

Fine needle aspiration cytology of benign breast lumps: a review of experience with 651 cases

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Abstract

A detailed cytomorphologic study was done on fine needle aspiration smears from 651 benign breast lumps. Cytological categorization enabled the distinction of proliferative from non-proliferative and infective lesions in the majority of the cases. Lumpectomy provided the histological diagnosis in 584 cases, most of which were proliferative lesions. Gross cystic disease and fibroadenoma were the most common lesions encountered. Microcysts with apocrine change, sclerosing adenosis, proliferative disease without atypia, atypical ductal hyperplasia, atypical lobular hyperplasia, and lobular carcinoma *in situ* were associated with the dominant lesion in many of the cases. In all these cases, retrospective analysis of the cytological smears was done in an attempt to identify cytological features which may indicate these lesions.

Key words: Breast, cytology, fibroadenoma, hyperplasia, carcinoma.

INTRODUCTION

Fine needle aspiration (FNA) cytology has not only proved to be invaluable in the distinction of malignant from benign breast lesions but has also replaced the era of positive-negative and suspicious cytological diagnosis with an ever enlarging potential of accurate morphological typing of various breast lesions, including benign lesions.¹⁻¹⁰ We present a morphological analysis of FNA cytological smears from 651 palpable breast lumps.

MATERIALS AND METHODS

From August 1981 to December 1989, 651 patients (598 females and 53 males) presenting in the surgery outpatient department of Lok Nayak Jai Prakash Narain hospital with clinically benign breast lumps were referred for FNA cytology. Their ages ranged from 14 to 63 years. All cases were examined by the cytopathologist (GJ) who then performed the aspiration using a 21 or 22 gauge needle attached to a 20 cc plastic syringe that was mounted on a handle for single hand grip. The aspirate was expelled onto clean glass slides, smeared, air dried, fixed in methanol and stained with May Grunwald Giemsa. In cases where fluid was aspirated, cytospin preparations of the fluid were made and stained. In cystic lesions, complete evacuation of the cyst was attempted and this was followed by needling of the wall of the cyst. The number of needle

passes in each case varied from two to four or five depending on the size and consistency of the lump. In 21 cases in which there was associated nipple discharge, cytological smears from the nipple discharge were prepared. The cytological smears were studied in detail and a clinico-cytological diagnosis (incorporating the clinical and cytological features in each case) was made. In 584 cases, excision biopsy was done. The material was processed routinely and detailed histological study was performed.

RESULTS

In most cases one and in a few cases more than one palpable breast lump was present. 21 females had, in addition, nipple discharge. In 15 cases the discharge was bilateral and could be expressed from multiple ducts. In six cases it was unilateral, with five having single duct discharge while one patient had discharge from two ducts. The discharge was serous or serosanguinous.

The histological diagnoses, correlated with the cytological diagnoses in 584 lumpectomized cases, are given in Table 1. A correct cytological diagnosis could be made in 539 cases (92.2%). Gross cystic disease (GCD) was the most common lesion followed by fibroadenoma (FA). The FNA cytological features of GCD, FA, phylloides tumor, gynaecomastia and duct papilloma are depicted in Table 2. GCD was characterized by fluid aspirate with mainly apocrine cells (Fig. 1)

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TABLE 1: Histo-cytologic correlation in 584 Cases

No.	Histological diagnosis	No. of cases	Cytological diagnosis	No. of cases
1.	Gross cystic disease*	247	Gross cystic disease	246
			Gross cystic disease with apocrine carcinoma	1
2.	Fibroadenoma**	223	Fibroadenoma	191
			Benign proliferative lesion	32
3.	Gynaecomastia***	52	Gynaecomastia	51
			Gynaecomastia with suspicion of carcinoma	1
4.	Benign phyllodes tumour	18	Benign phyllodes tumour	15
			Giant fibroadenoma	3
5.	Giant fibroadenoma	12	Giant fibroadenoma	8
			Benign phyllodes tumour	4
6.	Duct papilloma****	12	Duct papilloma/papillary hyperplasia/papillary carcinoma	10
			Benign proliferative lesion	2
7.	Fat necrosis	8	Fat necrosis	8
8.	Duct ectasia	7	Duct ectasia	7
9.	Papillary adenoma	1	Papillary adenoma	1
10.	Lactating adenoma	1	Lactating adenoma	
11.	Pilomatrixoma	1	Giant cell lesion	1
12.	Echinococcal cyst	1	Echinococcal cyst	1
13.	Tumour adenosis	1	Invasive lobular carcinoma	1
	Total	584	Total	584

Associated Changes:

Microcysts with apocrine change **21, ***1
 Sclerosing adenosis *9 **14
 Proliferative disease without atypia *142 ****5
 Atypical ductal hyperplasia *3 **6 ****1
 Atypical lobular hyperplasia *4 **2
 Lobular neoplasia in situ *2

and foam cells. The lobular pattern of GCD could be appreciated in a few cases and in an occasional case, apocrine cells showed admixture with myoepithelial cells (Fig. 2). Apocrine cell atypia in one case led to a false positive diagnosis of malignancy. 15 cases of GCD also had bilateral serous nipple discharge emanating from multiple ducts. Smears of nipple discharge showed scattered and clustered foam cells. Smears from FA were usually very cellular with monomorphic epithelial cells in cohesive clusters and antler horn pattern with many scattered bipolar naked nuclei and stroma fragments (Figs. 3 & 4). Cells in the periphery of the clusters often showed

cytoplasmic vacuolation (Fig. 5) that sometimes compressed or indented the nucleus. 32 cases where scattered bipolar naked nuclei were scanty and/or the clinical picture not characteristic were designated as benign proliferative lesions (BPL). 5 cases of FA showing nuclear atypia included two adolescent, one pregnant and one lactating patient, and one patient who had associated atypical ductal hyperplasia (ADH) (Fig. 6).

Giant FA showed the same cytological picture as FA and four cases that showed slightly hypercellular stroma fragments were mistaken for phyllodes tumor.

Stroma fragments in phyllodes tumour were

TABLE 2: Cytological features in benign breast lumps

	GCD	FA & giant FA	Phyllodes tumour	GM	Duct papilloma
Fluid	Present (straw coloured, turbid or greenish)	Absent	Infrequent	Absent	Absent
Cellularity	Mild to moderate	Usually high	Usually high	Moderate to high (young patients) low (old patients)	Moderate to high
Nonapocrine cells	Less frequent	Very frequent	Frequent	Frequent	Frequent (often in twisted or papillary pattern)
Apocrine cells	Very frequent	Less frequent	Less frequent	Infrequent	Frequent
Vacuolated cells	Infrequent	Frequent	Frequent	Frequent	Absent
Bipolar nuclei	Infrequent	Very frequent	Very frequent (often spindle & elongated forms)	Infrequent	Infrequent
Foam cells	Frequent	Infrequent	Less frequent	Infrequent	Infrequent
Stroma fragments	Absent	Frequent	Frequent, usually hypercellular, frequently pleomorphic	Absent	Absent
Apocrine cell atypia	Occasional	Absent	Absent	Absent	Absent
Nonapocrine cell atypia	Absent	Infrequent	Absent	Infrequent	Infrequent

GCD = Gross cystic disease ; FA = Fibroadenoma ; GM = Gynaecomastia.

more numerous and more cellular (Fig. 7) with some enlarged spindle shaped or plump stromal cells that showed mild atypia (Fig. 8). Elongated or spindle forms of naked nuclei were common. In four cases numerous ball-like masses of mucoid material (Fig. 9) and in two cases vascular myxoid tissue fragments (Fig. 10) were seen. The three cases mistaken for giant FA showed a picture similar to FA with a mild increase in the cellularity of stroma fragments and naked nuclei.

Smears from young males with gynaecomastia (GM) resembled fibroadenoma (Fig. 11), but bipolar naked nuclei were few and stroma fragments absent. In one of these cases there was focal mild to moderate nuclear pleomorphism which, combined with high cellularity, gave rise to an erroneous cytological diagnosis of carcinoma. Smears from elderly patients with

GM were poorly cellular.

6 out of 12 duct papillomas presented with nipple discharge. Smears from these showed small papillary clusters of ductal and foam cells admixed with spindle cells. Cells with cytoplasmic vacuolation and occasional signet ring forms were present. Cell in cell arrangement was seen in some of the clusters and dissociated cells were also present. The ductal cells sometimes showed degenerative changes. FNA smears from duct papilloma showed cohesive clusters of nonapocrine and apocrine epithelial cells admixed with spindle cells often in twisted pattern (Fig. 12), finger-like clusters and papillary clusters (some with fibrovascular core). 10 of these cases which included the six cases with nipple discharge, were designated on cytology as duct papilloma/papillary hyperplasia/low grade

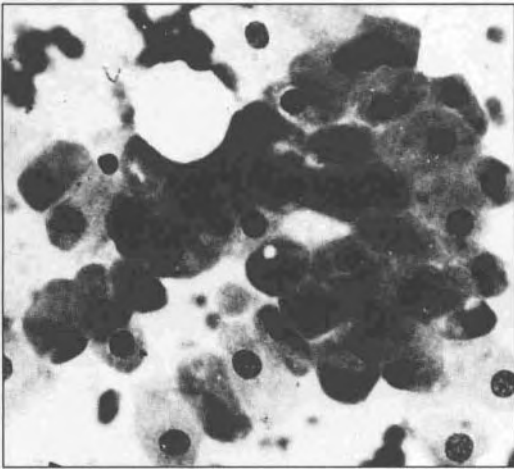


FIG. 1: Clusters of apocrine cells in gross cystic disease. MGG X 400.

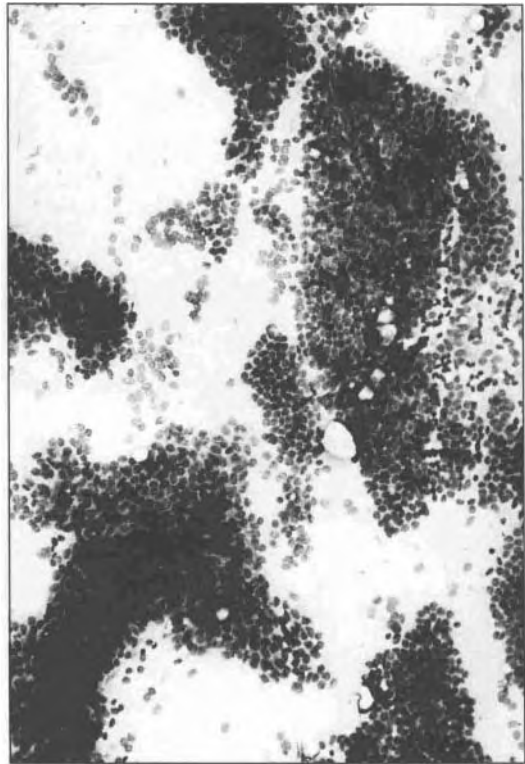


FIG. 3: Cellular smear with cohesive clusters of monomorphic cells in fibroadenoma. MGG X 250.

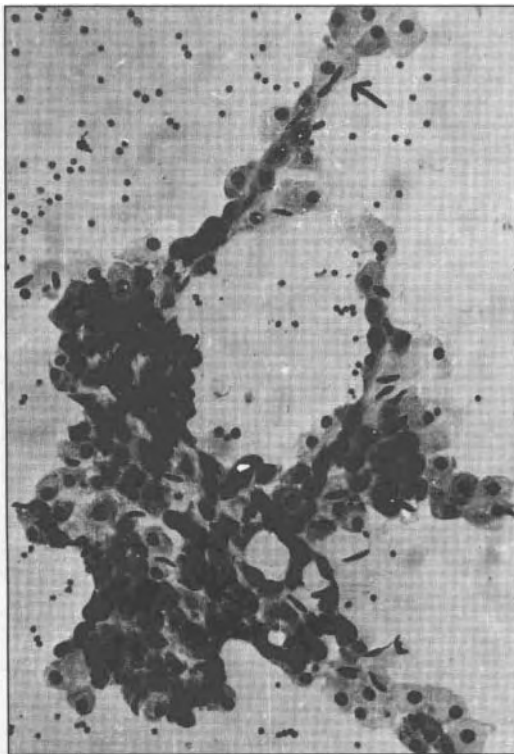


FIG. 2: Admixture of myoepithelial cells (arrow) with apocrine cells in gross cystic disease. MGG X 250.

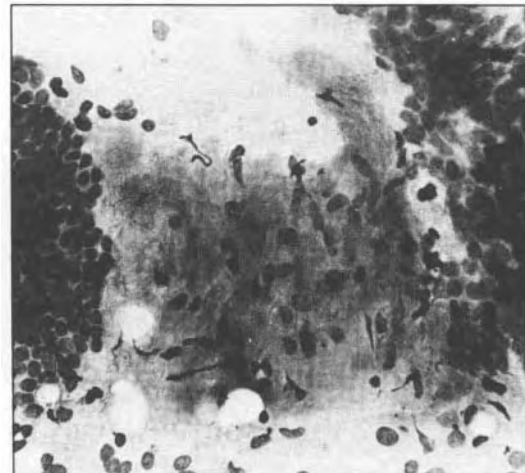


FIG. 4: Stromal fragments in fibroadenoma. MGG X 300.

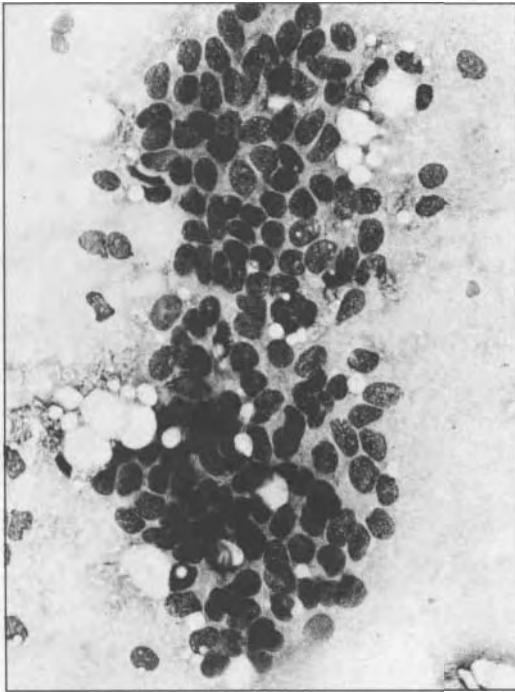


FIG. 5: Cytoplasmic vacuolations in cells of fibroadenoma. MGG X 400.



FIG. 7: Cellular stromal fragment in phyllodes tumour. MGG X 250.

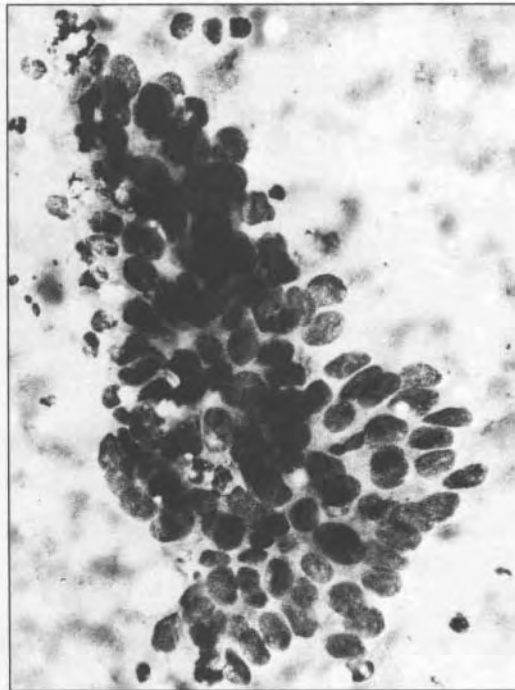


FIG. 6: Mild nuclear enlargement and pleomorphism in fibroadenoma associated with atypical ductal hyperplasia. MGG X 400.

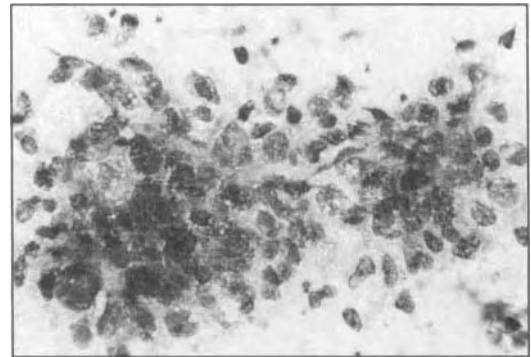


FIG. 8: Atypia of stromal cells in phyllodes tumour. MGG X 400.

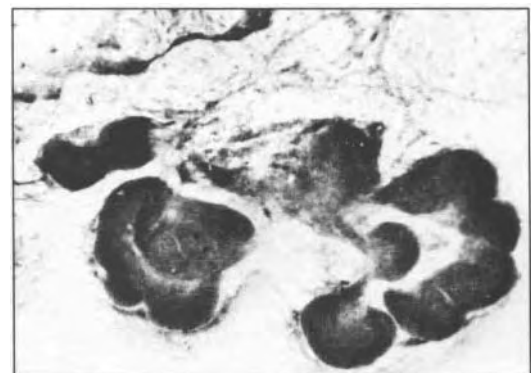


FIG. 9: Ball-like masses of mucoid material in phyllodes tumour. MGG X 150.

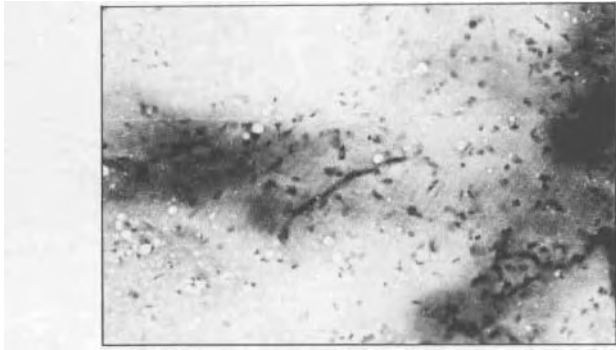


FIG. 10: Vascular myxoid tissue fragments in phyllodes tumour. MGG X 200.



FIG. 12: Apocrine cells and twisted pattern of nonapocrine epithelial cells in duct papilloma. MGG X 400.

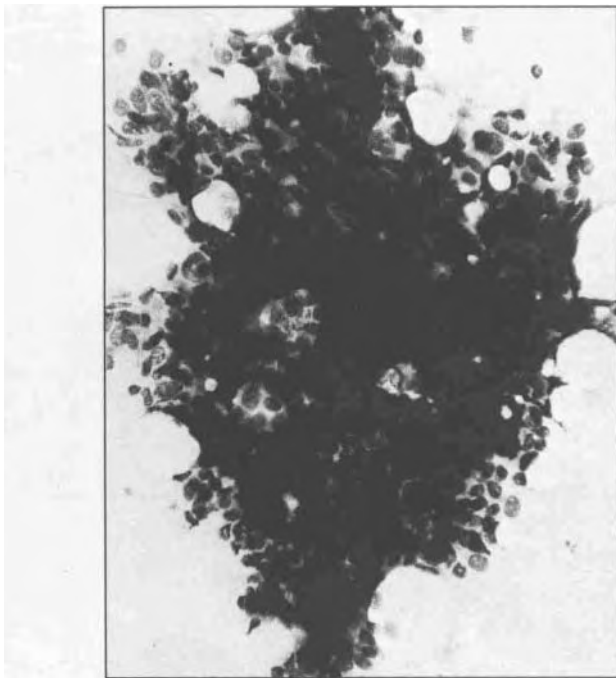


FIG. 11: Cohesive cluster of epithelial cells in gynaecomastia. MGG X 400.

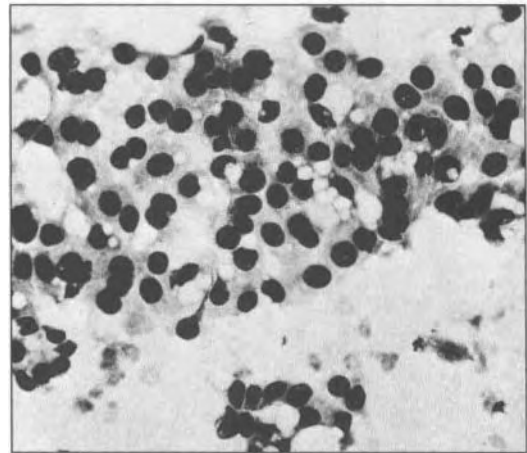


FIG. 13: Prominent cytoplasmic vacuolation in cell cluster in lactating adenoma. MGG X 350.

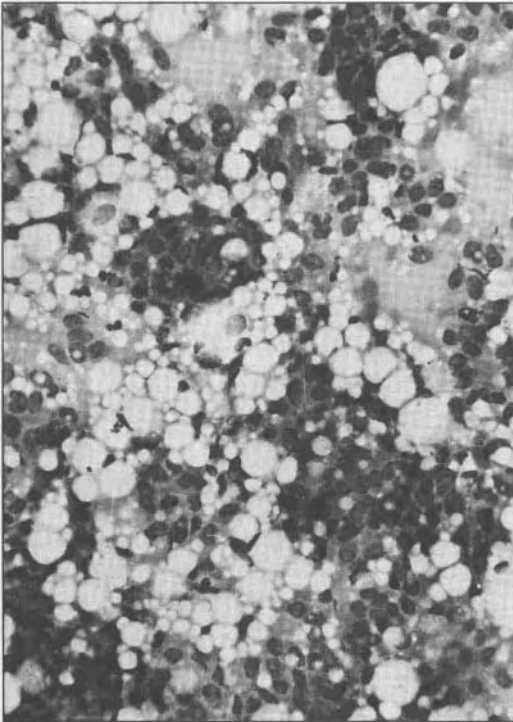


FIG. 14: Small clusters of monomorphic cells in close association with fat cells. MGG X 350.

papillary carcinoma. In two cases in which the papillary clusters were not prominent, a diagnosis of BPL was given. In the patient who had discharge from two ducts, surgery and histopathology demonstrated the presence of two duct papillomas. After six years, this patient developed intraductal solid and cribriform carcinoma which occurred in the same quadrant of the breast from which the papillomas were excised.

The solitary case of papillary adenoma of the nipple has been reported." The smears were highly cellular with cohesive clusters of epithelial cells, three dimensional tissue fragments, numerous bipolar naked nuclei, and papillary clusters of ductal cells (some with apocrine change) and occasional stromal fragment.

The solitary case of lactating adenoma showed cohesive clusters of epithelial cells with prominent intracytoplasmic vacuoles seen in almost all the cells (Fig. 13). Spindled out or elongated (myoepithelial) cells were interspersed with epithelial cells in a few clusters and stromal fragments were absent.

The single case of sclerosing adenosis presented with a palpable tumour (tumour adenosis). The mass was firm and poorly delineated, relatively fixed, clinically indistinguishable from carcinoma and measured

two centimeters in size. Smears were very cellular with small clusters of monomorphic cells and cells in acinar grouping closely associated with fat cells (Fig. 14). Smaller groupings of four to six cells, cells with vacuolated cytoplasm and cells with mild nuclear pleomorphism were additional features. This case was mistaken for invasive lobular carcinoma.

Seven cases of duct ectasia showed a subareolar small nodule and in five of them nipple retraction was present along with a history of difficulty in lactation. Thick yellow or brownish paste-like material was aspirated and smears showed acellular deeply staining material, a few foam cells and occasional ductal cells. In cases with associated periareolar or subareolar abscess, many polymorphs were also present.

Two out of eight cases of fat necrosis were clinically diagnosed as breast carcinomas. Smears showed amorphous acellular material with many foam cells, some multinucleate cells, clusters of fat cells with granular cytoplasm and scattered polymorphs and fibroblasts.

The case of pilomatrixoma has been described earlier.¹² Smears showed thick, deeply staining clumps of anucleate squames, numerous mononucleate histiocytic cells and a few multinucleate giant cells. A descriptive cytological report was given ruling out malignancy and suggesting a giant cell lesion.

The case of echinococcal cyst of the breast was clinically mistaken for GCD. Fluid was aspirated and cytopspin smears showed hydatid scolices. The patient developed a severe local hypersensitivity reaction subsequent to FNA cytology.

In one patient with a mobile left lateral breast nodule which clinically simulated FA, smears showed many microfilariae of *Wuchereria Bancrofti*. This case was not subjected to histopathological study as were 66 other cases which included 24 cases of breast abscess, 19 galactocoeles, nine cases of tuberculous mastitis and 14 granulomatous mastitis. Aspirates from breast abscesses were purulent, and composed of numerous degenerating and viable polymorphs. The material was sent for culture in all the cases.

Milky fluid was aspirated from galactocoeles. Smears showed amorphous material and lipid in the background with a few scattered lipid filled foam cells.

The cases of tuberculous mastitis have been described in detail.¹³ Epithelioid cell granulomas with giant cells, cheesy necrotic material and the presence of acid fast bacilli enabled cytological diagnosis and distinction from granulomatous

mastitis in which only non-caseating granulomas were present. The latter occurred almost invariably in lactating or pregnant females.

DISCUSSION

Incorporating clinical and cytological data, we could accurately categorize benign breast lesions in 92.2% of cases and this helped in deciding the therapeutic protocol (i.e. surgery versus conservative treatment, enucleation versus wider resection etc.) We also attempted to evaluate the scope of cytology in the distinction of the atypical ductal and lobular lesions¹⁴⁻¹⁷ which sometimes accompanied the dominant presenting lesion.

Fibrocystic disease (FCD) was the most common lesion in women in the reproductive years and was the most easily classified on clinicocytological basis. We agree with Suen *et al*¹⁴ that in the absence of fluid, the distinction of FCD from FA may not be possible. However, in this series we have taken only the FCDs presenting as palpable lumps i.e gross cystic disease (GCD). Stromal fragments which are usually seen in FA are absent in GCD and in the bilateral lumpy breasts of FCD, and bipolar naked nuclei, usually numerous in FA, are fewer in FCD and absent in GCD. Nonapocrine epithelial cells dominate in FA while GCD shows mainly apocrine cells. The cases of FA classified as benign proliferative lesions were clinically and/or cytologically uncharacteristic. GCD is an ideal target for FNA cytology with a high diagnostic accuracy and therapeutic significance.¹⁴ Apocrine cell atypia caused false positive cytodiagnosis in one of our cases of GCD. Single or syncytial fragments of apocrine cells with marked cellular and nuclear pleomorphism, irregular nuclear chromatin and multiple large nucleoli, have been found to be indicative of malignancy, while admixture of frankly benign appearing cells with atypical apocrine cells usually precludes malignancy.¹⁶⁻¹⁸ It is extremely unusual to aspirate sanguinous fluid in GCD and if blood is aspirated it is more likely to be an intracystic carcinoma.¹⁹ In all cystic masses, reaspiration of any residual mass is recommended" and even in the absence of a residual mass, we have found that reaspiration of the wall of the cyst yielded fairly cellular smears with more likelihood of viable epithelial cells. The cyst wall could also presumably be a good target for the detection of associated epithelial proliferative lesions with or without atypia (ADH or PDWA). Fluid may also be aspirated in pseudocysts and intracystic papilloma, turbid

yellow green in the former and bloody in the latter."

Phyllodes tumour could be distinguished in most of the cases from FA by virtue of the increased number and cellularity of stromal fragments, more numerous naked nuclei with many spindle and elongated forms. Mild to moderate nuclear atypia of stromal cells and in some cases ball-like masses¹⁴ of mucoid material or vascular myxoid tissue fragments were additional features. The cytomorphology of phyllodes tumour and their distinction from FA has been described in detail.^{6,16}

Cases of phyllodes tumour that were clinically uncharacteristic or in which stromal hypercellularity was overlooked, were misdiagnosed as FA. On the other hand, four cases of giant FA showing mild hypercellularity of stromal fragments were mistaken for phyllodes tumour. Giant FA has been used as a synonym for phyllodes tumour, which is unfortunate since the two conditions occur in different age groups, show different histopathological features, behave differently and require slightly different surgical procedures.^{16,20}

The cases of gynaecomastia (GM) all presented as retro-areolar nodules. While epithelial efflorescence was usual in younger patients of GM, smears from older patients showed only mild or moderate cellularity. Russell *et al*²¹ also described the presence of tall columnar cells with abundant wispy cytoplasm. Epithelial atypia prompted us to misdiagnose one case of GM as carcinoma. Pinedo *et al*²² noted epithelial atypia in GM due to chemotherapy and concluded that in some cases, distinction of atypia from carcinoma may be impossible. Male breasts may show the whole spectrum of changes seen in the female breast including sclerosing adenosis,²³ apocrine change and epithelial hyperplasia, mimicking an atypical pattern.

Duct papilloma may present with serous or sanguinous nipple discharge, breast lump or both. Discharge usually emanates from a single duct and smears show papillary clusters of ductal cells admixed with spindle cells, foam cells and occasional signet ring forms. Dissociated cells, degenerating ductal cells and occasional cell in cell arrangement can be present. FNA smears may resemble FA. In addition, however, papillary clusters, some with fibrovascular core, and twisted ductal cell fragments are frequent. Stromal fragments are absent and bipolar naked nuclei scanty. Distinction from papillary hyperplasia and low grade papillary carcinoma is difficult¹⁴ and so we have designated most of the lesions as

duct papilloma/papillary hyperplasia/low grade papillary carcinoma. Shu *et al*¹⁴ found absence of myoepithelial cells helpful in the distinction of papillary carcinoma from papilloma but their illustrations show a considerable degree of morphological overlap between the two lesions and we feel that biopsy is recommended in difficult cases. Distinction from ADH and PDWA may also be difficult¹⁴ and two cases with uncharacteristic morphology have been designated as BPL.

Papillary adenoma is a clinically characteristic lesion.²⁴ We have described the cytological picture which includes features of FA and duct papilloma.¹¹

Sclerosing adenosis may present as a palpable tumour (tumour adenosis)²⁴ and may project into mammary fat thus simulating carcinoma both clinically and histologically. The lobular configuration of the lesion and the circular pattern of cell infiltration, helpful in the histological distinction of sclerosing adenosis,²⁴ cannot be appreciated in cytological smears as brought out by our case which was mistaken for an invasive lobular carcinoma.

Epithelial proliferative lesions of the breast have been studied in depth by Page and Anderson¹⁵ with the idea of prognostication especially with regard to the subsequent risk of breast cancer in these cases. One of the aims of the present study was to explore the potential of FNA cytology in detecting associated epithelial proliferative lesions and their categorisation into atypical and nonatypical lesions.¹⁵ Epithelial hyperplasia has long been regarded as one of the component parts of the fibrocystic disease (FCD) complex¹¹ and as the change most likely to produce the elevated cancer risk in FCD. The presence of well preserved clusters of non-apocrine epithelial cells in GCD may be an indicator of accompanying proliferative disease without atypia (PDWA) or ADH. There were no cytological features of atypia to distinguish the latter from PDWA. This can be well expected in view of the fact that the "pattern criteria" or combined "pattern and cellular criteria" are today the basis of distinguishing ADH from PDWA.¹⁵

Bibbo *et al*¹⁷ had earlier used cytological atypia in the grading of epithelial proliferative lesions. Shu *et al*'s¹⁴ cytological illustration of smears from ADH show changes such as nuclear overlapping, prominent nucleoli, moderate to marked hyperchromasia and anisonucleosis which overlap with PDWA as well as frank carcinoma. The presence of non apocrine epithelial cells in 36 out of 105 cases of GCD in

which there was no proliferative epithelial change may detract from the significance attached to these cells as an indicator of epithelial proliferative change. On the other hand, the biopsied tissue in the latter may have failed to include the proliferative areas.

Cell configurations suggestive of expanded lobular units appear to imply lobular proliferations including atypical lobular hyperplasia (ALH) and lobular carcinoma *in-situ* (LCIS) as they were seen in half the cases in which ALD or LCIS accompanied GCD. Finely *et al*²⁵ have described such features in breasts of pregnant and lactating women and the illustration of LCIS by Sneige²⁶ is also similar. We believe that this feature can be expected in all pathological lobular lesions and also in physiological conditions in which the terminal ductular lobular unit fills up with cells e.g. lobular hyperplasia, pregnancy and lactation, lactating adenoma etc. The illustrations of lobular hyperplasia by Novotny *et al*²⁷ which resembles Sneige's²⁶ and our lobular hyperplasia gives credence to this belief. Since even lobular proliferations with a neoplastic connotation lack cytological atypia,²⁴ we feel that the scope of cytology is limited to suggesting a lobular proliferation. The intracellular lumina described in LCIS by Salhany and Page²⁸ were not seen in our cytological smears.

Since epithelial proliferation is a part of the spectrum of changes in FA and also duct papilloma, the presence of PDWA and ADH could not be singled out from the cytological features of the dominant lesion. Similarly, sclerosing adenosis (present in 14 cases of FA) and ALH (present in two cases of FA) could not be distinguished as both are lobular proliferative lesions and merge into the spectrum of changes seen in FA.

In this study FNA cytology has also been extremely useful in the segregation of non-proliferative lesions such as fat necrosis and duct ectasia (which may clinically simulate malignancy) and also in the diagnosis of infectious lesions including tuberculous mastitis.^{13,29,30} Non-tuberculous granulomatous mastitis^{31,32} and actinomycotic infection³³ of the breast have also been described by other workers. Rarely, echinococcosis and filariasis can present as breast lumps and in the former the aspiration procedure can lead to anaphylactic reaction.

Breast lumps are frequent, readily palpable and an ideal target for FNA cytology which is a single, rapid, and cost effective office procedure free of major complications. The high accuracy and specificity obtained with FNA cytology

