Closed pleural needle biopsy: predicting diagnostic yield by examining pleural fluid parameters

S. NUSAIR*, R. BREUER*, G. AMIR†, AND N. BERKMAN*

*Institute of Pulmonology and †The Department of Pathology, The Hadassah University Hospital and Hebrew University-Hadassah School of Medicine, Jerusalem, Israel

**Abstract**

Objective: Pleural fluid parameters that predict a diagnostic closed pleural needle biopsy were investigated.

Design: A retrospective analysis.

Setting: The Institute of Pulmonology, Hadassah University Hospital.

Patients and methods: Forty-four patients who underwent closed pleural needle biopsies were included in this study. Pleural fluid values of protein, glucose, lactate dehydrogenase (LDH), pH, and white blood cell count with differential cell counts, from patients with diagnostic and non-diagnostic pleural biopsies were compared.

Results: Thirteen patients (29%) had diagnostic biopsies. Malignancy was identified in 10 patients (23%), of whom 70% had adenocarcinoma. Three other patients had non-malignant specific diagnosis. LDH levels in pleural fluid from patients with diagnostic pleural biopsy were higher than in patients with non-diagnostic pleural biopsies (1436 ± 333 UI⁻¹ vs. 775 ± 109 UI⁻¹; P < 0.05). LDH levels less than 510 UI⁻¹ were highly predictive of a negative biopsy (negative predictive value of 86.6%). Follow up revealed malignancy including mesothelioma and lymphoma, in 10 of 30 (33%) patients with non-diagnostic biopsies, and one patient died of unrelated cause, while the pleural effusion either resolved, remained stable or an alternative benign process was identified in 19 patients (63%).

Conclusions: Low levels of LDH (< 510 UI⁻¹) were highly predictive of a negative pleural needle biopsy. Thus, LDH may serve as a useful guide in deciding whether to perform closed pleural biopsy or to proceed to thoracoscopically guided biopsy.

Available online at http://www.sciencedirect.com

Keywords pleural needle biopsy; exudative pleural effusion; adenocarcinoma; tuberculosis; lactate dehydrogenase.

INTRODUCTION

In adults with a newly detected exudative pleural effusion and no evidence of an acute infectious process (parapneumonic effusion), exclusion of malignancy or tuberculous pleurisy becomes a priority, especially, if there is lymphocyte predominance in the pleural fluid (1). If initial cytologic and microbiologic studies of the pleural fluid are not diagnostic, a pleural biopsy should be performed.

Closed pleural needle biopsy is a simple bedside procedure which can be performed on an ambulatory basis, has a high diagnostic yield for the detection of malignancy and tuberculosis, and has a low rate of complications in experienced hands. Thoracoscopy and the recently developed video-assisted thoracoscopic surgery are attractive alternative diagnostic methods that are minimally invasive with high diagnostic yield. Open surgical procedures such as thoracotomy with pleural biopsy has the highest diagnostic yield. The advent of minimally invasive thoracoscopy has led us to review our experience with closed pleural biopsy, in an attempt to identify pleural fluid parameters that may predict a diagnostic closed pleural biopsy, thereby allowing better selection of which patients should proceed directly to thoracoscopy-guided pleural biopsy.

METHODS

We performed a retrospective analysis of the medical charts of 44 adult patients, who underwent closed pleural needle biopsies at the Hadassah University hospital, during the time period from May 1993 until May 2000. In our institution, closed pleural biopsy is performed in patients with an exudative pleural effusion with no accompanying pleural or subpleural thickening or mass that can be sampled using imaging-guided needle biopsy (ultrasonography or computerized tomography), and in
whom at least one pleural fluid cytological examination is negative.

Pleural fluid from all patients was examined for pH, glucose, total protein, and lactate dehydrogenase (LDH) levels. White blood cell counts with differential counts were determined using an automated coulter. Cytologic examination of the fluid was performed on centrifuged concentrate using Papanicolaou stain. Fluid samples were routinely stained by Gram and Ziehl−Neelsen stains and sent for bacterial, fungal and mycobacterial cultures. The pleural fluid was classified as an exudate according to Light's criteria requiring one of the following: (1) fluid protein/blood protein ratio > 0.5; (2) fluid LDH/blood LDH ratio > 0.6; (3) fluid LDH greater than 2/3 of the maximal normal serum LDH levels (normal range is 300−620 U l−1 in our institution).

Pleural biopsies were obtained at the bedside using Abrams needle using standard technique (2). A pleural biopsy is considered adequate if at least three specimens containing pleural tissue were obtained.

Specimenswere processed and sectioned at 5 μm, and stained routinelywith hematoxylin and eosin; and when appropriate, Ziehl−Neelsen or special immunohistochemical stains. Pleural tissue was also submitted for mycobacteria and fungal cultures.

In cases where the pleural biopsy revealed only mesothelial tissue with varying degrees of acute and chronic inflammation, the biopsy was interpreted as non-specific pleuritis. Outcome of patients with such non-diagnostic pleural biopsies was determined by reviewing their medical records, and contacting patients and their physicians. When there was no specific diagnosis (malignancy or tuberculosis), an attempt was made to establish whether the pleural effusion had changed or resolved over time.

Statistical evaluation was performed using unpaired t-test to compare between groups, and a two-tailed P value < 0.05 was considered statistically significant.

RESULTS

Forty-four adult patients (average age 65 years, range 24−88 years) who underwent closed pleural needle biopsy were identified. All patients had adequate specimens. All patients had exudative pleural effusion according to Light’s criteria. The pleural effusion occupied at least 25% of the ipsilateral pleural space as estimated on posteroanterior chest X-ray film, and no accompanying pleural masses were identified. All patients had at least one previous negative cytologic examination of the pleural fluid, 31% had two negative examinations and 10% had three or more negative cytologic examinations.

Of 44 patients, closed pleural biopsy yielded a diagnosis in 29% (13/44) cases. Of these, a malignancy was detected in 10 patients (23%) (Fig. 1). In one patient, biopsy revealed the presence of tuberculous pleurisy, with a
caseating granuloma and positive culture. One patient had sarcoidosis and another extramedullary hematopoiesis. Thirty-one patients (71%) had findings of acute or chronic pleuritis with variable degrees of mesothelial atypia, and thus were classified as non-specific pleuritis.

Of the patients in whom a malignancy was identified on pleural biopsy, 70% (7/10) had adenocarcinoma. Two patients had metastatic malignant pleural effusion (breast carcinoma, papillary carcinoma of thyroid). One patient had bronchogenic squamous cell carcinoma, and the other poorly differentiated non-small cell carcinoma.

The major purpose of this study was to determine whether pleural effusion parameters predict a positive diagnostic yield from a closed pleural needle biopsy. Biochemical and cellular values in the pleural fluid of patients with diagnostic and non-diagnostic pleural biopsies are presented in Table 1. Although glucose and pH values were lower in the pleural fluid from patients with a diagnostic pleural needle biopsy, and protein and LDH levels were higher, only raised LDH values (1436 ± 333 U l−1 vs 775 ± 109 U l−1; P < 0.05) significantly predicted a diagnostic pleural biopsy (Table 1). Individual values of pleural fluid LDH available from 40 patients are presented in Fig. 2. Using absolute cutoff value of 510 U l−1, LDH values greater than 510 were found in 11 out of 13 cases with diagnostic biopsies. This cutoff value gives a sensitivity of 84.6%, specificity of 48.1%, positive predictive value of 44%, and a negative predictive value of 86.6% (Table 2).

Notably, there was no significant difference in the percentage of lymphocytes in the pleural fluid from patients with diagnostic pleural biopsies, compared to fluid obtained from patients with non-diagnostic biopsies.

Complications of pleural biopsy included vasovagal syncpoe (2 patients), and subcutaneous hematoma (1 patient). There were no cases of pneumothorax or hemothorax as a result of the procedure.
Clinical follow-up could be obtained in all but one of 31 patients with non-diagnostic closed pleural biopsy, with a median follow-up interval after biopsy of 39 months (range from 2 to 87 months). A malignancy was eventually diagnosed in 10/30 (33%) of these patients (Fig. 3). Two patients had mesothelioma diagnosed by thoracoscopy, and two patients had lymphoma. In one patient, lymphoma was diagnosed based on findings in axillary lymph node biopsy, and in the other recurrence of lymphoma was detected by a transbronchial biopsy from an accompanying pulmonary infiltrate. The other six patients had carcinoma, primary or secondary.

In 19 patients (63%) with an negative pleural biopsy, the pleural effusion either resolved, stayed stable or an alternative benign process (hypothyroidism and idiopathic eosinophilic pleuritis) was identified. One further patient died of non-related causes. From these data, we conclude that closed pleural biopsy has an overall diagnostic sensitivity for malignancy of 50% (62.5% for adenocarcinoma), and a specificity of 100%.

**DISCUSSION**

Patients with a diagnostic pleural biopsy had lower glucose levels and pH, and higher LDH and protein levels as compared with patients with non-diagnostic biopsies. However, only LDH levels were significantly different between the two groups. In patients with an LDH of less than 510 U l\(^{-1}\), a closed pleural biopsy is highly unlikely to
be diagnostic (negative predictive value of 86.6%). LDH levels greater than 510 U l^{-1} predict a positive diagnostic pleural needle biopsy in 44% of cases.

Pleural biopsy is recommended for patients with an undiagnosed exudative pleural effusion, especially if there is lymphocytic predominance in the pleural fluid (I). Although thoracoscopy-guided biopsy has a high diagnostic yield for both benign and malignant disease (95% for malignancy and 99% for TB) (3,4), in most patients, blind closed pleural needle biopsy remains a valid initial diagnostic option.

Pleural needle biopsy yielded a specific diagnosis in 29% of our patients. Previous studies show that pleural needle biopsy yields a specific diagnosis in one-third to one-half of patients, with about 80% of the diagnostic biopsies demonstrating malignancy, while tuberculosis is the second most common finding (5,6).

In our study, the diagnostic yield of pleural needle biopsy for detection of malignancy was 23%. This is somewhat lower than the yield found in most reports which ranges from 27–56% (7–9). Previous studies have shown a relatively higher yield for the detection of malignant cells within the pleural fluid than from pleural biopsy from patients with malignant pleural effusion (7,10). However, the combined diagnostic yield of pleural fluid cytology and pleural biopsy was the highest (58% for fluid examination, 43% for pleural needle biopsy and 64% for both procedures combined) (10).

In most of our patients who had a malignant pleural effusion, the underlying histology was adenocarcinoma, similar to previous reports (5,10). Other malignant processes that may involve the pleura such as mesothelioma and lymphoma are difficult to diagnose by histologic examination of closed needle biopsy material, and pleuroscopy or thoracoscopy may be preferred when these conditions are suspected.

The combination of pleural fluid and pleural biopsy examination with culture of specimens from these two procedures, is considered a highly sensitive diagnostic method for the detection of tuberculous pleural effusion (II). Only one patient in our series, had a pleural biopsy positive for TB, with no false negative biopsies. This probably reflects the low incidence of TB in our geographic area.

The major purpose of this study was to determine whether pleural fluid parameters could predict a diagnostic pleural needle biopsy. Glucose levels and pH of the pleural fluid are known to be lower in patients with a malignant effusion in whom there is a large metabolic burden of tumor cells. Although patients with a diagnostic pleural biopsy tended to have higher LDH and protein levels and lower glucose levels and pH as compared with patients with non-diagnostic biopsies, only LDH levels were significantly different between the two groups. All but two patients with a positive biopsy had an LDH value of greater than 510 U l^{-1} (Fig. 2). The sensitivity and the specificity for this LDH cutoff value were 84.6 and 48.1%, respectively. The practical value of LDH measurement in predicting outcome of biopsies lies in the high negative predictive value of this test (86.6%); thus, in patients with an LDH of less than 510 U l^{-1}, a closed pleural biopsy is highly unlikely to be diagnostic. LDH levels greater than 510 U l^{-1} predict a positive diagnostic pleural needle biopsy in 44% of cases. This value is significantly higher than the percentage of total positive biopsies (29%) in our patients. An LDH level greater than 510 U l^{-1} in undiagnosed exudative pleural effusion is more predictive of a positive closed biopsy than is the presence of lymphocyte predominance. On the other hand, LDH levels lower than 510 U l^{-1} suggest that pleural needle biopsy is less likely to yield a diagnosis, and one should proceed directly to thorascopically guided biopsy, whenever a malignancy is strongly suspected.

Our findings are consistent with previously described studies in which higher LDH levels predicted greater activity of pleural disease, such as greater residual pleural thickening after pleural TB (12), and more prominent pleural thickening on chest CT as a result of infectious or malignant processes (13). In the study of Harris et al., patients who underwent pleuroscopic pleural biopsy had a positive diagnostic yield that correlated with higher preoperative LDH levels in the pleural fluid (14). From our data, we also conclude that lymphocytosis in the pleural fluid was not helpful in predicting a diagnostic pleural biopsy.

Follow up of our patients with non-diagnostic biopsies extending over a median interval of 39 months (range 2–87 months) revealed that only 33% of these patients were eventually found to have a malignant process. Therefore, after excluding three patients in whom follow up could not be obtained, the sensitivity of closed pleural biopsy for diagnosing malignancy using Abrams needle was 50% (62.5% for adenocarcinoma) in our series, with a specificity of 100%, and a negative predictive value of 67.7%.

The outcome of patients with non-specific pleuritis was generally favorable with low morbidity and mortality, similar to previously published data (6,15). In patients who were initially diagnosed as non-specific pleuritis, malignancy was eventually found in 20–30%, and another 5% of the patients had TB. Sixty to 80% of the patients had a benign clinical course with gradual resolution of the fluid or the finding of an alternative non-malignant process.

**CONCLUSIONS**

In the presence of undiagnosed pleural effusion, closed needle pleural biopsy is diagnostic in one-third of patients, in whom most cases are malignancy, and specifically adenocarcinoma. Thirty percent of negative pleural biopsies will later prove to be malignancy related;
however, most of the patients with negative closed needle pleural biopsy will have a favorable outcome. Our data show that pleural fluid LDH less than 510 U/L is highly predictive of a negative closed pleural biopsy. In contrast, pleural fluid LDH greater than 510 U/L may be a better predictor of positive yield of closed pleural biopsy, than the currently used criteria.

REFERENCES