

Four quadrant fine needle aspiration cytology of non-palpable benign proliferative breast lesions

Gita JAYARAM, MD, MIAC,* Sangeeta LAMBA, MD** and Arun KAKAR, MS**

*"Department of Pathology, Faculty of Medicine, University of Malaya, Malaysia and **Maulana Azad Medical College & Associated Lok Nuik JaiPrakash Narain Hospital, New Delhi, India.*

Abstract

Seventy-eight symptomatic females without palpable breast lumps were subjected to bilateral four quadrant fine needle aspiration cytology. Cytological evidence of an epithelial proliferative lesion was seen in 44 of these cases. Based on the cytological evidence of proliferation, the site for open biopsy was determined. Histopathological study of the breast biopsies in these patients showed proliferative disease without atypia (PDWA) in 40 cases, atypical ductal hyperplasia (ADH) in two, atypical lobular hyperplasia (ALH) in one and ADH with ALH in one case. Cytology was thus useful in establishing the presence of proliferative activity, commenting on the extent of proliferation, and thereby roughly mapping out the area of the breast most suitable for biopsy. On cytological grounds, it was not possible to distinguish the atypical hyperplastic lesions from the proliferative diseases without atypia.

Key words: Breast, fine needle aspiration cytology, proliferative disease.

INTRODUCTION

The precursor lesions of breast cancer are poorly defined and controversial and a number of workers have tried to determine the relationship of benign breast disease to breast cancer.¹⁻¹⁰ Some of the benign proliferations of the breast may not present with palpable lumps. "Mammography¹²⁻¹⁸ is used for the evaluation of symptomatic women who do not have well defined breast lumps and also in screening populations for breast cancer. The cases labelled as normal on mammography, however, are not subjected to biopsy and therefore there is usually no histological study of mammographically normal lesions. Besides, in developing countries like India, the infrastructure does not permit screening mammography in all but a few major centres. This work has been done with two aims: (1) to explore the scope of fine needle aspiration (FNA) cytology as an alternative to mammography in benign non-palpable breast lesions and (2) to attempt to select, on the basis of cytology, the appropriate site in the breast to be sampled for histological assessment.

MATERIALS AND METHODS

Seventy-eight patients with symptoms of breast disease (nipple discharge, pain in breast, dis-

comfort/heaviness of breast), but with no well defined breast lump, were selected for the study. The majority of patients (71%) were in the third or fourth decades of life. The rest were in the fifth decade. Thirteen per cent of patients were nulliparous while 15% were uniparous. In the majority (72%) the parity was two to four. Using a 22 gauge needle attached to a 20 cc. plastic syringe that was mounted on a handle, FNA was done from all four quadrants of both breasts. Thus a minimum of eight smears were prepared in each case. In addition, areas of either breast showing vague nodularity or any localised area of tenderness were also needed. The material aspirated was dispelled on clean glass slides, smeared, air-dried and stained with May Grunwald Giemsa. In addition, in all patients with nipple discharge, cytological smears of the discharge were prepared and stained similarly. All the smears were subjected to detailed cytological study and based on the cytological evidence of maximum proliferative activity, the site for open biopsy was selected. If there was equal cytological evidence of proliferative activity in more than one area, then more than one area was subjected to open biopsy. The tissue obtained on open biopsy was processed entirely for histopathology. Histopathological study and cyto-histological correlation were done.

RESULTS

Cytological features

In 34/78 patients, the FNA cytological smears showed only fat cells, while in the remaining 44 cases, epithelial cells were present in smears from one or more quadrants, the cytomorphological features in these 44 cases are shown in Table 1.

Cellularity was inoderate in more than half of the cases, with smears showing cohesive clusters of rnomorphic epithelial cells. Intracytoplasmic vacuoles, large or small, were present in 18 cases (41%). These were more prominent in the cells at the periphery of the clusters (Fig. 1). They sometimes overlapped the nucleus or pushed the nucleus to one side, indenting it. Bipolar naked nuclei and apocrine cells were variable and an occasional case showed foam cells. Stroma fragments were absent in all the cases. Mild focal nuclear pleomorphism was observed in some cases.

All these cases were cytologically designated as benign proliferative Lesions - unspecified (BPL-U) and the area for open biopsy mapped out.

Of the 4 cases with nipple discharge, smears of the discharge showed foam cells in 6 and acellular smears in 3.

The histological diagnosis in these 44 cases were as follows: proliferative disease without atypia (PDWA) 40; atypical ductal hyperplasia (ADH) 2; atypical lobular hyperplasia (ALH) 1; ADH with ALH 1. The patient with ADH and ALH, who had bilateral pain and breast nodularity for eight years, had a needle aspiration of a left breast cyst (not subjected to cytological study) two years ago. Breast biopsy in

TABLE 1: Cytomorphological features in 44 cases with epithelial proliferative lesions

| Cytological features | No. | (%) |
|---------------------------|-----|--------|
| Cellularity: High | 4 | (9.1) |
| Moderate | 28 | (63.6) |
| Poor | 12 | (27.2) |
| Cytoplasmic vacuolation | 18 | (41) |
| Scattered naked nuclei | 20 | (45.5) |
| Mild nuclear pleomorphism | 10 | (22.7) |
| Apocrine cells | 14 | (31.8) |
| Foam cells | 2 | (4.5) |

this patient showed, in addition to ADH and ALH, microcystic change with apocrine cells and foci of sclerosing adenosis. Pre-operative mammography had been normal. Five months after open biopsy, the patient (a pathologist) opted for bilateral masieciomy. Sections of the mastectomy showed ADH, multifocal ductal carcinoma *in-situ* (DCIS), ALH and definite evidence of lobular carcinoma *in-situ* (LCIS) with pagetoid spread of lobular carcinoma into the ducts.

The histological spectrum of changes seen in PDWA is given in Table 2. Ductal epithelial hyperplasia was usually mild or moderate. Columnar alteration of the lobules was associated with epithelial hyperplasia in 26 cases and was the only change in two cases. Half of the cases showed microcysts with apocrine change.

Cytohystological correlation

In cases with ductal epithelial hyperplasia, the cytological smears showed varying degrees of cellularity consisting of clusters of predominantly monomorphic epithelial cells (Fig. 2). In 3 out of 4 cases of PDWA with florid hyperplasia and the case of ADH and ALH, the cellularity of smears prepared from the quadrant biopsied was high. In 4 out of 9 cases of cribriform PDWA, the cribriform pattern could be made out in some of the cell clusters (Fig. 3). Fourteen per cent of cases with microcysts showed apocrine cells in the cytological smears. Smears from cases with lobular hyperplasia, including ALH, showed, on retrospective analysis, configurations of cells that resembled filled up lobular units (Fig. 4). Smears from cases of ADH showed features similar to smears from cases with PDWA (Fig. 5), but focal pleomorphism of a mild degree was present in 2 of these 4 cases. Focal pleomorphism was, however, also present in smears from 6 cases of PDWA. Smears from

TABLE 2: Histological spectrum of 40 cases of proliferative breast disease without atypia

| Histological feature | No. | (%) |
|--------------------------------|-----|------|
| Ductal epithelial hyperplasia: | | |
| mild | 22 | (55) |
| moderate | 14 | (35) |
| florid | 4 | (10) |
| Lobular hyperplasia | 4 | (10) |

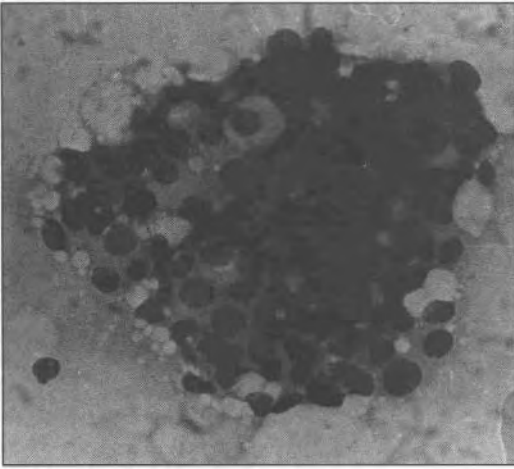


FIG. 1: Cluster of monomorphic epithelial cells, some with cytoplasmic vacuolation. MGG X400

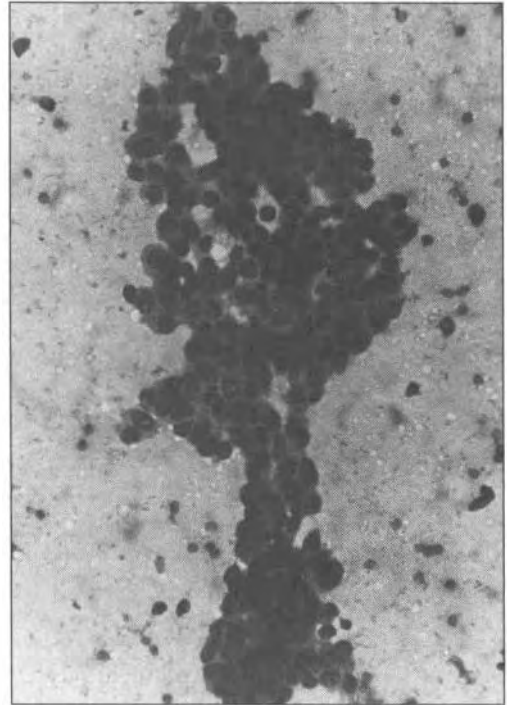


FIG. 3: Cluster of cells with a suggestion of cribriform pattern. MGG X400

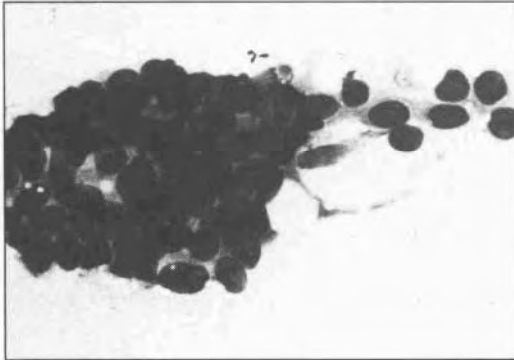


FIG. 2: Cohesive cluster of monomorphic epithelial cells in cases with epithelial hyperplasia. MGG X400

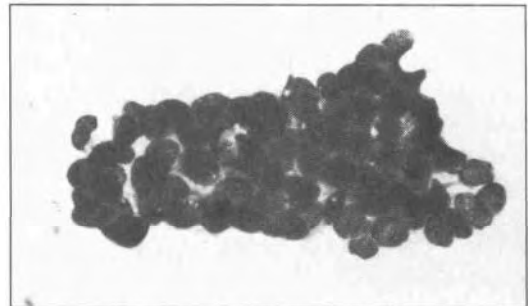


FIG. 5: Monomorphic epithelial cells in clusters in ADH. MGG X400



FIG. 4: Cell configurations suggestive of filled up and expanded lobular units. MGG X300

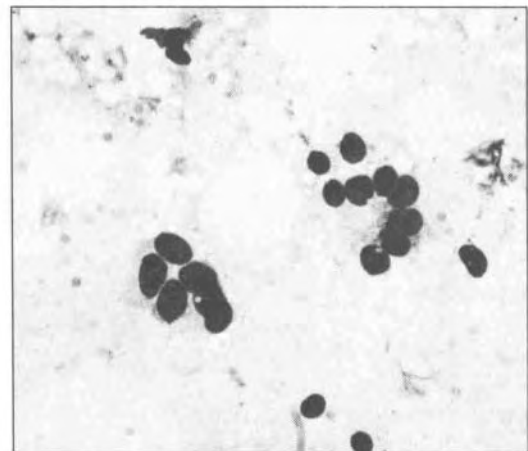


FIG. 6: Small cell groupings with attempted acinar pattern, in sclerosing adenosis. MGG X300

the case with sclerosing adenosis showed small collections of five to ten cells, sometimes in acinar pattern (Fig. 6), but this was a feature noted on retrospective analysis.

DISCUSSION

Mammography has been useful in the detection of significant numbers of clinically occult cancers, and needle¹⁹ and hooked wire²⁰ combinations, stereotaxic needle biopsies²¹⁻²³ and radiographically guided FNA cytology²⁴⁻²⁶ have been found to help in accurate localisation of these lesions. The mammographic features in epithelial proliferative lesions (many of which may be nonpalpable^{13,14}) may at times suggest malignancy.²⁷ The histopathological terminology for benign breast disease has undergone drastic changes over the years.^{2,7,8,11,28,29} Most troublesome at all times has been the interpretation and significance of epitheliosis. Page and Anderson⁸ stressed on the distinction of epithelial proliferations that carry a significantly increased risk of subsequent cancer from those that do not, labelling the former as ADH and ALH and the latter as PDWA. FNA cytology³⁰⁻³⁸ is widely used in the investigation of palpable breast lumps and enables distinction of benign from malignant lumps in the majority of cases. Cytological descriptions of nonpalpable breast lesions are few.^{27,39} Salhany and Page,³⁹ in a retrospective analysis of histologically proven cases of ALH, LCIS and infiltrating lobular carcinoma, found it difficult to distinguish ALH cytologically from LCIS. The cytological distinction of PDWA from ADH and lobular hyperplasia from ALH would understandably be more difficult. In the present study, cytological screening has been used as an alternative to mammography, and it enabled the detection of epithelial proliferative disease in 44/78 women (56.4%). In the remaining 34 patients, either there was no proliferative disease, or the FNA sample could have been inadequate. On cytological basis, the area for open biopsy was roughly mapped out and four atypical proliferative lesions could be diagnosed. Bibbo *et al*,²⁷ performing stereotaxic FNA of clinically occult breast lesions, used cytological grading to diagnose atypical ductal hyperplasia. We did not find it possible to distinguish PDWA from ADH on cytological basis. Since the diagnosis of ADH today rests more heavily on pattern criteria³¹ than on cellular atypia, this is to be expected.

Salhany and Page^{36,39} described prominent intracytoplasmic vacuolation and

intracytoplasmic lumina in smears from ALH & LCIS. We found intracytoplasmic vacuoles not only in ALH but also in all four cases with lobular hyperplasia and many cases of PDWA. We have also found this feature in many fibroadenomas (under publication) and, like Shu *et al*,⁴⁰ we are of the opinion that this feature is merely an indicator of a lobular origin for the cells. This type of vacuolization pattern characteristically affects cells in the periphery of the clusters and these vacuoles often coalesce at the periphery, sometimes overlapping or indenting the nucleus. These cells however, retain their normal size and shape and do not appear bloated up with secretory material. We did not observe intracytoplasmic lumina in any of our cases. Salhany and Page³⁹ did not comment on these vacuolations with regard to benign proliferations other than ALH and ADH. Additional features of interest in our cases of lobular hyperplasia and ALH were the configurations of cells simulating filled up lobular units. This has been described by Finley *et al*³⁰ in breast masses in pregnant and lactating women. They described them as "microtissue fragments with expanded and cellular lobules." We have also seen these configurations of cells in LCIS (under publication) and believe that this feature can be expected in physiological and pathological conditions in which the terminal ductular lobular unit (TDLU) fills up with cells, such as lobular hyperplasia, pregnancy, lactation, lactating adenoma and ALH. Since *in-situ* lobular proliferations rarely show cellular atypia,¹¹ the cytological distinction of ALH from other lobular proliferations would be difficult.

Although it has not been possible to cytologically distinguish ALH and ADH from PDWA, four quadrant FNA has been of great value in this group of women in identifying the presence and extent of epithelial proliferation and consequently in determining the area for biopsy. LCIS" (and therefore also ALH) is often bilateral and multicentric and cytology was advantageous in the patient who was cytologically diagnosed as bilateral BPL-U, and who, within five months, was shown to have ALH, ADH, and bilateral multifocal DCIS and LCIS. It is possible that she may have had DCIS and LCIS at the time of FNA. While the former could have been missed due to sampling error, the latter possibly merged into the cytomorphological spectrum of other lobular proliferations. At the time of our study, Ward *et al*²³ were also performing four quadrant FNA cytology of women at high risk for breast cancer

and were able to detect proliferative breast disease in 39% of their 52 cases, all of which were clinically and mammographically normal. Using Bibbo *et al*'s⁴ cytological criteria, they also graded the hyperplasia, but their cases lacked histological confirmation.

The main drawback of the present study remains that, without accurate radiographic needle localisation of both the FNA and the subsequent biopsy, it is not possible to know whether the exact area was sampled with both procedures. This facility, however, was unavailable to us. While a positive cytology can be taken as indicating proliferative disease, a negative cytology cannot rule out proliferation and some of the 34 cases where only fat cells were seen could be examples of inadequate FNA.

It is unlikely that the procedure tried by us will be used in developed countries where radiological localizing procedures have been greatly refined. Our idea, however, is to show the scope of cytology in the detection of proliferative lesions (some of which may be missed on mammography as noted by Ward *et al*²³ and as seen in one of our cases). Being an extremely cost effective diagnostic procedure its possible value as a primary diagnostic modality can also be considered in less developed countries for the screening of symptomatic women without definite breast lumps.

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