Immediate assessment of fine needle aspiration cytology of lung

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Abstract

Aims—To assess the value of immediate assessment of cytology in percutaneous fine needle aspiration (FNA) cytology of lung.

Methods—FNA specimens from 75 consecutive patients with suspected pulmonary neoplasms were subjected to immediate cytology assessment. Direct smears were prepared in the radiology department and stained using the Diff Quik method. The cellular content was assessed and, if possible, a provisional diagnosis offered. A second FNA was requested if the initial aspirate seemed of doubtful adequacy. The diagnostic accuracy was examined by review of clinical and radiological data in all patients, and by correlation with other histological or cytological material in 25 patients. Complications of the procedure were identified during the clinical review.

Results—Two of 75 specimens were inadequate for diagnosis. Satisfactory diagnostic material was obtained in 51 patients on a single aspirate and following a second FNA in 22 patients. Of the 73 satisfactory aspirates, 58 were malignant, one highly suspicious of malignancy and 14 reported as negative for malignancy. All malignant diagnoses were confirmed on clinical or pathological review. FNA accurately distinguished primary small cell and large cell carcinomas in those patients with pathological follow up. There were two false negative reports, one due to sampling error and the other due to misinterpretation of aspirate material. The diagnostic specificity was 100% and sensitivity 96.6%. Complications were recorded in seven (9.3%) patients, five of whom developed pneumothorax; a chest drain was required in one patient.

Conclusions—Percutaneous FNA cytology provides safe and accurate diagnosis in the investigation of pulmonary lesions. Immediate cytology assessment ensures that aspirate material is handled optimally, and those patients requiring further sampling or ancillary investigation identified rapidly. The number of unsatisfactory and false negative lung FNA are therefore reduced. The complication rate is minimised by decreasing the number of pleural punctures.

(J Clin Pathol 1996;49:839-843)

Fine needle aspiration (FNA) cytology offers safe, rapid and accurate diagnosis in patients with pulmonary mass lesions.¹⁻⁴ Numerous reports have shown that aspiration cytology is highly reliable, particularly in the diagnosis of lung carcinoma. A review of thoracic FNA by Sterrett *et al*⁵ revealed a specificity of 100% for a malignant diagnosis in many studies. A recent multicentre analysis by the College of American Pathologists, in which lung FNA was correlated with histology, also showed an overall positive predictive value of 99%.⁶ However, a negative result is generally less reliable and most reports document a false negative rate of 10-20% for lung aspiration cytology. The major contributing factor to the lower sensitivity of the technique has been failure to obtain diagnostic material.⁷ In addition, a variable number of aspirates are considered inadequate or unsatisfactory for evaluation.

Some studies have suggested that immediate cytology assessment of FNA specimens is of value in minimising the number of false negative and unsatisfactory specimens.⁸⁻¹² Smears from the aspirate are stained rapidly and examined in the radiology department by a cytopathologist, permitting assessment of cell yield and content. Repeat FNA can be advised if the initial aspirate seems inadequate or unrepresentative. This approach seems to be advantageous in that diagnostic material is handled optimally and immediate clinical and radiological correlation is possible, but it has not been advocated by all authors.^{13 14} We introduced a rapid cytology assessment protocol with lung FNA in 1994 and herein report 75 consecutive aspirates with immediate cytology assessment performed in our hospital between January 1994 and December 1995.

Methods

Consecutive lung FNA (n = 75) with immediate cytology assessment performed in Glasgow Royal Infirmary between January 1994 and December 1995 were studied. All patients had one or more discrete lung masses on radiological examination and the major clinical suspicion in all patients was of neoplastic disease.

The aspirates were performed using 21G needles attached to 20 ml syringes with fluoroscopic control for needle guidance in most cases; computed tomography and ultrasound were used occasionally. Following needle placement the aspirate was obtained by agitating the needle tip within the lesion, and four to eight direct smears were made immediately from the sample in the scanning room. The needle was rinsed thereafter in sterile normal saline. Two or more direct smears were stained

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Accepted for publication
16 July 1996

Keywords: fine needle aspiration, cytology, immediate assessment.

Table 1 Correlation of lung FNA with final clinical diagnosis

Lung FNA	Clinicopathological diagnosis	
	Malignant	Benign
Malignant (n = 58)	58	0
Suspicious (n = 1)	1	0
Benign (n = 14)	2	12

by the Diff Quik method for rapid assessment and the remaining slides dried in air and fixed in alcohol for routine May-Grünwald-Giemsa and Papanicolaou staining, respectively. If the first aspirate was considered of doubtful adequacy a second FNA was requested. No patient had more than two aspirates taken.

The needle rinses were not processed routinely. However, histochemical stains were performed on cytospin preparations in 21 patients, most commonly for demonstration of mucins in poorly differentiated large cell carcinomas. Immunocytochemistry was performed in five FNA, to confirm the epithelial nature of the tumour in three patients, to demonstrate endocrine differentiation in an atypical carcinoid tumour, and to confirm the mesenchymal nature of a benign spindle cell tumour. The needle rinse sample was submitted for microbiology in patients showing an inflammatory or reactive pattern on rapid assessment.

The major indication for immediate cytology assessment was to assess the adequacy of the specimen. However, a provisional diagnosis was also made whenever possible based on the rapidly stained smears.

CLINICAL AND PATHOLOGICAL CORRELATION

The accuracy of the lung FNA diagnoses was assessed in all patients by clinical follow up and by histological/cytological correlation with further specimens when these were available.

Hospital case records were reviewed in 69 patients and clinical information provided by referring physicians or general practitioners in six. A malignant diagnosis was confirmed by the patients' clinical course, the documentation of metastases and/or by progression of the radiological lesion.

A histological diagnosis was obtained subsequently in 19 patients, 15 of which were malignant and four benign. These included 10 lobectomy or pneumonectomy specimens, one necropsy and eight biopsy specimens. One

patient with multiple lung metastases had a history of biopsy confirmed transitional cell carcinoma of bladder. An independent cytological diagnosis was obtained in an additional five patients, four of whom had lung FNA diagnosis of small cell carcinoma and one an adenocarcinoma. These included FNA of cervical lymph node metastases in two patients and sputum, pleural fluid and cerebrospinal fluid cytology in one patient each.

Case records were also examined with reference to any complications of the FNA procedure.

The diagnostic specificity and sensitivity were calculated by standard methods.¹⁵

Results

Two aspirates were considered unsatisfactory. In both patients the pulmonary lesions were centrally located and a small pneumothorax noted after the first FNA. Therefore, second aspirates were not performed.

Seventy three FNA were satisfactory for examination. A single aspirate was adequate in 51 patients and a second aspirate requested in 22 patients. The results of lung FNA and the final clinicopathological diagnoses for the 73 satisfactory patients are summarised in table 1.

An unequivocal malignant diagnosis was made in 58 aspirates, all of which were confirmed on subsequent clinical or pathological review. Fifty seven patients were thought to have primary lung malignancy and one a metastatic transitional cell carcinoma of bladder. In one further patient the FNA was considered highly suggestive of large cell carcinoma but not completely conclusive as numerous inflammatory cells were also present. However, the cytology was considered sufficient for clinical management as the patient was not a candidate for radical treatment. This was a peripheral lesion which had shown slow growth over 20 months despite local radiotherapy and clinically was considered a low grade carcinoma.

Tumour subtyping in the 58 patients with malignancies was as follows: small cell carcinoma in seven patients; large cell carcinoma, not otherwise specified (NOS) in 25 patients; squamous carcinoma in 11 patients; adenocarcinoma in 12 patients; atypical carcinoid, metastatic transitional cell carcinoma and carcinoma NOS in one patient each.

Independent pathological material was available for correlation in 20 of the 55 primary malignant tumours (table 2). FNA distinguished accurately the clinically important subgroups of small cell carcinoma and large cell carcinoma in all patients. The more specific diagnoses of squamous carcinoma or adenocarcinoma were also confirmed in the 10 patients in which this distinction was possible on the aspirate. However, four of the six tumours regarded as large cell carcinoma NOS on FNA showed squamous or glandular differentiation in subsequent surgical resection specimens.

Fourteen aspirates were considered satisfactory for evaluation but with no evidence of malignancy. A benign clinical course confirmed the FNA assessment in 12 patients,

Table 2 Correlation with tumour subtyping in 20/55 primary lung carcinomas

FNA (number correlated/total)	Histological/cytological correlation			
	Small cell carcinoma	Large cell NOS carcinoma	Squamous cell carcinoma	Adenocarcinoma
Small cell carcinoma (4/7)	4*	—	—	—
Large cell NOS carcinoma (6/25)	—	2	2	2
Squamous cell carcinoma (6/11)	—	—	6	—
Adenocarcinoma (4/12)	—	—	—	4

*All confirmed on subsequent cytology specimens.

J Clin Pathol: first published as 10.1136/jcp.49.10.839 on 1 October 1996. Downloaded from <http://jcp.bmj.com/> on April 26, 2023 by guest. Protected by copyright.

Figure 1 Three dimensional cluster of slightly crowded but cytologically uniform cells from a bronchioalveolar carcinoma.

Figure 2 Well differentiated adenocarcinoma showing bronchioalveolar pattern of spread.

most of whom were subsequently thought to have had resolving pneumonic consolidation. Transbronchial lung biopsy was performed in two of these patients and showed an inflammatory process in both. Necropsy confirmed the FNA diagnosis of lung abscess in another patient. A specific benign diagnosis was made in only one FNA, this being a circumscribed peripheral lesion that was reported as a benign mesenchymal tumour and subsequently shown to be Schwannoma on excision biopsy.

There were two false negative FNA reports. The first was a 41 year woman with a history of respiratory insufficiency and patchy left upper lobe consolidation. The aspirate was mainly comprised of reactive epithelium and histiocytes but included a few crowded epithelial groups exhibiting papillary-like architecture. These groups showed orderly nuclear distribution, minimal cytological atypia and a low columnar border in areas (fig 1). No specific diagnosis was made on the aspirate material. Resection showed an adenocarcinoma of variable grade but with well differentiated foci

comprised of tall mucin secreting cells exhibiting a bronchioalveolar pattern of spread (fig 2). The second false negative FNA involved a left lower lobe lesion in a 56 year old woman with previously diagnosed squamous carcinoma of right bronchus. The aspirate mainly comprised reactive epithelium and haemosiderin laden histiocytes and the possibility of pulmonary haemorrhage or infarct was raised. The lesion persisted and subsequent lung and lymph node biopsy specimens showed a large B cell lymphoma. Review of the aspirate material showed occasional lymphoid cells but even in retrospect these seemed insufficient to suggest a diagnosis of lymphoma.

Complications were described in seven (9.3%) patients. One patient complained of severe pain following the procedure which settled with analgesia and another developed haemoptysis. There were five cases of pneumothorax, one of which was also associated with haemoptysis. A temporary chest drain was required in only one patient, who made a full recovery. No other complications were recorded.

Discussion

The role of immediate cytology assessment in radiologically directed FNA specimens has been the subject of controversy. Although this approach has been documented for many years it is not universally accepted. Disadvantages include the requirement for an experienced cytopathologist in, or close to, the radiology department and the increased time for the biopsy procedure due to staining and examination of smears.¹³ In addition, some reports have not documented improvements in diagnostic accuracy or a lowered complication rate when immediate cytology assessment is performed.^{13 14} However, other studies had shown a reduction in the number of inadequate specimens, an increased sensitivity for a malignant diagnosis and/or a decrease in the incidence of pneumothorax with rapid cytology examination of lung FNA specimens.^{8-12 16} Gasparini *et al* suggested recently that immediate cytology assessment offers both improvements in diagnosis and time and cost savings in the investigation of lung lesions.¹⁷

It is difficult to identify the unsatisfactory rate of lung FNA in some studies as inadequate aspirates have been excluded from analysis, not specifically documented or combined with negative reports. The importance of separating non-diagnostic from negative but adequate specimens had been emphasised by Zakowski *et al*.¹⁸ Crosby *et al*¹⁹ found that 16% of specimens were inadequate for evaluation, while Alonso *et al*²⁰ reported that 60/344 aspirates were unsatisfactory, reducing the sensitivity of lung FNA in their series from 93% to 71% when these patients were taken into account. A large series of thoracic aspirates from the Toronto General Hospital⁴ and a recent multi-centre analysis from US laboratories of more than 13 000 FNA⁶ recorded unsatisfactory rates of 6% and 9%, respectively. In this study only two (2.7%) of 75 FNA were unsatisfactory, the procedure in both patients being lim-

ited to a single aspirate because of pneumothorax. Like others⁸⁻¹⁰ we feel that immediate cytology assessment minimises unsatisfactory procedures by identifying those patients requiring further sampling.

The diagnosis of malignancy was confirmed in all our patients by clinical or pathological follow up, illustrating the well documented specificity of lung FNA cytology.^{7 19 21 22} Of more interest was the relatively high sensitivity of FNA in our study (96.6%) with only two false negative reports in 59 patients with malignancies. This compares with sensitivity rates of 78–94% in other recent studies of lung FNA^{7 17 22-25} and a range in sensitivity of 75–96% in a review of thoracic biopsy specimens by Sterrett *et al.*⁵ However, those studies in the latter review using a fine needle technique (needle smaller than 20G) generally reported a sensitivity of less than 90%. The factor which limits the sensitivity of lung FNA is sampling error in most patients, misinterpretation of the cytology material being relatively uncommon.^{3 4 18 26 27} Inadequate sampling was solely responsible for the 10% false negative rate reported in lung FNA by Cagle *et al.*⁷ Similarly, 11 of the 13 false negative reports in the series of Caya *et al* resulted from unrepresentative aspirates.²⁸ Zakowski *et al*¹⁸ found that FNA had a negative predictive value of 53%, the largest contributing factor being false negative specimens due to sampling error. False negative aspirates may include only normal or reactive elements but necrotic material is an additional source of error.^{15 27 29}

While the problem of sampling error cannot be entirely eliminated in lung FNA, we feel the risk is reduced by rapid cytology assessment. As with unsatisfactory specimens, a second aspirate is obtained if the initial FNA seems unrepresentative. Conces *et al*¹⁰ reported only two false negative FNA in 61 benign specimens using an immediate cytology assessment protocol similar, in most respects, to that in the present study. We agree with Weisbrod² that the close radiological correlation offered by immediate cytology assessment is of great value in the interpretation of lung aspiration cytology material, particularly in the context of an apparently ‘negative’ sample. In addition, should the initial aspirate show only degenerative or necrotic material, the radiologist can be guided to a more peripheral area of the lesion for further sampling. In this study a second FNA was requested in 22 patients, all of which finally included diagnostic material. There was only one false negative report due to sampling error, that of a malignant lymphoma. The aspirate in this patient was cellular but was considered suggestive of pulmonary haemorrhage or infarct. The other false negative report, in a patient with an adenocarcinoma with focal bronchioalveolar pattern, was principally an interpretative error as review showed that tumour cells were present in the smears. Bronchioalveolar carcinoma may present diagnostic difficulties in a variety of cytological specimens but the appearances of these tumours in lung FNA have been described in detail.^{30 31}

As occasional false negative results are inevi-

table, a benign lung FNA report must be interpreted with caution and further sampling advised when clinical and radiological suspicion of malignancy persist.³² Nevertheless, a negative report is often of value in permitting initial conservative management, and it may be possible to make a specific inflammatory or infective diagnosis on the cytology material.^{33 34} FNA therefore reduces the requirement for further investigation, including surgery, in some patients with benign disease. In addition, the need for diagnostic thoracotomy in cases of small cell carcinoma, which are usually treated with chemotherapy, inoperable primary large cell malignancies and metastatic tumours is minimised.^{4 22} Tao *et al*⁴ commented that surgery became unnecessary in approximately 35% of patients following the use of transthoracic and abdominal FNA, with resultant savings in mortality, morbidity and resources. Twelve of the 14 benign reports in this study proved to be accurate, a negative predictive value of 86%, and only one of these patients subsequently underwent surgery (to remove a Schwannoma). Rapid cytological assessment was also of value in selecting those cases in which microbiology was indicated as material from inflammatory lesions was submitted for culture.

FNA has been shown to be a safe technique. Nevertheless, as with any invasive procedure complications may arise. The most common complications are haemoptysis and pneumothorax, the latter occurring in 20–30% patients in most series although the range is wide.^{3 5} Only a minority of patients require chest drain insertion. Air embolism, needle tract implantation by tumour and death are extremely rare complications of lung biopsy and are generally associated with the use of large bore cutting needles (16–20G).^{2 5} The wide range in the reported complication rate of lung FNA can be partly explained by differences in patient selection and by the site of the lesions. However, the procedure is made safer by use of smaller needles (smaller than 20G) and by limiting the number of punctures.^{5 21 34} In our study satisfactory material was obtained in the initial FNA in approximately two thirds of patients, minimising the requirement for a further puncture. None of our patients underwent more than two punctures. Other authors have performed two aspirates routinely^{13 23} or up to three aspirates depending on visual inspection of the sample.^{21 32 34} De Gregoria *et al*²¹ noted a fall in the rate of pneumothorax from 23%, when three aspirates were performed routinely, to 13% when a single aspirate was used in most patients. We believe that restricting the procedure to a single aspirate in 51/73 diagnostic cases partly explains the low rate of pneumothorax of 6.7% in this study. Most lung FNA in our hospital are also performed by one experienced radiologist, an additional factor which reduces the risk of the procedure.

In conclusion, we have shown that FNA is a safe, accurate technique providing rapid diagnosis in patients with pulmonary mass lesions. In our view immediate cytology assessment provides optimum material for diagnosis,

minimises the number of inadequate specimens, ensures maximum specificity and sensitivity, and helps to limit the risk of complications.

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