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Audit of Transthoracic Fine Needle Aspiration of the Lung: Cytological Subclassification of Bronchogenic Carcinomas and Diagnosis of Tuberculosis

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ABSTRACT

Introduction: Transthoracic fine-needle aspiration cytology (FNAC) is a useful tool for evaluating neoplastic and inflammatory lung nodules. In view of the relative paucity of published audit studies regionally, such a study was undertaken to assess the use of the technique in our centre.

Methods: One hundred and fourteen FNACs were performed during 1997-1999. Immediate assessment for specimen adequacy was done. Diagnoses were correlated with clinical-pathological information and selective blind review performed.

Results: Cytologically, 65.8% of cases were malignant, 1.8% were atypical, 25.4% were inflammatory/non-malignant and 7% were inadequate. Cytological-histological tumour diagnostic concordance was 94.4%. Diagnostic sensitivity for malignancy: 93.4%, specificity: 95.8%, accuracy: 94%. Eight inadequate/benign cases (7%) proved to be malignant with clinical-pathological follow-up. Tuberculosis was confirmed (acid-fast bacilli detected) in six cases (5.3%) and suggested in a further 10 cases (8.8%). The cytological review showed 96% concordance with the original benign/malignant diagnoses. Pneumothorax rate was 18%.

Conclusion: FNAC is an accurate and safe method for the evaluation of lung nodules and it enables subclassification of bronchogenic carcinomas in the vast majority of cases. It is also useful for the diagnosis of tuberculous pulmonary nodules. Immediate assessment optimises specimen adequacy; inadequate/non-malignant smears in particular, need clinical correlation, close follow-up and re-biopsy, if necessary.

Keywords: transthoracic FNAC, follow-up, cytology

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INTRODUCTION

Fine-needle aspiration cytology (FNAC) is a well-established method of diagnosing both neoplastic and inflammatory conditions of the lungs[1]. Together with other cytological methods of diagnosis of lung diseases, it has resulted in a decrease in the performance of procedures that are more invasive in nature[2]. Transthoracic FNAC is regarded as the most effective of the cytological methods for diagnosing lung cancer, in particular peripherally-located lesions[3-6]. The concordance of FNAC classification of tumours with subsequent histological classification is as high as 70%-85%[6]. Notably, it demonstrates high accuracy in distinguishing between small cell lung carcinoma and non-small cell lung carcinoma, a clinically important differentiation.

Transthoracic FNACs is also useful for the diagnostic evaluation of lung nodules of infective aetiology, including tuberculosis, particularly when other non-invasive cytological methods (e.g. sputum cytology) fail to yield diagnostic material[7,8]. Chest infection by mycobacterium tuberculosis is known to have varied radiological manifestations, including the unusual presentation as a lung nodule or mass[9].

The quality of a lung FNAC service can be evaluated by the overall percentage of diagnoses, the review of routine cases as well as the correlation with histological and clinical follow-up[10-13]. In view of the relative paucity of published audit studies regionally, a retrospective audit study of the lung FNAC diagnoses in the Department of Pathology, National University of Singapore, National University Hospital between 1997 and 1999 was conducted. Our objective was to correlate our FNAC diagnoses with follow-up clinical-pathological data and to critically analyse and compare the data with published figures.

METHODS

A total of 114 transthoracic lung FNAC cases were carried out and diagnosed in our department between 1997 and 1999. There were 81 male patients and 32 female patients (one female patient underwent two separate lung FNACs). The age range was from 11 to 82 years (mean age of 60). Ninety-five patients were Chinese, nine were Malay, four were Indian and five were of other races.

Table I. General Results.

Diagnoses	Numbers (%)
Malignant	75 (65.8%)
Atypical	2 (1.8%)
Inflammation/necrosis	17 (14.9%)
Benign lesion	3 (2.6 %)
Negative	9 (7.9%)
Unsatisfactory	8 (7.0%)
Total	114 (100.0%)

Table II. Malignant Tumour Types.

Diagnoses	Numbers (%)
Adenocarcinoma	37 (49.4%)
Squamous cell carcinoma	12 (16.0%)
Small cell lung carcinoma	7 (9.4%)
Large cell lung carcinoma	2 (2.7%)
Carcinoma, NOS	6 (8.0%)
Carcinoma, anaplastic	1 (1.3%)
Carcinoma, metastatic	1 (1.3%)
Metastatic, others	3 (4.0%)
Metastatic adenocarcinoma	3 (4.0%)
Malignant neoplasm (melanoma favoured)	1 (1.3%)
Sarcoma	1 (1.3%)
Neoplasm, epithelial	1 (1.3%)
Total	75 (100.0%)

Table III. Correlation of lung FNA results with clinicopathological diagnosis.

Transthoracic FNAC diagnosis (n=100)	Clinical-Pathological Diagnosis Malignant	Benign
Malignant	71	1
Benign	5	23

sensitivity: 93.4%, specificity: 95.8%
positive predictive value (PPV): 98.6%,
negative predictive value (NPV): 82.1%, accuracy: 94%

The transthoracic FNACs were done either under CT or more commonly under fluoroscopy, using 22G biopsy needles. Vacuum aspiration was always used. Most patients required three or fewer passes for an adequate specimen. The aspirates were smeared onto glass slides. An air-dried smear was examined immediately by a senior cytotechnologist, to assess for adequacy, using a rapid-stain technique. Repeated passes were made when necessary. The remaining smears of the patients were either air-dried or alcohol fixed and stained with Papanicolaou (Pap) and Giemsa stains. They were examined in the Department of Pathology by the reporting pathologist. Immunocytochemistry, cytochemistry and microbiologic stains were carried out in 21 cases to aid in the diagnosis.

Prior and follow-up biopsy and cytology records of the cases as well as clinical-radiological data from case-sheets, hospital computer database and Singapore Cancer Registry were collated. This information constituted the final clinical-pathological diagnoses with which the FNAC diagnoses for all cases were correlated (Table III). A total of 28 cases (24.6%) that had original negative, unsatisfactory, atypical diagnoses, non-specified malignancy and other lesions that had discordant clinical outcome, were reviewed blindly by three of the authors (MST, AR, NB).

RESULTS

General Data

The general results are summarised in Table I. The tumour classification of the 75 malignant diagnoses is presented in Table II. Twenty (29.4%) of the 68 primary lung malignancies occurred in female patients; females constituted 15 (40.5%) of the 37 patients with primary lung adenocarcinomas.

Combined cytology-histology-clinical-radiological follow-up

Seventeen cases out of the 75 (22.7%) malignant FNAC diagnoses had follow-up lung biopsies that confirmed the diagnosis. These comprised seven primary adenocarcinomas, one metastatic adenocarcinoma, four primary squamous lung carcinomas, one primary small cell carcinoma, one non-specified epithelial neoplasm and one metastatic Wilm's tumour. One primary lung carcinoma, not otherwise specified, was definitively classified as adenocarcinoma with histology and the case of malignant neoplasm favoring melanoma was diagnosed as a neoplasm of uncertain histogenesis on histology. Only one case (1.3%) was discrepant: an FNA-diagnosed adenocarcinoma which turned out to be a sclerosing haemangioma (pneumocytoma) on histology (please see below). Five other cases (6.7%) had follow-up cytology that confirmed the diagnosis. These data indicate that when a cytological subclassification of type of bronchogenic carcinoma was attempted and a subsequent biopsy was available, a high concordance (94.4%) between both was obtained.

Forty-nine cytologically malignant cases (65.3%) had clinical-radiological courses that were consistent with the diagnoses, e.g. development of metastases, progression of radiological lesions, death due to the relevant malignancy or response to therapy. Of these, two cases had metastatic disease sites that were

Table IV. Cases with Immunocytochemistry, Cytochemistry or other Microbiologic Stains.

S/No.	Diagnosis	Special staining
1	Sarcoma	Vimentin +, Cytokeratin -
2	Metastatic renal cell carcinoma	Vimentin+ Cytokeratin +
3	Malignant neoplasm, favouring melanoma (*)	Vimentin & S-100 +, Cytokeratin, HMB45 -LCA -, Fontana-Masson + for melanin
4	Epithelial neoplasm	Cytokeratin & EMA+, HBME-1 & S-100 -
5	Carcinoma	D-PAS +
6	Metastatic renal cell carcinoma	Oil-red-O +
7	Tuberculosis	AFB +
8	Tuberculosis	AFB +
9	Tuberculosis	AFB +
10	Tuberculosis	AFB +
11	Tuberculosis	AFB +
12	Tuberculosis	AFB +
13	Histoplasmosis	PAS, GMS positive organisms
14	Inflammation	AFB -
15	Necrosis	AFB -
16	Caseous necrosis	AFB -
17	Inflammation	AFB -
18	Consistent with tuberculosis	AFB -
19	Necrosis	AFB -
20	Consistent with tuberculosis	AFB -
21	Granulomatous inflammation	AFB -

(*) After lobectomy, the final histological diagnosis was that of a neoplasm of uncertain histogenesis.

Table V. Selected results of cytology review.

S/No.	Original FNAC Diagnosis	Final Clinical-Pathological Diagnosis	Review of Cytology
1	Adenocarcinoma	Sclerosing haemangioma	Atypical glandular lesion
2	Atypia	Benign	Negative
3	Atypia	Malignancy	Atypia
4	Unsatisfactory	Malignancy	Unsatisfactory
5	Unsatisfactory	Malignancy	Unsatisfactory
6	Unsatisfactory	Malignancy	Unsatisfactory
7	Unsatisfactory	Malignancy	Unsatisfactory
8	Negative	Lymphoma	Unsatisfactory
9	Negative	Malignancy	Negative
10	Negative	Malignancy	Negative
11	Granulomatous inflammation	Malignancy	Granulomatous inflammation

biopsied. Histology of both of these matched the primary cytological diagnoses. Twenty-four cases of FNAC-diagnosed malignancies died from their disease. Notably, of the seven cases of FNAC-diagnosed small cell carcinomas, all but two of the patients have died of the disease at the time of writing, an observation consistent with the aggressive behaviour of these tumours. Three cases (4.0%) were lost to follow-up.

In the benign category of FNA diagnoses (including inflammatory, benign, atypia and negative – 31 cases), one case of atypia died of lung cancer later. One case initially diagnosed as negative, turned out to be a lymphoma on histology. One inflammatory and two benign cases had malignant clinical courses in the form of systemic metastases. Two cases died of unrelated malignancies (oesophageal carcinoma and hepatoma) and three cases were lost to follow-up. The rest of the cases had benign clinical courses.

Of the eight unsatisfactory FNACs, three cases had subsequent malignancy on biopsy: eventual histologies included adenocarcinoma, large cell lung carcinoma and a lymphoma. One case had a follow-up diagnosis of metastatic nasopharyngeal carcinoma. One other case had a benign follow-up biopsy and two cases had benign clinical courses. One case was lost to follow-up.

The malignant and benign FNA diagnoses were correlated with the final clinical-pathological diagnoses in Table III. The calculated sensitivity for a diagnosis of malignancy is 93.4%, the specificity is 95.8 %, the positive predictive value is 98.6%, the negative predictive value is 82.1% and the accuracy is 94%. Cases that were considered unsatisfactory at FNAC (eight cases) or that were lost to follow-up (six cases) were excluded from these calculations.

Special Stains

Immunocytochemistry and cytochemistry were added in six cases for tumour diagnosis (Table IV). Special

stains/microbiologic stains were performed in 15 out of 17 cases of inflammatory/necrotic lesions (Table IV). Tuberculosis (TB) was confirmed by the presence of acid-fast bacilli (AFB) using the Ziehl-Neelson staining method in six cases (5.3%). Ten other cases (8.8%) showed features of granulomatous inflammation, giant cells, caseous necrosis, inflammatory debris or inflammatory cells. The Ziehl-Neelson stain was performed in eight of these cases and all were negative. In four of these cases, there was clinical suspicion of TB. These results show that the FNA appearances were fully diagnostic or suggestive of TB in a high percentage of cases (14.1%). One other case showed GMS and PAS positive micro-organisms, with the morphological features of histoplasmosis.

Review of cytology specimens

The cytological specimens of a total of 28 cases were available for review, including all those diagnosed as negative for malignancy (nine cases), unsatisfactory (seven cases), granulomatous inflammation (one case), atypia (two cases), non-specified carcinoma (six cases), adenocarcinoma (one case), hamartoma (one case) and metastatic Wilm's tumour (one case). This blind review showed 96% concordance with the benign/malignant diagnoses reported originally, as well as full concordance among the reviewers. None of the malignancies in this group allowed further sub-categorisation on review. Some results of the review deserve highlighting and are shown in Table V.

Complications

Of the 20 patients who developed pneumothoraces (18%), all but one were small, and they were all successfully managed conservatively. Minor haemoptysis during biopsies was not recorded, but no episode of clinically significant haemoptysis occurred in any case during the post-biopsy inpatient stay.

DISCUSSION

Tumour types

The outcome of this review of the lung FNAC service at our department shows that the relative percentages of the general benign and malignant diagnoses are comparable with those in other studies. Of particular note, however, is the relatively larger percentage of primary adenocarcinomas compared to other studies[7,11-13]. In studies by Gouliamos[12] and Rajwanshi[7], primary squamous cell carcinoma of the lung was the commonest diagnosis. They also had relatively larger percentages of large cell carcinomas, undifferentiated/not otherwise specified. However, this may just reflect the overall difference in the frequency of specific lung cancer types. International figures have shown comparable incidences of primary lung adenocarcinoma and squamous cell carcinoma in the population[14], while the Singapore figures show relatively more adenocarcinomas[15]. Nineteen ninety-three to 1997 data from the Singapore Cancer Registry[15] showed that adenocarcinoma constituted 39.7% of lung cancers while squamous cell carcinomas made up 27.0% of lung cancers. Compared with this, our FNAC study shows an even higher proportion of adenocarcinomas (49.4%) than in the reported Singaporean population. This could be explained by the fact that adenocarcinomas are more often peripherally located[14] and thus more amenable to diagnosis by transthoracic FNAC.

Our study also found a high percentage of our FNAC-diagnosed adenocarcinomas patients were female (40.5%). This is higher than the overall female proportion of all FNAC-diagnosed primary lung cancers (29.4%) in this study as well as the female proportion of all lung cancers in Singapore[15]. This is in keeping with the fact that adenocarcinoma is the commonest lung cancer in females and that it tends to be peripherally located.

Adequacy of Samples

Adequacy of samples obtained by lung FNAC have been reported to be between 80%-95%[6,10]. Immediate assessment of the FNAC specimen by a cytotechnologist, with further passes made when necessary, has been shown to improve the adequacy rate of the technique[13], the figure remarkably reaching 100% in a prospective study by Santambrogio and coworkers[16]. We routinely practise immediate assessment of smears by a trained cytotechnologist, which explains our high adequacy rate of 93%.

Ancillary Techniques

O'Reilly et al showed that lung FNAC is well complemented by ancillary techniques such as immunocytochemistry, electron microscopy, mucin stains and microbiological stains[17]. In our study, immunocytochemical and cytochemical methods were used in only six cases for tumour classification. There was a need for these techniques for the characterisation of non-epithelial tumours and to confirm or establish the primary site of metastases to the lungs. In the vast majority of primary lung epithelial cancers, the diagnosis was solely based on the cytomorphology interpreted within the clinical context.

Our study reaffirms the use of FNAC in the diagnosis of pulmonary tuberculosis (TB)[7,8]. Our figure of 5.3% AFB positive cases is relatively high

by comparison with data by others. In series based on western populations, TB cases constituted 0.2-1.5% of all FNAC cases for lung nodules[12,17]. In studies from India, the corresponding figures range from 2.1% to 20%[7,8]. Clearly, TB figures prominently as an important differential diagnosis in the clinical problem of a solitary lung nodule, particularly in Asia.

Diagnostic accuracy and follow-up

All the follow-ups available on the cases considered generally showed good correlation between the original cytological diagnoses and the final clinical-pathological diagnoses; furthermore, in all except three cases, the blind review of the cytology material available concurred with the original diagnoses.

A few cases illustrate the importance of good characterisation of unsatisfactory and negative diagnoses. One of our cases was reported as negative but the consensus diagnosis on review was unsatisfactory; the post-lobectomy specimen turned out to be a lymphoma. Four additional cases originally considered to be unsatisfactory at FNAC turned out to be malignant when clinicopathological follow-up was available. These cases underline the importance of minimising unsatisfactory (inadequate) smears with the use of immediate assessment, the need to be able to recognise unsatisfactory smears and the carrying out of close follow-up/re-biopsy in such cases.

In the FNAC-diagnosed malignancies that had histological follow-up, the concordance of the tumour type diagnoses was 94.4%. Although our figures were small, we compare favourably with other published results[6]. Overall, our sensitivity, specificity and accuracy for diagnosing malignancy are comparable with those of other published results[10,11,13]. The single case of the FNA-diagnosed adenocarcinoma that turned out to be a sclerosing haemangioma underlines the potential difficulty in this cytological diagnosis. Its frequent presentation as a peripherally located solitary lesion and its cytological similarities to bronchioalveolar carcinoma, papillary carcinoma and carcinoid tumours requires attention[18].

Transthoracic core needle biopsy of lung nodules has become more popular over the last five years, particularly at sites where immediate cytologic specimen evaluation is not readily available. The availability of inexpensive, disposable spring-loaded needles that cut in place rather than firing forwards has increased the popularity of such biopsies, as this style of core needle has a lower risk of producing pulmonary haemorrhage or pneumothorax. We did not perform any biopsies using this type of needle in our study. More recently, our Department of Radiology continues to use fine needle cytology in the first instance and whenever feasible, and performs core needle biopsies only if fine needle biopsy consistently fails to deliver an adequate specimen.

Complications

Our observed complication (pneumothorax) rate is comparable with those reported by others, which vary from 9% to 24%[13,16]. This variability may be due to the differences in the definitions of significant complications and in the stringency in which they are reported.

CONCLUSION

Transthoracic FNAC is an accurate and safe method for the diagnosis of localised lung lesions. It can accurately sub-classify the type of bronchogenic carcinoma and suggest a possible primary site for those tumours metastasising to the lung. The vast majority of lung malignancies can be confidently diagnosed with cytomorphological characterisation in the right clinical context. Unsatisfactory and other non-malignant smears, in particular, need clinical correlation and close follow-up; re-biopsy may be necessary.

Our series shows one of the highest percentage of TB cases and affirms FNAC as a good method for the diagnosis of tuberculous lung nodules.

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