Breast pathology

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Abstract

Cellular pathology is a key component of the breast disease multidisciplinary team (MDT), representing the 'gold standard' in the diagnosis of breast cancer and providing crucial information for determination of prognosis and management. Material may be obtained for pathological examination using fine needle aspiration (FNA) cytology, needle core biopsy or surgical excision (histopathology). Common benign conditions include fibrocystic change, fibroadenomas, intraduct papillomas and radial scars. Carcinoma is by far the most common malignant tumour and may exist as in situ or invasive forms. The use of mammography in the NHS Breast Screening Programme (NHS BSP) has resulted in the detection of breast cancers at an earlier stage of development (e.g. in situ carcinoma and small, low-grade invasive carcinomas). A recent comprehensive independent review has acknowledged the risk of over-diagnosis, whilst supporting the continuation of the programme due to evidence of overall benefit in terms of a reduction in breast cancer mortality. A cellular pathology report for a malignant breast excision specimen should include comments on the factors most pertinent to prognosis and management, such as tumour type, size, grade, and presence of vascular invasion and lymph node metastases. Assessment of the proximity of the tumour to the surgical margins will inform decisions regarding further surgical excision and radiotherapy, while identification of lymph node metastases will prompt consideration for chemotherapy in suitable patients. Cellular pathology techniques can also be used in predicting the likelihood of tumour response to hormonal manipulation and newer treatments such as trastuzumab. The application of increasingly sophisticated genomic technologies to breast cancer has enhanced the classification of the disease whilst highlighting new levels of complexity, and may lead to an improvement in both prognostication as well as the ability to better identify patients who may particularly benefit from chemotherapy and novel molecularly targeted therapies.

Keywords Breast; carcinoma; diagnosis; histopathology; molecular classification; prognosis; screening

Introduction

Breast cancer is the most common malignancy in women. Cellular pathology plays a major role in the assessment of breast disease, both in initial diagnosis and in the determination of prognosis and future patient management. One of the most important roles of cellular pathology is therefore to differentiate between neoplastic and non-neoplastic breast disease and between benign and malignant tumours. This review will describe the pathological features of the most commonly encountered neoplastic and non-neoplastic lesions within the breast, and provide a brief update on recent developments in the molecular classification of breast cancer.

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Assessment of breast disease

Multidisciplinary team working in breast disease diagnosis

Breast cancer has led the way in the formation of cancer site-specific multidisciplinary teams (MDTs), which are now well-established in NHS practice. The MDT is made up of a small number of surgeons, oncologists, radiologists and pathologists as well as specialist nurses, radiographers and allied individuals such as administrative and coding staff, all of whom contribute to the provision of efficient and high-quality patient care. Optimal MDT working is reliant upon good communication between team members, usually in the form of regular MDT meetings at which individual patients are discussed.

Video conferencing can facilitate MDT meetings in geographically dispersed clinical networks. 'Telepathology' describes geographically remote reporting of diagnostic samples – such as fine needle aspiration (FNA) cytology specimens from a fast-track clinic – using a high-resolution image transmission system. Diagnoses made in this way usually require confirmation once the sample arrives in the cellular pathology laboratory.

'Triple assessment' in breast disease diagnosis: accurate diagnosis in breast disease is best achieved using 'triple assessment' which comprises a combination of clinical and radiological (mammography or ultrasonography) assessment together with either needle core biopsy or FNA cytology. This applies to lesions identified during breast screening as well as those presenting with symptoms. The findings from triple assessment should be reviewed at regular multidisciplinary team meetings.

FNA cytology is a fast, cheap and minimally invasive procedure that can confirm the presence of malignancy. Cytology cannot differentiate between in situ and invasive carcinoma. Breast core biopsy, however, can be performed under local anaesthetic in an outpatient setting and provides the ability to differentiate invasive from in situ carcinoma. Both techniques can be performed as manually guided methods on clinically palpable lesions or as image (ultrasound or X-ray)-guided sampling on radiologically detected abnormalities. The latter improves the chances of obtaining a sample from the correct area. In the context of the NHS Breast Screening Programme (BSP), identification of microcalcifications in a breast core biopsy sample helps to confirm sampling of the abnormal area of breast tissue in which microcalcifications have been detected on mammography. The results of FNA cytology or breast core biopsy may sometimes be equivocal and this usually results in the requirement for either repeat FNA, core biopsy including vacuum-assisted biopsy techniques designed to obtain larger tissue samples, surgical 'open' biopsy or excision.

Fast track 'one-stop' clinics: patients often undergo rapid assessment, usually for symptomatic breast disease, within dedicated clinics in which all of the required diagnostic modalities are available during one visit. Such clinics require the provision of a FNA cytology service with immediate assessment of the slides by a pathologist, which may be provided either within the clinic or via the use of telepathology. This is useful for making an initial diagnosis of benign lumps but a core biopsy is required for precise diagnosis. The technical processing steps required for core biopsies preclude their use in a one-stop setting, although a core biopsy may be taken during a clinic and a result often provided within 24–48 hours.

The NHS Breast Screening Programme (NHS BSP)

Cellular pathology plays an important role in the NHS BSP. The aim of the screening programme is the detection of carcinoma at an early (preferably pre-invasive) stage, to facilitate immediate surgical removal since there is evidence that this leads to improved survival. The possible risk of over-diagnosis of early disease that may not progress to invasive carcinoma and/or clinically significant disease during a woman's lifetime has been acknowledged in a recent independent review of the NHS BSP, but the review group's recommendation was that the screening programme should continue due to evidence of an overall reduction in breast cancer mortality among participants. Currently, invitations are sent to women aged 50–70 years for three-yearly mammography and an age extension trial is underway to invite women aged from 47 to 73 years to attend for mammographic screening. Recall for more detailed 'triple assessment' is then arranged for those in whom an abnormality such as microcalcification, tissue deformity/asymmetry or a mass lesion is found. The diagnosis may subsequently be confirmed with the aid of core biopsy or FNA cytology. Patients in whom the diagnosis remains uncertain may undergo diagnostic localization biopsy, where the position of the mammographic lesion is identified radiologically (using ultrasound scanning or X-rays) immediately prior to surgery. The NHS BSP guidelines indicate that surgeons should aim to remove no more than 20 g of tissue for a diagnostic localization biopsy. Therapeutic localization excision with radiological guidance can also be performed to remove impalpable lesions, if a preoperative biopsy diagnosis has been made.

The nature of breast lesions detected by screening differs to that in patients presenting with breast disease-related symptoms. Radial scars/complex sclerosing lesions, in situ carcinomas and small and/or low-grade invasive carcinomas are relatively over-represented within the screened population, because these lesions tend to be asymptomatic.

Non-neoplastic breast disease

Fibrocystic change

This very common condition comprises a spectrum of changes including *cyst formation, apocrine metaplasia* and alterations of lobules, especially *columnar cell change* and *sclerosing adenosis* (Figure 1). Fibrocystic change may present symptomatically with cyst formation, as a semi-discrete mass or an ill-defined thickening/nodularity. N.B. Columnar cell change may also occur in association with proliferative and malignant disease as described in the neoplastic disease section below.

Duct ectasia

This is dilatation of breast ducts that most commonly presents with nipple discharge in which cytological examination may reveal the presence of macrophages derived from the duct lumens. If an inflammatory process develops around the ducts, then acute inflammation, abscess formation and a fistula may develop in a condition known as periductal mastitis.

Epithelial hyperplasia

Epithelial hyperplasia of usual type ('epitheliosis') is a common non-neoplastic condition in which 'overgrowth' of epithelium of variable degree (mild, moderate or florid) occurs within ducts or lobules, often in association with one or more components of fibrocystic change (Figure 1). Patients in whom florid epithelial hyperplasia of usual type is identified appear to be at slightly increased risk of subsequent breast malignancy.

Radial scar and complex sclerosing lesion

These terms describe essentially the same lesion, with a rather artificial size cut-off of 10 mm used to separate radial scars (<10 mm) from complex sclerosing lesions (>10 mm). They are usually found incidentally or identified as stellate (star-shaped) lesions on mammography, when distinction between a radial scar and a small invasive carcinoma may be difficult or impossible on radiological grounds alone. The stellate architecture is very apparent on histological examination, which also reveals often quite florid benign epithelial hyperplasia and other components of fibrocystic change, occurring within a characteristic background elastotic tissue appearance. These lesions are in themselves benign although they may be spatially associated with invasive or in situ carcinoma. There is also some evidence to suggest that multiple radial scars may be a predictor of future breast malignancy.

Unusual non-neoplastic conditions

Sclerosing lymphocytic lobulitis (SLL): this unusual benign condition occurs most commonly in patients with autoimmune disease, especially insulin-dependent diabetes mellitus, and comprises perilobular and perivascular chronic inflammation within a fibrous background. SLL may present clinically as an irregular mass suspicious for malignancy, while FNA cytology often results in an insufficient sample, due to the presence of fibrosis, prompting surgical excision.

A *hamartoma* is a benign lesion comprising tissues normally found at a particular site but arranged in an abnormal manner. Hamartomas of the breast may present as clinically well-defined masses suggestive, for example, of a fibroadenoma. Macroscopic examination of the lesion reveals a variably defined nodule while microscopic examination reveals a semi-discrete jumbled arrangement of breast ducts and lobules, usually with some background adipose tissue and sometimes with smooth muscle fibres.

The breast may unusually become involved in systemic disease processes such as *vasculitis* (e.g. Wegener's granulomatosis) and *amyloidosis* (the latter may also exceptionally affect the breasts alone).

Neoplastic breast disease

Benign tumours of the breast

Fibroadenomas most commonly present in young women as a well-defined mobile mass. Histological examination reveals a