesis and a pleural biopsy no diagnosis is found in 10–25% of patients with malignant pleural effusions. A second thoracentesis and pleural biopsy can be performed when no diagnosis is obtained with the first one and there are reasons to suspect neoplasia and tuberculosis (9). If the effusion persists and no definite diagnosis can be achieved, diagnostic thoracoscopy should be performed (17).

On the other hand, as far as pleural tuberculosis is concerned, many authors stress the high sensitivity of the pleural biopsy for diagnosis (3,15,18,19) and the added effect of the culture (20). With both procedures, a global sensitivity of up to 87% is obtained (3) [60% for the culture, 80% for the biopsy and 87% for both; 94% in our experience (21)]. Recently, much interest has been focused on adenosine deaminase (ADA) for the diagnosis of pleural tuberculosis (22). Tuberculous pleural fluid contains higher levels of ADA than do most other exudates (6,23), but elevated pleural fluid ADA levels do occur with most empyemas (23), rheumatoid pleurisy (24), some lymphomas (23) and rarely with non-lymphoma malignancies (23). ADA has been recently separated into ADA1 and ADA2. Patients with tuberculous pleurisy had predominantly ADA2 and the determination of ADA iso-enzymes could overcome the problem of false-positive cases (21).

Even after extensive diagnostic work-up of the pleural fluid the aetiology of a number of pleural effusions remains undetermined (25). In these cases, some authors stress the yield of diagnostic thoracoscopy, particularly when pleural malignancy is suspected (26). In view of our results, thoracoscopy is not necessary for the
diagnosis of most malignant pleural effusions (91% of diagnostic yield with cytology and pleural biopsy). In any case, in centres with a lower prevalence of adenocarcinomas, it can be justified in cases of suspected malignant pleural effusions. Our studies also suggest that there is a very limited role for thoracoscopy in patients with a suspected tuberculous pleural effusion. The diagnostic yield of pleural fluid studies and pleural biopsy was 96-2% in a recent paper (21) and the use of ADA, and specially ADAI/ADAp has shown an accuracy of 91-2% and 99-02% respectively (21).

The goal of this paper was to determine the number of biopsy samples for optimum yield according to the type of pleural pathology. In pleural tuberculosis, 81% of the diagnoses could be obtained with a single good sample due to the disseminated nature of the disease, which affects different areas more or less homogeneously. We could not find any significant improvement in the diagnostic yield by taking four specimens instead of one. On the other hand, in malignant pleural pathology, a single biopsy sample only provides a diagnosis 54% of the time. When four samples were taken, diagnoses were obtained 89% of the time because the involvement of the pleura is not homogeneous, and the results depend on where the biopsy sample is taken (13).

One could argue that malignant pleural effusions are often mistaken for pleural tuberculosis and that one should always take at least four pleural biopsies. In a recent paper from our own group we found that only five patients out of 278 with pleural malignancies were suspected as having pleural tuberculosis (1-79%) before thoracentesis was performed (27).

In conclusion, a single good biopsy sample is generally sufficient when the suspected cause of the pleural effusion is tuberculosis, but four samples should be obtained when the suspected cause is malignant or unknown.

REFERENCES