

Leading Article

The legitimacy of the atypical (C3) breast cytology category

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Fine needle aspiration cytology (FNA) has been used as a diagnostic tool in many sites, for more than a century (1). Although, FNA was initially utilised in the evaluation of palpable masses, currently the procedure is employed in the assessment of both palpable and non-palpable pathologies. With improvement in imaging techniques, almost any lesion, anywhere in the body can now be safely targeted with precision. FNA is simple, easy to perform and minimally invasive. It is associated with negligible complications. Low cost of the procedure makes it ideal for resource poor or economically disadvantaged areas. The proven accuracy of FNA, when practiced by a team of dedicated workers, has been repeatedly demonstrated (2-4). FNA in this setting is comparable to surgical pathology in sensitivity and very similar to frozen section in specificity (5). FNA, when supported by rapid on-site evaluation (ROSE), can provide immediate feedback to help triage the patient and allow for collection of material for relevant investigations.

Breast FNA is a well-established diagnostic procedure for the investigation of palpable and screen detected lesions. Clear reporting

guidelines and quality assurance programs ensure the diagnostic utility of breast FNA. A standardised reporting system, complementing the clinical and radiological BIRAD systems, which combine to form the triple test, has been used for several decades (6-10). The most widely used cytological reporting protocol consists of a 5 tier categorical system which stratifies the risk of malignancy and provides clinical management directions. It contains the following categories: C1 (non-diagnostic), C2 (benign), C3 (atypical), C4 (suspicious) and C5 (malignant). This reporting system is endorsed by the Britain's National Health Service Breast Screening Programme (NHSBSP)(11), the National Cancer Institute (NCI) of the USA (12) and The Royal College of Pathologist of Australasia (RCPA)(6).

The benign (C2) and malignant (C5) categories, with well-defined cytological features, have high predictive values. There are enough evidence-based criteria to reliably categorise these lesions. A suspicious (C4) result usually suggests a high probability of cancer but is not as definitive as C5 either because of scant diagnostic material or low grade morphology (3,13,14). A non-diagnostic (C1) report provides limited information and highlights either sampling or technical problems. An atypical (C3) report is an ambiguous result and provides limited clinical value to the clinician (15). The Australian National Breast Cancer Centre defines C3 as

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“smears with benign features but also showing features which may be seen with malignancy or a lesion in which the cellularity is low with subtle cytological atypia” (6). Management of C3 reports require further investigation such as a repeat FNA, core biopsy or open surgical biopsy, which come at greater cost and more anxiety to the patient.

The percentage of C3 compared to total number of FNAs is variable. There are no performance standards for laboratories to follow, however, published studies show the percentage of C3 to range from 3.7-5.9% of overall FNAs (13,16-18). Our own atypical rate of 5.1% (484 C3 from a total of 9555 FNAs) over an 8 year period falls within this reported range.

The lack of well-defined evidence-based criteria for the atypical category is reflected in the heterogeneous mix of pathological outcomes following such a diagnosis. There is no benchmarking or standardised risk of malignancy for C3; however, the literature contains a number of studies which report a range of 16% to 52% of C3 cases resulting in a malignant outcome (16,17,19-22). We recently reviewed our C3 category to establish the histological outcomes and to investigate the underlying reasons for assigning cases to C3. Our review findings of 254 C3 cases with follow up showed an overall malignancy rate of 37.4% (23). The histological outcomes, most frequently encountered in the follow up of C3 lesions, largely fall into 2 general subgroups, namely benign proliferative lesions and low grade cancers. Our eight year experience is shown below as depicted in the figure 1(23).

Benign proliferative lesions form a subgroup of actively growing benign lesions and include papillomas, fibroadenomas (FA), radial scars (RS)/complex sclerosing lesions (CSL), sclerosing adenosis, proliferative fibrocystic change (FCC), usual epithelial hyperplasia and a small number of specific lesions such as adenomas, hamartomas and

benign phyllodes tumours. Due to their active growth they can produce very cellular smears with challenging architectural patterns. Benign papillomas and fibroadenomas were the most likely benign proliferative entities to be found in our C3 cases (23). Often a diagnosis of a benign papillary lesion is achievable with cytology, radiology and clinical symptoms, however, these lesions should remain in C3 because of the limitations of the FNA cytology. Fibroadenomas are commonly found in the C3 category, particularly when the cytological pattern displays high cellularity with marked nuclear enlargement and dissociation which may skew the diagnosis towards malignancy (24,25). Complex sclerosing lesions (CSL), radial scars and sclerosing adenosis are often placed in the C3 category due to high cellularity with complex microscopic features including tubules, bare bipolar nuclei and loss of cohesion, coupled with worrisome imaging findings (26–28). Proliferative fibrocystic change can produce cellular smears which can be particularly worrisome in post-menopausal women on hormonal replacement therapy (29,30).

The presence of malignant lesions in the C3 category undermines the intent of the C3 category. However, without this category, the negative predictive value of the benign (C2) category would suffer due to the possibility of including false negative cases in this category. Our study showed the most common cancers in C3 were low grade invasive ductal carcinoma (IDC), followed by invasive lobular carcinoma (ILC) and ductal carcinoma in situ (DCIS). Low grade IDC often displays minimal cytological changes but lacks overlying myoepithelial cells, diminished numbers of bare bipolar nuclei and subtle epithelial dissociation. The majority of low grade IDC cases in our study were screen detected. ILC also featured in the C3 group, mainly because of paucicellularity of the sample and the co-existence of benign epithelium. Low grade DCIS produces large sheets of epithelial cells with complex architecture which may be

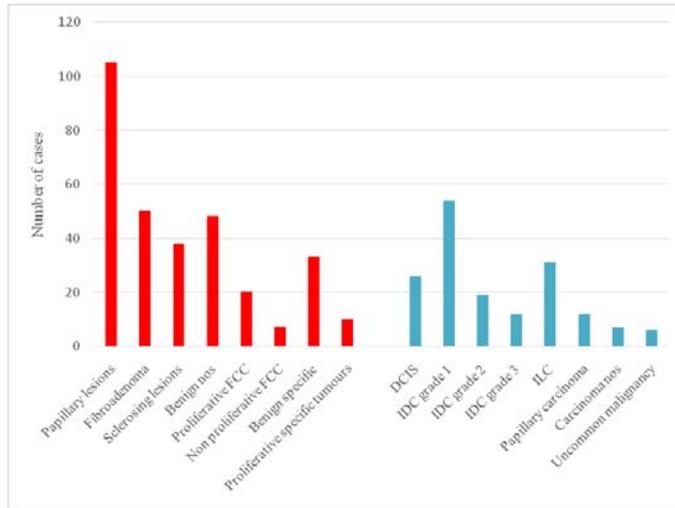


Figure 1. Histopathological outcomes of 478 atypical (C3) breast cytology cases seen over an 8 year period.

(FCC, fibrocystic change; DCIS, ductal carcinoma in situ; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma)

confused with papillary lesion or proliferative fibrocystic change. The ability of FNA to distinguish invasive carcinoma from in-situ lesions should not cause difficulty if the factors which influence the allocation of cases into the atypical category are both extrinsic and intrinsic (Figure 2). Extrinsic factors include samples with low cellularity, poor specimen preparation and lack of expertise in all aspects of the procedure (23,32). Rigorous smearing of fragile material or delayed fixation can falsely exaggerate cellular changes leading to an equivocal diagnosis. Low cellularity may be due to technical reasons such as poor FNA technique or inadequate sampling of the targeted lesion. These can be minimised with education and training of the team members. Inherently difficult lesions such as sclerotic lesions, sclerosing papilloma or lesions with strong desmoplastic reaction such as radial scars or invasive lobular carcinoma may not easily yield diagnostic material. Uncommon or unexpected pathological entities may not be correctly identified due to the lack of experience or unfamiliarity with the entity. Conflicting radiological and clinical impressions may mislead the pathologist, evoking a cautious but equivocal report. Intrinsic factors such as physiological characteristics of breast tissue, intralesional

heterogeneity and overlap between benign and malignant cytological features further compound the diagnostic dilemmas (33,34). Hormonal or treatment changes such as those seen during lactation or post radiation respectively may produce cytomorphological alterations leading to a C3 diagnosis. The clinical history in these situations is vital for accurate interpretation of the perceived changes. Heterogeneity within a lesion is always problematic for small sample biopsies. For example, benign papilloma can be colonised by DCIS or invasive cancer and a small needle sample may not be representative of the whole lesion. However, the greatest challenge for cytologists is the interpretation of lesions with overlapping benign and malignant microscopic features. Our study into C3 found 65.2% of cases were placed into the C3 category due to complex architectural features or aberrant cell morphology resulting in interpretation difficulties. This complex set of factors contributed to the diagnostic uncertainty and influenced the allocation of FNA results into the C3 category (23).

We used the results of our review to determine the specific microscopic features commonly associated with a C3 diagnosis. These cytomorphological features included

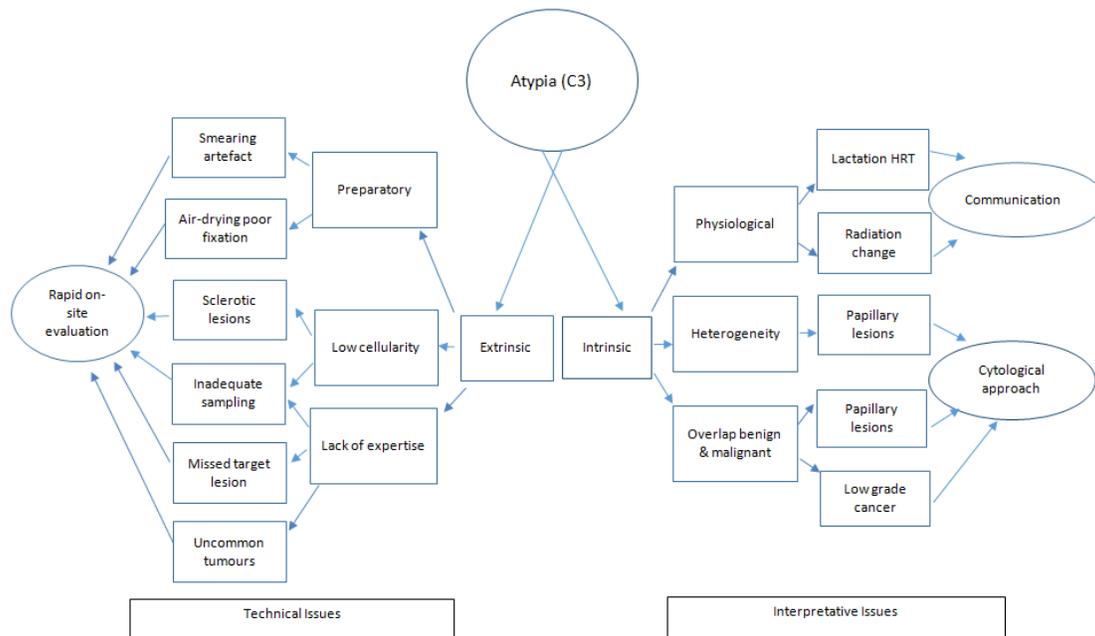


Figure 2. Factors influencing the allocation of cases into the atypical (C3) category and ways of minimising the use of C3 category without impacting on the integrity of the benign (C2) and the suspicious (C4) categories.

presence or absence of myoepithelial or bare bipolar nuclei, cohesion, cystic background, papillary fragments and tubules.

Myoepithelial cells, when overlying sheets of ductal epithelium, are good indicators of benignity. Similarly, stripped bare bipolar nuclei found in the background also point towards a benign cytological pattern. Cohesion of epithelial cells signals benignity, however, some of the low grade carcinomas, particularly tubular carcinoma can display a cohesive picture. In our study, a quantitative value of 5% or more of epithelial cells presenting as isolated single cells was set as a benchmark for cohesion. This was tested and found to be statistically significant (33). Most malignancies were not associated with a cystic background so this was found to be a useful predictor of benignity and reflected the large number of FCC and papillomas found within our study cohort. The presence of papillary

fragments was found to be predictive of papillary lesions, whereas, tubules were highly predictive of malignancy.

With the combination of the above criteria we were able to predict malignant, benign proliferative and papillary outcomes within C3 with reasonable accuracy (33). This led to the formulation of a cytomorphological approach to stratify the risk of malignancy, thereby potentially removing C3 cases with a higher probabilistic value into C4.

Various strategies can be implemented to minimise the effects of these factors within the C3 category. Control over the quality and quantity of aspirated material is fundamental to the formulation of a diagnosis. ROSE by an attending cytologist can ensure adequate cellularity of the targeted lesion with optimal sample preparation as well as providing immediate feedback to the FNA aspirator. A

dedicated team of pathologists, clinicians and radiologists with the necessary expertise and close communication can also minimise the diagnostic uncertainty in this setting. The Flowchart (figure 2) depicts the main reasons for the allocation of cases into the C3 category and shows ways to minimise such a diagnosis without impacting on the integrity of C2 and C4.

Despite the overwhelming published literature regarding the accuracy of FNA, there is currently a worldwide trend to replace FNA with core biopsy as the first line investigative procedure. Both FNA and core biopsies have a role to play in diagnosing and classifying breast pathologies. The lack of standardised criteria for the C3 category often leads to the use of core biopsy for clarification of the underlying pathology (35). However, some FNA limitations also apply to core biopsy. Undersampling or underestimation of the lesion, due to the biological nature of the lesion or intralesional heterogeneity, is just as subjective for histology as for cytology (36-41). A FNA service, when practiced by a skilled team can produce acceptable performance standards in these situations with benefits to patients, the medical fraternity and the public health sector (42). All of these studies cement our philosophy and approach to providing accurate results in a timely fashion with less physical and emotional trauma to the patient and a reduction in the financial burden on the community.

The future of breast FNA is dependent upon several pathways. The ease, simplicity and cost of a successful FNA procedure, places it in prime position to capitalise on future technologies. Cocktails of immunocytochemistry markers are being developed which may contribute to improving the diagnostic and therapeutic approaches to the breast lesions (43-46). Morphology is the foundation upon which the interpretation of these new ancillary technologies lies. With more powerful technology comes greater

evidence based knowledge and understanding. Indeed the five tier diagnostic reporting system in breast cytology is currently under review by the International Academy of Cytology (47). New technologies which provide greater understanding of specific tumours and their behaviour are changing traditional morphological based classification systems. Molecular testing of FNA material is becoming increasingly relied upon for providing diagnostic, prognostic and predictive information about individual patients and is likely to play an important role in precision/individualised medicine.

Our studies have shown atypia to be a legitimate reporting category in breast FNA cytology. This cannot be nor should it be totally eliminated. The atypical category preserves the integrity of the benign and malignant classes. However, cytology like any diagnostic test has limitations. These include subjectivity of opinions expressed, biological heterogeneity of lesions, sampling adequacy and dedication and expertise of the team involved in patient management. Our strategies help reduce these limitations.

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