Making sense of breast pathology

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An understanding of breast pathology is essential when caring for women with breast disease. Part five of this series discusses the spectrum of common benign and malignant conditions including the distinction between invasive and noninvasive breast cancer. It also aims to increase the general practitioner's confidence in understanding breast pathology reports, arranging appropriate referral for patients, and educating women about their disease.

There are three main categories of breast disease:

- Benign conditions – these may require treatment to relieve symptoms
- Malignant conditions – invasive carcinoma requires multidisciplinary assessment and treatment. Treatment may include surgery, radiotherapy, and chemotherapy; their use reflects the severity of disease and its mortality rate. Similarly, the pre-invasive form of breast carcinoma – ductal carcinoma in situ (DCIS) – requires treatment to ensure it does not directly progress to invasive carcinoma
- Conditions that identify the patient to be at increased risk of future breast carcinoma – these include conditions such as lobular neoplasia and atypical ductal hyperplasia (ADH). Patients with these conditions require close surveillance to detect any onset of breast carcinoma at an early stage, thereby maximising the effectiveness of therapy.

The investigation of a breast abnormality and the categorisation of any disease rely on a combination of clinical, imaging and biopsy techniques. These culminate in the examination of a cell or tissue sample by a pathologist.

Once the diagnosis of invasive breast carcinoma has been made, the pathologist is required to provide further information including a range of prognostic and predictive factors that help determine appropriate therapy. A prognostic factor is any measurement available at the time of diagnosis associated with disease free or overall survival such as tumour size or nodal status. A predictive factor is any measurement associated with response or lack of response to a particular therapy such as an oestrogen receptor positive tumour responding to tamoxifen.

The pathologist is an important member of the multidisciplinary team responsible for the care of patients with breast disease. For the patient with breast carcinoma, tailoring therapy for the individual has become the aim for all those involved. There is increasing dependence on accurate and reliable pathology reporting to reach this goal.

Breast biopsy techniques

The pathologist may be presented with a range of breast specimens. These may be obtained by fine needle aspiration (FNA), core biopsy, or open surgical biopsy.

Fine needle aspiration biopsy is a simple, inexpensive, reliable and rapid technique for obtaining cells from a targeted area of breast tissue. It does however, depend on the skill and experience of both the aspirator providing the specimen and the cytopathologist interpreting the cells.

A core biopsy involves obtaining single or multiple tissue cores from the breast by conventional or vacuum assisted means. A vacuum assisted core biopsy (eg. Mammotome®) results in a larger sample and may in some cases allow complete removal of the target abnormality in

the breast.

If the lesion is impalpable, the surgeon performing an open biopsy may require imaging localisation of the target lesion using mammography or ultrasound and hook wire placement.

For these sampling techniques, it is important that the pathologist receives all relevant information concerning the indication for biopsy and imaging findings.

Benign breast disease

In the past, benign breast changes were often referred to collectively by terms such as 'fibrocystic disease', 'mammary dysplasia' and 'benign mastopathy'. These terms were used to refer to a range of benign breast changes, from cyclical clinical nodularity to benign proliferative and nonproliferative pathological changes seen on biopsy. In the past 20 years, there has been a move away from using these poorly defined terms in favour of more specific pathological terms. These specific terms not only describe the particular lesion or breast tissue change with greater accuracy, but also provide an indication of the risk of future breast carcinoma development.[1]

Risk of carcinoma

There are several types of benign breast disease shown to increase the risk of developing breast carcinoma. The magnitude of the risk appears to be dependent on the degree of proliferative change and atypia seen in the biopsy material (*Table 1*).[2] Much of the information used in this risk assessment is derived from retrospective reviews of breast pathology. These reviews are obtained from the biopsies of thousands of women who continue to be followed up, in some cases for more than 20 years after the breast biopsy was performed.[3]

Proliferative benign breast disease in the form of ductal hyperplasia of moderate or florid type can therefore be considered a risk factor for developing invasive carcinoma (*Figure 1, 2*). The magnitude of risk is increased by other factors such as family history of breast carcinoma and nulliparity. It is important to note that this associated increased risk of future invasive carcinoma applies to both breasts, and continues to be seen for 15 or more years after diagnosis.[3]

Table 1. Benign breast disease and invasive carcinoma risk[2]

No increased risk
Adenosis, other than sclerosing adenosis
Duct ectasia
Fibroadenoma lacking complex features
Fibrosis
Mastitis
Mild ductal hyperplasia of usual type without atypia
Cysts, gross or microscopic
Simple, apocrine metaplasia without associated hyperplasia or adenosis
Squamous metaplasia
Slightly increased risk (relative risk 1.5–2.0)
Complex fibroadenoma
Moderate or florid ductal hyperplasia of usual type without atypia
Sclerosing adenosis
Solitary papilloma without atypical hyperplasia
Moderately increased risk (relative risk 4.0–5.0)
Atypical ductal hyperplasia
Atypical lobular hyperplasia

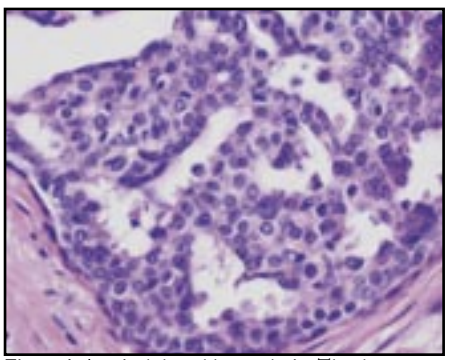

Figure 1. Atypical ductal hyperplasia. The duct shows a proliferation of atypical monomorphic cells whose appearance closely resembles that of low nuclear grade DCIS. The arrangement of the cells is irregular in contrast to those seen in Figure 5

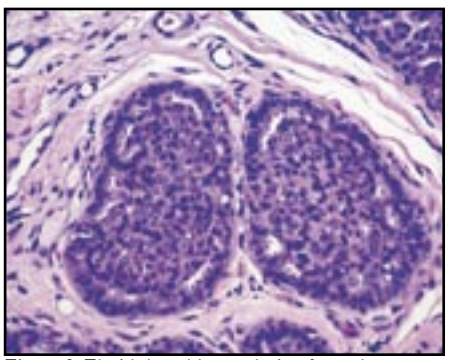

Figure 2. Florid ductal hyperplasia of usual type. The two ducts are filled by a mixed population of cells

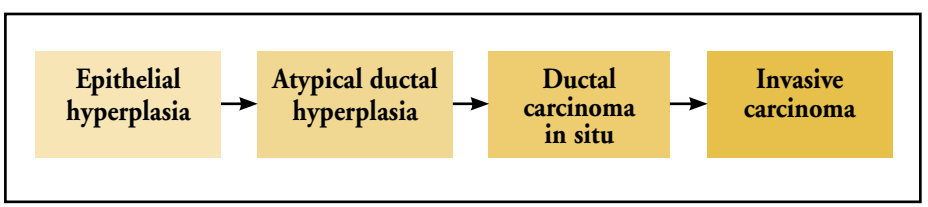

Figure 3. Continuum of change

Clinical implications

Common benign breast lesions include fibroadenomas, cysts, and intraduct papillomas. Breast lesions identified as risk factors for subsequent invasive breast carcinoma may require a different management strategy (*Table 2*).

Table 2. Clinical implications of benign breast disease

Fibroadenoma

- Carcinoma risk
  - no increased risk associated with fibroadenoma without hyperplasia
  - slightly increased risk of future breast carcinoma if hyperplasia, with or without atypia
- Management implications
  - no special management needed for women with fibroadenoma without hyperplasia
  - women with a previous fibroadenoma with hyperplasia have a slightly increased risk of future breast carcinoma (usually no special management is recommended as the increased risk is extremely small)

Cysts

- Carcinoma risk
  - conflicting evidence as to whether cysts lead to increased risk (some studies show no increase in risk,[4] others show a small increase in risk[5])
  - on balance there may be slight increase in risk, although not of clinical significance
- Management implications
  - no special management is required

Intraduct papilloma

- Carcinoma risk
  - a solitary intraduct papilloma results in a slightly increased risk
- Diagnostic difficulty
  - intraduct papilloma may be difficult to distinguish from intraduct papillary carcinoma on percutaneous biopsy
- Management implications
  - if a papilloma is suspected from FNA or core biopsy, surgical excision is recommended for full pathological assessment and to exclude intraduct papillary carcinoma

Ductal hyperplasia of usual type (HUT) and ADH

- Carcinoma risk
  - mild HUT without atypia carries no increased risk
  - ADH carries an increased risk (relative risk 4–5)
  - when associated with a family history of breast carcinoma in a first degree relative, ADH carries a 10 times increase in risk[3]
- Diagnostic difficulty
  - pathological distinction between the two conditions is often extremely difficult and reproducibility of diagnosis between pathologists is poor
  - difficult to distinguish ADH from DCIS (carries an even higher risk of direct progression to invasive carcinoma)
- Management implications
  - HUT needs no special management or surveillance
  - when ADH is suspected on FNA or core biopsy, excision of the lesion is recommended for further assessment as some will prove to be DCIS, or may be adjacent to foci of DCIS[6]
  - if an open biopsy specimen shows ADH (without DCIS) there is no need for further management of the lesion, however given the magnitude of risk, close surveillance by annual mammography and clinical breast examination is advisable

Atypical lobular hyperplasia (ALH)

- Carcinoma risk
  - carries an increased risk similar to ADH
- Diagnostic difficulty
  - some lesions displaying ALH on core biopsy are upgraded to carcinoma in situ or invasive carcinoma (usually ductal) after open biopsy[7]
- Management implications
  - increasing trend to surgically excise lesions that show ALH on core biopsy
  - women with previous ALH on a core or excision biopsy should be monitored in the same way as women diagnosed with ADH

The evolution of breast carcinoma

Invasive breast carcinoma has traditionally been regarded as the final stage in a continuum of proliferative changes in the breast (*Figure 3*). The concept of a continuum in the development of breast carcinoma is now being questioned, and classification of breast lesions is being reconsidered.

It is likely that both genetics and pathology will contribute to future classifications of benign and malignant breast lesions, and to our understanding of the progression between the two. Some benign proliferative lesions that show atypia increase the risk of future breast carcinoma. The lesions of DCIS and lobular carcinoma in situ (LCIS) are considered 'pre-invasive' malignant lesions, which are one step further along the spectrum toward invasive breast carcinoma. The management of these lesions is changing with a trend toward more aggressive management of proliferative and in situ lesions (surgical excision).

In situ breast carcinomas

In situ breast lesions include DCIS and LCIS. In DCIS, the epithelial cells have undergone malignant change, but the malignant cells have not invaded through the basement membrane of the duct or acini to become 'invasive' carcinoma. There are several types of DCIS subclassified by the pathologist into high, intermediate and low nuclear grade, according to the appearance of the cell nuclei (*Figure 4, 5*). High nuclear grade DCIS has a high rate of recurrence following treatment, and a high proportion of these recurrences are as invasive carcinoma (*Figure 6*). By contrast, low nuclear grade DCIS has a lower rate of recurrence and of progression to invasive carcinoma. Intermediate nuclear grade DCIS has an intermediate recurrence rate, between that of high and low grade lesions. However, low grade DCIS can recur at a constant rate over many years. Although the risks of local recurrence are lower at 5 years after initial treatment, the rates increase and approach that of high grade DCIS 10 years after initial treatment.[8]

Treatment of DCIS is therefore dependent to some extent on the classification of the lesion on pathological examination. The pattern of proliferation of the malignant cells in DCIS affected ducts is recorded, although the architecture of the lesion appears to

Table 3. In situ breast carcinoma pathology report

Nuclear grade
- high grade
- intermediate grade
- low grade

Lesion size

Pathological type/architecture
- comedo, solid, cribriform, micropapillary

Margin status
- margins involved with tumour, or
- margins clear of tumour cells (measure clearance in mm)

Associated microcalcification
- present or not

Presence of necrosis
- present or not (presence is a poor prognostic feature)

Hormone receptors
- can be tested (not routinely recommended)
- the role of hormonal agents such as tamoxifen remains unclear in this setting

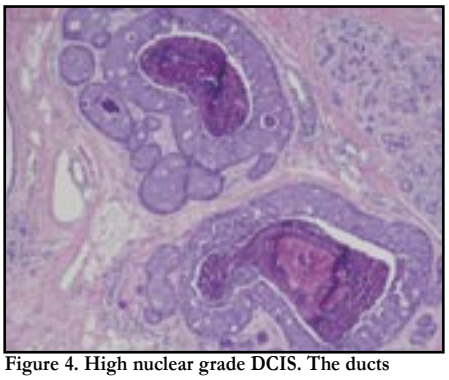

Figure 4. High nuclear grade DCIS. The ducts contain an increased number of large cells that remain confined within the duct. The centres of involved ducts contain necrotic cellular debris

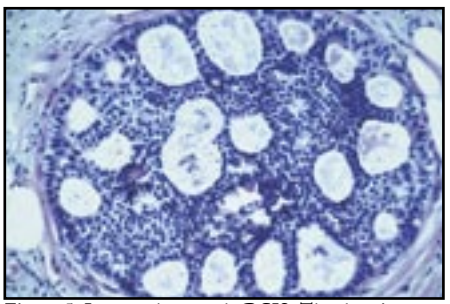

Figure 5. Low nuclear grade DCIS. The duct is expanded by a uniform population of cells forming a cribriform or 'sieve-like' pattern

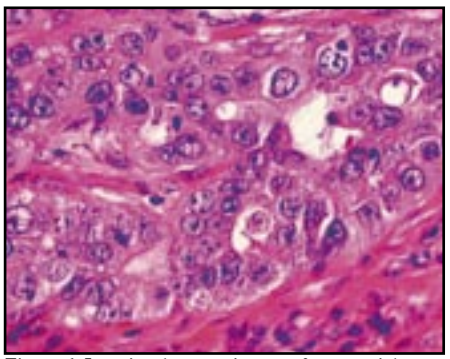

Figure 6. Invasive duct carcinoma of no special type, grade 3. Large pleomorphic carcinoma cells infiltrate the breast in groups forming irregular tubules

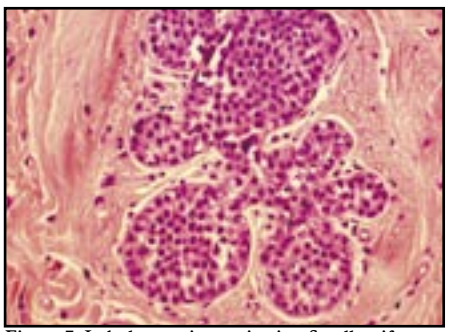

Figure 7. Lobular carcinoma in situ. Small uniform cells expand and fill the lobule

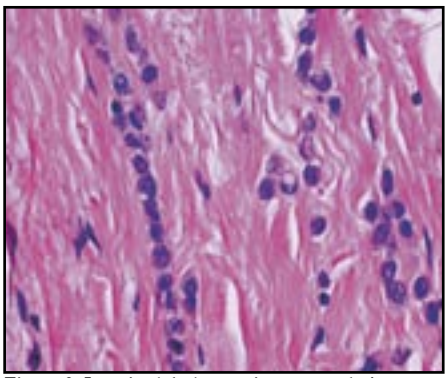

Figure 8. Invasive lobular carcinoma, grade 1. Carcinoma cells are small and uniform, and often infiltrate the breast in single file columns

have very little correlation with the clinical course of the disease All pathology reports of an open biopsy of DCIS should include the information listed in *Table 3*.

Lobular carcinoma in situ is currently thought of as a marker of increased risk of future invasive carcinoma, which may be of ductal, lobular or other histological type (*Figure 7, 8*). Lobular carcinoma in situ has no specific clinical or imaging properties and is usually diagnosed by the pathologist as an incidental finding in a breast biopsy performed for some other indication. It is not defined as or treated as 'breast cancer', however this thinking is changing. Issues related to cancer risk, diagnosis and management of DCIS and LCIS are given in *Table 4*.

Invasive breast carcinoma

The pathology report

In recent years, breast carcinoma pathology reports resulting from open breast biopsy, 'breast conservation' and mastectomy specimens have been increasingly standardised and expressed in summary or 'synoptic' format. Following the pathologist's description of the macroscopic appearance of the specimen, there is usually a summary of the critical features used to make treatment decisions. Each report should therefore contain all the important prognostic and predictive information required to guide prognosis and treatment. The pathology report should include all the information in *Table 5*.[12,13]

Table 4. DCIS and LCIS

DCIS

- Carcinoma risk
  - DCIS has the potential to develop into an invasive carcinoma (10 times risk)
  - after treatment DCIS can recur (may recur as invasive carcinoma rather than as DCIS[2])
  - future risk of in situ or invasive carcinoma elsewhere in the breast in women who have had DCIS
- Diagnostic difficulty
  - low nuclear grade DCIS can be extremely difficult to distinguish from ADH, and small foci of invasive carcinoma may be missed in an excision specimen
  - DCIS diagnosed in a core biopsy may be found to be invasive carcinoma when the lesion is excised (~15% of cases[9])
- Management implications
  - lesions diagnosed as DCIS on core biopsy require excision of the lesion for further assessment in case invasive carcinoma is present
  - lesions confirmed to be DCIS on excision need to be managed as high risk lesions, with all the principles of cancer management in mind (given that if the lesion recurs, it may be invasive)
  - complete excision of the lesion is necessary with attention to margins (mastectomy or wide local excision)
  - consider adjuvant treatment (radiotherapy) if a mastectomy has not been performed. The role of tamoxifen remains unclear
  - consider treatment of the axilla (not currently recommended for pure DCIS, but this is changing with the advent of sentinel lymph node biopsy and may be recommended in the future for large areas of high nuclear grade DCIS)
  - women with previous DCIS need close monitoring (as for women with previous invasive breast carcinoma) with the aim of detecting recurrence and new carcinomas elsewhere in the breast

LCIS

- Carcinoma risk
  - LCIS carries an increased risk of future breast carcinoma (either invasive ductal or invasive lobular carcinoma)
  - risk is in the order of 12% for future breast carcinoma (higher in women with previous LCIS than those with previous DCIS[10])
  - future breast carcinoma may occur in either breast (not just original LCIS)
- Diagnostic difficulty
  - the lesion may be underestimated on core biopsy and cannot be diagnosed on FNA biopsy
  - there is emerging evidence that a significant number of lesions showing LCIS on core biopsy are upgraded on excision biopsy to invasive carcinoma (either ductal or lobular)[11]
- Management implications
  - in the past, LCIS was considered to be a marker of future bilateral risk of invasive carcinoma rather than a lesion requiring treatment in its own right – this thinking is changing
  - there is a trend to consider excising lesions that show LCIS on core biopsy
  - lesions confirmed to be LCIS on excision biopsy are usually managed with ongoing close surveillance rather than further surgery
  - women with previous LCIS need close monitoring of both breasts as the risk of future invasive carcinoma in either breast is high[10]

Conclusion

An understanding of breast pathology is essential when caring for women with breast disease. There are many benign breast conditions that must be approached with caution. They may reflect an undersampled area of more serious breast pathology or carry an increased risk of invasive carcinoma in the future.

Conflict of interest: none declared.

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AFP

Table 5. The invasive breast carcinoma pathology report

Tumour size
- important prognostic factor

Histological type
- invasive ductal carcinoma accounts for 80% of breast cancers
- invasive lobular carcinoma accounts for 10–15% of breast cancers
- 'special' types: tubular, cribriform, and mucinous carcinomas (particularly good prognosis tumours[12])
- papillary, medullary and other uncommon histological types

Histological grade
- important prognostic factor
- grade 1–3 based on the combination of three pathological features: nuclear grade, tubule formation, and mitotic rate

Accompanying DCIS
- associated with local recurrence if 'extensive' in patients treated for invasive carcinoma by breast conservation surgery with close or positive margins [14]

Lymph node involvement
- important prognostic factor: the number of nodes dissected and the number involved with metastatic carcinoma

Margins of excision
- involvement of resection margins with invasive carcinoma or DCIS and margin distance from cancer cells
- these factors guide further treatment such as additional surgery or radiotherapy
- may also predict risk, local recurrence

Lymphovascular invasion (LVI)
- evidence of tumour cells invading into vessels
- Presence of LVI is a poor prognostic factor

Changes in adjacent breast tissue
- eg. DCIS, ADH, ALH, LCIS

Hormone and other receptors
- predict response to adjuvant treatment
- ER (oestrogen) and PR (progesterone) receptors
- HER2 receptor overexpression is a marker of poor prognosis and also of response of the carcinoma to Herceptin therapy. HER2 positive tumours may respond better to anthracycline type chemotherapy and are generally less responsive to endocrine therapy

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