

FORUM OF PATHOLOGY

Diagnostic Problems in Breast Pathology – How to avoid the pitfalls

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Introduction

Almost any breast lesion may produce diagnostic difficulty and a degree of selectivity is therefore necessary in a seminar such as this. This has been achieved by reference to two main sources: data on consistency of diagnosis from External Quality Assessment schemes in the United Kingdom organised by the National Co-ordinating Group for Breast Screening Pathology and in Europe organised by the European Breast Screening Pathology Group;¹⁻³ an informed audit of cases sent for second opinion from other departments. It is, perhaps, not surprising that both routes produce similar problem cases which fit into a relatively restricted group of diagnostic categories which can be considered under the headings shown in Table 1.

In practice the pitfalls described below may be avoided or reduced by the application of sound general histopathological principles. These include the application of strict diagnostic protocols and in this respect there is good world-wide agreement for most lesions. Participants in the symposium are referred to the standard breast pathology texts in the reference list, including UK and European breast screening pathology guidelines.⁴⁻⁸ It is interesting to note that many diagnostic difficulties arise with those lesions where complete agreement on diagnostic criteria has not yet been reached. The aim in this presentation is to emphasise practical points of distinction rather than to provide a comprehensive description of each lesion.

One further general point is pertinent. Experience has shown that in many cases difficulty in diagnosis is related to sub-optimal specimen preparation, mostly poor fixation or tissue processing. A comparatively minor investment of time and effort in improving the technical aspects of the diagnostic process will be rewarded by considerably better quality of preparations and a consequent decrease in unnecessary problem cases.

Sclerosing lesions

Some benign breast processes are characterised by a combination of epithelial proliferation, with or without a myoepithelial component, and stromal fibrosis and sclerosis which may result in formation of a mass lesion. The entities which can be placed within the umbrella of sclerosing lesions are sclerosing adenosis (SA), microglandular adenosis (MGA) and radial scar/complex sclerosing lesion (RS/CSL). They have many overlapping features and may all give rise to diagnostic problems clinically, on imaging (ultrasound and mammography) and histopathologically. Although they are frequently impalpable, both sclerosing adenosis and complex sclerosing lesion may produce palpable masses which can easily be mistaken for invasive carcinoma. Fine microcalcification is a common feature of all three entities and the appearances on mammography may be closely similar to those of low grade ductal carcinoma in situ (DCIS).⁹ In addition both SA and RS/CSL may be identified on mammography or ultrasound as an architectural distortion or spiculate mass which cannot be distinguished with confidence from carcinoma. In all these situations a tissue diagnosis must be established and increasingly this is obtained pre-operatively through needle core biopsy using one of the new spring loaded guns.¹⁰⁻¹² Diagnostic difficulty may be experienced histopathologically in interpreting such samples, and indeed in some circumstances excision biopsy specimens may also cause problems, the main differential diagnosis being invasive carcinoma, especially of tubular type.

The main morphological features of the sclerosing lesions and tubular carcinoma are shown in Table 2. **Sclerosing adenosis** is characterised by a disorderly proliferation of acinar and ductular epithelial cells, myoepithelial cells and intralobular stroma which results in expansion and distortion of lobules and an overall whorled appearance. Despite the apparent disorganisation of the cellular proliferation a lobulocentric architecture is maintained. The epithelial component may form microtubular structures but the compressed acini frequently show obliteration of their lumina. Nuclei are small and regular without atypia and mitotic figures are infrequent. Fine foci of microcalcification are frequently found within the lumina of epithelial structures.

In **microglandular adenosis** there is a disorderly proliferation of small round acinar structures, apparently infiltrating between normal ducts and lobules and extending into adipose tissue. There is no spindle cell proliferation and the growth pattern is not lobulocentric. The acini appear to be lined by a single layer of epithelial cells and the lumina often contain PAS positive, diastase-resistant, eosinophilic material which may, rarely, be calcified.

Classically **radial scar/complex sclerosing lesions** are composed of a radial arrangement of ductular structures around a central fibroelastotic core. In early lesions the central connective tissue is cellular and includes numerous myofibroblasts. The entrapped ductular or tubular structures are lined by a two-layered epithelium although epithelial proliferation is commonly present. Atypical ductal hyperplasia or lobular neoplasia may also be seen.¹³

As noted above the most important differential diagnosis for all these lesions is invasive carcinoma, especially the tubular type. In excision specimens sclerosing adenosis can usually be distinguished by its circumscribed lobulocentric low power morphology in contrast with the infiltrative pattern and desmoplastic stroma of tubular carcinoma, but care should be taken with needle core and frozen section specimens in which this feature may not be apparent. Furthermore, the architectural distortion produced in both these techniques may result in a mistaken diagnosis of infiltrating lobular carcinoma due to compression of the epithelial structures. In rare cases of sclerosing adenosis extension of the glandular components into perineural and vascular spaces is seen, a finding that must not be regarded as indicative of malignancy in the absence of confirmatory features. The presence of apocrine atypia may also raise the question of malignancy¹⁴ and this should be avoided by recognition of the benign features described above. Both ductal carcinoma in situ and lobular neoplasia have been recorded in the nodular form of sclerosing adenosis and may be mistaken for invasive carcinoma if the presence of

myoepithelial cells is not recognised.¹⁵ If the diagnosis is in doubt immunostaining with anti-smooth muscle actin will readily demonstrate their presence, thus excluding the diagnosis of invasion.

Microglandular adenosis can usually be distinguished from tubular carcinoma by its diffuse pattern and lack of central elastosis and desmoplastic stroma, although the sclerosing type of tubular carcinoma may provide a close mimic. A useful distinguishing feature is the fact that the glandular structures in MGA are usually uniform and rounded in contrast with the less regular, often angulated appearance in tubular carcinoma. Immunostaining for anti-smooth muscle actin is less helpful in MGA because in most recorded cases myoepithelial cells are said to be absent.^{16, 17} MGA may also be confused with the tubulo-lobular variant of infiltrating lobular carcinoma. However, careful examination in the latter always reveals cords of cells typical of the classical lobular type in addition to microtubular structures.

In the great majority of cases of RS/CSL the distinction from tubular carcinoma is relatively straightforward. The dense, sclerotic, poorly cellular stroma and elongated flattened tubules are quite different from the desmoplastic stroma and well formed oval structures in tubular carcinoma. However, more complex lesions with an admixture of sclerosing adenosis and epithelial hyperplasia may cause problems; it must also be remembered that both in situ and invasive carcinoma may be encountered **in association with** RS/CSL.¹³ If there is any doubt about the correct diagnosis immunostaining with anti-smooth muscle actin will help to clarify both these problems.

Great care should be taken in the interpretation of sclerosing lesions found on needle core biopsy because of the sampling problem. For example, the finding of part of a benign RS/CSL on core biopsy does not exclude the possibility of associated malignancy; it is, therefore, still our policy to excise all parenchymal distortions or architectural deformities.

Papillary lesions

These lesions cause diagnostic problems because papillary structures are found in benign **and** malignant processes and the differences between the two are often subtle and difficult to assess; the entities concerned are shown in Table 3. In practice few problems should be encountered with small single benign intraduct papillomas which are usually centrally placed under the nipple and removed by microdochectomy. However, potential pitfalls will be encountered with all of these processes on needle core biopsy, partly because of sampling error and partly related to architectural distortion due to crush artefact. Our early experience with pre-operative use of needle core biopsy, based on the manual Tru-Cut needle lead us to advise caution when benign papillary structures were identified, because of the risk of a false negative diagnosis. It is undoubtedly true that some invasive papillary carcinomas arise in a pre-existing benign papilloma, almost always of the multiple type. The finding of benign papillary structures on needle core biopsy does not necessarily mean, therefore, that malignant change is not present elsewhere in the lesion. It is our practice to issue a report with a non-specific conclusion of 'papillary lesion present', and local excision is advised. This would come into the B3 category - lesion of uncertain malignant potential - in the revised United Kingdom National Health Service Breast Screening Service (NHSBSP) Guidelines for Pathologists. It should also be noted that multiple duct papillomas are usually peripheral and often associated with florid epithelial proliferations, including usual and atypical ductal hyperplasia. In excision specimens adequate sampling is required to exclude the presence of associated ductal carcinoma in situ (see also below – borderline lesions).

Some benign papillary lesions form relatively well defined solid masses with a dominantly sclerosed architecture. In the past the term ductal adenoma was applied to such lesions, but they are now believed to arise from sclerosis of duct papillomas and we prefer to use the term ***complex sclerosing papillary lesion***. Epithelial proliferation is relatively common and a minor degree of nuclear atypia may be seen, especially if there is apocrine change. They are, in fact, entirely benign and care must be taken not to overdiagnose malignancy, especially if entrapped tubular structures are found. There is considerable morphological overlap with sclerosing adenosis and radial scar/complex sclerosing lesion and in some cases it may be impossible to make a firm distinction.

Encysted papillary carcinoma (papillary carcinoma in situ) may be confused with invasive papillary carcinoma, especially on needle core biopsy. This relatively uncommon lesion is now being detected with increasing frequency in mammographic screening. Because of their soft, cystic structure encysted papillary carcinomas are rarely palpable clinically, but are seen on mammography in older women as well circumscribed mass lesions. Astute radiologists quickly develop a suspicion of the correct diagnosis when they encounter an unusual degree of haemorrhage on needling the lesion. Using a multi-disciplinary team approach this information enables the pathologist to assess the papillary structures seen on needle core biopsy more accurately. The presence of multi-layering and genuine cytological atypia point towards a diagnosis of encysted papillary carcinoma rather than a benign intracystic papilloma but care must be taken not to overinterpret the presence of entrapped tubules as evidence of invasion. In any event all such circumscribed impalpable papillary lesions should be managed by complete local excision rather than mastectomy in the first instance. Attention must be paid to excision margins, since local recurrence is related both to the presence of ductal carcinoma in situ in adjacent ductal structures and completeness of excision.¹⁸ As with needle core biopsy areas of possible invasion around the periphery of the excised lesion should be assessed with caution. There is usually a broad fibrous 'capsule' and 'pseudoinvasion' due to the presence of entrapped tubules is a frequent finding. Invasive carcinoma may, rarely, be associated with encysted papillary carcinoma, but should only be diagnosed when epithelial structures extend into adjacent breast or adipose tissue. Encysted papillary carcinoma has a good prognosis and complete excision appears to be curative.¹⁸

‘Borderline’ lesions

The language used in medicine is fascinating and it is interesting to observe how insidiously words such as ‘borderline’ creep into our vocabulary without due thought to their impact on clinical practice. It is difficult to establish when the term was first applied to breast lesions but it appears to have been in use for at least 25 years to encompass those lesions characterised by epithelial proliferation. The main problem with the term is that it implies a sharp division between entities and this is usually interpreted as providing a separation between benign and malignant lesions with a consequent effect on clinical management protocols. In reality such sharp distinctions rarely occur and certainly where breast epithelial lesions are concerned we are dealing with a **spectrum** of changes. This has been emphasised in recent years by molecular genetic studies which have shown loss of heterozygosity in usual epithelial hyperplasia, atypical ductal hyperplasia and ductal carcinoma in situ (DCIS); this data implies that even usual epithelial hyperplasia, in some cases, is a clonal, and therefore neoplastic, process.¹⁹⁻²² Nevertheless, from the practical viewpoint stratification **is** required so that individual patients receive appropriate treatment. The entities concerned are the epithelial hyperplasias of usual and atypical subtypes, in situ carcinoma and so-called ‘minimal’ invasive carcinoma. In my view it is more appropriate to regard these lesions as occupying a **borderland** between entities which are definitely benign and those which are unequivocally malignant. Some years ago we devised the scheme outlined in Table 4 to indicate the gradual transition from risk factor (for subsequent invasive carcinoma) to established malignancy. This concept now needs to be re-evaluated for two main reasons; there are definite problems in reproducibility of diagnosis of such entities as atypical ductal hyperplasia (ADH) and more appropriate cut-off points are required to stratify patients for clinical and therapeutic management.

The debate concerning the utility of the term atypical ductal hyperplasia has continued for the past 20 years. Page and colleagues have promoted the view that epithelial proliferations which closely resemble DCIS of low grade type, but which do not exhibit all the precise morphological characteristics to make that diagnosis with confidence should be designated as ADH.^{23, 24} Although this concept has received wide acceptance doubts remain. Some,^{1, 3, 25} but not all,²⁶ reproducibility studies have shown poor agreement for the entity suggesting that there is a lack of agreement on the diagnostic criteria. It is therefore worth emphasising some key distinguishing features, as set out below:

- a DCIS of low grade type has a population of evenly spaced, uniform cells with uniformly oval to rounded nuclear features, comprising without doubt the entire population of cells throughout at least two membrane-bound spaces (a measure of the extent of the lesion). Secondary spaces have smooth rounded ‘punched out’ borders of geometrical structure (cribriform architecture - cribrum - sieve - Latin) and rigid non-tapering bars can be found. Micropapillary structures are bulbous and regularly placed around the space.

NB Epithelial proliferations of high grade cytology, with or without comedo necrosis qualify as DCIS, regardless of lesional size.
- b ADH exhibits partial involvement of the basement membrane-bound space by a cell population of the type defined above for DCIS of low grade type. A second cell population is usually present, consisting of columnar, polarised cells of the type seen in the ductal lamina positions immediately above the basement membrane. There is general agreement that lesions with these features which measure more than 2-3 mm in diameter are more likely to represent DCIS than ADH. ADH is, therefore, almost without exception, a tiny lesion.

In summary, we use the following rules of thumb.

- 1 We do not entertain a diagnosis of ADH unless low grade DCIS has been considered seriously in the differential diagnosis.

- 2 ADH is a very small, microfocal, process; the larger the lesion the more likely it is to be DCIS.
- 3 It follows that if there is any doubt about the differential diagnosis further levels and blocks should be examined. In our experience this usually resolves the problem, almost always by revealing evidence of low grade DCIS.
- 4 If changes resembling ADH are found in a needle core biopsy they should be regarded as either indicative of uncertain malignant potential (B3) or suspicious of malignancy (B4). Excision biopsy is mandatory and usually reveals unequivocal low grade DCIS.^{10, 12, 27}

In recent years there has been a proliferation of classifications for ductal carcinoma in situ.^{7, 28-30} Despite differences in terminology all identify an aggressive comedo, poorly differentiated, high grade subtype and a relatively indolent subtype - non-comedo, well differentiated, low grade. In the United Kingdom it has been recommended that to avoid problems with the definitions of comedo necrosis and architectural pattern a simpler nuclear grading system is adopted for use in the National Health Service Breast Screening Programme (NHSBSP), and the same classification has been accepted by the European Commission Working Party on Breast Screening Pathology.^{6, 7} However, problems with reproducibility still exist and only average agreement has been obtained in studies to date.

We are still left with the dilemma of correlating the morphology of these epithelial proliferative lesions and their management. Table 5 provides a somewhat speculative personal attempt to achieve this. Epithelial hyperplasia of usual type, with its low relative risk factor of x2, needs no treatment or follow-up. The size rule should still be applied to define atypical ductal hyperplasia, but, in my view, both ADH and low grade DCIS measuring less than 3 mm can be managed in the same way, by follow-up alone. There is no doubt that the prognosis for all types of ductal carcinoma in situ is excellent, provided that complete local excision is achieved. The same is true for so-called 'microinvasive carcinoma' (which will be referred to further below) and small invasive carcinomas as defined in Table 5. Note that the small invasive tumour size in Table 4 has been raised to 15 mm from 10 mm because no difference in prognosis between the two was found in the Nottingham Tenovus Primary Breast Cancer Study.⁴ This group of patients can therefore be treated by complete local excision, with or without axillary dissection. Local irradiation may be appropriate, but systemic therapy is not indicated.

Experience from both anecdotal consultation cases and early data from the UK NHSBSP indicate that microinvasion in DCIS is over-diagnosed by many general histopathologists. Because of this perception and the lack of consensus throughout the world on diagnostic criteria the definition recommended for use in the NHSBSP is very restrictive.⁷ The lesion is composed predominantly of DCIS (almost always of high grade type), but with foci of **definite** invasion outside the specialised lobular stroma measuring not more than 1 mm in maximum diameter. There is no limit on the number of such foci. Care must be taken not to confuse as microinvasion extension of DCIS into lobules, branching of ducts containing DCIS, tangential cutting, crush and cautery artefact. Particular difficulty may be encountered in cases with marked periductal fibrosis and inflammation. In general terms the diagnosis of microinvasion should not be made unless there is convincing invasive carcinoma extending into interlobular stroma or adipose tissue. Multiple levels should be examined in suspicious cases and we have found in our laboratory that immunostaining for anti-smooth muscle actin may be helpful in distinguishing in situ from invasive elements. Immunostaining for basement membrane components (type IV collagen, laminin) is of less value. Pathologists are taught in general that when in doubt over a 'borderline' diagnosis to give the more malignant interpretation in order to avoid under treatment. It should always be borne in mind when considering a diagnosis of microinvasive carcinoma that some surgeons will carry out an axillary dissection or clearance in such cases but not, of course, for DCIS, and overdiagnosis therefore leads to unnecessary surgery. Furthermore, there is no evidence to date which has demonstrated that microinvasive carcinoma has a

different prognosis from that of high grade DCIS. In my view, therefore, the diagnosis should only be made in those rare cases with unequivocal evidence of invasion.

Fibroepithelial lesions

Fibroepithelial lesions may give rise to a number of diagnostic problems but the most important concern **phyllodes tumour**. At the benign end of the diagnostic spectrum difficulty is occasionally encountered in distinguishing a cellular fibroadenoma from a benign phyllodes tumour. At the malignant end the criteria for the separation of benign and malignant phyllodes tumour are often misinterpreted with consequent overdiagnosis of malignant phyllodes tumour.

Classically fibroadenomas are usually encountered in women under the age of 30 years whilst phyllodes tumours are seen much more frequently in middle aged or older women. However, there is considerable overlap between the two entities at both ends of the age range and a significant minority of phyllodes tumours occurs in adolescents and young women.³¹ Size alone is of no value as a distinguishing feature; although most fibroadenomas are small, measuring less than 20 mm in diameter and phyllodes tumours tend to be larger than this, there is marked variation in the size of both lesions. We have certainly encountered a number of phyllodes tumours measuring no more than 10 mm in diameter. Nevertheless, most problems are encountered with relatively large fibroadenomas in younger women when the presence of an intracanalicular pattern with leaf-like foci and cellular stroma raise the possibility of benign phyllodes tumour. Relative uniformity of stromal nuclei and a lack of mitoses favour a diagnosis of fibroadenoma. Further blocks should always be examined but it may be very difficult to make a clear distinction in some cases. It may be prudent to issue a cautious report in such cases, especially if the lesion extends to resection margins, since risk of local recurrence in phyllodes tumour is related to incomplete excision.

In the past phyllodes tumour gained an unwarranted aggressive reputation largely based on data from tertiary referral centres which, by their very nature, tend to acquire the more difficult cases for treatment. In addition there has been a general lack of agreement on the morphological criteria which should be used to designate malignancy in an individual tumour. As a result some pathologists, in an understandable attempt to avoid under-diagnosis, are inclined to err on the malignant side in assessing the histological appearances. It is now accepted that the majority of phyllodes tumours are, in fact, entirely benign; in our own community based study in Nottingham two thirds of the cases were classified as benign on morphological grounds and only 16 per cent had malignant features.³² We therefore prefer to use the term 'phyllodes tumour' rather than cystosarcoma phyllodes and believe that the latter, with its innate implication of malignancy, should be abandoned.

Based on semiquantitative criteria^{33, 34} we divide phyllodes tumour into three categories, benign, borderline and malignant.³² Benign tumours have a pushing margin, minimal stromal overgrowth, cellularity and nuclear pleomorphism with stromal mitotic counts less than 10 per 10 fields (field diameter 0.152 mm²). In malignant lesions the margin is infiltrative, there is marked stromal overgrowth, cellularity and nuclear pleomorphism and mitotic counts are greater than 10 per 10 fields. Cases are placed in the borderline category if they fulfil some, but not all, of the criteria for malignancy, eg, a pushing margin, but moderate nuclear pleomorphism and an intermediate mitotic count. Interestingly we found that none of these morphological features was useful in predicting local recurrence, which was strongly related to completeness of local excision. Metastasis is very uncommon in phyllodes tumour and only occurs in tumours with a malignant phenotype. It is our policy to excise benign phyllodes tumours with a clear margin of at least 10 mm; re-excision may be appropriate in some cases if completeness of excision is not achieved at the first operation. Mastectomy is advisable for patients with malignant phyllodes tumours and is also offered to women with very large benign lesions to avoid a poor cosmetic result. The borderline category is useful in preventing over-diagnosis of malignancy and therefore potential over-treatment. Optimum local therapy depends on the size of the tumour. Local excision is imperative, but only if this cannot be achieved with a satisfactory cosmetic result need mastectomy be considered.

Effects of previous therapy

An increased proportion of patients now have breast conserving therapy rather than mastectomy for first line surgical treatment of breast carcinoma. This is frequently followed by radiotherapy to the breast. Both pre- and post operative chemotherapy may also be utilised in different treatment regimes of patients with primary breast cancer. Fine needle aspiration cytology (FNAC) specimens or biopsies of clinical or mammographic abnormalities in the residual breast may thus show changes due to irradiation or systemic therapies which may mimic residual, recurrent or second malignancies. It is therefore vital that adequate clinical information is given about previous treatments when any specimen is sent to the laboratory.

Second malignancies, both mammary and non-mammary in origin are also seen in patients treated for breast cancer and these must be considered when new clinical or radiological lesions are identified.

Within the breast parenchyma both the stromal component and the epithelium may show **radiation changes**. Stromal fibrosis with reactive 'radiation fibroblasts', as seen elsewhere in the body, can be identified. The nuclei of these fibroblasts may be variable in size and hyperchromatic or hypochromatic with 'smudged' outlines; nucleoli may also be visible.³⁵ The fibrosis may be extensive and a severe reaction is a particular complication of radiotherapy in patients with underlying connective tissue diseases. Elastosis is also seen in association with radiotherapy but this is a non-specific feature which may be present in benign breast conditions and after surgery alone and is thus of little diagnostic help.

The most characteristic radiation changes, however, involve the terminal duct lobular units where atypical epithelial cells are present within the surrounding lobular stroma which is usually hyalinized and sclerotic.³⁶ The epithelial changes are seen in all irradiated patients but show considerable variation in severity, apparently unrelated to radiation dose. Nuclei are hyperchromatic and enlarged but nucleoli are inconspicuous and chromatin is homogeneous without the 'clumping' seen in malignancy. The cytoplasm of the cells is often vacuolated. Myoepithelial cells are reported to be unaffected by radiotherapy.

The epithelial atypia described may mimic residual or recurrent carcinoma. However, although the epithelial cells are plump and may appear to fill the terminal duct lobular units, the latter are not significantly distended and a lack of stratification and mitotic activity may be helpful in determining that the features are due to irradiation. Neither the monotony of the regular cells of lobular carcinoma in situ nor the pleomorphism, conspicuous nucleoli, mitoses and loss of polarity of ductal carcinoma in situ (DCIS) within lobules ('cancerization of lobules') is present. Although epithelial atypia may be seen in larger ducts, as reported with chemotherapy, this is always accompanied by the more characteristic changes in the terminal duct lobular unit. Necrosis is not usually identified.

The epithelial features associated with radiotherapy may also be seen in foci of sclerosing adenosis thus making histological interpretation more difficult. The overall architectural pattern on low power examination is then not that of carcinomatous infiltration but remains lobulo-centric and this is a useful discriminatory feature. To diagnose residual or recurrent carcinoma in these circumstances may be a particular problem in frozen section material and a definite diagnosis may not be possible on such preparations. In general frozen section requests should be discouraged when small foci of recurrent carcinomas are suspected in patients who have had radiotherapy. It is worth noting however that recurrent breast carcinomas are usually similar in appearance to the original tumour and review of the previous reports and histological slides may be invaluable.

The lack of the architectural assistance gained from histological examination of an excision biopsy specimen may make the assessment of needle core and cytological preparations from the irradiated breast very difficult. It has been reported that the cytological features in particular may be indistinguishable from malignancy. Caution is required in the interpretation of cytological atypia in FNAC from irradiated tissues³⁷ and the cellularity of the sample is more useful diagnostically;

paucicellular samples are uncommon from foci of recurrent or residual malignancy but are usual from the non-neoplastic irradiated breast. If scanty highly atypical cells are seen in a smear it may be necessary to issue a C4 - 'suspicious' rather than a C5 - 'malignant' report and the same is true for needle core biopsies.

The tissue changes present in residual breast carcinoma cells after radiotherapy are essentially similar in nature to those seen in non-neoplastic breast tissue. Cytoplasmic vacuolation may be identified and carcinoma cell nuclei may show marked pleomorphism with the presence of bizarre forms and extensive tumour necrosis may be encountered. As described above the fibrosis of the stroma may lead to difficulties in distinguishing small foci of carcinoma cells which have become entrapped from radiation changes in sclerosing adenosis and non-neoplastic conditions. In these circumstances immunohistochemistry with epithelial markers and smooth muscle actin may be invaluable; the epithelial nature of the cells can be confirmed but smooth muscle actin immunoreactivity will be seen surrounding entrapped benign tubules.

Chemotherapy in the residual non-neoplastic breast causes changes similar to those in the irradiated organ. Atrophy of epithelial structures is seen in lobules with a variable degree of intralobular fibrosis.³⁸ Indeed lobular atrophy occurs in up to 65% of cases and is seen in both pre- and post-menopausal women.³⁹ Bland fibrous obliteration of acini may occur and fibrous or fatty involution of the stroma elsewhere in the breast may be identified, possibly related to suppression of ovarian function. Epithelial atypia is present in the lobules in approximately 30% to 50% of cases but, unlike irradiation change, is equally common in ducts where this feature may be seen in 40-50% of specimens.^{38, 39} Epithelial cells may be enlarged with prominent nuclei, small nucleoli, thick nuclear membranes and pale vacuolated cytoplasm, essentially similar to the features of irradiation in breast tissue. The nuclear membrane remains well-defined and hyperchromasia is less prominent than in residual or recurrent carcinoma cells. Uncommonly, necrosis and consequent calcification may occur within the duct lumen and can thus produce a suspicious mammographic appearance necessitating FNAC or biopsy.

Residual carcinomatous foci may show similar histopathological changes as a result of chemotherapy to those described following irradiation. These features may be degenerative and transient.³⁹ It has been reported, however, that malignant cells can be mistaken for histiocytes with increased quantities of vacuolated eosinophilic cytoplasm and eccentric, sometimes hyperchromatic, vesicular nuclei.³⁸ Vacuolization of the cytoplasm is seen in approximately 60% of cases and may also be seen in metastatic deposits within lymph nodes. Chromatin clumping and prominent nucleoli may be seen and multinucleated forms identified. Significant difficulties in diagnosis can occur when small foci of residual or recurrent carcinoma are admixed with genuine histiocytes and foreign body type giant cells adjacent to the site of a previous biopsy.

Although some authors have reported that carcinoma cells retain an overtly malignant appearance after chemotherapy we believe that in difficult cases immunohistochemical profiles may be invaluable; carcinoma cells retain cytokeratin and epithelial membrane antigen (EMA) expression post chemotherapy despite the alteration in morphological appearance. It is of interest to note that infiltrating lobular carcinomas are said not to show the cytological effects of chemotherapy seen in other types of breast carcinoma.⁴⁰

Fibrous scarring after **surgery** is seen in about one quarter of women and may mimic residual or recurrent carcinoma clinically and mammographically. Biopsy may be required to exclude malignancy although some authors suggest that fine needle aspiration cytology is cost effective and reliable in distinguishing scar tissue from carcinomatous foci within scar lesions.⁴¹ As with radiotherapy, FNAC samples from residual carcinomatous foci are usually cellular with overtly malignant cells compared with smears from areas of fibrous scarring which are almost acellular, usually with a predominance of macrophages. Mammographic calcifications may be identified in patients who have had wide local excision of a primary breast carcinoma with subsequent

radiotherapy. A high index of suspicion should be retained for new calcifications in the post-irradiated breast which are more often associated with residual or recurrent carcinoma than non-neoplastic irradiation changes.⁴²

Prognostic factors in invasive breast carcinoma

The management of patients with breast carcinoma has changed radically in the last decade for a number of reasons. The range of therapeutic options for both local and systemic therapy has widened considerably with choices between conservation surgery (with or without post-operative irradiation) and mastectomy and hormonal or cytotoxic therapy. It has also been shown unequivocally that invasive breast carcinoma is not a single entity, but should be regarded as a neoplastic spectrum with a prognostic range from excellent to poor.^{43, 44} Improved health education and the introduction of mammographic screening have led to the identification of a greater number of cancers at the better end of this prognostic range and it is self-evident that such patients require different treatment to those with more aggressive disease. It is therefore increasingly important that clinicians are given the most accurate prognostic information on which to base the appropriate therapy for women on an individual basis. In this way both over and under treatment can be avoided. This clinical need for information has fostered an ever widening search for the ideal prognostic factor, but despite an extensive literature devoted to newer techniques such as molecular biology, traditional histopathological examination of breast cancer specimens still yields the most useful information. It is now recognised throughout the world that the minimum data set provided by histopathologists should comprise an accurate measurement of tumour size, histological type and grade, assessment of lymph node status and a record of the presence or absence of lymphovascular invasion.^{6, 7, 45} Although there are no specific diagnostic pitfalls in the assessment of these factors studies designed to examine the accuracy of histopathological reporting, particularly those associated with the UK NHSBSP and the European Group for Breast Screening Pathology, have highlighted problems in consistency and reproducibility.¹⁻³

In order to assess the accuracy of assessment of **tumour size** the participants in the UK scheme were asked to measure the maximum extent of the invasive component on the histological sections.¹ It was assumed, somewhat naively, that this would be the most consistent of all the factors, but, initially, large variations were encountered. Although 80% of measurements were within ± 3 mm of the median value some results were well outside this range, eg, estimates of 5 and 22 mm recorded for a 15 mm tumour. More detailed instructions were then issued,⁷ with explanatory diagrams and these have led to improvements in this area (data as yet unreported).

The level of consistency in reporting the morphological subtypes was disappointingly poor in the early reports from the UK scheme, with an overall kappa value of 0.21, a result which could almost have been achieved by chance alone. Similarly, poor consistency for histological grading was obtained by the non-co-ordinators, although the co-ordinators, with more experience in breast pathology, achieved a value of 0.46, in the average range. The results for tumour type were, perhaps, understandable, because at the time of the original circulations, now over eight years ago, the scheme had not focused specifically on this issue and few pathologists recorded this feature routinely. The poor performance with grading was rather more of a concern, since the method recommended is summarised in the document *Pathology Reporting in Breast Cancer Screening*,⁷ now in its second edition and had been shown to have an acceptable level of consistency and reproducibility in several other studies.⁴⁶⁻⁴⁸ It is likely that, as with type, relatively few pathologists were grading breast cancer at the time of the study and it is also possible that too little attention has been paid by participants to the published criteria.

Better levels of agreement have been achieved in the European scheme, involving only 20-25 pathologists, all with a specific interest in breast pathology.³ There is also evidence from the UK scheme that participation itself improves performance. Indeed now that both schemes have been in operation for a number of years it appears from recent unpublished results that kappa values for both typing and grading of about 0.6, in the 'good agreement' range, can be obtained. These results are extremely encouraging and there seems to be little doubt that consistent and reproducible results can be obtained for the traditional pathological prognostic factors, especially if agreed diagnostic protocols, as recommended in the European Community guidelines are used.

It is also clear that attention now needs to be paid to accuracy of the pathological assessment of lymph node status, especially in view of the development of sentinel node biopsy.⁴⁹ The management of individual patients is increasingly dependent on these factors and pathologists have a duty of care to ensure that they provide the most accurate information possible.

Part 2: Slide Seminar

Pitfalls in Breast Pathology

Case 1

Clinical history

At the age of 57 years routine screening mammography showed an ill defined parenchymal deformity in the upper outer quadrant of the left breast. The lesion was shown to be a complex sclerosing lesion and no further action was taken. Subsequent mammography at the age of 62 years showed another ill defined parenchymal deformity, this time in the right upper outer quadrant. The lesion was impalpable. Ultrasound-guided needle core biopsy (NCB) was performed.

Needle core histology – A,B

Part of a lesion with desmoplastic and elastotic stroma containing entrapped epithelial elements; some of these appear normal and others show squamous features with atypia, possibly lacking a myoepithelial layer. The appearances are those of a sclerosing lesion with areas suspicious of invasive carcinoma (B4).

Action

In an attempt to clarify the picture staining with anti-smooth muscle actin was performed (C). This confirmed the suspicion of malignancy but was not conclusive.

Conclusion

Sclerosing lesion with foci suspicious of malignancy.

Triple approach summary

Imaging – Category A (probably malignant)

Clinical – not relevant

Histology – suspicious, B4

Management

Repeat needle core biopsy – this revealed definite invasive carcinoma – B5.
Accordingly wide local excision and axillary sampling were carried out.

Final histology – D-G

The section shows a low grade adenosquamous carcinoma arising in association with a complex sclerosing lesion (CSL), including papillomas. The tumour is shown best by immunostaining by Cam 5.2 (G).

Learning points

- Actin immunostaining can help in distinction between CSL and carcinoma but may not be conclusive.
- Repeat needle core biopsy saved a two stage operation.

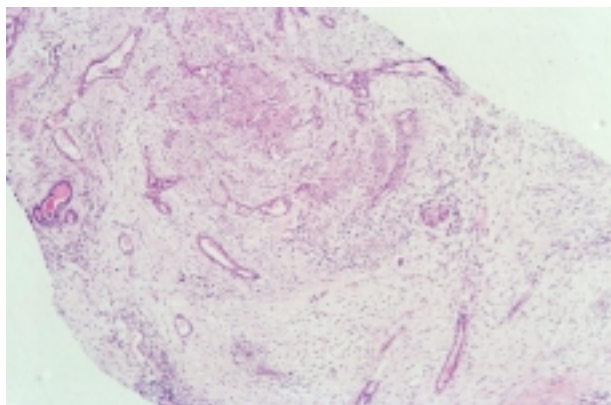


fig. 1a

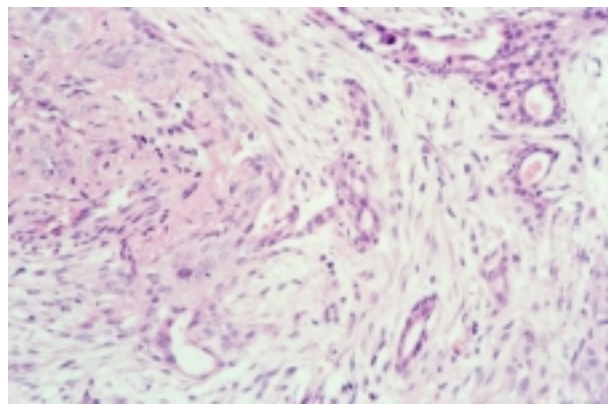


fig. 1b

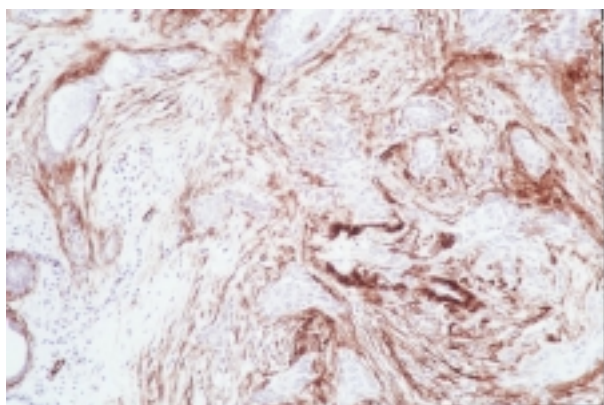


fig. 1c

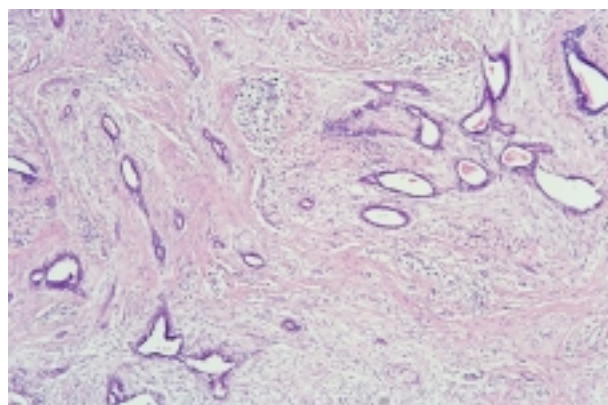


fig. 1d

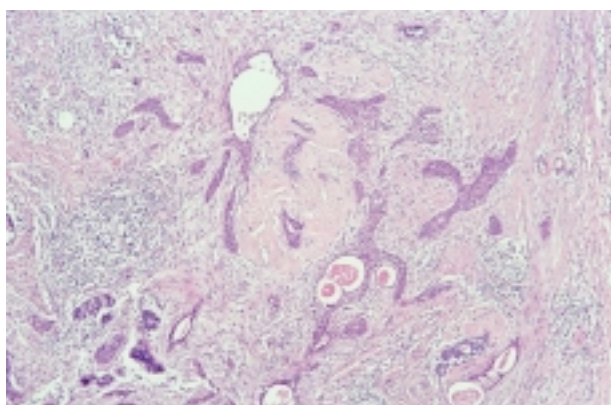


fig. 1e

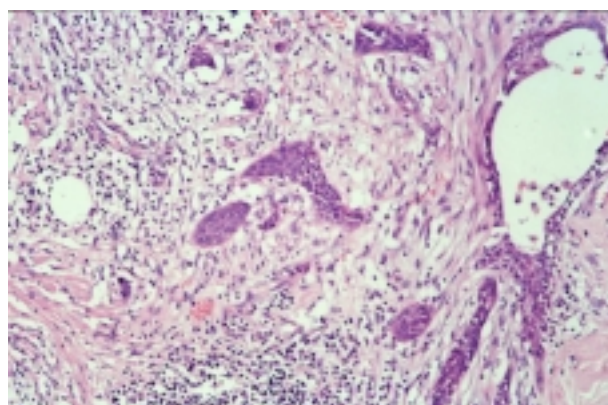


fig. 1f

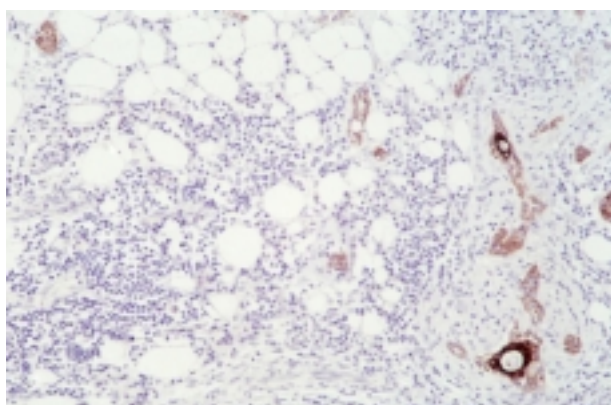


fig. 1g

Case 2

Clinical history

A 54 year old female attended for her first mammographic screen. A spiculate parenchymal deformity was identified in the lower outer quadrant of the right breast. The lesion was impalpable. NCB showed part of a sclerosing lesion with no overt evidence of malignancy.

Triple approach summary

Imaging – Category A

Clinical – not relevant

Histology – uncertain malignant potential B3

Management

In view of the suspicious imaging appearances, excision of the lesion is mandatory, despite the absence of definite malignant histological features. A diagnostic wire guided excision biopsy was therefore performed.

Histological appearances – A-C

Initial sections confirmed a complex sclerosing lesion with florid usual epithelial hyperplasia and foci of low grade ductal carcinoma in situ. Further blocks were taken and in one a 3 mm focus of invasive carcinoma, ductal NST, grade 2, was identified.

Further management

Re-excision of biopsy site – clear margins obtained. Axillary sampling – all four nodes negative.

Final Diagnosis

Complex sclerosing lesion with associated in situ and invasive carcinoma.

Learning points

- All mammographic parenchymal deformities must be excised.
- Value of adequate tissue sampling in excision specimens.

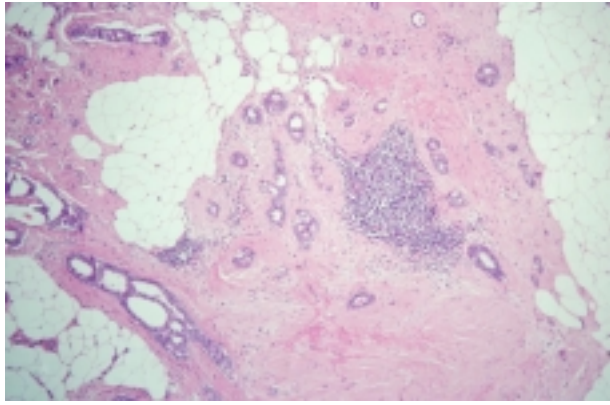


fig. 2a

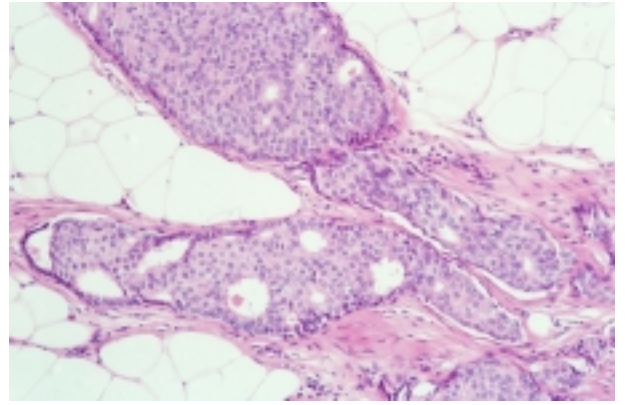


fig. 2b

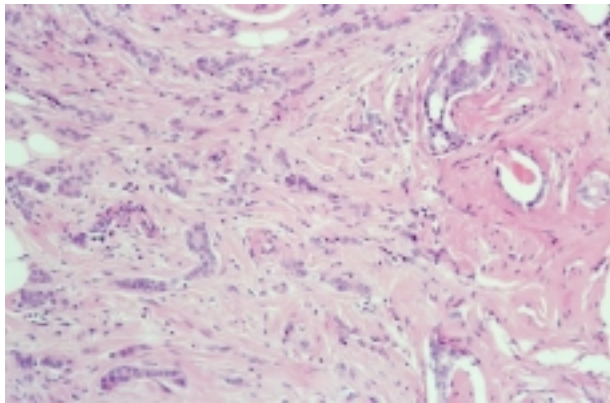


fig. 2c

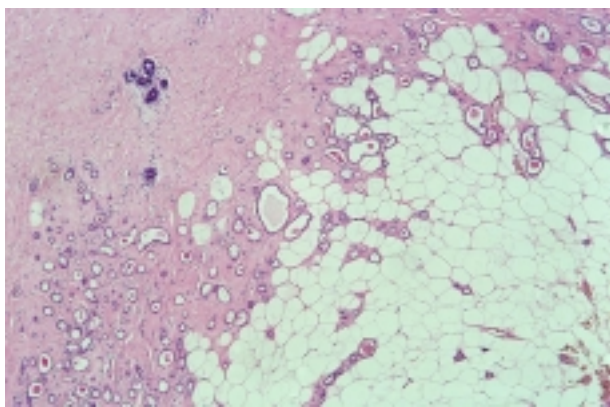


fig. 3a

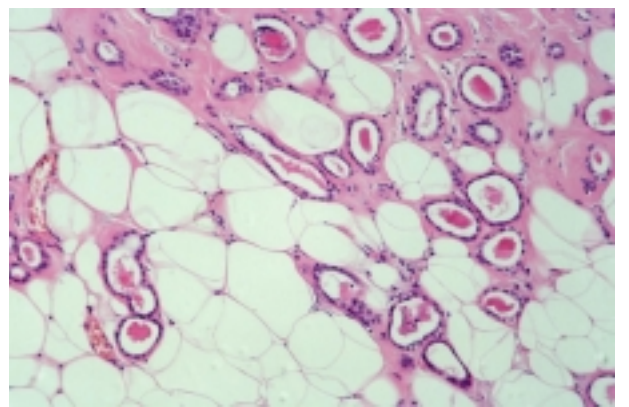


fig. 3b

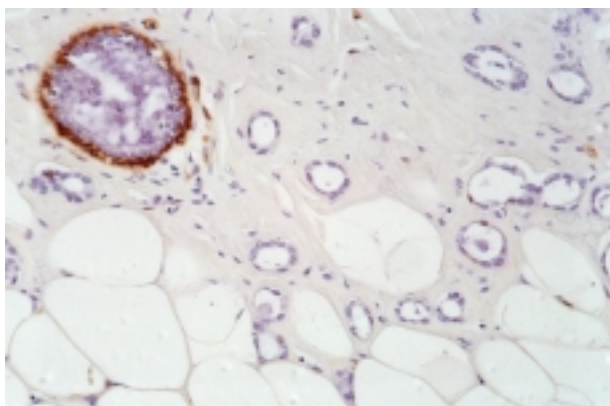


fig. 3c

Case 3

Clinical history

A female of 54 years presented to the Breast Clinic with an ill defined lump in the upper outer quadrant of the right breast. No abnormality was seen on imaging and there was a palpable mass, suspicious of malignancy. Fine needle aspiration cytology (FNAC) revealed a benign sample – C2. A diagnostic excision biopsy was therefore performed.

Histological appearances – A-C

Sections from the biopsy reveal a diffuse collection of small, rounded tubular structures infiltrating into stromal and adipose tissue, together with some essentially normal lobular structures. Nuclei are small and regular, with no discernible difference between the two elements. Immunostaining with anti-smooth muscle actin shows that the tubules lack a myoepithelial layer.

Differential diagnosis

Microglandular adenosis
Tubular carcinoma

The features which favour a diagnosis of microglandular adenosis are as follows:

- Diffuse pattern – no stellate structure (NB, care needs to be taken in interpreting the sclerosing type of tubular carcinoma).
- Lack of desmoplastic and elastotic stroma.
- Lack of angulation of tubules.
- Regularity of nuclei and similarity to those in adjacent normal nuclei.

NB Demonstration of the absence of a myoepithelial layer is unhelpful since this is a feature of both entities.

Final Diagnosis

Microglandular adenosis

Learning points

- Microglandular adenosis may mimic tubular carcinoma.
- Overall architectural pattern is the most useful distinguishing feature.
- Immunostaining with anti-smooth muscle actin is usually unhelpful.

Case 4

Clinical history

A female aged 36 years presented to the Breast Clinic with diffuse lumpiness in the left breast. On examination a dominant mass was found, but considered to be benign. Imaging was not performed. FNAC showed a cellular aspirate of benign cells – C2. Diagnostic excision biopsy was carried out at the request of the patient.

Histological appearances – A-C

The sections show a nodular area composed of a disorderly arrangement of lobular structures, ie, tubules, myoepithelial cells and stroma. There is focal epithelial hyperplasia, some of which appears to involve lobules.

Differential diagnosis

Sclerosing adenosis
Tubular carcinoma
Usual epithelial hyperplasia
Lobular neoplasia
Ductal carcinoma in situ

Although tubular carcinoma should always be considered when making a diagnosis of sclerosing adenosis, the lobulocentric structures and lack of desmoplastic stroma favour the latter. Furthermore, immunostaining for anti-smooth muscle actin shows that all tubular structures have a myoepithelial layer.

There are no architectural features to suggest ductal carcinoma in situ, but the monotonous small cell epithelial proliferation within lobular acini is indicative of lobular carcinoma in situ.

Final Diagnosis

Sclerosing adenosis with associated lobular neoplasia and usual epithelial hyperplasia.

Management

Because the presence of lobular neoplasia is a risk factor for subsequent invasive carcinoma (either breast) the patient is followed-up in the 'high risk' clinic – annual clinical examination and biennial mammography until age 50, then normal screening cycle.

Learning points

- Lobular neoplasia is sometimes associated with sclerosing adenosis.
- Care must be taken not to overdiagnose invasive carcinoma.
- The presence of lobular neoplasia indicates the need for close follow-up.

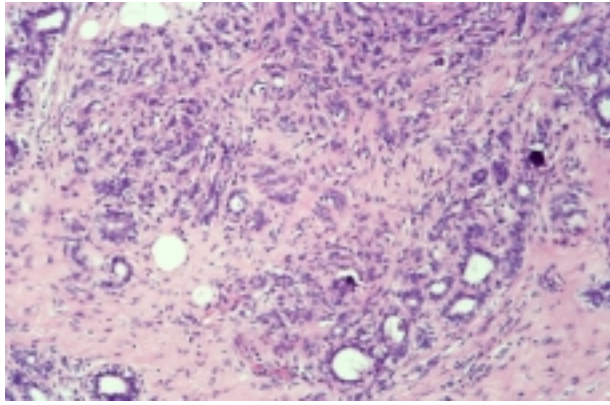


fig. 4a

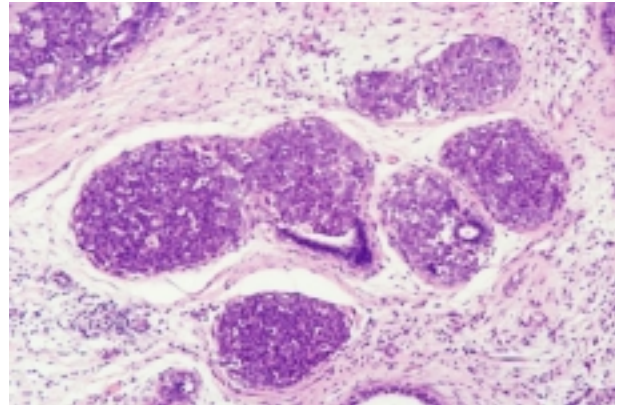


fig. 4b

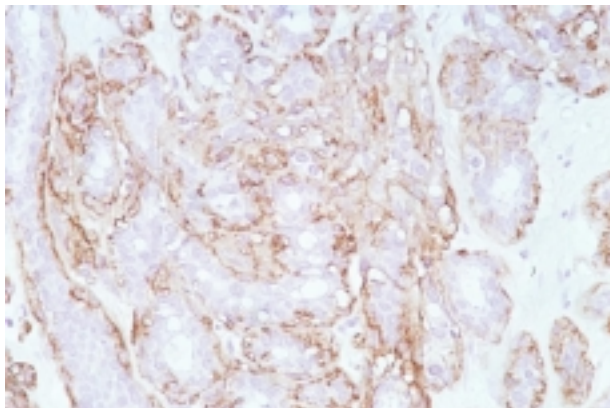


fig. 4c

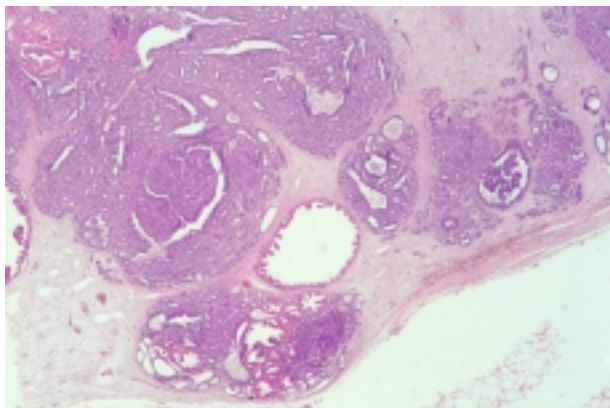


fig. 5a

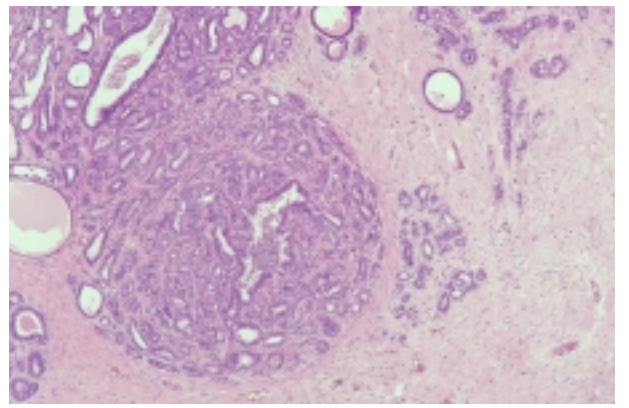


fig. 5b

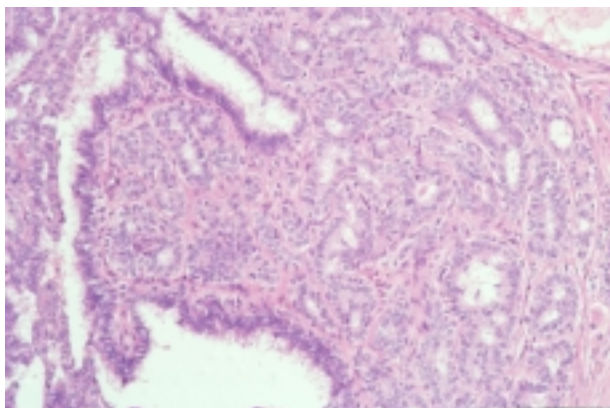


fig. 5c

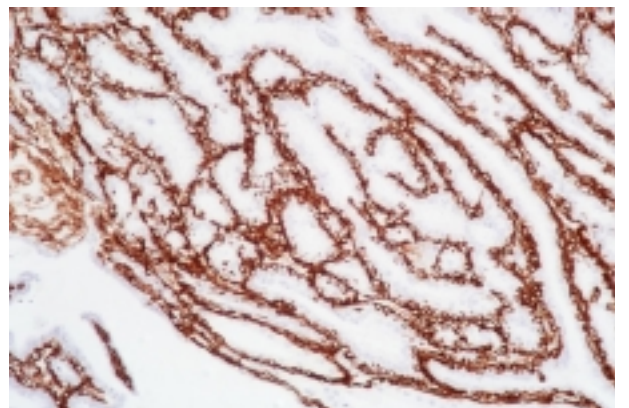


fig. 5d

Case 5

Clinical history

This 31 year old patient presented with a palpable mass in the left breast. Imaging (ultrasound) was indeterminate. NCB showed some papillary structures – uncertain malignant potential – B3. In view of this a diagnostic excision biopsy was performed.

Histological appearances – A-D

The section shows a nodular lesion with a complex pattern of changes, with a mixture of papillary areas, adenomatous structures including sclerosing adenosis, cysts with apocrine change and associated fibrosis. Some focal entrapped tubules are present. The papillary and adenomatous foci are composed of epithelial structures with a bilaminar configuration and there is no nuclear atypia.

Differential diagnosis

Florid fibrocystic change
Complex sclerosing lesion
Complex sclerosing papillary lesion
(Ductal adenoma)
Papillary carcinoma in situ

The bilaminar pattern and lack of nuclear atypia rule out a malignant process. It is highly likely that the benign processes noted above form a spectrum, with considerable overlap with complex sclerosing lesions. Because of the presence of a significant number of papillary structures, and the overall nodular nature we prefer to use the term ‘complex sclerosing papillary lesion’.

Final diagnosis

Complex sclerosing papillary lesion

Further management

No follow up required

Learning points

- Immunostaining with anti-smooth muscle actin is useful in confirming a bilaminar pattern and excluding malignancy.
- Terminology in these lesions should be based on the dominant architectural pattern.

Case 6

Clinical history

Mastectomy for left-sided breast carcinoma 20 years previously. Presented with a one month history of a lump in the right breast. Imaging showed a well defined mass lesion, suspicious of malignancy; clinically the lump also appeared malignant. Needle core biopsy was performed.

Histological appearances – A,B

Sections show part of a papillary lesion in which there is a moderate degree of nuclear atypia and a focal cribriform architecture. The appearances are suspicious of a papillary carcinoma in situ.

Triple approach summary

Imaging (mammography and ultrasound) – Category A

Clinical – Category A

NCB – Suspicious, B4

Comment

Had the NCB shown benign papillary features, the correct category would have been B3 – uncertain malignant potential.

Management

Wide local excision performed, without axillary dissection.

Histological appearances – C-F

The sections confirm a 30 mm circumscribed area of papillary carcinoma in situ, intermediate grade. Entrapped epithelial structures are seen within a pseudocapsule (E) but this is not interpreted as invasion. DCIS of intermediate grade is present in adjacent ducts (F). Local excision is complete.

Further management

Follow up only, in view of patient's age.

Learning points:

- Most papillary lesions should be classified as benign of uncertain malignant potential – B3, because of sampling issues.
- However, in the presence of nuclear atypia a suspicious diagnosis may be appropriate.
- Care must be taken not to overdiagnose invasive carcinoma in the presence of entrapped epithelial structures in the 'capsule'.

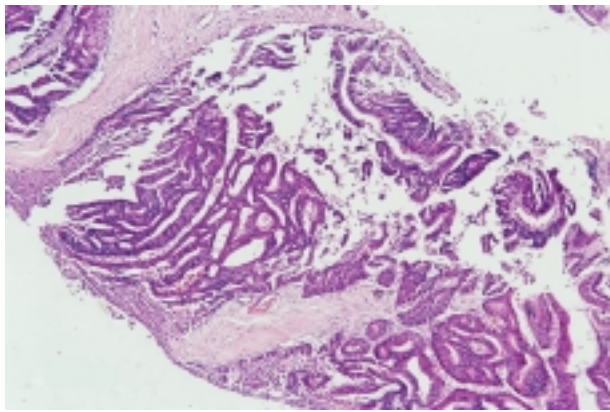


fig. 6a

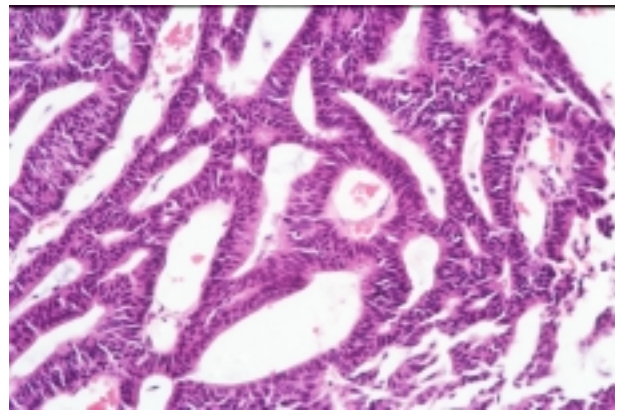


fig. 6b

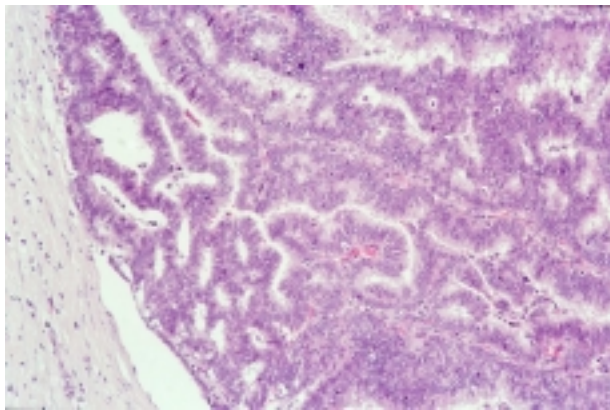


fig. 6c

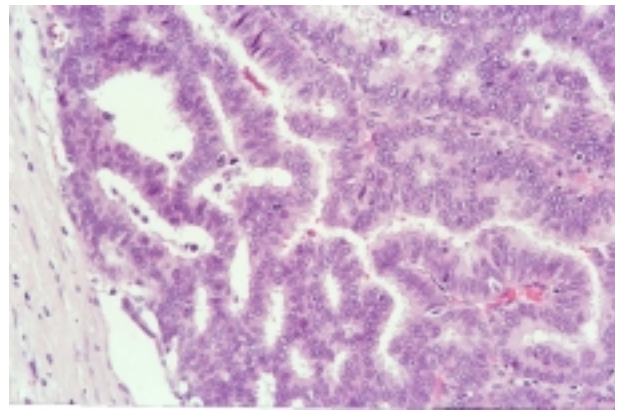


fig. 6d

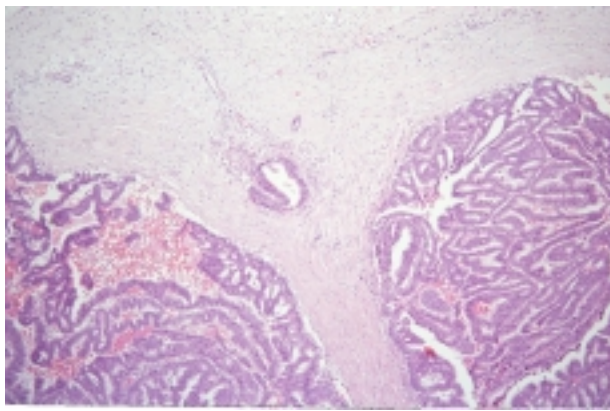


fig. 6e

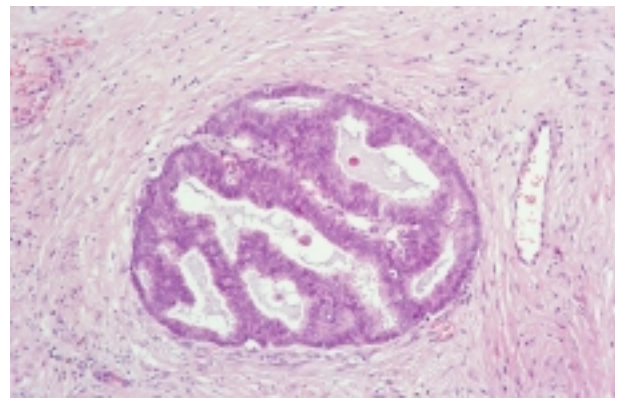


fig. 6f

Case 7

Clinical history

This 44 year old woman had had two previous biopsies from the right breast which showed multiple benign duct papillomas with associated epithelial hyperplasia, but no atypia. Close follow-up was carried out and a further palpable lump occurred, in the same quadrant as the previous biopsies. Repeat excision biopsy performed.

Histological appearances – A-C

The sections show multiple duct papillomas in association with fibrocystic change, including florid epithelial hyperplasia of usual type. In addition, there are focal areas in which the epithelial proliferation has an incomplete cribriform pattern, without significant nuclear atypia.

Interpretation

In our view the architectural pattern was insufficiently developed for a definite diagnosis of low grade DCIS of cribriform type. A diagnosis of multiple papillomas with atypical ductal hyperplasia (ADH) was made.

Management

In view of the increased risk of subsequent invasive carcinoma from multiple duct papillomas, especially when associated with ADH and the history of multiple biopsies the patients was advised to undergo a subcutaneous mastectomy. She declined and close follow-up was therefore maintained. Three years later she developed another palpable lesion and, following needle core biopsy, a subcutaneous mastectomy was performed.

Histological appearances – D-F

In addition to further background epithelial proliferative changes as noted above, intermediate grade DCIS is present, together with a grade 1 invasive carcinoma of tubular mixed type.

Final diagnosis

Multiple ductal papillomas with associated ductal carcinoma in situ and invasive carcinoma.

Learning points

- Multiple duct papillomas give an increased risk for subsequent invasive carcinoma.
- The risk is increased by the presence of associated ADH.
- Close follow-up of such patients should be carried out.

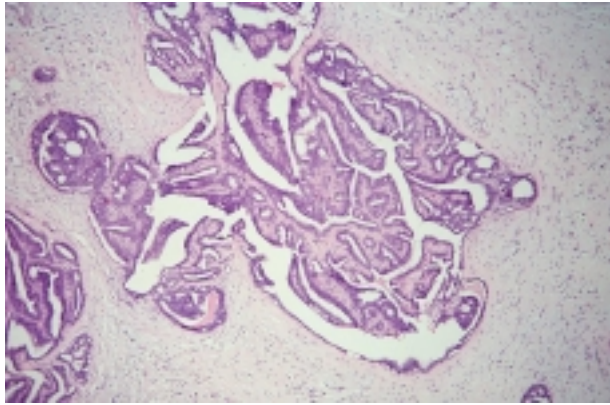


fig. 7a

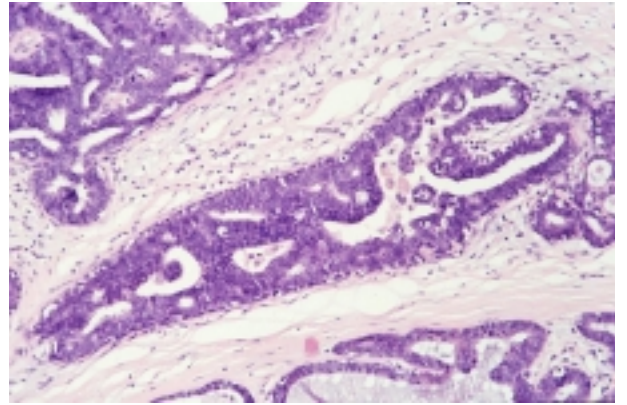


fig. 7b

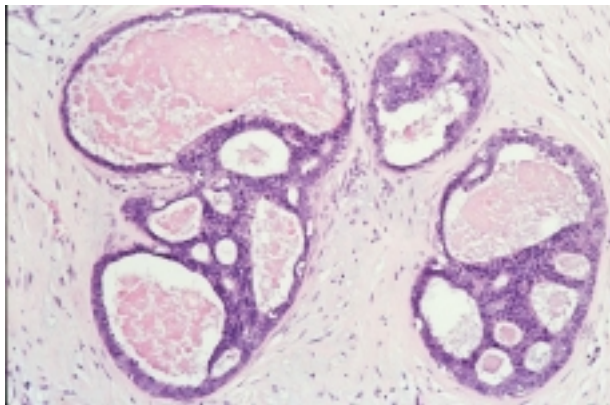


fig. 7c

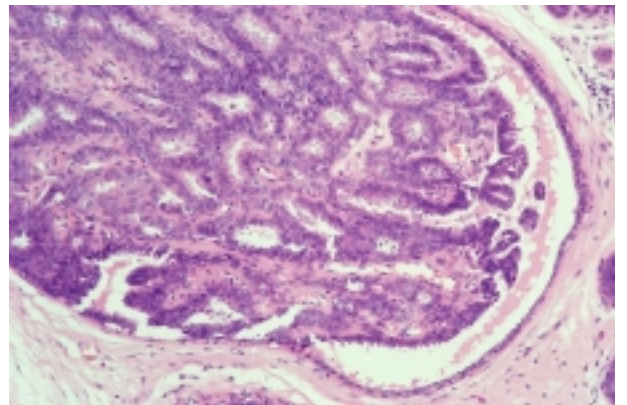


fig. 7d

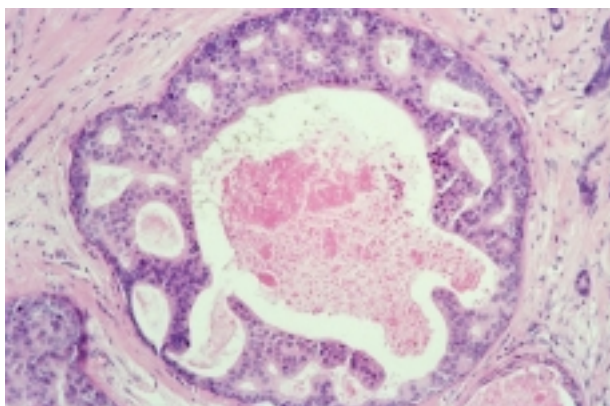


fig. 7e

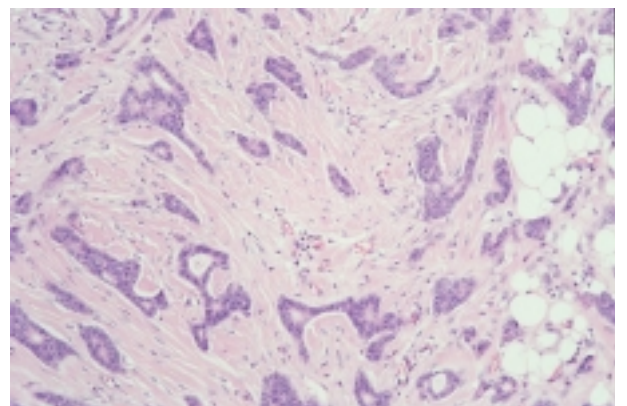


fig. 7f

Case 8

Clinical history

A female of 52 years presented for her first mammographic screen. An area of fine microcalcification was noted in the left upper outer quadrant – indeterminate category. No palpable lesion was identified. Needle core biopsy showed DCIS.

Triple approach summary

Imaging – Category B

Clinical – not relevant

Needle core histology – DCIS

Management

Wide local excision performed, without axillary dissection.

Histological appearances – A-C

The section shows a florid epithelial proliferative lesion with areas, which taken alone, do not meet the diagnostic criteria for DCIS and other areas which do. Overall, taking into account the size of 20 mm, the appearances are those of low grade ductal carcinoma in situ of predominantly cribriform type. No invasive carcinoma seen.

Further management

Local excision was complete – margins greater than 10 mm. Post-operative radiation therapy to the breast. No systemic therapy. Clinical follow-up will be maintained.

Learning points

- The distinction between ADH and DCIS rests, in part, on overall lesion size.
- Needle core biopsy is the most appropriate method for the investigation of microcalcifications.
- Axillary dissection is contraindicated in DCIS, especially of low grade.

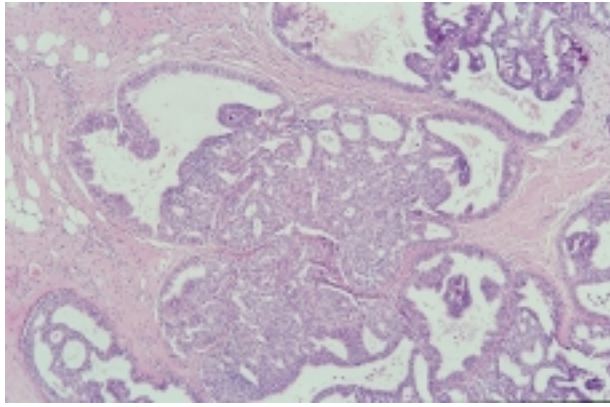


fig. 8a

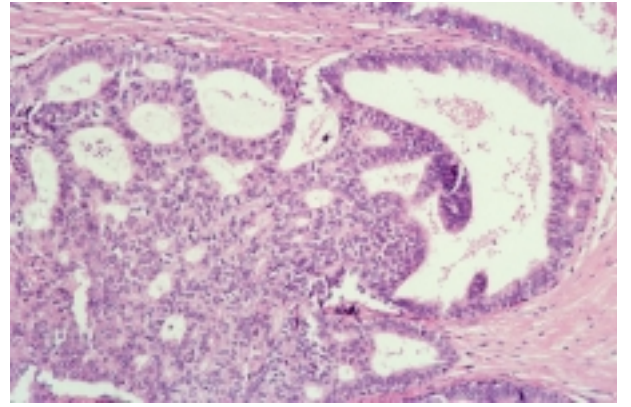


fig. 8b

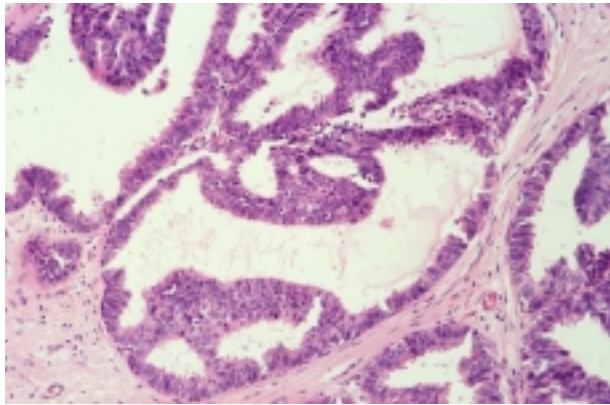


fig. 8c

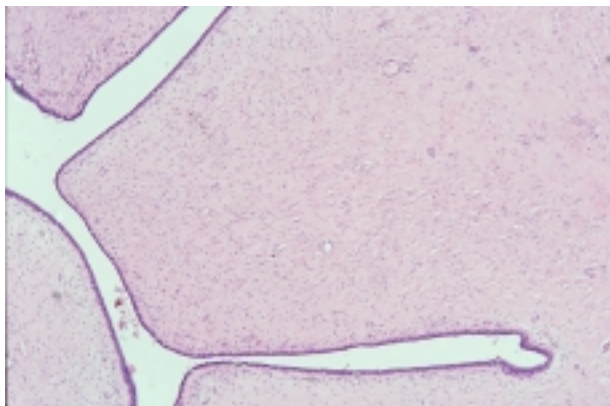


fig. 9a

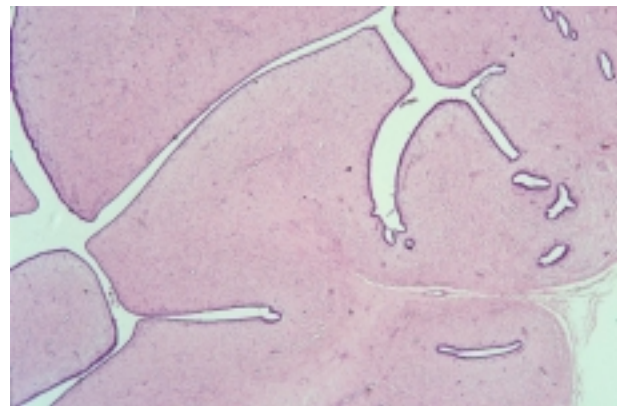


fig. 9b

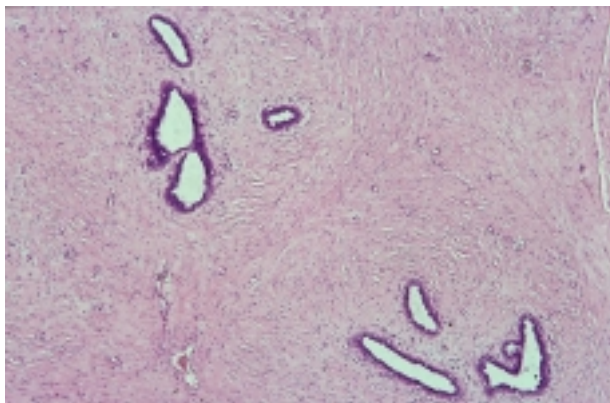


fig. 9c

Case 9

Clinical history

This 24 year old female presented to the Breast Clinic with a large, rapidly growing mass in the right breast, causing distortion and thinning of the overlying skin. Clinically the lesion was felt to be suspicious of malignancy, possibly a sarcoma. Imaging was not performed. FNAC showed benign cells only – C2. The mass was excised.

Histological appearances – A-C

The section shows a large fibroepithelial lesion composed of deep epithelial clefts and stroma. The clefts have a normal bilaminar structure whilst the stroma is of relatively low cellularity with focal sclerosis.

Differential diagnosis

Juvenile fibroadenoma
Hamartoma
Phyllodes tumour

The overall pattern is that of a fibroadenoma with an intracanalicular pattern, but the presence of deep clefts with a leaf-like pattern raises the possibility of phyllodes tumour. However, the latter diagnosis is ruled out by the lack of a cellular stroma and the regularity of the stromal nuclei. Hamartoma can also be excluded because of the lack of ducto-lobular structures.

Final diagnosis

Juvenile fibroadenoma

Case 10

Clinical history

Female 42 years. Six years previously she had a fibroadenoma removed from each breast. She was sent back to the Breast Clinic because she had developed two further lumps in the right breast. Ultrasound showed both to be solid and well defined. FNAC from both showed benign cells only – C2. Excision biopsies were performed because the larger of the lesions measured more than 3 cm clinically.

Histological appearances – A-D

Two blocks from the larger lesion are provided. In one the typical appearances of a fibroadenoma are seen (A) with an intracanalicular pattern and loose cellular stroma. The latter shows no nuclear atypia. In the other block from a different area of the lesion (B-D) there are definite leaf-like structures with deep epithelial clefts, and the stroma is very cellular with closely packed spindle-shaped nuclei, some showing slight nuclear atypia. Mitoses are infrequent.

Differential diagnosis

‘Cellular’ fibroadenoma
Phyllodes tumour

The combination of the leaf-like pattern and cellular stroma in part of the lesion point to a diagnosis of phyllodes tumour arising in a pre-existing fibroadenoma. The edge is well defined, there is little nuclear pleomorphism and the mitotic count is low, all features of a benign phyllodes tumour.

NB The other lesion in the breast was a simple fibroadenoma.

Final diagnosis

Benign phyllodes tumour arising in a fibroadenoma.

Learning points – Cases 9 and 10

- Size alone is not a helpful distinguishing feature between fibroadenoma and phyllodes tumour.
- A diagnosis of phyllodes tumour requires a combination of deep epithelial clefts **and** a cellular stroma.
- Some phyllodes tumours appear to arise in pre-existing fibroadenoma.
- Adequate sampling is required to make the correct diagnosis in large fibroepithelial lesions.
- The main points of distinction between benign and malignant phyllodes tumour are margin definition, stromal nuclear pleomorphism and mitotic counts.

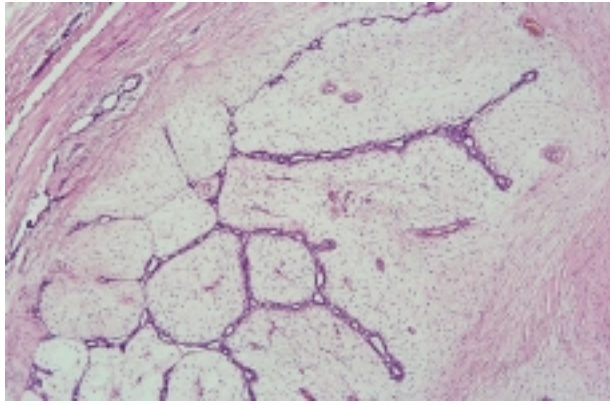


fig. 10a

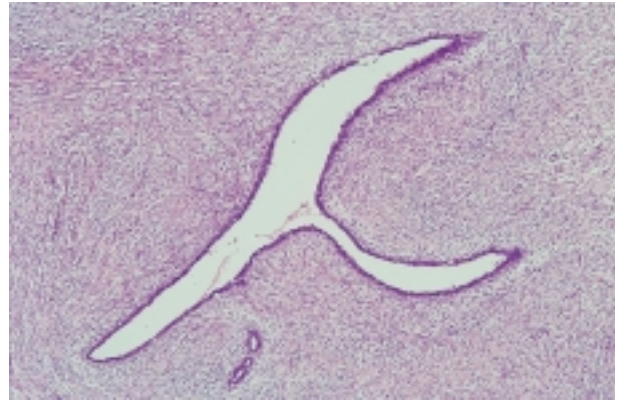


fig. 10b

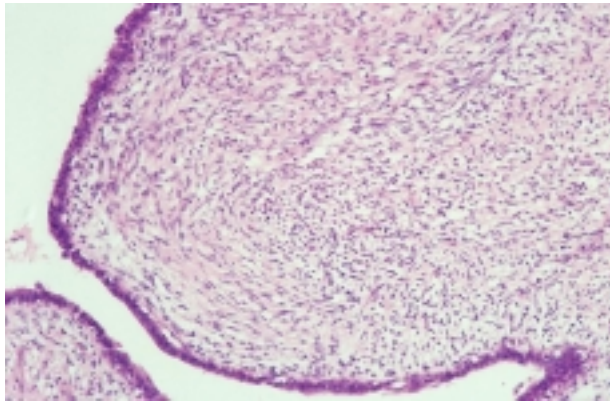


fig. 10c

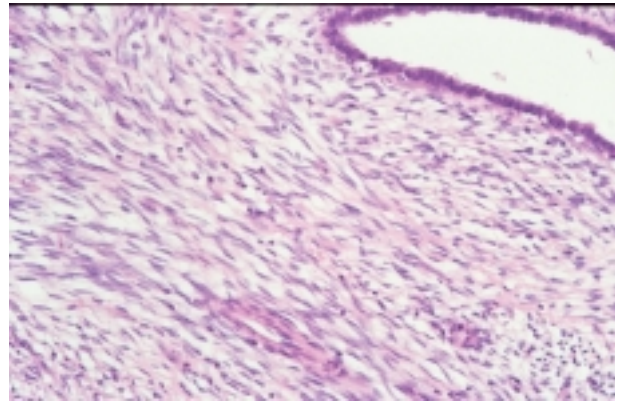


fig. 10d

Case 11

Clinical history

This patient presented at the age of 37 years with a four week history of a lump in the left breast. This felt malignant on clinical examination, imaging was suspicious and FNAC revealed malignant cells. A wide local excision and axillary sample were carried out, followed by breast irradiation and chemotherapy. Nine months later she was found to have a recurrent mass at the site of the previous surgery. FNAC was inadequate – C1 and an excision biopsy was performed.

Histological appearances – A-E

There is a background of focal fibrocystic change and involutonal lobules, some of which show marked sclerosis and nuclear atypia (A,B). Extensive fibrosis is present, in which large atypical fibroblasts are present. Within the fibrous stroma are numerous highly atypical cells, singly and in groups (C,D).

Differential diagnosis

Radiation change
Recurrent carcinoma

The atypical cells noted above have appearances strongly suspicious of malignancy. Confirmation of their epithelial nature is obtained by positive immunostaining for cytokeratins (eg, Cam 5.2 (E)).

Final diagnosis

Recurrent carcinoma

Further management

Mastectomy was performed, and extensive recurrent disease found. Her original Nottingham Prognostic Index was 5.5 (tumour size 2.5 cm, histological grade 3, lymph node stage 3 – Poor Prognostic Group). Despite systemic chemotherapy she died two years after diagnosis.

Learning points

- The distinction between radiation fibroblasts and recurrent or residual carcinoma cells can be made with the help of immunostaining for epithelial markers.
- Always obtain details of previous therapy in post-malignancy follow-up cases.

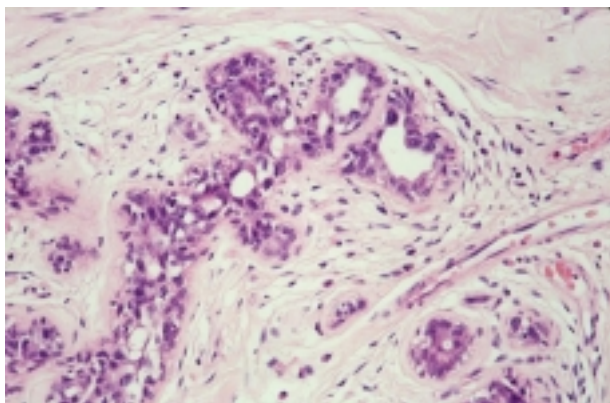


fig. 11a

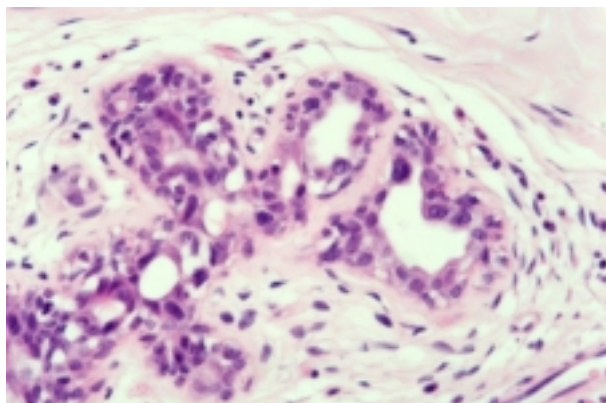


fig. 11b

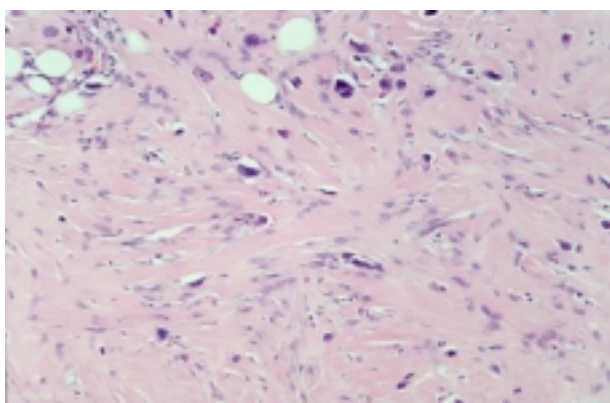


fig. 11c

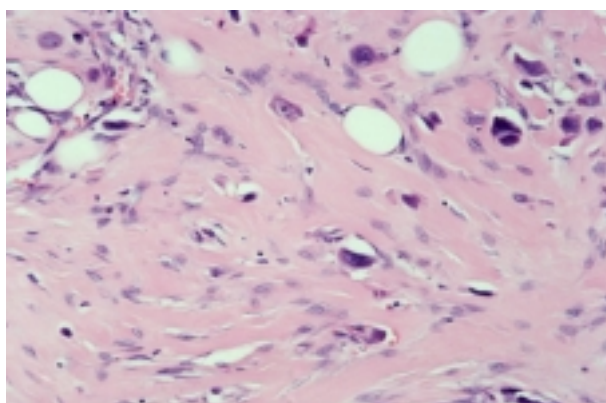


fig. 11d

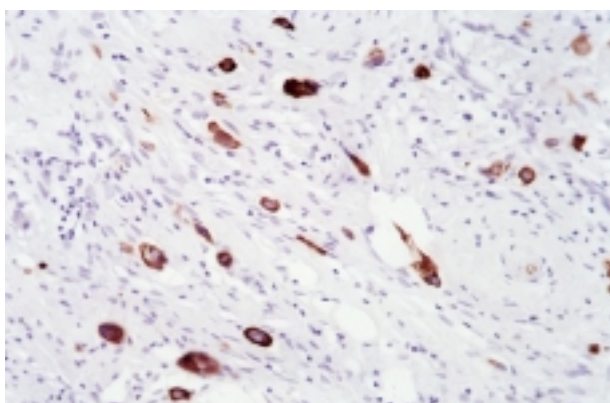


fig. 11e

Case 12

Clinical history

Female aged 54 years. She presented with a palpable lump in the right breast. This was clinically malignant and FNAC revealed malignant cells. A wide local excision and axillary dissection were carried out.

Histological appearances – A-E

The section shows an invasive carcinoma with a curious architectural pattern – clusters of tumour cells surrounded by clear peripheral spaces (A,B). Glandular differentiation is seen only focally (T3), there is marked nuclear pleomorphism (P3) (C) and intermediate numbers of mitoses (M2) – grade is therefore assigned as 3.

Possible explanations for architectural pattern

Vascular invasion
Fixation artefact
Special tumour type

The pattern is not due to vascular invasion (VI) – vascular markers are negative (eg, CD34 (D)), although VI is present at the tumour periphery in other blocks. The tumour is well fixed and little true shrinkage artefact is seen. Immunostaining for epithelial mucin antigen (EMA) shows that the tumour cells have a reverse polarity (E). This type was first described by Peterse¹ as a tumour with an inside-out pattern, but subsequent authors have applied the term invasive micropapillary carcinoma.²⁻⁴ They tend to be of high histological grade and frequently exhibit vascular invasion and lymph node metastases.²⁻⁴ Most series demonstrate poor long-term survival.

Diagnosis

Invasive micropapillary carcinoma, grade 3

Learning points

- Tumours with distinctive architecture can, and should, be assigned to special subtypes, especially if this provides prognostic information.

References

- 1 Peterse JL. Breast carcinomas with an unexpected inside out growth pattern. Rotation of polarisation associated with angioinvasion. *Pathol Res Pract* 1993; 189: 780.
- 2 Siriaunkul S, Tavassoli FA. Invasive micropapillary carcinoma of the breast. *Mod Pathol* 1993; 6: 660-662.
- 3 Luna More S, Gonzalez B, Acedo C et al. Invasive micropapillary carcinoma of the breast. A new special type of invasive mammary carcinoma. *Pathol Res Pract* 1994; 190: 668-674.
- 4 Middleton LP, Tressera F, Sobel ME et al. Infiltrating micropapillary carcinoma of the breast. *Mod Pathol* 1999; 12: 499-504.

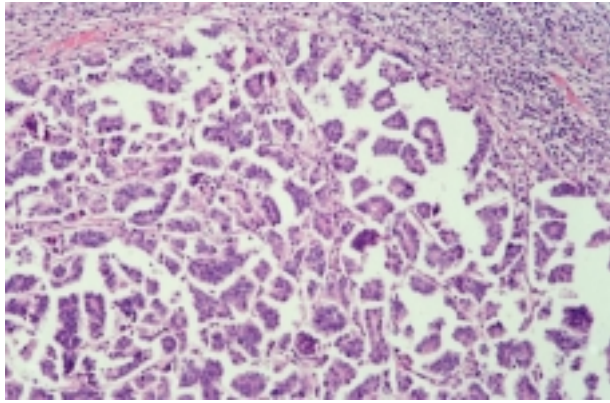


fig. 12a

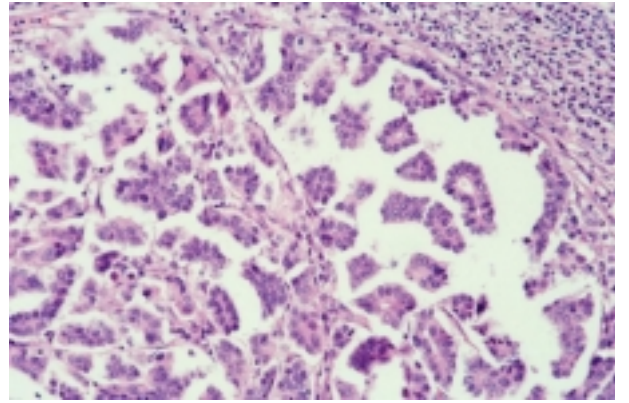


fig. 12b

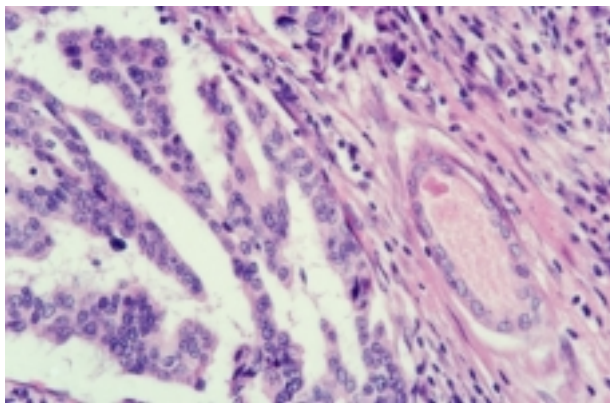


fig. 12c

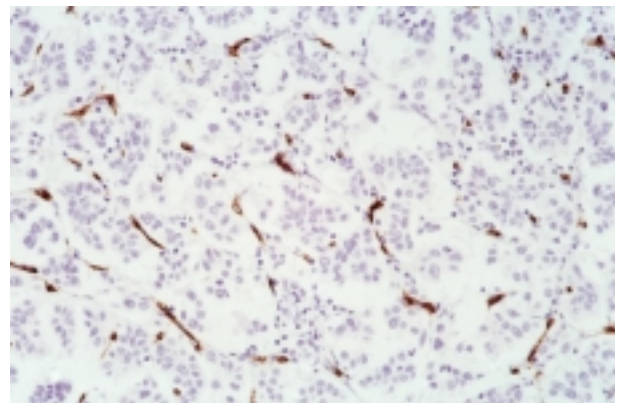


fig. 12d

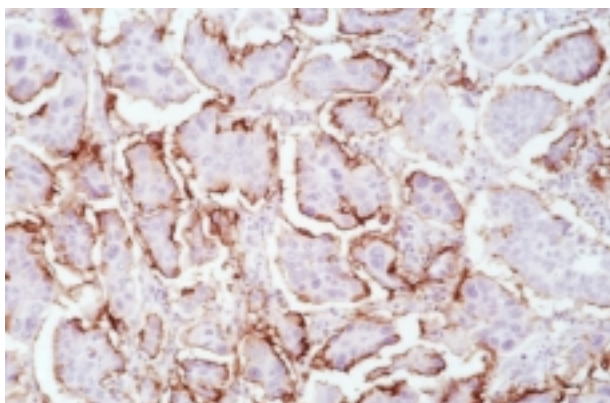


fig. 12e

Table 1

Main categories of lesions which lead to diagnostic pitfalls in breast pathology

<ul style="list-style-type: none">• Sclerosing lesions• Papillary lesions• « Borderline » lesions• Fibroepithelial lesions• Effects of previous therapy• Pathological prognostic factors

Table 2**Differential diagnosis of sclerosing lesions**

Tubular carcinoma	Sclerosing adenosis	Microglandular adenosis	Radial scar
Infiltrative, often stellate architecture	Lobulocentric architecture	Infiltrative, disorderly architecture	Complex, stellate architecture
Desmoplastic stroma Central elastosis frequent	Often central cellularity with sclerotic periphery	Fibrotic stroma	Variable stromal cellularity
Well formed, angulated tubules	Distorted, compressed tubules Frequent obliterated lumina	Uniform, round tubules	Distorted tubules
Abundant eosinophilic cytoplasm, often with apical snouts	Infrequent apical snouts	Clear, vacuolated or granular epithelial cytoplasm. No apical snouts	No apical snouts
Absent myoepithelial cells	Prominent admixed myoepithelial cells	Occasional myoepithelial cells described	Myoepithelial cells seen
Patchy, incomplete basement membrane	Uniform basement membrane	Prominent basement membrane	Basement membrane seen
Intraluminal secretion or microcalcification may be seen	Intraluminal microcalcification may be seen	Intraluminal colloid-like material which may be calcified	Intraluminal secretion uncommon. Microcalcification may be seen
Frequent associated low grade cribriform or micropapillary DCIS	May be associated apocrine metaplasia. Associated DCIS or lobular neoplasia are rare but described	Atypical features rarely described (see text)	Associated cysts, sclerosing adenosis, epithelial hyperplasia and rarely in situ or invasive carcinoma

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Systemic Pathology 3rd Ed- The Breast. London: Churchill Livingstone, 1998.*

Table 3

Spectrum of papillary lesions of the breast

- | |
|--|
| <ul style="list-style-type: none">• Single intraduct papilloma• Multiple duct papillomas• Complex sclerosing papillary lesion• Encysted papillar carcinoma (papillary carcinoma in situ)• Invasive papillary carcinoma |
|--|

Table 4**« Borderline » lesions of the breast**

Epithelial hyperplasia	
Benign	
Usual Type	
<hr/>	
Atypical ductal hyperplasia	
Lobular neoplasia	
Ductal carcinoma in situ	
Micropapillary / cribriform	
Solid	
Comedo	
Increasing risk factor	
Microinvasive carcinoma	
Minimal invasive carcinoma	
< 10 mm)
Special type) + lymph node negative
Grade I)
<hr/>	
Invasive carcinoma	
Malignant	

Table 5

Proposal for « borderland » epithelial proliferative lesions which correlates morphological structure with clinical management

Lesion	Clinical significance
Epithelial hyperplasia Usual Type	Follow up not appropriate
Lobular Neoplasia Atypical ductal hyperplasia Ductal carcinoma in situ Low grade < or = 3 mm	Risk factor Follow up only required No specific therapy
Low grade > 3 mm Intermediate grade High grade (Microinvasive carcinoma) « Small » invasive carcinomas < 15 mm special type grade I	Excellent prognosis lesions Complete excision required +/- axillary dissection +/- local irradiation no systemic therapy
Invasive carcinoma	Local and systemic therapy based on evaluation of prognostic factors

References

- 1 Sloane JP, National Co-ordinating Group for Breast Screening Pathology. Consistency of histopathological reporting of breast lesions detected by screening: findings of the UK National External Quality Assessment (EQA) Scheme. *Eur J Cancer* 1994; 30: 1414-1419.
- 2 Sloane JP, European Commission Working Group on Breast Screening Pathology. Consistency achieved by 23 European pathologists in categorizing ductal carcinoma in situ of the breast using five classifications. *Hum Pathol* 1998; 29: 1056-1062.
- 3 Sloane JP, European Commission Working Group on Breast Screening Pathology. Consistency achieved by 23 European pathologists for 12 countries in diagnosing breast disease and reporting prognostic features of carcinomas. *Virchows Arch (A) Pathol Anat* 1999; 434: 3-10.
- 4 Elston CW, Ellis IO. *Systemic Pathology 3E The Breast*; vol 13. London: Churchill Livingstone, 1998.
- 5 Elston CW. Breast Cancer Screening. In: Anthony PP, ed. *Diagnostic Pitfalls in Histopathology and Cytopathology Practice*. London: Greenwich Medical Media, 1998: vol, 39-53.
- 6 European Commission. *European Guidelines for Quality Assurance in Mammography Screening*. de Wolf CJM, Perry NM, eds. 2nd ed; Luxembourg: Office for Official Publications of the European Communities, 1996.
- 7 Royal College of Pathologists Working Group for Breast Screening Pathology. *Pathology Reporting in Breast Cancer Screening*. 2nd ed; NHS BSP Publications No 3, 1995.
- 8 Royal College of Pathologists Working Group for Breast Screening Pathology. *Guidelines for Pathologists*. 2nd ed; NHS BSP Publications No 3, 1997.
- 9 Spencer NJB, Evans AJ, Galea M, et al. Pathological-radiological correlations in benign lesions excised during a breast screening programme. *Clin Radiol* 1994; 49: 853-856.
- 10 Dahlstrom JE, Jain S, Sutton T, Sutton S. Diagnostic accuracy of stereotactic core biopsy in a mammographic breast cancer screening programme. *Histopathol* 1996; 28: 421-427.
- 11 Nguyen M, McCombs ME, Ghandehari S, et al. An update on core needle biopsy for radiologically detected breast lesions. *Cancer* 1996; 78: 2340-2345.
- 12 Litherland JC, Evans AJ, Wilson ARM. The impact of core biopsy on pre-operative diagnosis rate of screen detected cancers. *Clin Radiol* 1996; 51: 562-565.
- 13 Sloane JP, Mayers MM. Carcinoma and atypical hyperplasia in radial scars and complex sclerosing lesions: importance of lesion size and patient age. *Histopathol* 1993; 23: 225-231.
- 14 Simpson JF, Page DL, Dupont WD. Apocrine adenosis - a mimic of mammary carcinoma. *Am J Surg Pathol* 1990;3:289-299.
- 15 Resbridge SA, Millis RR. Carcinoma in situ involving sclerosing adenosis: a mimic of invasive breast carcinoma. *Histopatho* 1995; 27: 269-273.
- 16 Eusebi V, Foschini MP, Betts CM, et al. Microglandular adenosis, apocrine adenosis and tubular carcinoma of the breast. *Am J Surg Pathol* 1993; 17: 99-109.

- 17 Millis RR, Eusebi V. Microglandular adenosis of the breast. *Adv in Anat Pathol* 1995; 2: 10-18.
- 18 Carter D, Orr SL, Merino MJ. Intracystic papillary carcinoma of the breast. After mastectomy, radiotherapy or excisional biopsy alone. *Cancer* 1983; 52: 14-19.
- 19 Lakhani SR, Collins N, Stratton MR, Sloane JP. Atypical ductal hyperplasia of the breast: clonal proliferation with loss of heterozygosity on chromosomes 16q and 17p. *J Clin Pathol* 1995; 48: 611-615.
- 20 Lakhani SR, Slack DN, Hamoudi RA, et al. Detection of allelic imbalance indicates that a proportion of mammary hyperplasia of usual type are clonal neoplastic proliferations. *Lab Invest* 1996; 74: 129-135.
- 21 Stratton MR, Collins N, Lakhani SR, Sloane JP. Loss of heterozygosity in ductal carcinoma in situ of the breast. *J Pathol* 1995; 175: 195-201.
- 22 Lakhani SR. The transition from hyperplasia to invasive carcinoma of the breast. *J Pathol* 1999; 187: 272-278.
- 23 Page DL, Dupont WD, Rogers LW, Rados MS. Atypical hyperplastic lesions of the female breast. A long-term follow-up study. *Cancer* 1985; 55: 2698-2708.
- 24 Page DL, Rogers LW. Combined histologic and cytologic criteria for the diagnosis of mammary atypical hyperplasia. *Hum Pathol* 1992; 23: 1095-1097.
- 25 Rosai J. Borderline epithelial lesions of the breast. *Am J Surg Pathol* 1991; 15: 209-221.
- 26 Schnitt SJ, Connolly JL, Tavassoli FA, et al. Interobserver reproducibility in the diagnosis of ductal proliferative breast lesions using standardised criteria. *Am J Surg Pathol* 1992; 16: 1133-1143.
- 27 Liberman L, Cohen MA, Dershaw DD, et al. Atypical ductal hyperplasia diagnosed at stereotaxic core biopsy of breast lesions: an indication for surgical biopsy. *Ajr Am J Roentgenol* 1995; 164: 1111-1113.
- 28 Holland R, Peterse JL, Millis RR, et al. Ductal carcinoma in situ: a proposal for a new classification. *Semin Diagn Pathol* 1994; 11: 167-207.
- 29 Poller DN, Silverstein MJ, Galea M, et al. Ductal carcinoma in situ of the breast. A proposal for a new simplified histological classification. Association between cellular proliferation and c-erbB-2 protein expression. *Mod Pathol* 1994; 7: 257-262.
- 30 Silverstein MJ, Poller DN, Waisman JR, et al. Prognostic classification of breast ductal carcinoma-in-situ. *Lancet* 1995; 345: 1154-1157.
- 31 Rajan PB, Cranor ML, Rosen PP. Cystosarcoma phyllodes in adolescents and young women: a study of 45 cases. *Mod Pathol* 1997; 10: 24A.
- 32 Moffat CJC, Pinder SE, Dixon AR, et al. Phyllodes tumours of the breast: a clinicopathological review of 32 cases. *Histopathol* 1995; 27: 205-218.
- 33 Pietruska M, Barnes L. Cystosarcoma phyllodes. A clinico-pathologic analysis of 42 cases. *Cancer* 1978; 41: 1974-1983.

- 34 Ward RM, Evans HL. Cystosarcoma phyllodes. A clinicopathologic study of 26 cases. *Cancer* 1986; 58: 2282-2289.
- 35 Girling AC, Hanby AM, Millis RR. Radiation and other pathological changes in breast tissue after conservation treatment for carcinoma. *J Clin Pathol* 1990; 43: 152-156.
- 36 Schnitt SJ, Connolly JL, Harris JR, Cohen RB. Radiation-induced changes in the breast. *Hum Pathol* 1984; 15: 545-550.
- 37 Filomena CA, Jordan AG, Ehya H. Needle aspiration cytology of the irradiated breast. *Diagn Cytopathol* 1992; 8: 327-332.
- 38 Kennedy S, Merino MJ, Swain SM, Lippman ME. The effects of hormonal and chemotherapy on tumoral and non neoplastic breast tissue. *Hum Pathol* 1990; 21: 192 - 198.
- 39 Rasbridge SA, Gillett CE, Syemour AM, et al. The effects of chemotherapy on morphology, cellular proliferation, apoptosis and oncoprotein expression in primary breast carcinoma. *Br J Cancer* 1994; 70: 335-341.
- 40 Brifford M, Spyrtos F, et al. Sequential cytopunctures during preoperative chemotherapy for primary breast carcinoma. Cytomorphologic changes, initial tumor ploidy, and tumor regression. *Cancer* 1989; 63: 631-637.
- 41 Malberger E, Edoute Y, Toledano O, Sapir D. Fine-needle aspiration and cytologic findings of surgical scar lesion in women with breast cancer. *Cancer* 1992; 69: 148-152.
- 42 Solin LJ, Fowble BL, Troupin RH, Goodman RL. Biopsy results of new calcifications in the postirradiated breast. *Cancer* 1989; 63: 1956-1961.
- 43 Clark GM. Do we really need prognostic factors for breast cancer? *Br Cancer Res Treat* 1994; 30: 117-126.
- 44 Galea MH, Blamey RW, Elston CW, et al. The Nottingham Prognostic Index in primary breast cancer. *Br Cancer Res Treat* 1992; 22: 207-219.
- 45 Connolly JL, Fechner RE, Kempson RL, et al. Recommendations for the reporting of breast carcinoma. *Hum Pathol* 1996; 27: 220-224.
- 46 Dalton LW, Page DL, Dupont WD. Histologic grading of breast carcinoma: a reproducibility study. *Cancer* 1994; 73: 2765-2770.
- 47 Frierson HF, Wolber RA, Berean KW, et al. Interobserver reproducibility of the Nottingham modification of the Bloom and Richardson histological grading scheme for infiltrating ductal carcinoma. *Am J Clin Pathol* 1995; 105: 195-198.
- 48 Robbins P, Pinder S, de Klerk N, et al. Histological grading of breast carcinomas. A study of interobserver agreement. *Hum Pathol* 1995; 26: 873-879.
- 49 Lee AHS, Ellis IO, Pinder SE, et al. Pathological assessment of sentinel lymph node biopsies in patients with breast cancer. *Virchows Arch (A) Pathol Anat* 2000;436: 97-101.