Fine Needle Aspiration Cytology: Does It Have a Role in the Management of Clinical Solitary Thyroid Nodules?

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**SUMMARY**

Fine needle aspiration cytology is a safe and cost-effective diagnostic method for thyroid abnormalities. It is recognised as the first line investigation for solitary thyroid nodules. We analysed 443 thyroid aspirates, carried out in this Postgraduate Medical Institute. Aspirations were done in an outpatient FNA clinic by the pathologist, under local anaesthesia. Slides were stained with May–Grunwald Giemsa and Papanicolaou methods. On cytological examination these aspirates were categorised as follows: Unsatisfactory for diagnosis = 22, non Neoplastic = 155, Indeterminate but benign 31, Follicular adenoma / Follicular neoplasm = 67, Hyperplastic colloid nodule Vs Follicular adenoma = 111, Suspicious malignant = 40 and malignant = 17. Where appropriate, excision biopsy was suggested. In 97 (21.9%) cases, surgical excision specimens were available for comparative analysis. Although a degree of overlap was observed in benign thyroid lesions including hyperplastic colloid nodules and follicular adenomas and one microscopic sized papillary carcinoma was misdiagnosed as benign due to sampling error, the remaining aspirates were correctly labelled as either, benign or malignant. Most of the suspicious malignant aspirates turned out to be malignant on histology. No significant complications occurred after the FNA procedure. Despite, the overlap of the spectrum of cytological features of different thyroid lesions, FNA cytological examination of solitary thyroid nodules is strongly recommended.

**INTRODUCTION**

Fine needle aspiration (FNA) cytology is a safe and expedient diagnostic method for thyroid abnormalities. The procedure is of great importance in the examination of thyroid swellings because of its convenience, accuracy, sensitivity and utility in obviating the need for open tissue biopsies of this richly vascular organ. It is not only useful in selecting patients for surgery, thereby avoiding un-necessary operations, but it may also be therapeutic for cystic lesions. Although FNA is now recognised to be the first line investigation for a solitary thyroid nodule, however, the principal area of difficulty in thyroid aspiration cytology is the distinction between cellular non-neoplastic nodules, follicular adenomas and follicular carcinomas.

Our experience with fine needle aspiration cytology of palpable breast lesions and space-occupying lesions in liver has been reviewed previously. The present study is cytology in the management of solitary thyroid nodules. Cytomorphological features of different thyroid lesions are described. In cases where follow-up excision biopsies were carried out, the histological diagnosis are compared with the original cytological diagnosis and pitfalls in thyroid aspiration cytology are discussed.
MATERIAL AND METHODS

From 1991 to 1995, 443 aspirates of the thyroid gland were carried out in Shaikh Zayed Postgraduate Medical Institute, Lahore. These aspirates from solitary thyroid nodules, were initially detected by the clinicians. With rare exception, most of these were "cold" nodules on radio-isotope uptake studies. The aspirates were performed by the pathologist in an FNA outpatient clinic, after careful palpation of the thyroid gland and examining the accompanying thyroid scan. After a brief explanation to the patient, the procedure was performed under local anaesthesia. The patients were either sitting upright or were in a supine position with neck extended, supported by a small pillow under the shoulder. The skin was cleaned with an antiseptic and using a 21 or 23 gauge needle attached to 10 nil disposable syringe, aspirations were performed by applying constant suction pressure on the syringe plunger. In most patients two passes were made. However, depending on the material aspirated, upto 4 passes were carried out in some cases. Where the lesions were cystic, most of the cyst fluid was aspirated first and then a second aspirate was taken from the cyst wall to obtain an adequate, cellular aspirate. The patients were asked not to talk or swallow during the aspiration procedure, to avoid movements of the thyroid gland.. After the procedure, a piece of cotton swab pressed firmly against the needle puncture site(s) prevented any haematoma formation. Slides were prepared in a manner similar to that for blood smears. On average 4-8 slides were prepared in each case. Half of the slides were air dried, and the remaining were immediately fixed in 95% alcohol. Any cyst fluid aspirated was transferred to the laboratory as such, for subsequent centrifugation and slide preparation from the sediment. In addition to cytology smears, aspirates with sufficient tissue particles were used to make conventional paraffin embedded blocks.

The labelled unstained slides, accompanied with the cytology request forms were taken to the main laboratory. The air dried smears were stained with May - Grunwald Giemsa method, and the alcohol fixed were stained with Papanicolaou method. 3 - 4 um sections were cut from the paraffin blocks and stained with conventional haematoxylin and eosin stain. The stained slides were examined and screened by the pathologist and when the aspirate was considered adequate, a diagnosis was made, as specific as possible. In most cases, reports were available to the clinician within 1 to 4 days.

As recommended by Lioe et al, all reports of the thyroid aspirates performed were retrieved and categorised into the following groups:

- Unsatisfactory for diagnosis.
- Non-neoplastic; including cysts, colloid goitre and inflammatory conditions.
- Indeterminate but benign.
- Follicular adenoma / Follicular neoplasm.
- Hyperplastic colloid nodule vs. Follicular adenoma.
- Suspicious malignant.
- Malignant.

An attempt was made to subclassify malignant lesion. Out of these 443 aspirates, in 97 (21.9%) cases, subsequently performed excision biopsies of the thyroid lesions were available for comparison with the cytodiagnosis.

Statistical analysis

Correlation between cytology and histopathology was evaluated using Chi-square analysis. Phi co-efficient was used to increase the strength of correlation. A P value ≤ 0.05 was considered significant.

RESULTS

The 443 aspirates comprised of 379 (85.55%) female and 64 (14.45%) male patients. The breakdown of different diagnostic category was as follows (Table - 1).

1. Unsatisfactory for diagnosis

Twenty two (4.9%) aspirates were considered inadequate for diagnosis. Majority of these were either acellular or contained very few epithelial cells. Reaspiration was done during the subsequent visit of the patient or excision biopsy was suggested.

2. Non-neoplastic

One hundred and fifty five (34.9%) non-neoplastic lesions were diagnosed. These included 101 (22.8%) patients of multinodular goitre / hyperplastic colloid nodule, 47
Table 1: FNA cytodiagnoses of the thyroid gland aspirates included in this study (n = 443).

<table>
<thead>
<tr>
<th>Categories</th>
<th>No. Of Patients (%)</th>
<th>SEX</th>
<th>Age (Years)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Male</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inadequate for diagnosis</td>
<td>22(4.97)</td>
<td>2</td>
<td>17 - 70</td>
<td>35.2</td>
</tr>
<tr>
<td>Indeterminate but benign</td>
<td>31(6.99)</td>
<td>3</td>
<td>14 - 70</td>
<td>36.9</td>
</tr>
<tr>
<td>Follicular adenoma Vs. Hyperplastic colloid nodule.</td>
<td>111(25.05)</td>
<td>13</td>
<td>13 - 90</td>
<td>32.2</td>
</tr>
<tr>
<td>Follicular adenoma/follicular neoplasm</td>
<td>67(15.12)</td>
<td>10</td>
<td>16 - 70</td>
<td>37.4</td>
</tr>
<tr>
<td>Suspicious malignant</td>
<td>40(9.03)</td>
<td>6</td>
<td>10 - 75</td>
<td>40.0</td>
</tr>
<tr>
<td>Malignant</td>
<td>17(3.84)</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follicular carcinoma</td>
<td>3</td>
<td>0</td>
<td>25 - 50</td>
<td>41.7</td>
</tr>
<tr>
<td>Papillary carcinoma</td>
<td>4</td>
<td>1</td>
<td>24 - 35</td>
<td>29.0</td>
</tr>
<tr>
<td>Anaplastic carcinoma</td>
<td>6</td>
<td>3</td>
<td>34 - 80</td>
<td>57.0</td>
</tr>
<tr>
<td>Carcinoma NOS</td>
<td>4</td>
<td>3</td>
<td>52 - 60</td>
<td>57.3</td>
</tr>
<tr>
<td>Non neoplastic Lesions.</td>
<td>155(34.99)</td>
<td>23</td>
<td>6 - 75</td>
<td>36.3</td>
</tr>
<tr>
<td>Benign cyst</td>
<td></td>
<td>47</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MNG / HPCN</td>
<td></td>
<td>101</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abscess</td>
<td></td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hashimoto’s</td>
<td></td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thyroiditis NOS</td>
<td></td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Granulomatous</td>
<td></td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOTAL:</td>
<td>443(100%)</td>
<td>64(14.45)</td>
<td>379(85.55)</td>
<td>6 - 90</td>
</tr>
</tbody>
</table>

MNG, Multinodular goitre; HPCN, Hyperplastic colloid nodule; NOS, Not otherwise specified.

Table 2: Analysis of the thyroid aspirate cytodiagnoses compared with the histological diagnosis of excision specimens (n=97).

<table>
<thead>
<tr>
<th>FNA Cytology</th>
<th>Histological Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cyst</td>
</tr>
<tr>
<td>Inadequate</td>
<td>3</td>
</tr>
<tr>
<td>Cyst</td>
<td>6</td>
</tr>
<tr>
<td>FA / FN</td>
<td>19</td>
</tr>
<tr>
<td>HPCN / MNG</td>
<td>23</td>
</tr>
<tr>
<td>FA Vs. HPCN</td>
<td>26</td>
</tr>
<tr>
<td>Benign NOS</td>
<td>5</td>
</tr>
<tr>
<td>Suspicious Malignant</td>
<td>10</td>
</tr>
<tr>
<td>Malignant</td>
<td>5</td>
</tr>
<tr>
<td>TOTAL :</td>
<td>97</td>
</tr>
</tbody>
</table>

FA / FN, Follicular adenoma / Follicular neoplasm; HPCN / MNG = Hyperplastic colloid nodule / Multinodular goitre; NOS, Not otherwise specified
*Non-specific inflammation, fibrosis and calcification.
**Microscopic sized papillary carcinoma.
(10.6%) benign cysts, 2 (0.45%) inflammatory lesions NOS, 2 (0.45%) non-specific abscesses (AFB negative), 2 (0.45%) granulomatous thyroiditis (AFB negative) and a single patient of Hashimoto's thyroiditis.

3. Indeterminate but benign (Benign not otherwise specified, NOS)
Thirty one (6.99%) aspirates contained benign follicular epithelial cells of non-descript type with no associated or background features to support a specific disease entity. These aspirates were labelled as benign thyroid lesions with the concluding remarks that no malignant cells were present.

4. Follicular adenoma / Follicular neoplasm
In 67 (15.12%) cases the diagnosis of follicular adenoma / Follicular neoplasm was made. In these patients the cytological features were characteristic enough for rendering this diagnosis.

5. Hyperplastic colloid nodule Vs. Follicular adenoma
This group comprised of 111 (25.05%) patients. The lesions were grouped as benign and, due to the inherent inability to distinguish follicular adenoma from a well differentiated follicular carcinoma cytologically, a diagnosis of "follicular neoplasm" was made in the presence of mild cellular and nuclear pleomorphism or marked cellularity of the aspirate. An excision biopsy was strongly suggested in these cases. On balance one or the other diagnosis was suggested as more probable. However, no specific diagnosis was chosen among these two entities.

6. Suspicious malignant
Forty (9.03%) aspirates were labelled as suspicious malignant based on equivocal cellular and nuclear pleomorphism or scanty atypical cells. Excision biopsies were strongly suggested in these cases.

7. Malignant
In 17 (3.84%) patients a definite diagnosis of malignancy was made. These comprised of 3 follicular carcinomas, 4 papillary carcinomas, 6 anaplastic carcinoma and 4 malignant lesions NOS.

- Sensitivity: Out of 13 malignant cases examined histologically, 12 were detected cytologically, suggesting an overall sensitivity of 92.3%.
- Specificity: Out of 84 histologically benign cases, the cytological diagnosis of benign lesions was given in 81 cases with 3 false positive cases. The specificity therefore was 96.4%.
- Positive predictive value for malignancy on FNA thyroid is = 80%.
- Negative predictive value for malignancy on FNA thyroid is = 98.8%.
- False negative rate = 7.7%.
- False positive rate = 3.6%.

Significant correlation was found between cytology and histopathology evaluation of FNA and biopsy results using Chi-square analysis (P < 0.001).
A Phi coefficient of 0.836 indicated a very strong correlation between FNA cytology and histology of thyroid lesions.

CYTOMORPHOLOGICAL FEATURES

Clinical and radio-isotope scan findings were always correlated with the cytological picture in each case. The cytological features found helpful in the diagnosis of multinodular goitre / hyperplastic colloid nodule were epithelial cells with regular nuclei, oxyphilic cells, large follicles, honeycomb pattern, moderate to abundant colloid material and foamy macrophages (Figs. 1, 2) as also described by Harach et al11.

The cysts were usually obvious at the time of procedure when large quantities of brown, colloid stained fluid was aspirated. The smears prepared from the centrifuged deposit were mostly cellular containing few degenerate cells, necrotic debris and abundant brown pigment laden macrophages with dirty, colloid stained background.

Follicular adenomas (Fig. 3) were characterised by good cellularity, large sheets of cells with prominent microfollicular pattern and three dimensional tissue fragments. Smaller numbers of loose follicular cells and scanty colloid material was also seen12. Nuclear enlargement was frequent finding in follicular adenomas (Fig. 4).
Fig. 1: Multinodular colloid goitre: Uniform cells are arranged in monolayers with vague, microfollicular pattern. Giemsa stain.

Fig. 2: Multinodular colloid goitre: In this field from the same case as Fig 1, there are foamy macrophages and colloid material. Giemsa stain.

Fig. 3: Follicular adenoma. Hypercellular aspirate containing 3-dimensional tissue fragments. Papanicolaou stain.

Fig. 4: Follicular neoplasm / Adenoma. There is multi nuclear pleomorphism. The follicular arrangement is striking in this example. Giemsa stain.

Aspirates from papillary carcinomas showed papillary tissue fragments, intranuclear inclusions and nuclear grooves (Fig. 5)\textsuperscript{13,14,15}. Psammoma bodies and "chewing - gum" colloid were not seen in our cases, although these features were detected by other authors\textsuperscript{4}.

Follicular carcinomas yielded hypercellular, dyscohesive aspirates, showing obvious cellular and nuclear pleomorphism. The nuclei were large with irregular contours and the chromatin was clumped. Many prominent nucleoli were seen and there was minimal colloid and follicular differentiation\textsuperscript{16}.
Anaplastic carcinomas were characterised by marked cellular and nuclear pleomorphism with hyperchromasia. Spindle shaped and multinucleated, tumour giant cells were present. Prominent one or more nucleoli were seen and there was tumour diathesis in the background (Figs. 6, 7).

Fig. 6: Anaplastic carcinoma. Markedly pleomorphic, discohesive and hyperchromatic malignant cells. Note the large tumour giant cells. Giemsa stain.

Fig. 7: Anaplastic carcinoma. In this example, there is cellular pleomorphism and nuclear hyperchromasia associated with striking cellular discohesion. Tumour diathesis can be seen in the background. Giemsa stain.

In 97 (21.9%) cases, surgical excision biopsies were available for histological examination and comparison with the cytdiagnosis, as shown in Table – 2.

Analysis of the 97 surgically excised specimens show that we did make mistakes in reaching a specific diagnosis on FNA cytology. In the 47 (10.6%) cytologically diagnosed cysts, 6 were subsequently excised. In these, 4 turned out to be follicular adenomas and 2 multinodular goitres showing cystic degeneration. In the 26 cases from the category of "follicular adenoma vs. hyperplastic colloid nodule", after histological examination 15 were multinodular goitres, 10 follicular adenomas and 1 benign cyst. To highlight further the heterogeneity in the cytomorphology of these lesions, 3 follicular adenomas (on cytology) were in fact, hyperplastic colloid nodules in multinodular goitres on histology and 4 multinodular goitres (on cytology) were follicular adenomas when surgical excision specimens were examined. Out of 40 cases
of cytologically suspicious malignant lesions, in 10
patients surgical excision specimens were available.
In these 2 were follicular adenomas and 1
multinodular goitre while the remaining 7 were
confirmed as malignant. Five cytologically
diagnosed definite malignant lesions were confirmed
histologically as carcinomas.

DISCUSSION

Fine Needle Aspiration (FNA) cytology is an
in expensive,atraumatic technique for the diagnosis
of disease sites. The most obvious advantages of
FNA cytology over surgical and large needle biopsy
are that it is quicker to perform and report, less
painful, less technically demanding and easily
repeatable. It is far more convenient and may be set
up in any clinical situation. There is little doubt
that FNA cytology has in part replaced frozen
sections and tissue biopsies, particularly for the
diagnosis of cancer. However, the great danger of
the method lies in erroneous interpretation of the
sample by inexperienced observer without sufficient
cognizance of the many diagnostic pitfalls.

Carcinoma of the thyroid is relatively
uncommon, however thyroid nodules occur
frequently. It is the clinically solitary, non-toxic
(cold) thyroid nodule which has usually been a
strong indication for surgery because it is
considered to be a highly suspicious sign of
carcinoma. As FNA cytology has a higher
sensitivity for the detection of malignancy compared
with ultrasound and radio-isotope scan, and with
experienced aspirator in a well organised service, an
FNA cytology clinic is highly cost effective,
resulting in considerable savings in resources, it
has become an important aid in the diagnosis and
management of palpable thyroid nodules. The
technique is now recognised to be the first line
investigation for a solitary thyroid nodule.

In the present study only 4.9% aspirates were
considered inadequate for diagnosis. A review of
the literature revealed a wide range of inadequate
aspirates from 2.2% to as high as 25% in
thyroid aspirates. Various authors have stressed the
importance of multiple aspirates in one patient and
an expensive cytopathologist making the aspirate
him/herself as a screening tool for the selection of
cases requiring excision and histological
examination to make the definitive diagnosis of an
adenoma or carcinoma on the basis of the
architectural features. Some authors recommend
that aspirates from follicular adenomas and
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"follicular neoplasm" on FNA cytology and this
cyto diagnosis should be an indication for removal
of the nodule. The distinction of a follicular
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...
differentiated follicular carcinoma. Consequently, follicular neoplasm reported by FNA that subsequently prove by histologic examination to be follicular carcinomas should not be regarded as false negatives. Certain features are helpful in making a diagnosis of follicular carcinoma on FNA cytology in comparatively less well differentiated lesions. These include good cellularity, cellular dyscohesion, three dimensional tissue fragments and more importantly cellular and nuclear pleomorphism, hyperchromasia, clumped chromatin and prominent and frequent nucleoli. Based on these features we picked up 3 follicular carcinomas.

Due to its typical features, papillary carcinomas should be diagnosed even cytologically with high accuracy. Similar is the case with anaplastic carcinoma where the aspirate contains very pleomorphic obviously malignant cells. Minor degrees of cellular pleomorphism is common in benign thyroid lesions including multinodular goitre and follicular adenomas. In our suspicious malignant category both benign and malignant lesions were represented in cases where histology of the excision specimens was available. Interestingly, one of the suspicious lesion was Hurthle cell adenoma on histology, in which cellular and nuclear pleomorphism is a well known and common feature to the extent that it can be misinterpreted as carcinoma on cytological examination.

"Cysts" are well recognised diagnostic pitfall in FNA cytology of thyroid, as a diversity of thyroid lesions can exhibit cystic degeneration which appear as solitary cold nodules on radioisotope scans. These include multinodular colloid goitre, follicular adenomas and more importantly papillary carcinomas. It is due to this reason that it is recommended to obtain an adequate cellular aspirate from cyst wall, after emptying the cyst contents, for proper cytological assessment of these lesions. This certainly is the case in recurrent cysts requiring repeated aspirations and these should be excised surgically for proper diagnosis.

Excluding papillary and anaplastic carcinomas, the diagnostic accuracy of FNA cytology of the thyroid gland is limited in distinguishing between aspirates from cellular colloid nodule and follicular adenoma, because of similar and overlapping cytologic findings. A substantial proportion (25.05%) of this study belonged to this quivocal category. However in all cases a diagnosis of benignity was made and one of the two diagnosis was considered more probable in each patient. In cases where histology was available, significant overlap between these two diagnostic categories was noted.

There are very occasional reports of complications arising due to the FNA thyroid including haematoma formation, partial or complete infarct of the tumour and needle tract implantation of papillary carcinoma of the thyroid. We did not encounter any of these complications in our series, apart from very few patients developing transient vasovagal shock when aspiration was attempted in an upright sitting position. These patients quickly recovered when laid down in supine position and the FNA procedure was successfully completed afterwards.

**CONCLUSION**

Because of the overlap of the spectrum of cytological features, FNA cytology of the thyroid gland is considered a difficult area. Despite this difficulty analysis of 97 cases where both FNA cytology and histology results were available, revealed that we were able to separate benign from malignant lesions apart from a single case of "missed" papillary carcinoma, due to the inherent sampling error. Most of the "suspicious malignant" lesions on cytology did turn out to be malignant on histological examination. If performed by an experienced cytopathologist, non-neoplastic lesions can be confidently separated from neoplastic conditions in most cases. The cytological features of papillary and anaplastic carcinomas are characteristic enough to make these straightforward diagnosis on FNA cytology. The technique is certainly cost effective and is a valuable diagnostic tool in countries with limited resources, reducing greatly the number of unnecessary surgeries in thyroid gland. The use of FNA cytology in the evaluation of solitary thyroid nodules is, therefore, strongly recommended. Due to the frequent occurrence of cystic degeneration in a diversity of thyroid lesions, both benign and malignant any "recurrent cyst" should be excised surgically for correct diagnosis.

**ACKNOWLEDGEMENT**

We wish to thank Dr. Asrshad Kamal Butt for
his help in statistical analysis of the results. We are also particularly thankful to the Surgeons and Physicians of Shaikh Zayed Postgraduate Medical Institute for referring the cases for FNA cytology of thyroid.

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