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Cytological analysis of breast lesions: A review of 780 cases

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Abstract

780 breast cytology samples obtained over a one year period at the Breast Clinic of the University Hospital, Kuala Lumpur were reviewed. These included 745 fine needle aspirates (FNA's) and 35 nipple smears. The broad categories of cytodiagnoses were as follows: malignant: 95, suspicious or equivocal: 26, benign: 543, no proliferative lesion: 58 and inadequate: 58. The benign and malignant lesions were also subcategorized on cytological basis. The suspicious or equivocal lesions were subjected to biopsy and 17 of these proved to be malignant. 194 cases that were subjected to histological confirmation and 34 cases that were considered to be undisputably malignant (on the basis of clinical features, recurrences, metastases, etc.) were subjected to statistical analysis (total 228 cases). If the cytologically suspicious/equivocal category was considered as "test positive" the sensitivity of cytodiagnosis was 97.4% and the specificity 92%. The high degree of cytodiagnostic sensitivity and specificity make breast cytology a valuable adjunct in the evaluation of breast lesions.

Key words: Fine needle aspiration cytology, breast, nipple cytology.

INTRODUCTION

Fine needle aspiration (FNA) cytology has been established as a highly reliable technique in the initial evaluation of palpable and nonpalpable breast lumps.[1-6] Although the primary goal of FNA is to separate malignant lesions that require more radical therapy from benign ones that may be conservatively managed, the scope of cytology in identifying the subtypes of malignant and benign lesions can be exploited for the purpose of planning the therapeutic protocol and eventual follow-up.

In order to evaluate the efficacy of cytology in the diagnosis of breast cancer and to explore its scope in the identification of subtypes of malignant and benign lesions, we analysed 780 breast cytology samples obtained during the first year of onset of the Breast Clinic at the University Hospital, Kuala Lumpur.

MATERIALS AND METHODS

The 780 cases included 730 FNA samples from palpable lesions, 35 nipple smears, 13 FNA's done under stereotactic guidance and two under ultrasonographic guidance. FNA was done with a 21 or 22 gauge needle attached to a 20 c.c. plastic syringe mounted on a syringe holder for single hand grip.

Smears in all cases were routinely air-dried, fixed in methanol and stained with May Grunwald Giemsa (MGG). In selected cases, additional smears were wet fixed in ethanol for subsequent special staining procedures. All cystic lesions were evacuated following which the wall of the cyst was needled. The cyst fluid was also subjected to cytological study.

RESULTS

The cases were broadly categorized on cytological basis as follows: malignant, equivocal/suspicious, benign, no proliferative lesion and inadequate (Table 1). In 194 cases, histopathological study was possible from tissue obtained in the form of mastectomy, lumpectomy, open biopsy or hook wire-localization and excision. The broad cytohistological correlation in these cases is given in Table 2. Of 93 cytologically benign cases, 3 turned out to be malignant. Of 26 cases reported cytologically as equivocal/suspicious, 19 proved

TABLE 1: Broad category of cytodiagnosis in 780 breast lesions

Category of cytodiagnosis	No	%
Malignant	95	12.2
Suspicious/Equivocal	26	3.3
Benign	543	69.7
No proliferative lesion	58	7.4
Inadequate	58	7.4
Total	780	100

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TABLE 2: Cytohistological correlation in 194 breast lesions

Cytology	No.	Histopathology	
		Benign	Malignant
Benign	93	90	3
Equivocal/Suspicious	26	7	19
Malignant	61	1	60
Inadequate	14	11	3
Total	194	109	85

malignant. Of 61 cases diagnosed cytologically as malignant, 1 turned out to be benign. Of the inadequate aspirates 3 subsequently proved to be malignant. For statistical evaluation, 34 cases diagnosed on cytology as malignant and proved to be undisputably malignant (on the basis of clinical features, metastases, recurrences) were added to the 194 cases in which histopathological confirmation was available (total 228 cases). If the cases diagnosed cytologically as equivocal1 suspicious were considered as positives, the sensitivity of cytological diagnosis was 97.4%, specificity 92.4% and the false positive cytodiagnostic rate 6.6%.

Cytological subcategorization

Table 3 shows the cytological subcategorization of 543 cases diagnosed as benign. *Fibrocystic condition* (FCC) and *fibroadenoma* (FA) were the most common benign cytological diagnoses constituting 39.8% and 32.8% respectively. Smears from FCC usually showed apocrine and foam cells and occasionally nonapocrine cells. Apocrine cells not uncommonly showed degenerative atypia. Smears of FA were cellular with monomorphic epithelial cells in cohesive clusters, intracanalicular and 3-dimensional pattern. In 11.2% of cases there was evidence of benign epithelial proliferation and the clusters often showed lobular configurations and cytoplasmic vacuolation. There were no clinical or cytological features of FA-like stroma fragments or abundance of bipolar nuclei nor features of FCC such as cystic change or apocrine metaplasia. These cases were labelled cytologically as *"benign lobular proliferative lesions"* (BLPL). 7.7% of cases that were similar but lacked lobular configurations were labelled as "benign proliferative lesion."

TABLE 3: Distribution of 543 cytologically benign breast lesions

Cytological diagnosis	No.	%
1. Fibroadenoma	178	32.8
2. Fibrocystic condition	216	39.8
3. Phyllodes tumour	11	2
4. Duct papilloma/papillary proliferative lesion	8	1.5
5. Benign proliferative lesion	42	7.7
6. Benign lobular proliferative lesion	61	11.2
7. Inflammatory/granulomatous	20	3.7
8. Fat necrosis	2	0.4
9. Duct ectasia	5	0.9
Total	543	100

Cytodiagnosis of *phyllodes tumour* (FT) was made in 2% of cases. Smears in these cases resembled FA but the stromal fragments were often large and hypercellular and in the background spindled-out or elongated stromal cells were seen that sometimes showed mild atypia.

When small or large papillary clusters with many 3-D fragments, twisted epithelial fragments and apocrine cells were seen, a diagnosis of *duct papilloma/papillary proliferative lesion* was suggested with a cautionary note that intraductal papillary carcinoma could not be ruled out on cytological basis.

Non-proliferative breast lesions were labelled as inflammatory/granulomatous lesions, duct ectasias and fat necrosis.

Histological correlation was possible in 109 benign lesions in which some form of biopsy was done. Table 4 shows the cytohistologic correlation in these cases. Of 60 FA's, 44 had been correctly designated on cytology, 1 was mistaken for FT, 1 for FCC, and in one the cytological picture was equivocal. In 8 the lesion was too small or too sclerotic yielding inadequate cytological material. 5 lacked distinctive cytological features of FA and were labelled as BLFL. As most cases of FCC were

TABLE 4: Cytohistological correlation in 109 cytologically benign breast lesions

		Cytodiagnosis							
Histopathology	No.	FA	PT	FCC	DP/PPL	BLPL	Infl/Gran	E/S/M	NP/Inadeq
DP	**6**	-	-		4			2	
TA	1	1	-						
Infl/gran	11	-	-				10	1	
FA	**60**	**44**	1	1		5		1	8
FCC	22	3	-	3	2	4		4	**6**
PT	8	2	4	-		1			1

FA : fibroadenoma, PT : phyllodes tumour, FCC : fibrocystic condition, DP : duct papilloma, PPL : papillary proliferative lesion, BLPL : benign lobular proliferative lesion, Infl : inflammatory, Gran : granulomatous, E : equivocal, S : suspicious, M : malignant, NP : no proliferative lesion, Inadeq : inadequate, TA : tubular adenoma

subjected to therapeutic aspiration, histological material was available for correlation in only 22 cases. In these cases excision was done for one of the following reasons: high risk group, suspicious mammographic findings, patient anxiety, clinical suspicion of malignancy, equivocal cytology etc. 3 of these cases had been correctly designated as FCC, 3 mistaken for FA, 2 for DP/PPL and in 6 cases the aspirate was inadequate or showed no evidence of epithelial proliferation. In 5 cases the presence of a BLPL was suggested and 4 cases showed apocrine atypia that was severe enough to place them in the equivocal/suspicious cytological category. In 4 of 6 cases of duct papilloma the clinico-cytological picture was characteristic. 2 cases that were placed in the equivocal category showed focal cytological atypia. 4 out of 8 cases of PT were correctly designated, 2 were mistaken for FA, 1 labelled as BLPL and in 1 the aspirate was inadequate. The inflammatory/granulomatous category included one very unusual case of inflammatory pseudotumour in which highly reactive epithelial cells and young fibroblasts with large nuclei and prominent nucleoli led to a false positive cytodiagnosis of malignancy.

Malignant lesions

In 85 cytologically malignant lesions, histological material was available for study in the form of lumpectomy or mastectomy. The cytohistologic correlation in these cases is given in Table 5. 50

TABLE 5: Cytohistological correlation in 85 breast lesions subjected to histopathological study

Histodiagnosis	No.	Cytodiagnosis	No.
IDC (NST)	70	Ca (NST)	50
		Suspicious	17
		Inadequate	3
Paget's with DCIS	2	Paget's	2
Medullary Ca	3	Ca (NST)	2
		Medullary Ca	1
Mucous Ca	2	Mucous Ca	2
Infiltrating Pap Ca	2	Pap Ca	1
		BPL	1
DCIS	3	Suspicious	1
		FCC with apocrine atypia	1
		BPL	1
Infiltrating comedo Ca	1	Medullary Ca	1
Tubular Ca	1	ILC	1
ILC	1	Ca (small cell type)	1

Ca = Carcinoma; IDC-NST = invasive ductal carcinoma of no special type; Pap = Papillary; DCIS = Ductal carcinoma in-situ; BPL = benign proliferative lesion; ILC = invasive lobular carcinoma.

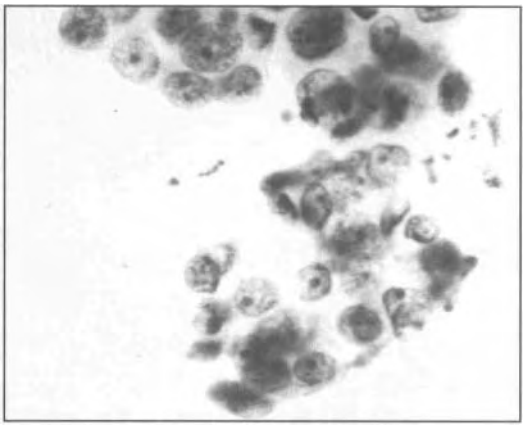

FIG. 1: **Pleomorphic malignant cells with prominent nucleoli in an invasive ductal carcinoma of no special type. Pap x 400**

of 70 ***invasive ductal carcinomas of no special type*** (IDC-NST) had been correctly designated. Smears in these cases showed high cellularity with dissociated and clustered large cells with nuclear pleomorphism, prominent nucleoli (Fig. 1) and brisk mitotic activity. Features such as acinar-ductal pattern, papillary pattern and intracellular mucin were variable. 17 cases were designated as cytologically suspicious either because the atypia was not pronounced, lack of cell cohesion was not evident or because numerous benign cells were admixed with the atypical ones. **3** cases in which the aspirate was inadequate had presented with peau d'orange lesions that were then subjected to tru-cut biopsy to confirm the clinical diagnosis. In both cases of ***Pager's disease*** (Fig. **2)** smears from the eczematoid nipple lesion showed pleomorphic malignant cells some with clear cytoplasm (Fig. **3)** and occasional cell in cell pattern. All **3** cases of ***medullary carcinoma*** showed highly

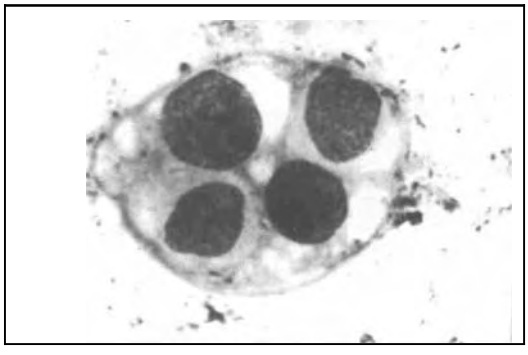

FIG. 3: Nipple smear showing Paget cells with clear cytoplasm. MGG **× 800.**

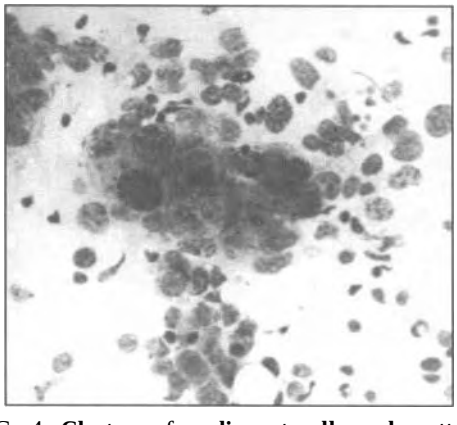

FIG. 4: **Clusters** of **malignant cells and scattered lymphoid cells in medullary carcinoma.** MGG **× 400**

pleomorphic epithelia1 cells in clusters (Fig. **4)** and dissociated pattern (Fig. 5) with scattered lymphoplasmacytic cells around them. (Figs. **4** & 5) The latter were however overlooked in **2** of the cases.

Mucoid carcinomas showed a very distinctive cytological picture consisting of sheets of monotonous bland small to medium sized

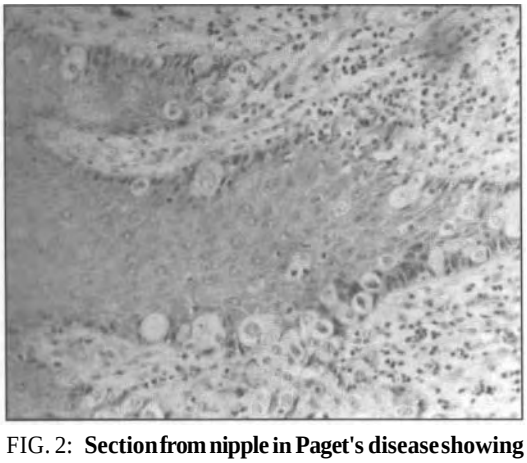

FIG. 2: **Section from nipple in Paget's disease showing Paget cells.** H&E **x 250**

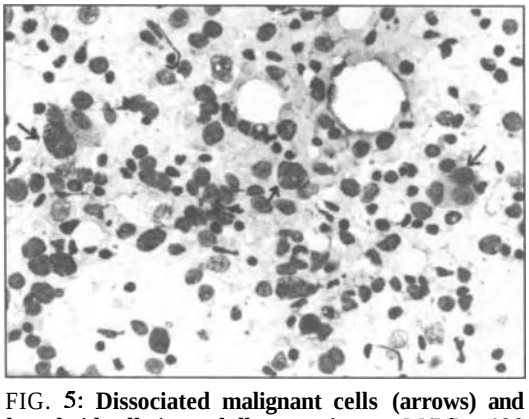

FIG. **5: Dissociated malignant cells (arrows) and lymphoid cells in medullary carcinoma. MGG × 400**

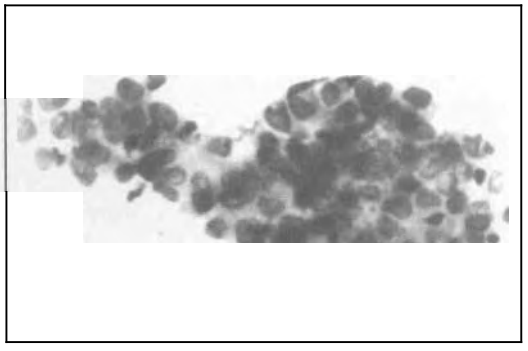

FIG. 6: Cluster of monotonous bland tumour cells in mucous carcinoma. MGG x 400

epithelia1 cells (Fig. 6) floating in whirlpools of mucin that often stained metachromatic with the MGG stain. Intracellular mucin was seen in occasional cells. In spite of the uniformity of the cells, the characteristic morphology enabled correct cytodiagnosis in both cases of mucoid carcinoma which were confirmed on histopathology (Fig. 7).

One of the two cases of ***papillary carcinoma*** showed papillary clusters of tumour cells as well as isolated cells while the other showed no obvious papillary pattern or atypia and was labelled as benign on cytology. The three cases of ***in-situ ductal carcinoma*** (DCIS) also showed a cytologically benign or equivocal pattern. One case each of ***infiltrating comedocarcinoma, invasive lobular carcinoma*** (ILC) and ***tubular carcinoma*** were labelled correctly as malignant on cytology but were incorrectly typed. Smears from ILC showed small cells with occasional cytoplasmic vacuolation in dissociated pattern

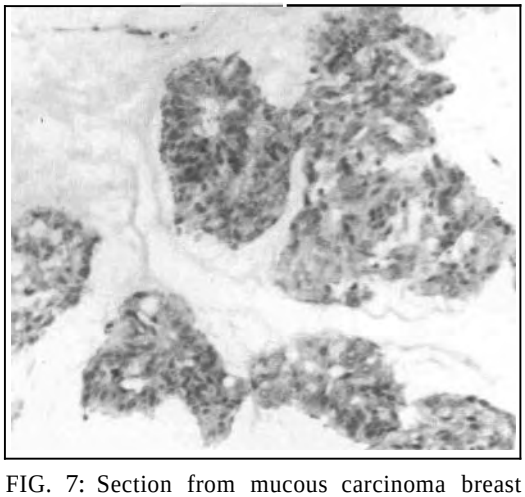

FIG. 7: Section from mucous carcinoma breast showing papilloglandular structures with abundant extracellular mucin. H&E x 250

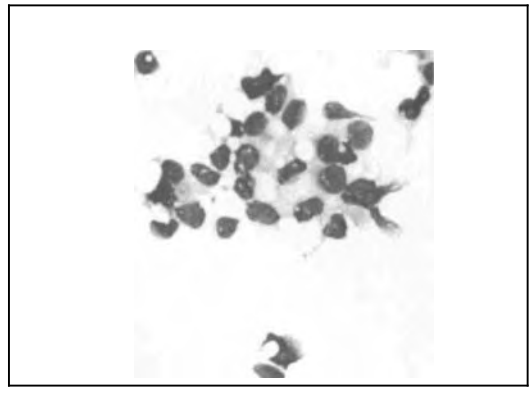

FIG. 8: Clustered and dissociated small cells with focal cytoplasmic vacuolation in invasive lobular carcinoma. MGG × 400

and small clusters (Fig. 8) that led to a cytological diagnosis of carcinoma breast (small cell type). Histological sections of the tumour showed the typical targetoid and Indian file pattern characteristic of ILC. The case of tubular carcinoma showed a relatively bland cytological picture (Fig. 9) that was taken as suggestive of ILC.

DISCUSSION

Cytology has moved gradually but unswervingly from an era of 'positive,' 'negative' and 'suspicious' diagnosis to an era of specific morphological typing of benign and malignant neoplasms as well as non-neoplastic lesions[7] and the breast is no exception. FNA today occupies an extremely important role in pre-operative evaluation of breast lesions and in most centres patient management is decided on the basis of the cytological report.

Although prior cytological typing of breast carcinoma may have little influence on the surgical management of a case, awareness of certain types of carcinoma (e.g. tubular, mucinous, lobular) is necessary to correctly identify these lesions.[8] Furthermore, reconfirmation of prognostically favourable histological types is necessary to select patients for pre-operative chemotherapy.[7]

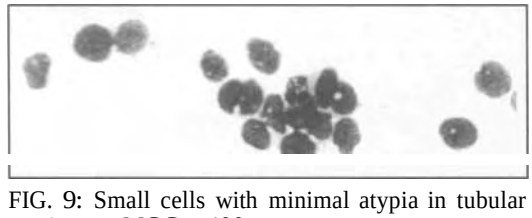

FIG. 9: Small cells with minimal atypia in tubular carcinoma. MGG × 400

In this study it was possible to categorize with ease cases of IDC (NST), mucoid carcinoma and Paget's disease. .About half of the cases of medullary carcinoma and papillary carcinoma could also be correctly typed. With increasing experience, we believe it would be possible to correctly type cases of ILC and tubular carcinoma, both of which have a bland cytological appearance and overlapping morphological features.[7]

While Masood *et al*[9] and Sneige *et al*[10] found it difficult to distinguish DCIS from invasive ductal carcinoma on FNA, Venegas *et al*[11] described distinctive cytological criteria indicative of DCIS. In our 3 cases, it was more difficult to distinguish DCIS from benign proliferative lesions as the former lacked significant atypia.

Lesions classified cytologically as 'benign' can be followed up clinically or removed only if the patient so desires for cosmetic or psychological reasons.[12] As described and illustrated in detail by one of us (GJ) in an earlier series,[13] we were able to type most of the cases of FA and FCC as well as many of the other benign lesions. Cytological typing is very useful in FCC because FCC (in the absence of epithelial proliferation) can be managed by therapeutic aspiration and clinical, mammographic and cytological follow-up. The cytological distinction of 50% of PT's from FA's enabled excision with a wider margin (which is the treatment of choice in PT).

The papillary nature of the proliferation was cytologically discernable in 4 of 6 cases of DP enabling microdochotomy or excision depending on the clinical setting. In 2 cases it was not possible to distinguish DP from PC. Dawson and Mulford,[14] in a retrospective analysis of 29 papillary breast lesions, found markedly increased cellularity and numerous single cells to favour a diagnosis of papillary carcinoma.

The most valuable role of cytology in benign lesions was in the distinction of epithelial proliferative lesions from non-proliferative and inflammatory or granulomatous lesions. Aspirates in the latter could be stained for microorganisms and/or sent for microbiological culture.

Data on the limited number of cases in the first year of our breast clinic justify the approach using FNA to evaluate and guide the treatment in palpable and non-palpable breast lesions. FNA of breast in experienced hands has a sensitivity of 90%, specificity of 95% and a positive predictive value of 95%.[15,16] With increasing confidence in cytodiagnostic accuracy cytological evaluation will no doubt provide the basis worldwide for planning of definitive treatment in breast lesions.

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