

Fine needle aspiration cytology of the thyroid – a review of experience in 1853 cases

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Abstract

1853 thyroid lesions subjected to cytological sampling (either by the fine needle aspiration or fine needle capillary sampling technique) from January 1992 to December 1997 at the University Hospital, Kuala Lumpur, were reviewed. Nodular goitre was the most common thyroid lesion needed (67.35%). Among the neoplastic lesions, follicular neoplasms predominated (64%), followed by papillary carcinoma (29.4%). In 325 cases, partial or total thyroidectomy had been done, providing material for histological review and cyto-histological correlation. Cytological diagnosis was found to have high sensitivity and specificity rates of over 75%. Besides, most non-neoplastic thyroid lesions could be diagnosed on cytology. The scope of cytology in the diagnosis of lymphomas, anaplastic and metastatic tumours rendered diagnostic biopsies (or thyroidectomy) unnecessary in these cases. Being a cost-effective technique and having the capacity to provide exact morphological diagnosis in a large variety of thyroid lesions, cytology is obviously the method of choice in the assessment of thyroid nodules.

Key words: Fine needle aspiration, fine needle capillary sampling, thyroid.

INTRODUCTION

A solitary nodule of the thyroid is a common problem in clinical practice, and the vast majority of thyroid nodules are benign.¹ While scanning evidence of a hyperfunctioning nodule is a fairly reliable indicator of its benign nature, the converse is not true² and the incidence of malignancy in solitary cold nodules has been shown to vary from 10.4 % to 44.7%.^{2,4} The pressing need for a pre-operative investigative modality that can discriminate between benign and malignant thyroid nodules has been fulfilled to a great extent by fine needle aspiration (FNA) cytology.⁴⁻⁸ In the last decade the fine needle capillary (FNC) sampling technique (non-aspiration fine needle cytology) technique has also proved its utility as an excellent method of sampling the thyroid.^{9,10}

We present herein a detailed review of our experience in 1853 thyroid lesions evaluated by FNA or FNC cytology technique at the University Hospital, Kuala Lumpur from the years 1992 to 1997.

MATERIALS AND METHODS

From January 1992 to December 1997, 1853

thyroid lesions were subjected to cytological study at the University Hospital, Kuala Lumpur. All cases were initially seen at the outpatient clinics and then referred for cytological study. 1457 cases presented as solitary nodules and 396 as diffuse goitres. Samples were obtained in all cases by the cytopathologists using either the FNA⁸ or FNC cytological techniques.¹⁰ For both techniques a 22 or 23 gauge needle was used, which for the FNA technique was attached to a disposable 20cc plastic syringe that was in turn mounted on a handle for single-hand grip. Smears obtained were grossly inspected for cellularity, air dried, fixed in methanol and stained with May Grünwald Giemsa (MGG).

In selected cases (where a neoplastic lesion was clinically suspected or where cellularity could not be definitely ascertained on gross inspection of the freshly prepared smears), a Diff-Quik stain was done at the bedside on one smear and examined under a microscope. Based on the findings of the Diff-Quick stained smear, needling was repeated (if required) to obtain additional smears for any subsequent special or immuno-staining techniques. These additional smears were wet-fixed in 95% ethanol. In every case, care was taken to ensure representative

sampling of the lesion.

At the time of review of the cytological material, histological correlation was found to be available in 325 cases (17.53%) in which a lobectomy or total thyroidectomy had been done. The cytological smears as well as the histological sections were subjected to detailed morphological analysis and cyto-histological correlation was done.

RESULTS

The cytological diagnosis in 1853 cases and the cyto-histological correlation in 325 cases are shown in Tables 1 & 2. Nodular goitre (NG) was the most common lesion subjected to cytological study, constituting 67.35% (1248 cases). Of these, histological correlation was available in 182 cases (14.5%). In 148 cases the histological diagnosis concurred with the cytological diagnosis. 32 cases diagnosed as NG on cytology turned out to be neoplastic lesions. These included 28 follicular adenomas (FAs), three follicular carcinomas (FCs) and one Hurthle cell tumour (HCT). Two cases diagnosed as NG proved to be nodular presentations of Hashimoto's thyroiditis (HT).

In 70 of 138 follicular neoplasms (FNs) diagnosed on cytology, histological material was available for review. 36 cases (51.42%) proved to be FAs on HPE and 8 cases (11.42%) turned out to be FCs. Of 26 remaining cases, 10 turned out to be papillary carcinoma (PC), 13 were NGs and three proved to be HCTs. The solitary case diagnosed as FC on cytology was confirmed on HPE.

Of 44 cases diagnosed cytologically as PC, only 26 were operated and all of these proved to be PC. Six out of 10 cases diagnosed as HCT on cytology were operated. Although only two of these six cases turned out to be HCT on HPE, five cases proved to be neoplastic. These included one case each of FA, FC, PC, HCT and Hurthle cell carcinoma (HCC).

Three of nine cases with a cytological diagnosis of medullary carcinoma of thyroid (MCT) were confirmed on surgery and HPE. Of seven cytologically diagnosed cases of anaplastic carcinoma (AC), one was operated and confirmed on HPE. The solitary case diagnosed cytologically as a primitive neuroectodermal tumour (PNET) proved to be a malignant teratoma with predominantly neuro-epithelial differentiation.

12 of 38 cases that were cytologically equivocal were operated. Eight of these proved

to be neoplastic (four FAs, two FCs and two PCs) and four non-neoplastic (three NGs and one HT).

Of 157 cases that were considered inadequate, inconclusive or unsatisfactory on cytology, 13 were operated; eight turned out to be NGs, two proved to be FCs and there was one case each of FA, PC and HCT. 10 of 87 cases in which a cytological report of "no malignancy" was given were operated. These consisted of seven NGs, two FAs and one case of PC.

Smears from NG showed variable amounts of colloid in the background, often admixed with blood. The cellularity ranged from mild to moderate and consisted of monomorphic follicular cells (Fig. 1) that were in mono-layered clusters as well as in focal acinar pattern. These clusters were often superimposed by colloid that took up globular shapes (colloid globi). Variable numbers of foam cells often containing haemosiderin pigment were present (Fig. 1). Occasional cases showed foci of Hurthle cell change.

Of three cases cytologically diagnosed as NG and showing very prominent Hurthle cell change, two turned out to be HT and one HCT. 31 FNs (28 adenomas and three carcinomas) were misdiagnosed as NG on cytology. Review of cytological smears in these cases showed sub-optimal cellularity, small size of follicular cells and presence of colloid either in the background or as colloid globi superimposing follicular cells.

Smears from HT usually showed a polymorphous population of cells in the background that included mature and transformed lymphocytes, plasma cells and histiocytes. Lymphoid cells were also found to be infiltrating follicular cells (Fig. 2) and

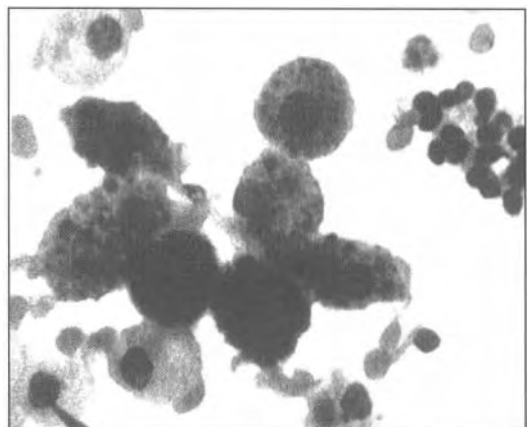


FIG. 1: Pigment-laden foam cells and follicular cells (right) in nodular goitre. MGG \times 400.

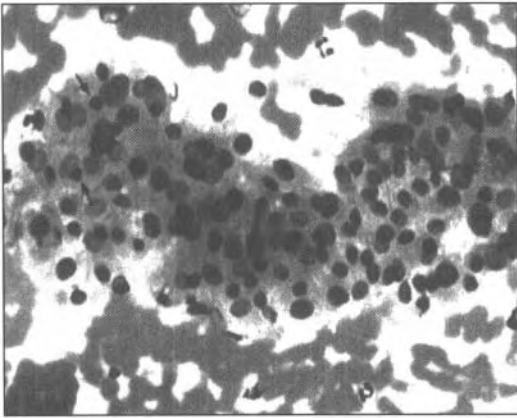


FIG. 2: Lymphocytes (arrows) infiltrating follicular cell clusters in Hashimoto's thyroiditis. MGG \times 200.

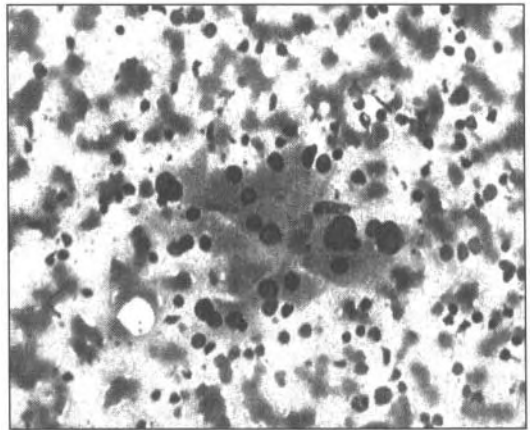


FIG. 3: Hurthle cells showing focal nuclear atypia (centre) and lymphocytes in the background in Hashimoto's thyroiditis. MGG \times 200.

follicular collections of lymphoid cells and lympho-histiocytic cells were often present. Hurthle cell change was variable and when present, Hurthle cells showed focal nuclear atypia and were surrounded (and occasionally infiltrated) by lymphoid cells (Fig. 3).

A few cases of HT were less characteristic with only a minimal lymphoid population with occasional follicular cell clusters showing degeneration and infiltration by lymphoid cells. In all 77 cases diagnosed as HT (Table 1), the clinical features and thyroid function tests (TFTs) were compatible with the cytological diagnosis and anti-thyroid antibodies were significantly raised in at least 50%. All of these cases are under annual follow-up FNA cytology. None of the cases diagnosed as HT on cytology were subjected to surgery. However two cases of HT that were misdiagnosed as NG on cytology were operated and review of cytological smears in these cases showed an insignificant lymphoid population that had been overlooked on cytological assessment.

Smears from subacute thyroiditis (SAT) were dominated by the presence of multinucleated foreign body and Langhansoid type of giant cells (Fig. 4). Epithelioid cell collections were present in about half of the cases and follicular cellularity was variable. Small numbers of lymphocytes and polymorphs were scattered in the background in a minority of cases. Neither follicular cell infiltration by lymphoid cells nor Hurthle cell change was present in any of these cases. Most cases of SAT presented with tender, minimally enlarged, soft or firm goitres, marked reduction in the I^{131} uptake, increased blood levels of T3 and T4 and reduction in the serum thyroid

stimulating hormone (TSH) levels.

Smears from cases of Graves disease (GD) showed moderately cellular smears with follicular cells in mono-layered clusters in a bloody background devoid of colloid. The follicular cells showed lacy or cobweb-like cytoplasm and fire-flare appearance was seen in 50-100% of the follicular cells (Fig. 5). Focal nuclear pleomorphism and clear cell changes were seen in a few of the cases. In 10 cases of NG a small percentage of follicular cells (usually 10 - 20%) showed fire-flare appearance. These were considered to reflect foci of hyperplasia and possible hyperfunction in NG. None of the cases diagnosed as GD were operated during the period of study. TFTs in all of these cases were however consistent with a diagnosis of GD.

Smears from follicular adenoma and carcinoma (diagnosed broadly as FN on

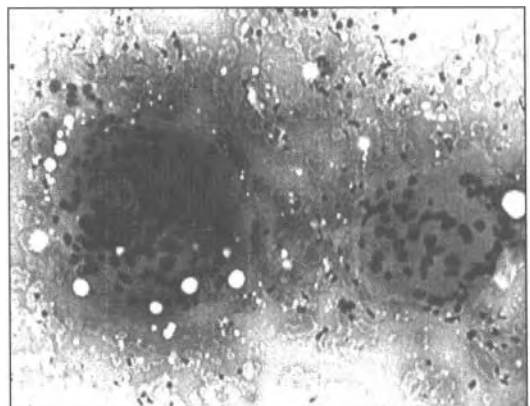


FIG. 4: Multinucleated giant cells in subacute thyroiditis. MGG \times 200.

TABLE 1: Cytological diagnosis in 1853 cases

Cytodiagnosis	No. of cases	Percentage
Nodular goitre	1248	67.35%
Hashimoto's thyroiditis	77	4.16%
Sub acute thyroiditis	13	0.70%
Graves disease/thyrotoxicosis	7	0.38%
Thyroglossal cyst	3	0.16%
Follicular neoplasm	138	7.45%
Follicular carcinoma	3	0.16%
Papillary carcinoma	44	2.37%
Hurthle cell tumour	10	0.54%
Medullary carcinoma	8	0.43%
Anaplastic carcinoma	7	0.38%
Non Hodgkin's lymphoma	6	0.32%
Primitive neuro-ectodermal tumour	1	0.05%
Sarcoma	1	0.05%
Metastatic carcinoma/Undifferentiated carcinoma	4	0.22%
No malignancy	87	4.70%
Inconclusive/inadequate/unsatisfactory	158	8.53%
Equivocal	38	2.05%
Total	1853	100%

cytology) showed moderate to marked cellularity in a bloody background devoid of colloid. All cases showed a prominent acinar pattern (Fig. 6) and monolayered clusters were present in 90%. Three-dimensional (3-D) clusters of follicular cells were seen in a minority of cases and papillary pattern was unusual. Follicular cells were uniformly enlarged with a monomorphic appearance in the majority of cases. Pleomorphism was present in only 10%. Focal fire-flare appearance and Hurthle cell change were present in 13% of cases.

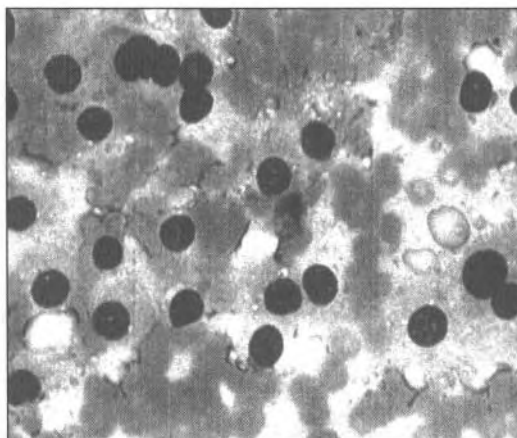


FIG. 5: Follicular cells showing fire-flare appearance in Graves' disease. MGG × 400.

The cytological appearance in FA and FC were similar and distinction was made on the basis of histological study for evidence of capsular and/or vascular permeation. The single case diagnosed as FC on cytology was so diagnosed on the basis of metastatic lymphadenopathy confirmed on FNA. 13 cases of NG and three cases of HT misdiagnosed as FN on cytology showed moderate to high cellularity with prominent acinar pattern and smear background devoid of colloid and lymphoid cells. Histological sections in these cases showed foci of follicular hyperplasia.

Smears in PC were hypercellular in a background of blood, sometimes admixed with

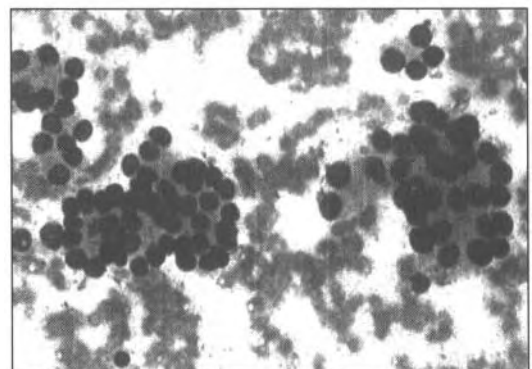


FIG. 6: Follicular cells in acinar pattern in follicular neoplasm. MGG × 200.

colloid. 3-D clusters, papillary clusters with peripheral scalloping and mono-layered clusters were the dominant features. Most of the papillary clusters were devoid of vascular core; a few however showed a vascular core. The follicular cells were invariably enlarged with dense (metaplastic) cytoplasm and intra-nuclear cytoplasmic (INC) inclusions and nuclear grooves (Fig. 7) were present in more than half of the cases. Squamous metaplasia was seen in 12% and Hurthle cell metaplasia in 23%. Multinucleated giant cells of foreign body type were seen in one third of the cases and foam cells in two thirds. Psammoma bodies were uncommon in cytological smears from PC (5%). Fire-flare appearance was an occasional feature (9%).

Review of ten cases of PC that were diagnosed cytologically as FN showed a predominantly acinar pattern with no characteristic INC inclusions or metaplastic cytoplasm. A few papillary clusters and 3-D fragments were however present. Histological sections from these cases showed six of them to be follicular variants of PC while four showed a predominantly follicular pattern.

Smears from HCT showed isolated and monolayered clusters of Hurthle cells that showed abundant cytoplasm, polygonal cell shapes and round, vesicular nuclei with prominent nucleoli. Cytoplasm was granular in occasional cells and a few binucleate forms were seen (Fig. 8).

One case each of FA, FC, and PC that were misdiagnosed as HCT showed a prominent Hurthle cell component. One case of HT

misdiagnosed as HCT showed very high cellularity with pleomorphic Hurthle cells in clustered pattern and an insignificant lymphoid population. Dissociated Hurthle cells were absent in this case. The cytological appearances were similar in HCA and HCC and the distinction was made as usual by demonstration of capsular and/or vascular permeation in histological sections of the latter.

Smears from MCT showed a predominantly dissociated pattern of round or spindle cells that varied in size. The round cells showed eccentric, round, vesicular nuclei and frequent binucleate and trinucleate forms. Parachute-like forms of binucleate cells (Fig. 9) were particularly characteristic. Cells at the edges of the smears often showed reddish cytoplasmic granules (Fig. 10). Amyloid was demonstrable in cytological smears in three of eight cases diagnosed as MCT. These smears were stained with Congo Red (after de-staining) and birefringence demonstrated under polarising light. Although only three of the cases diagnosed as MCT were operated, all eight cases were proven to be MCT on the basis of immunocalcitonin staining of the tumour cells in alcohol-fixed wet smears of FNA or FNC material.

In all seven cases diagnosed as AC, the patients were elderly and presented with a rapidly growing thyroid mass that led to dysphagia, dyspnoea or hoarseness. Smear cellularity varied depending on the amount of tumour necrosis seen in individual cases. Tumour cells usually included giant and spindle cells (Fig 11 & 12). One case however showed a predominantly round cell type of morphology with eccentric nuclei

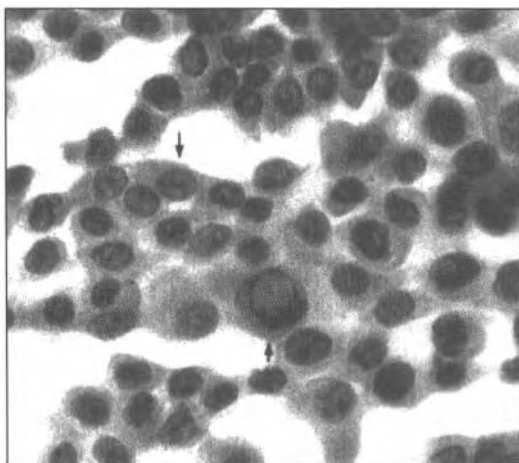


FIG. 7: Intranuclear cytoplasmic inclusions (arrow) and nuclear grooves (arrows) in papillary carcinoma. MGG \times 400.

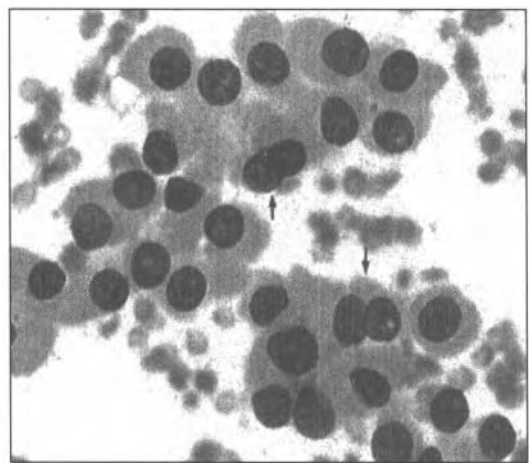


FIG. 8: Monolayered clusters of Hurthle cells in Hurthle cell tumour with a few binucleate forms (arrows). MGG \times 400.

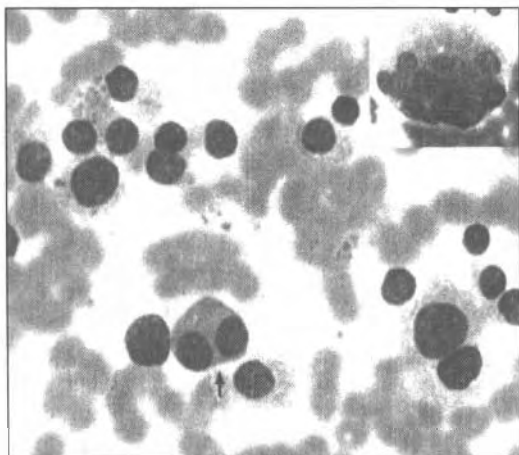


FIG. 9: Dissociated tumour cells in medullary carcinoma with a parachute form (arrow) and multinucleation (inset). MGG \times 40; Inset - MGG \times 200.

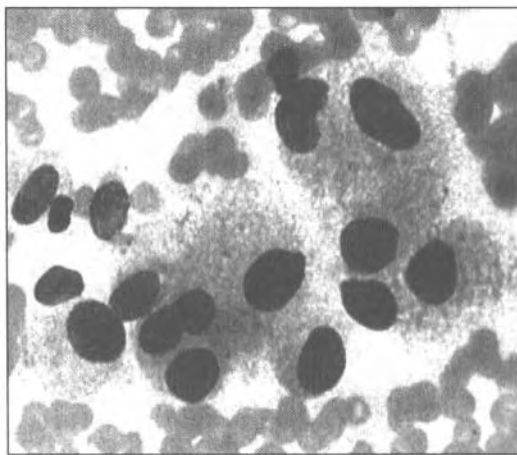


FIG. 10: Cytoplasmic granules in cells of medullary carcinoma of thyroid. MGG \times 400.

giving a plasmacytoid appearance to the cells. The giant cells in AC were pleomorphic and bizarre (Fig 11) with frequent mitosis. The spindle cells also showed a moderate degree of pleomorphism and were dissociated or clustered (Fig 12). Polymorphs and necrotic material were often present in the background (Fig 11). Immuno-cytochemical stains done in four cases showed the presence of cytokeratin and vimentin within the tumour cells. Histological confirmation was available in only one case. The remaining cases were inoperable and the patients expired within two to five months of presentation.

The solitary case of malignant teratoma (MT) of thyroid showed highly cellular smears with a monotonous population of small or intermediate sized round cells that were dissociated or in attempted rosette-like pattern. An exhaustive panel of immuno-cytochemical stains done on ethanol-fixed wet smears showed the tumour cells to express only neuron secretory enolase and chromogranin. Hence a cytological diagnosis of primitive neuroectodermal tumour (PNET) was given. Multiple sections from the thyroidectomy specimen showed a malignant teratoma with a predominantly neuroepithelial component that formed clusters and primitive neural tubules. Occasional foci of squamous and glandular epithelium could be seen giving testimony to the teratomatous nature of the

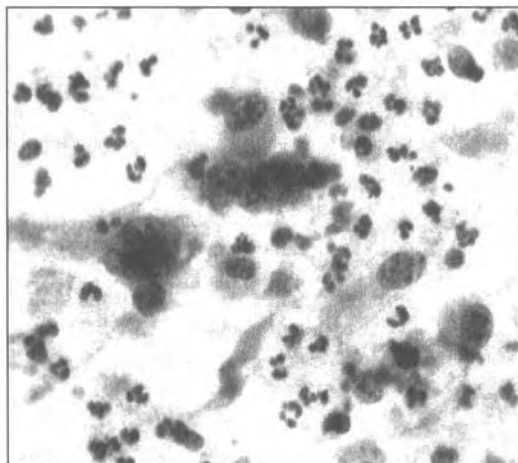


FIG. 11: Pleomorphic multinucleated giant cells in anaplastic carcinoma with polymorphs and necrotic material in the background. MGG \times 400.

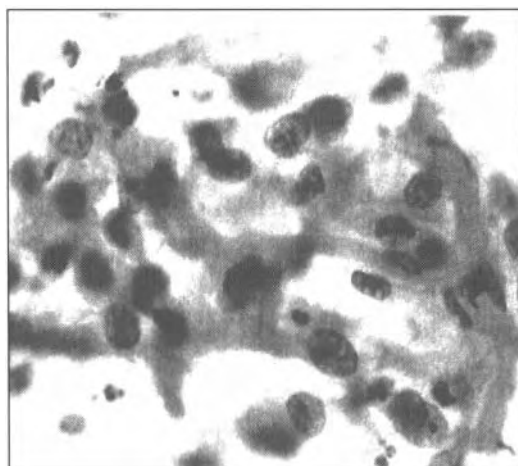


FIG. 12: Cluster of pleomorphic spindle cells in anaplastic carcinoma. MGG \times 400.

tumour. The patient, a young female, developed cervical and mediastinal lymphadenopathy soon after initial presentation. She had a total thyroidectomy and while on postoperative radiotherapy developed extensive vertebral, liver, paracaval and paraaortic lymph node metastases and expired 15 months after presentation.

Six cases of Non-Hodgkin's lymphoma (NHL), one spindle cell sarcoma and four cases of metastatic carcinoma (table 1) that were diagnosed on cytology did not have any histological confirmation. All cases of NHL were high grade lymphomas with smears showing a predominant population of large cleaved and non-cleaved lymphoid cells admixed with a few reactive mature lymphocytes and histiocytes. Many cells were present as naked nuclei and the mitotic index was high. All six cases were proven to be B-cell lymphomas on the basis of immunocytochemical reactivity of the large cells to CD20 (pan B-cell marker). Two of these cases had cytological evidence of pre-existing HT as seen from samples taken from areas of the thyroid other than the clinically dominant nodule.

Following thorough investigation to rule out a metastatic lesion, the solitary case of spindle cell sarcoma was proven to be a primary thyroid sarcoma. Tumour cells showed strong immunocytochemical reactivity to vimentin (but not to cytokeratin). Of four cases diagnosed as metastatic carcinoma/undifferentiated carcinoma, two had primaries in the breast. Location of the primaries in the other two cases could not be ascertained as the patients were lost to follow up.

Smears in cases that were diagnosed as "cytologically equivocal" generally showed higher follicular cellularity than that usually seen in NGs or thyroiditis, with no colloid, inflammatory or lymphoid components. All cases that received an equivocal cytological report were advised surgery and HPE to rule out neoplasia. Of 12 equivocal cases that were operated, eight (66.7%) turned out to be neoplastic. On the other hand, of 13 cytologically inadequate/unsatisfactory cases that were operated, only four turned out to be neoplastic. Three of 10 operated cases with a cytological report of "no malignancy" proved to be neoplastic (two FAs and one PC). Review of smears in the case of PC showed a significant lymphoid and Hurthle cell component that simulated HT. A cytological diagnosis of HT however was not given, as there was neither follicular cell infiltration by lymphoid cells nor any

transformed lymphocytes in the smears. The two cases of FA showed suboptimal cellularity in the cytological smears.

Considering a cytological diagnosis of neoplastic and equivocal (Table 2) as "positive" the sensitivity of cytological diagnosis was found to be 78% i.e.

$$\frac{\text{Total Positives (139)}}{[\text{Total Positives (139)} + \text{False Negatives (39)}]} \times 100$$

If "equivocal" was considered as "test negative" then the sensitivity was reduced to 73.15% i.e.

$$\frac{\text{Total Positives (139)}}{[\text{Total Positives (139)} + \text{False Negatives (51)}]} \times 100$$

Although only three cases of MCT were operated, all eight cases that received a cytological diagnosis of MCT had been confirmed by demonstrating immuno-calcitonin reactivity of tumour cells. Likewise although only one case of AC was operated, all seven cases were clinically anaplastic tumours progressing rapidly and killing the patients within a few months. All six cases of NHL and the single case of spindle cell sarcoma had been confirmed on the basis of immuno-cytochemical stains. Two cases of metastatic carcinoma had been confirmed as being of breast origin. If these cases (MCT, AC, NHL, sarcoma and metastatic carcinoma) are added (with equivocal cases taken as positive), the sensitivity of cytodiagnosis increases to 80.3% i.e.

$$\frac{\text{Total Positives (159)}}{[\text{Total Positives (159)} + \text{False Negatives (39)}]} \times 100$$

If equivocal cases are eliminated, the sensitivity decreases to 75.7% i.e.

$$\frac{\text{Total Positives (159)}}{[\text{Total Positives (159)} + \text{False Negatives (51)}]} \times 100$$

Calculating the specificity of cytodiagnosis, with equivocal cytology considered as positive (Table 2), the overall specificity was found to be 89.9% i.e.

$$\frac{\text{Total Negatives (186)}}{[\text{Total Negatives (186)} + \text{False Positives (21)}]} \times 100$$

If equivocal was considered "test negative" the specificity increased to 91.62% i.e.

$$\frac{\text{Total Negatives (186)}}{[\text{Total Negatives (186)} + \text{False Positives (17)}]} \times 100$$

DISCUSSION

Analysis of several reported series of FNA

TABLE 2: Cytological diagnosis correlated with the histopathological diagnosis in 325 cases

Cytodiagnosis	Histopathological diagnosis										Total
	FA	FC	PC	MCT	HCA	NG	AC	HT	MT	HCC	
Nodular goitre	28	3	0	0	1	148	0	2	0	0	182
Follicular neoplasm	36	8	10	0	0	13	0	3	0	0	70
Follicular carcinoma	0	1	0	0	0	0	0	0	0	0	1
Papillary carcinoma	0	0	26	0	0	0	0	0	0	0	26
Hurthle cell tumour	1	1	1	0	1	0	0	1	0	1	6
Medullary carcinoma	0	0	0	3	0	0	0	0	0	0	3
Anaplastic carcinoma	0	0	0	0	0	0	1	0	0	0	1
Primitive neuroectodermal tumour	0	0	0	0	0	0	0	0	1	0	1
Equivocal cytology	4	2	2	0	0	3	0	1	0	0	12
No malignancy	2	0	1	0	0	7	0	0	0	0	10
Inadequate/Unsatisfactory	1	2	1	0	1	8	0	0	0	0	13
TOTAL											325

FA = Follicular adenoma; FC= Follicular carcinoma; PC= Papillary carcinoma; MCT= Medullary carcinoma thyroid; HCA= Hurthle cell adenoma; NG=Nodular goitre; AC= Anaplastic carcinoma; HT= Hashimoto's thyroiditis; MT=Malignant teratoma; HCC= Hurthle cell carcinoma

cytology of thyroid indicate that whereas a positive cytological report raises the probability of malignancy to at least 85% - 90%, a benign cytological diagnosis lowers the probability to about 1%.¹¹ The inclusion of a "cytologically equivocal" category appears to be inevitable in most centres routinely performing and interpreting thyroid cytology.¹²⁻¹³ In the present study it was possible to achieve a fairly high degree of sensitivity (78%) that increased to 80.3% if cases not operated but confirmed by immunocytochemical means or clinical and other parameters were included. This essentially means that using the cytological method of evaluation only about 10% of thyroid neoplasms would be missed.

Before the introduction of FNA cytology, only patients with obvious cancers underwent surgery and numerous malignancies were missed. In addition, using conventional diagnostic modalities alone (such as clinical assessment, radionuclide scans etc.), only about 10 - 25% of all surgically removed nodules proved to be malignant, giving an unacceptably low specificity rate of 10 - 25%.¹ The specificity in the present study was 89.9% when equivocal cytology was considered as test-positive and 91.62% if it was

considered as test-negative. If equivocal cytology is taken as test-positive, around 10% of operated cases would turn out to be benign, whereas in the latter situation 11-12% would prove to be benign. The disadvantage of considering equivocal cytology as test negative would be the reduction in the sensitivity rate from 78% to 73.15%. Therefore we prefer to consider the equivocal cases in the positive category and to advise surgery. The wisdom of this decision has been born out by previous studies^{12,13} and the fact that eight of 12 operated cases that were cytologically equivocal turned out to be neoplastic.

NG was the most common lesion subjected to FNA cytology (Table I). The cytological picture in NG has been well described and documented.^{8,14} The problem of distinguishing cellular NG with minimal colloid storage from a follicular neoplasm with moderate colloid storage is also well known.⁵ 13 cases diagnosed as FN in the present series turned out to be NGs; conversely, 31 cases diagnosed as NG turned out to be FNs. The combination of high cellularity and a microfollicular pattern is highly predictive of FN¹⁵. **3-D**, crowded and overlapped, syncytial-like aggregates of microfollicles are also

characteristic of FN. Another fairly constant finding in FN is the uniform increase in nuclear size, an uncommon feature in non-toxic NG¹. The chromatin may be coarse but nucleoli are infrequent.^{15,16}

Problems encountered in the interpretation of Hurthle cell populations in thyroid FNA have been highlighted from time to time.^{17,18} Besides HT and HCT, Hurthle cells can be seen in a variety of thyroid lesions including NG, GD, SAT, FN and PC.^{5,8,19,20,21,22} The interpretation of Hurthle cells in thyroid cytology must therefore be taken in the context of the clinical profile and the other cytological features. If the cellularity is very high and consists predominantly of Hurthle cells that are clustered and dissociated and showing prominent nucleoli with no lymphoid cells in the background, a neoplastic lesion must be suspected and HCT is very high on the probability list. On the other hand, if the smear background shows lymphoid cells and Hurthle cells, albeit pleomorphic, are seen only in clusters, a diagnosis of HT must be suspected even if the cellularity is very high. In such cases, a careful search will usually show a few non-oxophilic follicular cells or even Hurthle cells that are infiltrated by lymphoid cells. Transformed lymphocytes and even plasma cells may be seen in the smears.

Some cases of PC show lymphoid cells as well as Hurthle cells but the added presence of non-oxophilic follicular cells with characteristic dense (metaplastic) cytoplasm and INC inclusions usually allow distinction from HT and HCT. FNs with prominent Hurthle cell change may be mistaken for HCT as occurred in two of our cases. Since the management is similar in HCT and FN, this distinction does not appear very relevant. The presence of Hurthle cells is not a pre-requisite for the diagnosis of HT. The characteristic appearance in HT is that of a smear showing a high lymphoid:follicular epithelial cell ratio with lymphoid cells (including mature and transformed lymphocytes) that are often seen to be infiltrating degenerating follicular cells. Clinical and thyroid functional profiles were compatible with the cytological diagnosis of HT in all of our cases. In difficult cases, thyroid antibody profiles and follow up FNA cytology are of great use.

SAT also showed a characteristic smear pattern dominated by large multinucleated giant cells with a variable epithelioid cell population. Although SAT and GD are usually clinically characteristic and not usually sent for FNA cytology, atypical cases may require a

morphological diagnosis. On the whole, cytology is an excellent method for studying inflammatory and auto-immune thyroid lesions and it is the diagnostic method of choice as these are non-surgical goitres. A closed needle biopsy may provide equal or even less information than cytological sampling since the closed needle cannot sample different parts of the gland the way a fine needle can. Of all thyroid lesions, PCs are probably the easiest to diagnose on cytology,^{15,23} particularly if they are predominantly papillary in architecture. Highly cellular smears with 3-D clusters, mono-layered sheets and papillary clusters (with or without vascular cores) provide the hallmark to the diagnosis of PC.^{5,15,24-26} Follicular cells of PC are invariably larger than benign follicular cells, show a moderate amount of dense (metaplastic) cytoplasm and well-defined cell margins. INC inclusions, nuclear grooves, multinucleated giant cells, squamous metaplasia and Hurthle cell change are seen in a variable proportion of cases. Follicular variant of PC may be mistaken for FN as occurred in 10 cases. INC inclusions, nuclear grooves and/or metaplastic cytoplasm are useful features in the distinction of follicular variant of PC from FN. These features were however absent in our cases.

A mixed round and spindle cell pattern of predominantly dissociated tumour cells with eccentric nuclei is characteristic of MCT. Binucleate (parachute) forms of tumour cells and amyloid (if present) provide additional cytological evidence of MCT. Immunocalcitonin stains of wet-fixed cytological smears are very useful in confirming the cytological diagnosis of MCT and in distinguishing variant forms of MCT (oncocyctic, papillary, giant cell) from HCT, PC and AC with which they may be occasionally confused.²⁷⁻³⁰

Cytology is probably the only method of diagnosing AC that presents as a rapidly growing large thyroid mass that often leads to compression symptoms. The cytological picture is fairly characteristic with bizarre giant and spindle cells (or squamous cells in a few cases). Extensive tumour necrosis may lead to hypocellular smears.²⁷ If a spindle cell population predominates, sarcoma must be considered in the differential diagnosis (especially if the clinical picture is uncharacteristic). Immunocytochemical demonstration of keratin (with or without vimentin) in the tumour cells is helpful in distinguishing AC from sarcomas that do not show keratin. Immunocytochemical reactions for keratin may however be inconsistent or even

negative in spindle cell areas of AC.¹ As in the present series, ACs are usually inoperable tumours that rapidly kill the patient in less than a year.

While low grade lymphomas may be difficult to distinguish from HT, high grade NHLs pose no problem in cytological diagnosis and immunophenotyping can also be done on cytological material.³¹⁻³² All six cases in the present study were shown to be high grade NHLs of B-cell type, facilitating the institution of prompt chemotherapy. Remnants of HT such as Hurthle cells and degenerated follicular epithelium may be present, as seen in two cases.

Two of four cases diagnosed as metastatic/undifferentiated carcinoma were proven to be metastases from breast carcinomas. Tumours metastasising to the thyroid pose a special problem in cytological diagnosis as they too present as solitary cold nodules, sometimes after a long delay following therapy.^{1,33-35} A variety of benign and malignant lesions have to be considered in their differential diagnosis.³⁶ If the cytological appearance is that of a neoplasm, then a metastatic lesion must be distinguished from a new primary so that unnecessary surgery can be avoided. Rarely, a thyroid metastasis may be the presenting manifestation of a clinically occult primary (such as renal cell carcinoma).¹ It is worth remembering that most thyroid nodules, even in patients with known extra-thyroid malignancy, are benign.³⁷ The most common sources of thyroid metastasis are from colorectal, breast, lung and renal carcinomas and melanomas.^{35,38-39} Laryngeal carcinoma frequently invades the thyroid by direct extension.⁴⁰ Careful clinical evaluation, knowledge of the cytological appearance of benign thyroid lesions and differentiated thyroid cancers and awareness of a pre-existent malignancy at an extra-thyroidal site (with review of histologic slides of the previous cancer) are useful in the distinction of primary from metastatic thyroid lesions.

FNA and FNC are quick and easy, relatively non-traumatic techniques that are ideally suited for the evaluation of nodular and diffuse thyroid lesions. In experienced hands, complications are negligible and sensitivity and specificity of cytodiagnosis are higher than with any other investigative modality used in thyroid lesions.^{3,4,12,13} Being cost-effective and having the capacity to provide exact morphological diagnosis in a large variety of thyroid lesions, cytology is obviously the method of choice in the assessment of thyroid nodules.

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