Cyto-morphologic correlation of equivocal C3 and C4 breast lesions

[1]Yusuf I, [1]Atanda AT, [1]Imam MI and [2]Alfa AS

[1]Department of Pathology, Faculty of Medicine, Bayero University/[2]Department of Pathology, Aminu Kano Teaching Hospital, Kano, Nigeria

Abstract

Background*: National Cancer Institute (NCI) formulated a five-tiered system for reporting cytological smears from the breast. Of these, C1, C2 and C5 are usually unequivocal. The equivocal categories C3 (atypical probably benign) and C4 (suspicious probably malignant) need to be evaluated to determine their cyto-morphologic correlation and thus provide useful information on the degree of clinical weight that can be put on them in patient management.*

Methods*: A retrospective study of cytological smears made from palpable breast lesions performed over a 5-year period from 2008 to 2012. The C3 and C4 smears were then compared with final histological diagnoses for these categories and their diagnostic value calculated.*

Result*: There were 1,162 smears taken in the five years, 200 (17.2%) of which had subsequent histology. Of the 200 smears 20 were C3 and 27 were designated as C4. Subsequent histology upgraded 7 (35%) of the C3 cases to malignant and downgraded 4 (14.8%) of the C4 cases to benign. The overall Suspicious Rate was 23.5% with sensitivity of 76.7%, specificity of 76.5%, positive predictive value and negative predictive values of 85.2% and 65.0% respectively.*

Conclusion*: A fair degree of clinical reliance can still be placed on cytologically categorized C3 and C4 breast smears. However, the rate of reporting of these categories can be reduced with availability of ancillary radiological techniques such as mammography and ultrasonography.*

Keywords: Atypical, Suspicious, Cytology, Breast, Smears, C3, C4

Introduction

In a bid to ensure uniformity in the reporting of Fine Needle Aspiration Cytology (FNAC) of palpable breast lesions, the National Cancer Institute (NCI)[1] formulated a five tiered system for reporting these smears. These include C1 for unsatisfactory smears; C2 for benign smears; C3 for atypical probably benign; C4 for suspicious probably malignant; and C5 for malignant smears. This system has been a valuable tool for the surgeon to triage his patients for different treatment modalities[2]. The value of FNAC has also been enhanced by the simplicity of the technique, its relatively lower cost as well as its high sensitivity which has been shown to be in the range of 76% to 99%.[3]

Correspondence to: **Dr Ibrahim Yusuf,** Department of Pathology, Aminu Kano Teaching Hospital, Kano, PMB 3452, Kano, Nigeria Post code: 700001 E-mail: yusufeebrah@gmail.com

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In spite of the high diagnostic values demonstrable for FNAC, most developed countries have shown greater inclination to core needle biopsies (CNB) because wider use of mammography allows for early diagnosis of non-palpable lesions among their women.[4] Currently in these countries the indications for which FNAC still hold appeal are for evaluating cystic breast lesions, diagnosing recurrent or metastatic lesions, confirmation of locally advanced cancer and axillary staging of patients with invasive breast cancer.[5] For developing countries, in contrast, FNAC still holds pride of place in the diagnostic armamentarium at the surgeon's disposal. This is not only because most women in these poorer countries present with advanced cancers[6,7] but also because FNAC has been shown to have greater sensitivity than CNB in the evaluation of palpable breast masses.[8]

In this regard, C2 and C5 cases have been associated with a high degree of diagnostic accuracy and thus do not constitute diagnostic conundrum. C3 and C4 cases however, require further evaluation either by core needle or incisional biopsy for histological characterization. It is these two latter categories that have generated continuing controversy. Thus there is need to evaluate these two subcategories to assess their diagnostic reliability so as to guide the surgeon in the decision making process with regards to treatment options for patients.

Method

A retrospective study of cytological smears made from palpable breast lesions performed over a 5-year period from 2008 to 2012. Aspirates were obtained using 25G needles, using either free- hand or attached to 20ml syringe/syringe holder. Smears were fixed both in 95% alcohol and air dried and stained with Papanicolaou and Diff Quik (Giemsa) stains respectively. Prepared slides were reviewed and reported according to NCI guidelines: C1, unsatisfactory smear; C2, unequivocally benign; C3, atypical but more probably benign; C4, suspicious more probably malignant; and C5, unequivocally malignant. Follow up histological reports for these cases were then retrieved and compared based on whether benign or malignant. Sensitivity, Specificity, Positive Predictive Value (PPV) and Negative Predictive Values (NPV) of FNAC were then calculated. The False Positive Rate (FPR), False Negative Rate (FNR) and the Suspicious Rates (SR) were also calculated.

Results

In the five years studied, only 17.2% (200 of 1,162) breast lumps on which FNAC was done had been subjected to histopathological follow up. As shown in Table 1, there were 20 C3 and 27 C4 smears. Seven (35.0%) of the 20 C3 (atypical more probably benign) diagnoses turned out to be benign fibroadenomas (FA); 5 (25%) turned out to be malignant Invasive Ductal Carcinomas (IDC); and 3 (15%) turned out to be benign fibrocystic changes (FCC). Other, less frequent, entities accounted for the remaining 25% of C3 cases. On the other hand, 18 (66.7%) of the 27 C4 (suspicious more

Table 1: Cytomorphological correlation of the breast lumps

Histological Diagnosis	C3	C4	Total
Fibroadenoma	7	1	**8**
Fibrocystic change	3	-	**3**
Benign Phylloides	2	1	**3**
Blunt Duct Adenosis	1	-	**1**
Fat Necrosis	-	1	**1**
Ductal Hyperplasia	-	1	**1**
Invasive Ductal Carcinoma	5	18	**23**
Invasive Lobular Carcinoma	1	2	**3**
Medullary Carcinoma	-	1	**1**
Papillary Carcinoma	1	1	**2**
Apocrine Carcinoma	-	1	**1**
Total	**20**	**27**	**47**

probably malignant) FNAC diagnosis turned out to be IDC and 2 (7.4%) turned out to be Invasive Lobular Carcinomas (ILC). One each of Papillary, Medullary and Apocrine carcinoma were also labeled on FNAC as C4.
As depicted in Table 2, subsequent histology upgraded 7 (35%) of the 20 C3 cases to malignant and downgraded 4 (14.8%) of the 27 C4 cases to benign. Five of the C3 cases which turned out to be malignant were IDC with the two others being ILC and Papillary carcinoma. The downgraded C4 FNAC diagnosis turned out to be a case each of FA, Usual Ductal Hyperplasia (UDH), Low grade Phyllodes and Fat necrosis.

Table 2: Histological diagnoses of the upgraded C3 and downgraded C4 lesions

Upgraded C3	Number	%	Downgraded C4	Number	%
Invasive Ductal Carcinoma	5	**71.4**	Fibroadenoma	1	**25**
Invasive Lobular Carcinoma	1	**14.3**	Benign Phylloides	1	**25**
Papillary Carcinoma	1	**14.2**	Fat Necrosis	1	**25**
			Ductal Hyperplasia	1	**25**
Total	**7**	**100**		**4**	**100**

The overall SR was 23.5% with sensitivity of 76.7%, specificity of 76.5%, positive predictive value and negative predictive values of 85.2% and 65.0% respectively.

Discussion

The frequency of diagnosis of suspicious breast lesions by FNAC either as atypical probably benign (C3) or suspicious probably malignant (C4) in this study was 23.5%. This rate is higher than the rate of 7.6% recorded by Deb *et al*[9] and the 15.7% documented in a study[10] from Korea. These lower rates, compared with ours, reflect availability of mammography reports as aids in the interpretation of atypical or suspicious cases. Our rate is however closer to the 21.1% documented by Erra and Costamagna[11] in Italy.

The high rate in our study may reflect the low rate of mammography utilization due to poverty, unavailability and poor awareness.[12] Consequently our cytopathologists have a low threshold for suspicion. Similar precaution and varying degrees of reluctance to assign a C5 assessment by different cytopathologists was also observed by Nguasangiam and collegues[13] in their study. In addition to this, other factors that may influence the rates of suspicion are technical issues, level of experience of the cytopathologist and overlap of benign versus malignant features on cytology.[14] The technical issues are minimized in our centre by virtue of the cytopathologist, as opposed to the surgeon, being the aspirator, thus inadequate (C1) smears are infrequent as repeats are taken in the FNAC unit within the department. Inexperience on the other hand played a role that could not readily be ascertained because of subjectivity. Most of the smears given an atypical or suspicious appellation exhibited mixed malignant and benign features.

A case each of FA, Usual Ductal Hyperplasia (UDH) and Low grade Phyllodes constituted the histological diagnosis in the 3 C4 lesions downgraded to benign. These cases were associated with atypical appearing cells focally in multilayered clusters suggestive of

malignancy, which, in retrospect, might have been due to smearing technique. Lim and colleagues[15] have also shown that these lesions, particularly FA, may show overlap of benign and malignant features on cytology. Yet, as did Nguansangiam *et al,*[13] we conclude that the surgeon can still place diagnostic reliance on FNAC diagnosis of Fibroadenoma in view of diagnostic accuracy of 85.7% for this lesion from our study and 90% from the earlier study. The misinterpretation of atypical appearing cells of ductal hyperplasias, as occurred in our report is similar to observations in other breast cyto-morphologic correlation studies.[14, 16]

The fourth case given a C4 diagnosis in our study was diagnosed as fat necrosis on histology. The dirty background seen on smears in such lesions as well as macrophages with irregular enlarged nuclei and condensed non-vacuolated cytoplasm simulate atypical epithelial cells and thus raise the suspicion of the cytopathologist. Gottschalk and Glick[17] made similar observations in their report of two cases and suggested identification of multinucleated forms and foamy cells with similar morphologic features as being useful in preventing errors. The presence of atypical cells as well as variations in stromal to epithelial ratios, necessitating a diagnosis of C4 for our

Low grade Phyllodes, highlights the need for observation of subtle criteria in the reporting of this lesion. Several authors[18,19] have suggested that stromal atypia and hypercellularity may be more reliable pointers to their histological type than epithelial atypia. The observed 35% likelihood of our C3 cases turning out malignant on histology is slightly higher than the 32% reported by Deb et al[11] but similar to the 36% reported by Chaiwun and colleagues.[20] However, better still, the 14.8% likelihood of our C4 lesions being benign is lower than the 19% reported in each of the latter two studies while the 85.2% confirmed by histology to be malignant is in the range of 81 to 97% reported by others[21-23] The 7 C3 cases upgraded to malignant share similar features. Of these, 5 cases were IDC and occurred in women whose ages ranged from 19 to 43 years (mean 31.6years). They had no axillary lymphadenopathy, suspicious skin changes or mammographic reports. Their cytology smears showed nuclear uniformity occurring in monolayered clusters and background with bare nuclei devoid of necrosis. However few clusters of cells demonstrated mild nuclear irregularity. Thus the young ages, absence of suggestive examination findings and lack of mammography contributed to the lower index of suspicion in these cases.

The papillary carcinoma rendered a C3 at cytology, in retrospect, ought to have been given a minimum of C4. Though there was no background necrosis and even though there were bare nuclei, the epithelial cells showed moderate pleomorphism, and papillae formation. The invasive lobular carcinoma given a C3 designation in our study also exemplifies the diagnostic difficulties often encountered with smears from such lesions. A high index of suspicion is required as such lesions tend to be hypocellular, only focally exhibiting characteristic Indian file pattern, and may readily simulate lymphocytes.

Overall, the sensitivity of 76.7%%, specificity of 76.5%, positive predictive value and negative predictive value of 85.2% and 65.0% respectively for our atypical and suspicious breast cytology in our study fall within the ranges (sensitivity, 48 – 94%; specificity, 35 – 98%, PPV, 99.5 – 100%; NPV, 51 – 97%) documented in other studies.[24, 25]

From the foregoing, it can be concluded that a fair degree of clinical reliance can still be placed on cytologically categorized C3 and C4 breast smears. However, the rate of reporting of these categories can be reduced with availability of ancillary radiological techniques such as mammography and ultrasonography.

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