Non-operative breast pathology

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An update on current practice

In recent years, core needle biopsy has become an integral part of the triple approach for the diagnosis of breast cancer lesions in screening programmes. This technique has undoubtedly changed diagnostic breast pathology practice and new diagnostic challenges have emerged. This issue of the *Journal of Clinical Pathology* contains a series of reviews addressing troublesome areas of non-operative breast pathology, including columnar cell change and flat epithelial atypia, lobular neoplasia, apocrine change and hyperplasia, ductal hyperplastic and neoplastic lesions, and metastasis to the breast, written by diagnostic breast pathologists based in the UK. The aim of this series of reviews is to provide an update on recent clinicopathological, immunohistochemical and molecular data on these rather difficult lesions and offer some guidance as to how these lesions should be managed.

With the advent of the National Health Service Breast Screening Programme (NHS BSP) in the late 1980s, the ethos of obtaining a preoperative (or non-operative) diagnosis of breast abnormalities became firmly established and subsequently has been applied to both symptomatic and screening practice; frozen section diagnosis as a routine for breast lesions is a largely historical technique in the UK. The highest levels of accuracy in breast non-operative diagnosis are achieved using the triple approach, combining imaging and clinical examination assessment with pathological results; it is worth emphasising that fine needle aspiration cytology (FNAC) and core biopsy diagnosis from palpable lesions should not be interpreted in isolation, but it has been recognised for many decades that a combination of the three disciplines results in accuracy of over 99%.¹ The non-operative identification of the nature of a lesion in the breast, by either FNAC or core biopsy, allows rapid diagnosis and subsequent discussion with the patient regarding treatment options, including the benefit of avoiding unnecessary surgery for benign lesions, unless requested. Conversely, surgery for malignant lesions can be planned, both clinically and logistically.

Historically FNAC was the more widely used non-operative technique, but the introduction of automated core biopsy techniques led rapidly to its extensive utilisation in both screening and symptomatic disease assessment. This was largely as a result of a recognition that the targets defined for the preoperative diagnosis of breast carcinomas defined by the NHS BSP were not being met in many breast units using FNAC alone,² along with publications reporting very high sensitivity and specificity for core biopsy. Application of the NHS BSP targets allows evaluation of performance³; these include a preferred target of >80% for absolute sensitivity, >90% for complete sensitivity, >85% full specificity positive predictive value and >99.5%, with a suspicious rate ideally <5%. Although some units continue to use FNAC with great success, many use core biopsy as the predominant non-operative biopsy technique; problem lesions and histological difficulties in breast core biopsy diagnosis will be addressed in the reviews published in this issue.⁴⁻⁸

This is not a static area of clinical practice and methods for, and application of, non-operative diagnosis, continue to be investigated in the research setting and developed in clinical practise. Some breast units have access to wider gauge needles, such as 11 gauge or 8 gauge cores utilising a vacuum-assisted technique, which can be used to target lesions with ultrasound or stereotaxis. These are most frequently applied to the assessment of microcalcifications, especially those that are mammographically of low or moderate suspicion, with a consequent reduction in the diagnostic biopsy rate reported.⁹ Such larger gauge core guns have the advantage of providing more tissue from often histologically difficult lesions, many of which are more specifically addressed by other authors in this issue.⁴⁻⁸ Other applications for these vacuum-assisted methods (such as the Mammotome device) include the removal of benign lesions, such as fibroadenomas, some papillary lesions and sub-areolar ducts; this is increasingly being undertaken, with the advantage to the patient of avoiding a surgical procedure.¹⁰⁻¹¹ Data

suggest that this is well tolerated by patients, and has few and minor complications.¹¹ A second surgical procedure is relatively rarely required, particularly if there is no evidence of epithelial atypia on a preceding 14 gauge core sample. If, however, a 14 gauge core biopsy shows epithelial atypia (such as atypical ductal hyperplasia or lobular in situ neoplasia), the risk of associated carcinoma is in the region of at least 40–50%¹²; it would therefore seem sensible that such patients are advised to undergo a diagnostic surgical procedure rather than 11 or 8 gauge vacuum-assisted excision.

Recent publications, and ongoing research into preoperative evaluation, indicate that lymph nodes from patients with invasive breast carcinoma may be sampled by either core biopsy or FNAC,¹³⁻¹⁵ and in this way a proportion of those with nodal metastases from breast cancer can be identified preoperatively (thus avoiding a second surgical procedure in these individuals); indeed such core biopsy and FNAC specimens are increasingly being received in the routine setting in pathology laboratories.

BASIC PRINCIPLES

Accurate histological interpretation and reporting of core biopsy samples (whether 14 gauge, 11 gauge or 8 gauge), requires knowledge of the clinical and mammographic findings. It is, for example, essential to know whether one is searching for microcalcification within a core biopsy or an explanation for a breast mass. Receipt of a fully completed request form is essential; reporting samples in isolation of patient and clinical information is imprudent. Information should include full clinical details, radiological findings and the site of biopsy. Information on the date at which the case will be discussed at the multidisciplinary meeting is also helpful. In addition to details of the radiological findings, biopsy specimens taken for microcalcification should be x rayed and the cores sent with a specimen x ray; any radiological comment regarding the presence of representative microcalcification in the sample is valuable. It may be helpful for those cores which contain the microcalcification to be separately identified (in a separate pot, capsule or marked with dye); in this way laboratory and histological resources can be targeted on the appropriate portions of the sample.

As for all other breast samples, good fixation is essential for core biopsy specimens. This is, however, not in general a significant problem; the specimens should be placed quickly in sufficient fixative and sent to the laboratory. Ideally, biopsy specimens should be fixed

routinely for a minimum of 6 h in order to optimally assess hormone receptor status and morphology,¹⁶ although it has been recognised for a long time that samples can be fixed more quickly with the aid of heat or microwave techniques.¹⁷ This can be performed if a particularly urgent result is required. More recently rapid processing techniques, when applied to breast cores, have been reported to produce good results for both H&E and immunohistochemical examination,¹⁸ although this is, as yet, not globally accepted or very widely used.

With regard to fixation, there are, conversely, reports of loss of microcalcification from specimens left in formalin or other aqueous solution for periods of time, and there is some data to suggest that this may occur relatively quickly, for example within 3 days¹⁹; this could be a potential difficulty for specimens that remain in fixative over a weekend without processing. If, however, microcalcification is not readily visible, it is important to remember to search for calcium oxalate crystals, which may not be seen on H&E sections but are a common cause of mammographic microcalcification,²⁰ and can be readily seen with polarised light²¹ (fig 1A,B). For larger breast specimens, high quality processing, section cutting and staining is essential. In some laboratories, a single level is examined for mass lesions, while cores from microcalcifications are assessed with a minimum of three levels stained with H&E. In practice, many laboratories choose to examine all core biopsy specimens from breast lesions with at least three levels initially, particularly those derived from screen-detected abnormalities; such issues will clearly differ between laboratories according to local preference and resources. It is helpful in such cases to retain the material between those levels examined with H&E, ideally on coated slides, in order to undertake immunohistochemistry, if required.

REPORTING CATEGORIES

Although the inexperienced may imagine that all lesions can be specifically diagnosed on core biopsy specimens, particularly larger 11 gauge or 8 gauge samples, it must be noted that the main aim of histological examination of breast core biopsy specimens in the NHS BSP is to fulfil the assessment process and apply pathology categorisation (B1–B5) as part of the triple assessment process.³ Thus the primary aim within the NHS BSP is not to give a definitive diagnosis although, fortunately, this is possible in the vast majority of cases. Although most core biopsy specimens can be classified as normal (B1), benign (B2), or malignant (B5), a small proportion cannot. These lesions fall in the borderline categories of B3 (lesion of uncertain malignant potential) or B4 (suspicious). These borderline categories are most often applied to screen-detected abnormalities which are also frequently the more difficult lesions to classify on surgical excision specimens when abundant material is submitted for assessment; it should be no surprise that these lesions in small core biopsy specimens cannot be unequivocally categorised.

It must also be noted that the reporting categories for breast cores apply purely to the histological appearances within the specimen, and the choice of diagnostic “B” category should be based solely on the features present in the sample, and not altered by the clinical or imaging characteristics. Clearly this pathology interpretation should be discussed in collaboration with the multidisciplinary team meeting and it is only in this setting that judgement can be made as to whether the sample is (i) adequate and (ii) representative of the mammographic lesion.

Within the B3 group of lesions of uncertain malignant potential are a variety of lesions that are either known to be heterogeneous (e.g., phyllodes tumours) or to be associated with a malignant

lesion more often than one would expect by chance. Although the term “risk” of malignancy is used, it should be noted that this does not reflect increased risk in the future (in either the ipsilateral or contralateral breast), as most commonly applied. Indeed, although some of the lesions are associated both with future bilateral risk in an individual patient and with risk of there being adjacent malignancy at the time of biopsy, for example, atypical ductal hyperplasia,^{12–22} some are not generally recognised to be associated with significant future bilateral risk of developing breast carcinoma when there is no associated epithelial proliferative disease, for example, radial scar.²³

Also within the B3 category are included lesions showing epithelial atypia and thus raising a low suspicion of being derived from malignancy. Higher suspicion lesions should be categorised as B4 (suspicious). Even within these two categories, therefore, there is a grey area, particularly for epithelial intraductal proliferations regarding correct classification as either B3 or B4, although fortunately this is not generally clinically highly important and such lesions typically require more tissue for assessment, either in the form of repeat core biopsy (often with a wider bore needle, e.g. 11 gauge) or diagnostic surgical excision.

These borderline lesions are the topic of articles from various authors in this issue. These are derived from a sub-group of lectures from the NHS BSP Breast Pathology Update Course on Non-operative Diagnosis, Spring 2006. A portion of this course addressed borderline and/or difficult lesions in breast core biopsy and some of those individuals who gave presentations on the course have provided the reviews presented in this issue. These are areas that either currently cause diagnostic difficulties or have been the subject of recent reviews, updates or controversy.

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Figure 1 Enlarged terminal duct-lobular unit affected by columnar cell change and apocrine metaplasia, containing luminal secretions and calcium oxalate crystals (A). Note that the crystals become readily visible under polarised light (B).

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