

Atypical and suspicious categories in fine needle aspiration cytology of the breast: histological and mammographical correlation and clinical significance

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ABSTRACT

Introduction: This study aims to correlate fine-needle aspiration specimens diagnosed as C3 (atypical, probably benign) and C4 (suspicious, probably malignant) with histology and mammography, and to evaluate these two cytology categories in terms of diagnostic usefulness and patient management.

Methods: All fine-needle aspiration (FNA) specimens in categories C3 or C4 at the Maharaj Nakorn Chiang Mai Hospital, Thailand between 2000-2004 were reviewed. Results were correlated with available histological and mammographical studies.

Results: 148 FNA specimens were identified, comprising 43 category C3 and 105 category C4. Histology was available in 90 cases. 14 (64 percent) C3 cases showed benign histology on biopsy and eight (36 percent) were malignant. 13 (19 percent) C4 cases were benign on biopsy, whereas 55 (81 percent) were malignant. Mammographical studies were available in 56 of the histologically-proven cases. All seven cases with benign mammograms had benign histology, and all 26 cases called "highly suggestive of malignancy" were malignant on histology (five C3 and 21 C4). Of the 23 cases called "suspicious abnormality" on mammography, 14 turned out to be malignant on biopsy (one C3 and 13 C4).

Conclusion: Our study supports maintaining cytology categories C3 and C4. About two-thirds of C3 cases were benign on biopsy whereas 81 percent of C4 cases were malignant (p-value is less than 0.001). There was complete correlation between histological and mammographical studies except those with equivocal mammograms. Our study supports the combined use of clinical, mammographical and cytological findings for optimal patient management. This is especially important for patients with C3 aspiration results, in order to avoid unnecessary surgery for benign lesions.

Keywords: breast biopsy, breast cancer, cytology, fine-needle aspiration, mammography

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INTRODUCTION

Fine-needle aspiration (FNA) of breast masses is widely accepted as a reliable diagnostic tool with both high sensitivity and specificity. Our previous study of over 2,000 cases showed a sensitivity of 84.4% and specificity of 99.5%⁽¹⁾. Although, many centres now recommend needle core biopsy instead of FNA, we have advocated keeping FNA as a first-line diagnostic procedure, at least in areas under economic restriction⁽¹⁾. Correlation of FNA results with the clinical and imaging studies is sometimes referred to as the "triple test"^(2,3). Some studies have demonstrated 100% diagnostic accuracy using this approach⁽²⁾. The National Cancer Institute recommends five categories for the diagnosis of breast aspiration cytology⁽⁴⁾ in order to bring a degree of uniformity to the diagnostic reporting. These categories are: unsatisfactory (C1), benign lesion (C2), atypical, probably benign (C3), suspicious, probably malignant (C4) and malignant (C5). However, some authors believe that C3 and C4 should be categorised in the same group⁽⁵⁾. In order to investigate this hypothesis further, we reviewed our FNA cases in categories C3 and C4, and correlated the results with the available histological findings at subsequent surgery. Moreover, we correlated the cytology and histology results to the mammography findings to determine the accuracy of this test for breast lesions diagnosed in the C3 and C4 categories.

METHODS

All FNAs performed at the Maharaj Nakorn Chiang Mai Hospital in Chiang Mai, Thailand between January 2000 and June 2004 were surveyed. Cases diagnosed as atypical, probably benign (C3) and suspicious, probably malignant (C4)⁽⁴⁾ were selected for further study. Biopsies from subsequent operations on these cases were reviewed for correlation with the FNA results. All specimens were reviewed by two

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Table I. Correlation of results of FNA with histology.

Cytological diagnosis	No. of cases	No. of cases with histology	No. of cases with benign histology	No. of cases with malignant histology
C3	43	22 (51%)	14 (64%)	8 (36%)
C4	105	68 (65%)	13 (19%)	55 (81%)

Table II. Correlation of results of mammography with histology.

Mammography results	No. of cases	C3 cases with histology		C4 cases with histology	
		Benign	Malignant	Benign	Malignant
BI-RADS 1	1	1	0	0	0
BI-RADS 2	3	1	0	2	0
BI-RADS 3	3	3	0	0	0
BI-RADS 4	23	2	1	7	13
BI-RADS 5	26	0	5	0	21

pathologists for uniformity of reporting. Clinical data was obtained by chart review. The study was approved by the Research Ethics Board of the hospital.

Mammography studies were reviewed for the cases in the C3 and C4 categories that also had histological confirmation. All cases were reviewed by a breast radiologist. The mammographical studies were reported using the Breast Imaging Reporting and Data Systems (BI-RADS) that includes categories: BI-RADS 1 (negative lesion), BI-RADS 2 (benign lesion), BI-RADS 3 (probably benign), BI-RADS 4 (suspicious abnormality), and BI-RADS 5 (highly suggestive of malignancy)^(6,7). Diagnostic value of cytological diagnoses and mammographical studies were assessed by comparing the percentage of benign or malignant histological diagnoses in categories C3 and C4 and by using the χ -square test of significance.

RESULTS

From January 2000 to June 2004, 3,016 breast FNAs were performed at the Maharaj Nakorn Chiang Mai Hospital in Chiang Mai, Thailand. Out of 2,491 satisfactory specimens, 148 cases (5.9%) were diagnosed as atypical, probably benign (C3) or suspicious, probably malignant (C4). All lesions in this study were palpable. The age range of the patients was 21 to 79 years. All patients, except one, were female. Subsequent operations were performed in 90 cases of those diagnosed in the C3 and C4 categories. Of those 90 cases, 56 cases had mammographical studies.

Of the 148 cases selected for review, 43 (29%) cases were category C3 and 105 (71%) cases were category C4. Histology was available in 51% of category C3 and 65% of cases in category C4

(Table I). About 64% of cases in category C3 had final histological diagnoses of benign lesions, whereas only 19% of cases in category C4 group did. The benign histological diagnoses for cases in category C3 included: fibroadenoma (7), papilloma (2), fibrocystic changes (1), gynaecomastia (1), lactational change (1), epidermal cyst (1), and epithelial hyperplasia (1). For the C4 category, the benign histological diagnoses included: fibroadenoma (5), fibrocystic change (4), papilloma (3) and granulomatous inflammation (1).

Malignancy was found in 36% of cases in category C3 but in over 80% of cases in category C4. All malignant diagnoses were invasive ductal carcinoma except one case of invasive lobular carcinoma in category C4. There was a significant difference between the number of benign and malignant diagnoses for cytologic categories C3 and C4 ($p < 0.001$). Individual cases with histological correlation are shown in Figs. 1-3. Benign cytology and histology from categories C3 and C4 are illustrated in Figs. 1 and 2, respectively, while a malignant case from category C4 is shown in Fig. 3.

The correlation between the mammography, cytology and histology results is presented in Table II. All seven cases in the BI-RADS 1, 2 and 3 categories (negative, benign, probably benign) had benign histology on biopsy and were in cytology category C3. Of the 23 cases in category BI-RADS 4 (suspicious abnormality), 14 (60.9%) had malignancy on biopsy, with one of these cases in cytology category C3 and the other 13 in cytology category C4. All 26 cases in category BI-RADS 5 (highly suggestive of malignancy) had malignant diagnoses on biopsy, with 19% in cytology category C3 and 81% in cytology category C4.

DISCUSSION

From our study based on over 3,000 cases of breast FNA, the equivocal diagnostic categories C3 and C4 comprised approximately 6% of the total. This proportion is in the range (4-17.7%) reported by others^(5,8-13), indicating these categories are not being underused or overused in our centre. The diagnosis of category C4 was almost 2.5 times as common as C3. In this study, the three most common lesions contributing to the diagnosis of categories C3 and C4 were fibroadenoma, fibrocystic change and papilloma, which is similar to what has been reported by others^(5,10,14,15). The other less common lesions included: lactating adenoma, non-specific inflammatory process, gynaecomastia, and granulomatous inflammation.

The most common malignant lesion diagnosed as category C3 or C4 was invasive ductal carcinoma, particularly with low nuclear grade. Occasionally, lesions were placed in the equivocal categories C3 and C4 because of technical factors such as air-drying effect, bloody background and small number of malignant cells. This problem is generally avoided in our FNA clinic, in which specimens are evaluated immediately at the time of the aspiration, and any unsatisfactory specimens are repeated during the same procedure.

Of the cases in category C3 that proceeded to surgery, over 35% had a malignant diagnosis on biopsy. This result is also in line with reported literature values that range between 8.6% to 52%, with most reports having over 30%^(5,8,9,12,16). The decision to proceed to biopsy in our centre relies, whenever possible, on the "triple test"^(2,3) correlating the FNA results with the clinical and radiological studies. With this approach, the cases in category C3 that had clinical and imaging studies suspicious for malignancy were recommended for biopsy, thereby accounting for the seemingly high proportion of malignant cases in this category. Our study supports the recommendations of others⁽¹⁷⁾ that the use of the "triple test" is important for proper management of patients with FNA results in category C3, and whether such patients need to proceed to surgery, or can simply be followed.

For cases in the C4 category, our study showed that approximately 80% of patient turned out to have malignant lesions, which is similar to the range of 81% to 97% reported by others^(5,8,9,12,16). Thus, as have been recommended by some authors^(5,18), we believe that patients in cytology category C4 should have the diagnosis confirmed by histological examination. Despite this recommendation, in our study, only 65% of patients in category C4 had surgery performed.

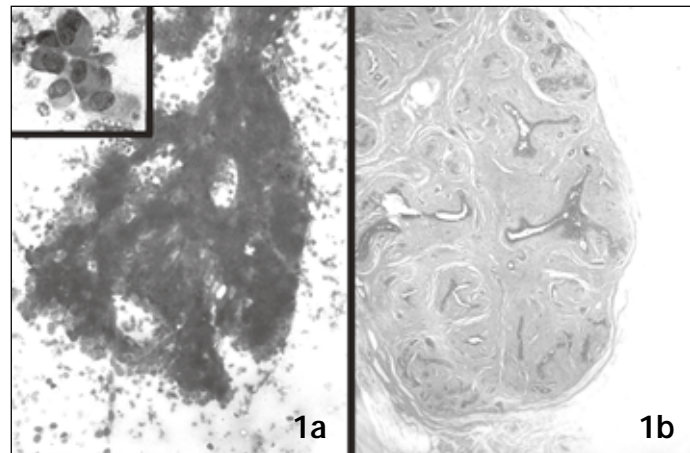


Fig. 1 Benign case from cytology category C3 (atypical, probably benign) (a) A large sheet of benign-looking epithelial cells with cribriform arrangement is shown [x100]. Some bipolar naked nuclei are noted in the background. The inset (upper left) shows a cluster of atypical cells [x400]. (b) The corresponding histological photomicrograph shows a fibroadenoma with epithelial hyperplasia [x40].

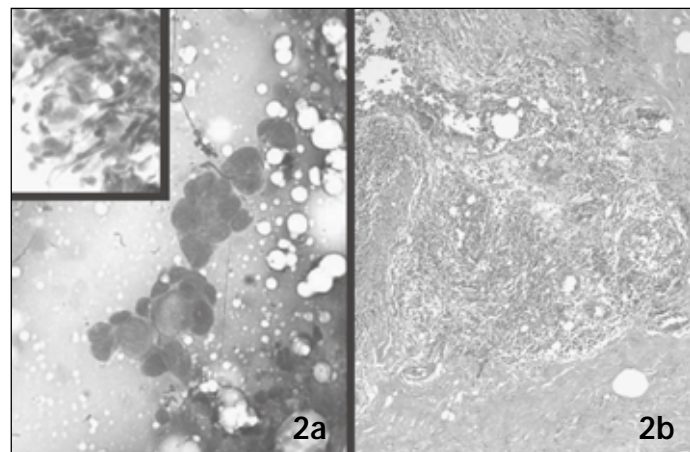


Fig. 2 Benign case in cytology category C4 (suspicious, probably malignant) (a) Clusters of atypical epithelial cells are noted with sheet of epithelioid histiocytes [x400] (inset, upper left) [x400]. (b) The corresponding histological photomicrograph shows a granulomatous mastitis with reactive change of epithelial cells [x200].

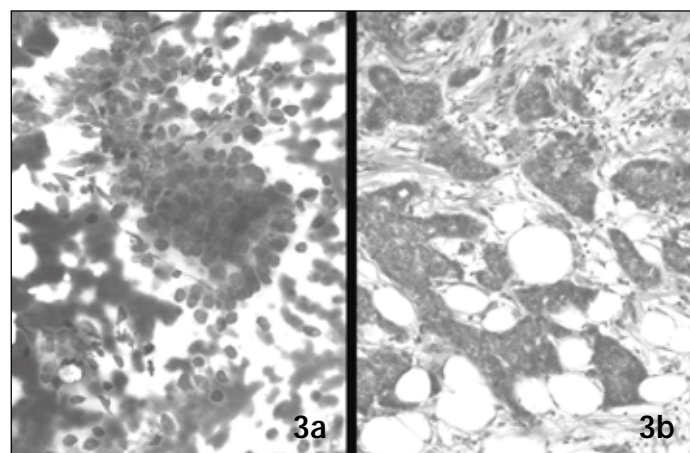


Fig. 3 Malignant case from cytology category C4 (suspicious, probably malignant) (a) Clusters of rather small epithelial cells with overlapping nuclei are noted as well as loose cohesion at the periphery [x400]. (b) The corresponding histological photomicrograph shows invasive ductal carcinoma [x400].

The remainder may have had the operation done in other hospitals, particularly private hospitals.

Considering mammography and cytology together, it would appear that both techniques are equally accurate in predicting benign versus malignant diseases for lesions that are in the mammographical categories of BI-RADS 1-3. For lesions in category BI-RADS 4, cytology was a better predictor of which lesions were benign or malignant. Only 14 out of 23 cases in this category were actually malignant, but 13 of those 14 cases were in cytology category C4. However, this difference did not reach statistical significance because of the small number of cases. For lesions in the radiological category BI-RADS 5, mammography was the better predictor since all those cases were malignant on biopsy, yet almost 20% of those cases were in cytology category C3.

In conclusion, it is important for both pathologists and clinicians to understand not only the benefits but also the limitations of cytological diagnosis from FNA specimens. Immediate evaluation of specimen adequacy is useful to eliminate equivocal diagnoses caused by technical factors. We feel it is still useful to maintain the equivocal diagnostic categories C3 and C4, since in our study, approximately two-thirds of patients who were diagnosed as category C3 had benign lesions, whereas about 80% of those in category C4 had malignant diagnoses. This difference was statistically significant ($p < 0.001$). Combining the mammography and cytology data together with the clinical findings (the "triple test") allow for proper management for each patient, determining which should proceed to surgery and which can be closely followed, hence avoiding an unnecessary operation.

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