Cytodiagnosis of Breast Lesions An Atlas and Text



Malcolm M. M. Hayes Gia-Khanh Nguyen 2014

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Chapter 1

GENERAL CONSIDERATIONS

Over the last 50 years the use of cytology in the diagnosis of breast abnormalities has waxed and waned. In areas of the world where medical litigation is rife, the enthusiasm for the use of fine needle aspiration (FNA) cytology for investigating breast lesions has been replaced largely by needle core biopsies. However, the pros and cons of these techniques are still hotly debated (Westenend 2001). There is no doubt that FNA can provide an accurate, rapid and cost effective diagnosis for most breast abnormalities. The technique is particularly applicable to cystic lesions and breast masses and has some use for the investigation of architectural abnormalities. It may provide rapid confirmation of the diagnosis of recurrent, metastatic or inflammatory breast cancer. Imprint cytology of the breast is also used as intra-operative assessment of margins of partial mastectomy procedures and to identify metastatic carcinoma in sentinel lymph node biopsies. However, in the absence of a mass lesion, calcifications are better investigated by tissue biopsy techniques. Additional cytological techniques that are of use include the analysis of nipple imprints or scrapes, nipple discharges and mammary duct brushings or lavage. The duct brushings and lavage require specialized cannulas and equipment and their use is restricted to a few major medical centres. In this monograph FNA and nipple discharge cytology of important breast lesions are presented and discussed. Relevant clinical features, imaging characteristics, and histopathological features are also included to aid comprehension of the cytological picture. The text is referenced with selected historical publications and relevant current literature. The cytological features of problematic areas are illustrated lavishly.

A. FINE NEEDLE ASPIRATION

FNA for cytological evaluation of breast lesions has a long history. Martin and Ellis (1930) were the first investigators to report on FNA of tumours of different anatomic sites including the breast. In 1952 Saphir recommended FNA of breast lesions occurring during pregnancy and lactation and for rapid diagnosis of malignant and benign breast lesions. In 1956, Godwin used FNA to diagnose deeply located palpable lesions of the breast that were difficult to explore surgically. Zajdela (1954) recommended the use of FNA for the diagnosis of palpable breast lesions and, in 1969 Verhaeghe and Cornillot formalized the triple test, combining clinical, radiological and cytological examination for the diagnosis of breast lesions. Since then numerous reports attesting the value of FNA in the cytological evaluation of breast lesions have appeared in the literature and breast FNA has become a routine diagnostic procedure worldwide. However, with the advent of widespread use of core biopsy FNA of breast lesions has fallen out of favour in many

institutions. Nevertheless, it is still considered a useful investigative technique in many centres throughout the world today (Abdel-Hadi, et al. 2010, Rosa et al. 2012; Simsir 2012)

TECHNICAL CONSIDERATIONS

The technique of FNA depends upon whether the abnormality is palpable or nonpalpable – detected by imaging studies. Palpable lesions are best investigated by manual FNA technique in which the mass is anchored with one hand and the needle manipulated with the other, making several passages through the lesion in different directions employing a back-and-forth oscillating drill-like motion. In our experience a bare 25-guage needle held by the hub provides excellent results but some aspirators prefer to attach a syringe to provide suction – usually used in conjunction with a "gun" or syringe holder. The sample is expressed onto glass slides and spread. Then, the needle can be rinsed for preparation of a cellblock or cytospin preparations. Air-dried smears are suitable for staining with May Grunewald Giemsa or DiffQuik techniques. Alternatively, smears can be fixed immediately in alcohol and stained with H&E or Papanicolaou stain. We prefer to have both Giemsa- and Papanicolaou-stained smears available. Excess aspirated material is used for preparation of a cellblock for histologic evaluation and immunohistochemical studies, if indicated. If smears are not made directly on site, the aspirate can be rinsed into a fluid-based medium such as Cytolyte, transferred to the laboratory, and processed as cytospin preparations, ThinPrep or SurePath slides. Multiple ThinPrep or SurePath preparations can be made from the same aspirate as an alternative to making a cellblock to provide material for immunostaining. The immunostaining technique must be optimized for such smear preparations. Non-palpable cystic or mass lesions are localized under imaging guidance (ultrasound, mammography or MRI) and then aspirated and handled in a similar manner. Lesions thought to be suspicious for malignancy on imaging techniques can also be sampled by core biopsy technique in the same session and the location marked by inserting a metal clip. This is our standard procedure for cases in which the diagnosis of malignancy is favoured based on the imaging and/or clinical data, so providing suitable material for the assessment of invasion and for immunostaining for breast biomarkers.

TRIPLE TEST: INFORMATION REQUIRED

Cytopathology cannot be practiced in a vacuum and the cytological changes need to be interpreted in the light of the clinical findings and the imaging characteristics of the lesion. These factors form the basis of the "Triple Test" for breast cytodiagnosis. The following questions must be asked before a final clinicopathological diagnosis is rendered.

• Does the clinical history suggest a malignant lesion?

- Do the imaging features suggest a malignant lesion?
- Do the cytological features suggest a malignant lesion?

Only if the answer to all three questions is concordant should a definite diagnosis of a benign or malignant process be rendered. This clinicopathological assessment is achieved best in the context of a multidisciplinary review meeting.

DIAGNOSTIC ACCURACY

In our opinion, FNA of the breast has several limitations because of the inability to assess tissue architecture. Thus, it cannot allow one to distinguish reliably between in situ and invasive carcinoma, cannot differentiate between usual ductal hyperplasia and atypical ductal hyperplasia, and cannot distinguish between follicular and diffuse lymphomas. Furthermore, it cannot identify vascular or lymphatic invasion. If a lymphoid neoplasm is suspected, FNA must be used together with flow cytometry. Stromal changes are more difficult to assess than epithelial changes because of sampling issues. Therefore, it is often impossible to distinguish between fibroadenoma and benign or borderline phyllodes tumour using FNA cytology. Because of these limitations, FNA cytology is often combined with a tissue biopsy for some breast lesions. However, FNA can provide a cost-effective, rapid and accurate diagnosis of many benign lesions of the breast enabling tissue biopsy to be avoided.

The diagnostic accuracy of breast cytology is highly operator dependent. The sensitivity of FNA for palpable and non-palpable malignant lesions performed under imaging guidance (by mammography or ultrasound) is comparable. The sensitivity for malignancy ranges from 65 to 98% and specificity ranges from 34 to 100%. False-positive results occur in 0 - 2% and false-suspicious results occur in 1 - 13% of cases. False-negative results may occur because of error in sampling, interpretation or both. The majority of breast cyst fluids are benign but about 2% are malignant and these are typically associated with complex cystic lesions. In a recent study, Shabb, et al. (2013) showed that approximately 2% of FNA cases show an overlap in morphology between benign and malignant lesions and constitute the true "grey-zone". Diagnostic accuracy of breast cytology using the liquid-based technique is reported to be slightly lower than for standard FNA smears (Ryu, et al. 2013).

Reasons for a false-negative aspirate:

- Sampling error
- Interpretive error: Causes include -
 - Human error every cytopathologist makes some errors of interpretation
 - Hypocellular neoplasm e.g. Lobular carcinoma
 - Low-grade carcinoma
 - Malignancy masked by benign cells
- Failure to use the Triple Test

Reasons for a false-positive aspirate:

- Interpretive error: Major traps
 - Atypia in benign lesions especially fibroadenoma, papilloma, gynecomastia, fat necrosis and inflammatory lesions. Fibroadenoma, papilloma and complex sclerosing lesions may yield highly cellular aspirates that contain atypical poorly cohesive ductal cells
 - Histiocytes in inflammatory lesions misinterpreted as malignant ductal cells
 - Degenerative changes seen in nipple discharges from papilloma, papilloma in dilated cystic ducts, and in some apocrine cysts.
 - Post-radiation atypia
- Failure to use the Triple Test

Unsatisfactory samples – Definition:

- We prefer to use the term "Insufficient for cytological diagnosis"
- Less than 6 well-preserved clusters of at least 5 epithelial cells
- Exceptions to this rule include:
 - o Cyst contents/fluid- which are sometimes acellular
 - Lipoma or other stromal lesions
 - Clinically benign breast tissue
- In these circumstances, we believe it is acceptable to use the phrase "Consistent with the clinical diagnosis of a simple cyst, lipoma, or benign breast tissue."

REPORTING TERMINOLOGY AND FORMAT

The cytopathology report should follow the Bethesda reporting guidelines and include the following information:

1) The exact site of the biopsy -

- a) Side
- b) Quadrant involved or the position on the clock
- 2) The type of sample FNA, nipple discharge etc.
- 3) A brief description of the cytological features including nuclear grade if malignant.
- 4) Comments, for example:
 - a) Further investigation (e.g. Histological assessment by open or core tissue biopsy for an atypical or suspicious result) or follow up imaging requested
 - b) Confirmation of invasion by histological examination in any cases of a "malignant" diagnosis
- 5) Conclusion/Result: One of the 5 following conclusions/results should be given.
 - i) Insufficient for cytological diagnosis
 - ii) Benign

- iii) Atypical (Atypical cells present, favour benign)
- iv) Suspicious for malignancy (Atypical cells present, favour malignant)
- v) Malignant

BREAST MARKER STUDIES

Increasingly, oncologists are demanding that breast marker studies be performed on fine needle aspiration samples of primary, metastatic and recurrent carcinomas. Although this does not conform to current ASCO guidelines, several studies have confirmed the accuracy of breast markers (ER, PR, Her2-neu) and markers of basal-type cancer assessed by immunohistochemistry and FISH on cell blocks of FNA material provided that it has been fixed in 10% buffered formalin. Immunostains may also be performed to detect the presence or absence of myoepithelial cells. Such material may also be used for molecular studies. However, in primary breast carcinoma one cannot distinguish between in-situ and invasive carcinoma, which limits the standard breast marker studies to some extent except in the metastatic setting. Furthermore, the immunostaining technique must be optimized for the staining of cytology preparations and must be appropriately validated.

MORPHOMETRIC ANALYSIS OF FNA MATERIAL

A few studies have shown some added benefit of morphometric analysis in the diagnosis of problematic aspirates. Both nuclear DNA content and textural features have been used. However, these technologies are not used in common practice. A morphometric study in our laboratory based on DNA ploidy assessed in Feulgen-stained smears failed to detect some cases of carcinoma that were evident on examination of routine smears.

B. NIPPLE DISCHARGES

The history of nipple discharge (ND) cytology dates back to the 1940s. Saphir (1950) reported the first detailed cytological description of breast secretions. Since then several reports on this topic have appeared in the literature.

ND is present in 7 to 14% of asymptomatic, non-pregnant, non-lactating women. It can be physiological or pathological. Physiological discharges are typically related to pregnancy or recent lactation. Pathological conditions such as prolactinoma can result in nipple discharge and ND is also seen in response to some medications such as antidepressants, administration of exogenous hormones and endocrine disorders of the thyroid. Inflammatory conditions in the breast such as acute mastitis and abscess can cause a purulent discharge, but these conditions are uncommon. Most bilateral discharges occur in association with fibrocystic changes. The discharge in fibrocystic changes can be clear, greenish or brownish in colour. Frankly bloodstained discharges occur with intraductal papilloma and intraductal carcinoma. Any nipple discharge that contains erythrocytes or hemosiderin-laden macrophages requires investigation of the underlying duct to exclude the latter conditions. According to one study, cancer is most prevalent when the ND is bloody (4%) and less prevalent when it is purulent (0.8%), serous (0.2%) and milky (0.1%).

Technical considerations: ND can be expressed and put directly onto glass slides and spread to make a smear in the similar manner as making a blood film. The smears are air-dried for staining by the MGG method or fixed in 95% ethanol for the Papanicolaou staining technique. Cytopathologic examination of nipple discharges may be challenging. Ductal cells from benign lesions that shed into the discharge undergo degenerative changes, resulting in nuclear enlargement and irregularity. Therefore a conservative approach to diagnosis is required.

Diagnostic accuracy: ND is useful in identifying intraductal cancers or intraductal papilloma. Papillomas occur mostly in women aged <40 years whereas intraductal carcinomas occur mostly in those >40 years. A diagnostic sensitivity ranging from 41-85%, a specificity of 97%, a positive predictive value of 92%, a negative predictive value of 94% have been reported for ND cytology.

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Chapter 2

DIAGNOSTIC IMAGING OF BREAST LESIONS

(Images supplied and text supplemented by Christine M. Wilson MD, BC Cancer Agency, Vancouver, BC)

Patients referred for diagnostic breast imaging typically present with a palpable mass, nodular breast tissue, a painful lesion, axillary lymphadenopathy or a nipple discharge. Otherwise, imaging studies are performed for purposes of screening and diagnostic workup. Accredited imaging modalities include mammography, ultrasound (US) examination, Magnetic Resonance Imaging (MRI) and Positron Emission Tomography (PET) scan. Mammography is the standard screening modality. This can detect mainly the following abnormalities:

- 1) Mass lesions
- 2) Calcifications
- 3) Architectural distortion
- 4) Asymmetrical focal density of parenchyma

Ultrasound examination detects mass lesions and can distinguish between solid and cystic masses but is less helpful in delineating calcifications and architectural abnormalities. MRI, which highlights areas of increased metabolic activity, is useful for detecting abnormalities in patients with dense breasts, especially those at high risk for malignancy such as familial cancer syndromes. FNA sampling can be directed under these three imaging modalities in order to sample the abnormal lesion. Typically, FNA biopsy is used for investigating cysts or masses and is less useful in the investigation of calcifications or areas of architectural distortion. The latter lesions are better assessed by tissue core biopsy. Enlarged axillary lymph nodes can also be targeted for FNA. The degree of suspicion for malignancy is summarized by the radiologist in one of 6 BI-RADS (Breast Imaging-Reporting and Data System) categories (Table 1).

Table 1: BI-RADS Categories for Imaging Interpretation

Category	Interpretation
1	Normal
2	Benign
3	Probably benign
4	Suspicious for malignancy
5	Highly suspicious for malignancy
6	Biopsy-proven malignant

Imaging features that favour benign lesions include the following:

- 1) Simple cysts broader than tall, anechoic, sharp posterior wall, enhanced through-transmission on ultrasound.
- 2) Masses with smooth circumscribed margins
- 3) Masses elliptical in shape
- 4) Masses with stable non-pleomorphic calcifications (coarse, round or punctuate, or curvilinear)
- 5) Masses stable in size and morphology over time

Many of these lesions with benign characteristics are not sampled for cytological assessment but some are aspirated at the discretion of the radiologist. In these lesions, the likelihood of malignancy is <2%. These fall into the BIRADS 2 or 3 categories.



Figure 2.1 Mammographic studies showing a mass with smooth margins typical of a fibroadenoma.

Malignant lesions that can simulate a benign lesion on imaging studies include the following:

- 1) Phyllodes tumour simulating fibroadenoma (Fig. 2.2)
- 2) High-grade invasive breast cancer simulating fibroadenoma
- 3) Mucinous carcinoma or medullary carcinoma simulating fibroadenoma
- 4) Invasive lobular carcinoma simulating fibrocystic changes or dense breast tissue
- 5) Encapsulated papillary carcinoma simulating a complex cyst or fibroadenoma



Figure 2.2 Phyllodes tumour presenting as a smooth circumscribed mass on mammogram.

Imaging features that may be associated with malignancy include the following:

- 1) Spiculated masses approximately 75% are malignant
- 2) Multinodular, irregular masses without spiculated margins approximately 25% are malignant
- 3) Masses containing pleomorphic calcifications or changing calcifications
- 4) Masses increasing in size over time
- 5) Masses with bright enhancement on MRI
- 6) Masses with FDG-avidity on PET scan
- 7) Asymmetric densities
- 8) Architectural distortions
- 9) Masses taller than wide on US
- 10) Complex cysts cysts with mural nodules or partially cystic lesions.

Benign lesions that can simulate a malignant mass on imaging studies include:

- 1) Radial scar
- 2) Complex sclerosing lesions/sclerosing papilloma
- 3) Granular cell tumour
- 4) Intraductal papilloma
- 5) Fat necrosis

- 6) Clustered cysts and ruptured cysts
- 7) Silicone mastopathy
- 8) Idiopathic granulomatous lobular mastitis
- 9) Pseudoangiomatous stromal hyperplasia
- 10) Gynecomastia-like hyperplasia
- 11) Intramammary lymph node
- 12) Ductal adenoma
- 13) Sclerosing adenosis

In addition to mammography, MRI may be helpful in separating benign from malignant breast lesions especially in the context of dense breasts. The MRI features of some common breast lesions are summarized in Table 2. MRI may be negative in in-situ carcinoma unless it is high grade comedoDCIS. PET may also be useful in differentiating benign from malignant breast lesions. Typically, malignant lesions are highly FDG-avid reflecting their high metabolic rate. Invasive cancers are more FDG-avid than are in-situ lesions. Importantly, as in all imaging modalities, some malignant neoplasms such as lobular carcinoma may produce false negative results and some benign lesions can produce false-positive results. Approximately 33% of invasive cancers that measure less than 1cm. in size are missed by PET scan. PET scan is less useful for diagnosing in-situ disease unless the DCIS is high grade. Inflammation and post-operative or post-biopsy changes hamper the utility of this diagnostic modality. Therefore, this technique is not recommended for routine screening for breast cancer. One must remember that invasive lobular carcinoma may be missed on all imaging modalities or may simulate a benign lesion. Table 2: MRI Enhancement kinetics illustrating the different patterns in benign and malignant breast lesions.



Enhancement Kinetics





Danger signs on radiology reports:

A: Mammography

New mass on comparative films Irregular spiculated mass Architectural distortion Pleomorphic calcifications Amorphous calcifications Linear and branching calcifications New calcifications especially clustered and irregular in shape Changing calcifications on comparative films Segmental distribution of calcifications Increasing mammographic density over time

B: Ultrasound

Irregular solid mass Enlarging mass on comparative examinations Hypoechoic Taller than wide Non-parallel to the chest wall Marked posterior acoustic shadowing

<u>C: MRI</u>

Mass enhancement – intense and heterogeneous Ring or rim enhancement Irregular angular margins T2-sequence low signal intensity compared with fat Fast initial phase – rapid enhancement Delayed kinetics – "wash-out" or plateau

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Chapter 3

NORMAL BREAST

A. HISTOLOGY

Normal breast tissue varies considerably between individuals in its ratio of epithelial and stromal elements, and typically becomes less dense with age. Similarly it varies from region to region throughout an individual breast and this imparts patchy variations in radiodensity that can be interpreted as abnormalities. Normal breast consists of a system of branching modified sweat ducts that originate as down-growths of the epidermis of the nipple region. Each duct begins as a lactiferous duct and the branches of this duct give rise to a mammary lobe. The size of the lobes varies greatly and the margins of the breast lobes are not circumscribed or contained within a capsule. The distal branches of the ducts are the terminal ducts that end in a grape-like cluster of blind sac-like dilatations termed acini (Fig. 3.1A&B). This structure constitutes the terminal duct-lobular unit. A dual layer of cells – an inner luminal cell layer and an outer myoepithelial cell layer, which are separated from the periductal stroma by a basement membrane, lines the ducts and lobular acini. The stroma of the breast consists of the specialized periductal or lobular stroma, vascularized loosely woven delicate collagen fibres and stromal fibroblasts. The non-specialized interstitial stroma is composed of adipose tissue and dense collagenous fibrous tissue that is hypocellular and contains coarse closely packed collagen bundles. Other mesenchymal elements including lymphatics, blood vessels, nerves, fibroblasts and myofibroblasts are found in the stroma (Fig. 3.2). Occasionally, these mesenchymal components give rise to neoplasms of the breast similar to those encountered in soft tissues elsewhere in the body.



Fig. 3.1A: Schematic drawing to illustrate the branching ductal system of the normal breast.



Figure 3.1B: Thick section of breast viewed under a dissecting microscope to show the terminal duct-lobular units forming grape-like clusters. Photograph provided by Professor Maria-Pia Foschini, University of Bologna, Italy.





Fig. 3.2. Normal breast tissue:

A. Terminal duct-lobular unit and fibro-adipose tissue stroma.

B, C. Terminal duct lined by an inner layer of columnar epithelial cells and an outer layer of myoepithelial cells.

D. Terminal duct and acini lined by an inner layer of epithelial cells and an outer layer of myoepithelial cells with clear cytoplasm. (H&E stain)

B. CYTOLOGY

Normal breast cells and minute fragments of breast tissue may be seen in some fine needle aspirates. These elements are easily identified. Ductal epithelial cells are columnar in shape and show benign, oval nuclei and granular, defined cytoplasm. They are commonly seen in small cohesive sheets with a honeycomb pattern or in small clusters. Myoepithelial cells appear singly, have oval hyperchromatic nuclei and are either bipolar or show no visible cytoplasm. Acinar cells are polygonal in shape and display oval nuclei, inconspicuous nucleoli and clear or granular cytoplasm. The acinar cells appear singly, in small clusters or groups. Lobules of acinar cells partially surrounded by a thin basement membrane are observed occasionally. (Fig. 3.3)







Fig. 3.3. Normal breast showing in FNA:

- A. Stroma adipose tissue with interspersed capillaries
- B. Cluster of ductal epithelial cells with a few attached myoepithelial cells
- C. Myoepithelial cells
- D. Lobular (acinar) cells

E, F. Lobular unit partially surrounded by thin metachromatic basement membrane (MGG stain)

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Chapter 4

BENIGN NON-NEOPLASTIC LESIONS

1. Fibrocystic changes

Fibrocystic changes (FC) are common in the reproductive years but can occur at any age. They are rare in children and adolescents and can occasionally be seen in male breast.

The clinical presentations of mammary fibrocystic changes include: tender breasts that often fluctuate with the menstrual period, focal thickening, "granularity" and multinodularity. The cysts can cause a localized mass. A nipple discharge – clear or greenish may occur. Imaging abnormalities include: cysts – simple or complex, irregular stromal densities, irregular masses and calcifications.

Histopathological findings in breast tissue with FC include cysts, apocrine metaplasia, ductal hyperplasia of usual type (epitheliosis, papillomatosis), lobular hyperplasia, duct ectasia, stromal fibrosis and inflammation around ruptured cysts. The balance of changes varies from case to case. Many patients present with simple cysts alone while others exhibit predominantly hyperplastic features. (Figs.4.1 and 4.2)







Fig.4.1. Histology of breast tissue with fibrocystic changes (H&E stain):

A. Enlarged lobules, dilated ducts and cysts containing eosinophilic granular secretions

- B. Apocrine cysts
- C. Apocrine cysts with Liesgang rings
- D. Adenosis and ductal hyperplasia of usual type





Fig.4.2. A, B. Histology of breast tissue with fibrocystic changes showing an area with ductal epithelial hyperplasia and collagenous spherulosis. (H&E stain)

Cytological findings (Figs. 4.3-4.5):

1. Cysts: Cytological contents may include:

- Foamy histiocytes some with brown pigment
- Cell debris
- Liesgang rings and calcifications
- Apocrine cells arranged in cohesive sheets
- In liquid preparations (ThinPrep and Cytospin), the apocrine cells may form ball-like clusters
- 2. Ductal hyperplasia:
 - Aspirates are usually highly cellular
 - Cohesive groups and sheets of uniform ductal cells are characteristic
 - Myoepithelial cells are present within the cell groups
 - Some small hyaline stromal globules may occur
 - Some stripped nuclei occur less numerous than seen in aspirates from fibroadenoma
 - Mild pleomorphism of ductal cell nuclei may be observed
- 3. Stromal hyperplasia:
 - Irregular mildly cellular stromal fragments lacking the clubbed or "cloverleaf" shape of those seen in fibroadenoma
 - Small hyaline stromal globules in collagenous spherulosis

4. Absent:

- •
- Marked nuclear pleomorphism Dissociated (dyshesive) atypical ductal cells •



4.3A







Fig.4.3. Breast fibrocystic changes showing in FNA: A. Irregular sheets and clusters of apocrine epithelial cells from a cyst aspirate (Pap stain)

- B. Sheet of benign apocrine cells from a simple cyst (MGG stain)
- C. Sheets and clusters of proliferated ductal epithelial cells and apocrine cells and single apocrine cells
- D. Sheets of benign ductal cells with interspersed myoepithelial cells (MGG stain)
- E. Higher magnification of the sheet of ductal epithelium seen in D to show spindle-shaped, darkly stained myoepithelial cell nuclei (MGG stain).




4.4B

Fig.4.4. Hyperplastic epithelial cells and collagenous spherulosis: A, B. A sheet of crowded benign hyperplastic ductal cells and myoepithelial cells showing oval nodules of metachromatic basement membrane matrix material (MGG stain)



Fig.4.5. A Liesgang ring (MGG stain)

Atypia in Fibrocystic Disease

Rarely one may encounter marked cytological atypia of the apocrine cells in aspirates from inflamed cysts (Fig. 4.6 A-F) and in radiated breasts. It is thought that this is a form of degenerative change akin to "symplastic" atypia encountered in "ancient" schwannoma and in bizarre leiomyoma of the uterus. Awareness of this entity and correlation with the imaging features will prevent a misdiagnosis of malignancy in these cases.







Fig 4.6: Atypia of apocrine cells in inflamed cysts. Note the degenerative appearance of the cells and the numerous foamy histiocytes. (A) Papanicolaou stain (B-F) Giemsa stain.

2. Breast abscess

Breast abscess is usually caused by a Staphylococcal infection that enters the breast through a cracked nipple traumatized by breast-feeding. In some patients it is unassociated with lactation and presents as a tender mass. Occasionally, when the clinical diagnosis is not obvious the lesion is evaluated by FNA. The cytological findings of breast abscess vary with the phase of inflammation (acute versus chronic) (Fig. 4.7).

- Very cellular sample
- Sheets of neutrophils, histiocytes and cell debris in acute phase
- Distorted ductal cells showing reactive atypia
- Granulation tissue fragments
- More chronic lesions can have a high content of lymphocytes and histiocytes.





4.7C

Fig.4.7. Breast Abscess showing in FNA:

A. Acute phase showing numerous neutrophils, some histiocytes, fibrin and cell debris

B. Chronic phase showing abundant lymphocytes with scattered loose aggregates of histiocytes

C. Loose aggregates of large histiocytes can be mistaken for crowded poorly cohesive groups of highly atypical or suspicious ductal cells (false-positive diagnosis)

3. Periareolar abscess or fistula

Plugging of lactiferous duct by ductal squamous metaplasia causes dilation, inflammation and ruptures of the duct with formation of a sinus. FNA of the lesion may be formed to rule out a neoplastic lesion. On imaging the lesion is superficially located adjacent to the nipple.

- Highly cellular aspirate with sheets of neutrophils (Fig. 4.8)
- Histiocytes and multinucleate histiocytic giant cells present and histiocytes
 may aggregate to form loose granulomas
- Lymphocytes and plasma cells are sometimes seen and histiocytes predominate in chronic lesions
- Squamous cells from squamous metaplasia of the duct lining cells
- Anucleate squamous cells may be seen





Fig.4.8. A & B: Periareolar cyst/fistula showing in FNA sheets of squamous epithelial cells, numerous anucleate squames, neutrophils, histiocytes and scattered multinucleate histiocytic giant cells (MGG stain)

4. Fat necrosis

This lesion is caused by necrosis of mammary or subcutaneous fatty tissue. Clinical features of fat necrosis are variable. Some patients give a history of trauma to the breast. Physical examination may reveal a superficial tender mass, overlying ecchymosis. Some present with a non-tender mass. Regional lymphadenopathy may be present. Old lesions can become cystic or assume a stellate mass-like appearance on imaging and abnormal calcifications may be present suggesting a malignancy.

- Lipid debris and fat vacuoles may be seen (Fig. 4.9)
- Hemosiderin pigment may be present sometimes within histiocytes
- Predominantly histiocytic infiltrate with few or no ductal cells
- Histiocytes with foamy cytoplasm, enlarged nuclei and prominent nucleoli
- Loose histiocytic aggregates mimicking groups of atypical ductal cells
- Metachromatic reactive stromal fragments may be present





4.9C

- Fig.4.9. Breast fat necrosis showing in FNA:A. Cell debris and foamy histiocytesB. Loose sheets of foamy histiocytesC. Cell debris and foamy histiocytes some with large nuclei (MGG stain)





Fig. 4.10. Histopathology of fat necrosis showing foamy histiocytes and giant cells encircling cysts formed by necrotic adipocytes with adjacent reactive fibrosis (H&E).

5. Silicone mastopathy (Granuloma)

Silicone has been used for augmentation mastoplasty until recent years. The most common technique was insertion of a breast prosthesis filled with silicone gel but some patients have had silicone injected directly into the tissues. Rupture of the prosthesis and leakage of the silicone into the breast tissues elicits a granulomatous reaction, fibrosis and calcification. The silicone can be transported to the regional lymph nodes, which also show a granulomatous reaction.

FNA shows many multinucleate histiocytic giant cells and aggregates of histiocytes containing spherules of silicone within their cytoplasm (Fig.4.11 A-D). Free-lying extracellular silicone globules are also seen in the smears. The presence of silicone globules can be accentuated by lowering the condenser or viewing under polarized light (Fig. 4.11 E&H). The histological changes are illustrated in Fig 4.12. The differential diagnosis includes a granulomatous reaction to injected paraffin oil, which is used as an augmentation technique in some countries. Here, the foreign material may be very difficult to delineate and the vacuoles appear empty. Rarely, silicone and saline prostheses are complicated by superimposed lymphoma usually of anaplastic large-cell type (see later).







4.11F

Fig. 4.11 A-F: FNA of Silicone mastopathy showing aggregates of histiocytes and histiocytic giant cells containing intra-cytoplasmic spherules of silicone and free-lying silicone globules (MGG stain).



Fig. 4.12 A&B: Histopathology of silicone mastopathy showing a foreign body granulomatous reaction to engulfed silicone particles – refracted in "B" (H&E)

6. Idiopathic Granulomatous Lobular Mastitis

Idiopathic granulomatous lobular mastitis is an inflammatory lesion of the breast of unknown aetiology that can simulate carcinoma clinically. Most patients are women in the 20-45 year age group who present with an indurated, irregular palpable mass at the periphery of the breast. There may be tethering to skin. The mass may be tender. Regional lymph nodes can be enlarged.

FNA shows a predominance of inflammatory cells including numerous neutrophils, lymphocytes, plasma cells and aggregates of histiocytes (Fig. 4.13). The histiocytes often have an epithelioid morphology and can be misinterpreted as malignant ductal cells. Some of the histiocytes form multinucleate giant cells. A similar cytological picture may occur with mycobacterial and fungal infections of the breast or cat-scratch disease so cultures are required to exclude these infections.

On histology, a suppurative granulomatous process is present centred on the breast ducts and lobules. Characteristically, lipid vacuoles form spaces in the centres of the granulomas and special stains for organisms are usually negative (Fig. 4.14). This disorder may be the result of an abnormal immunological response to breast secretions or due to infection with Corynebacteria that is difficult to culture unless special media are employed.









4.13G

Fig. 4.13 A-G: FNA of Idiopathic granulomatous lobular mastitis showing mixed inflammatory background containing multinucleate histiocytes and groups of epithelioid histiocytes forming loose granulomas.



4.14A



Fig.4.14 A&B: Histopathology of idiopathic granulomatous lobular mastitis showing granulomas centred on lobules with central lipid vacuoles (H&E)

7. Lactational Changes and Lactational Adenoma

Pregnancy-induced secretory or lactational changes are sometimes encountered in FNA's from women in the reproductive age group. Lobules in the breast that have undergone secretory or lactational hyperplasia can form large masses with circumscribed borders that resemble a fibroadenoma and are termed lactational adenomas (Fig. 4.15). Most lactational adenomas are really nodular aggregates of hyperplastic lobules rather than neoplasms but some represent lactational changes within a pre-existing fibroadenoma or tubular adenoma. Occasionally, secretory changes can occur outside of pregnancy in patients who have prolactinoma, hypothyroidism or who are on exogenous hormones or antidepressant drugs. These changes cause enlargement of ductal cell nuclei, prominence of nucleoli and loss of cohesion and, in the context of a cellular aspirate from a breast mass, can be confused with carcinoma.



Fig. 4.15: Histopathology of lactating adenoma showing the cystic ducts filled with eosinophilic secretions (A) and acini lined by cells with enlarged round vesicular nuclei containing central nucleoli (B).

- In the pre-lactational secretory phase the FNA shows a cellular aspirate containing sheets of epithelial cells with vacuoles/foamy cytoplasm, uniform medium-sized round nuclei and central nucleoli (Fig. 4.16)
- In the lacational phase there is loss of cellular cohesion and a predominance of stripped round nuclei associated with lipid droplets and cell debris in background













Fig.4.16. Lactational adenoma showing in FNA:

A. Cohesive enlarged lobulated epithelial fragments

B-F. Cohesive sheets of ductal cells with vacuolated cytoplasm, large nuclei and prominent nucleoli

- G. Stripped nuclei, uniform in size, round, and 1-2 central nucleoli
- H. Stripped nuclei and lipid droplets (MGG stain)

8. Galactocele

A complication of lactation is the development of a galactocele, which is essentially a pool of milky secretions lying in the breast stroma secondary to the rupture of a duct. These lesions may form a palpable mass or a circumscribed mass on imaging and may be associated with calcifications.

FNA biopsy yields milky fluid, which in smears contains greenish floccular material and occasional intact histiocytes. The secretions are eosinophilic on cellblock preparations (Fig. 4.17). Histology shows secretory breast lobules and an aggregate of eosinophilic secretion surrounded by reactive stoma and histiocytes. Fine calcification of the contents may be seen.







Figure 4.17 A-F: Galactocele

FNA showing floccular greenish secretion with occasional histiocytes (A & B) that is eosinophilic and foamy in the cell blok (C). Core biopsy showing secretory breast lobules (D), and a pool extra-ductal secretion surrounded by fibrous stroma, reactive fibroblasts and histiocytes typical of a galactocele (E &F).

9. Hyperplastic Intramammary Lymph Node

Occasionally intramammary lymph nodes present as abnormal mass lesions on imaging studies and these are subject to FNA aspiration. Typically, these are located in the upper outer quadrant of the breast and are not associated with calcifications.

The FNAB yields sheets of lymphocytes that are morphologically benign. Reactive nodes contain a more pleomorphic population of small, medium-sized and large transformed lymphocytes together with tingible body macrophages (Fig. 4.18). If the node is larger than 1.5cm, the possibility of lymphoma has to be entertained and flow cytometry for lymphocyte immunotyping is recommended for diagnosis. Intramammary lymph nodes can also be the focus of metastatic carcinoma from the breast or rarely from extra-mammary sites.



Fig. 4.18: FNA of a reactive intramammary lymph node. Note the mixture of small and large lymphocytes (MGG stain).

10. Gynecomastia

Breast development in the male is limited to proliferation of ducts and stroma without formation of lobules. When this forms a palpable mass it is termed gynecomastia. It may occur as a physiological condition in teenage boys but can develop at other ages and can raise the clinical question of breast carcinoma, especially in elderly men. Some men treated for prostate cancer develop gynecomastia and both breast carcinoma and prostate carcinoma occur in patients who have the BRCA2 hereditary genetic defect. Gynecomastia may occur as a side effect of some drugs, liver disease, as a paraneoplastic phenomenon and in cannabis smokers. Although aspirates from gynecomastia can be highly cellular and associated with cytological atypia, the cell groups are cohesive and are associated with myoepithelial cells. Carcinoma almost never occurs in a teenage male. One should be aware that in addition to gynecomastia almost every disorder of the breast encountered in females can be seen in the male breast (Singh 2012; Rosa 2012)

- Aspirates may be cellular showing cohesive or papillary epithelial cell groups that have a myoepithelial component (Fig. 4.19)
- Nuclear atypia can be striking
- Irregular metachromatic stromal fragments in active phase
- Apocrine cells may occur










Fig. 4.19. FNAs from cases of Gynecomastia showing:

A-E: Many cohesive groups or sheets of ductal cells with sharp borders geographic shapes, variable crowding of nuclei and scattered stripped nuclei. Some have a pseudo-papillary architecture. Some superimposed small dark nuclei of myoepithelial cells are evident. F: Apocrine cells in a case of gynecomastia. G: Stripped nuclei similar to those seen in aspirates from a fibroadenoma (MGG stain). H-J: Metachromatic stromal material surrounding cell clusters (MGG stain)

11. Sclerosing adenosis, Complex sclerosing lesions, Sclerosing Papilloma and Radial Scar

Sclerosing adenosis usually presents as multiple benign or indeterminate calcifications on mammography without mass lesions and is seldom sampled by FNA. However, nodular forms of adenosis produce mass lesions or "Complex sclerosing lesions" that may be subjected to FNA. Some of these lesions have a papillary component and have been termed "Sclerosing papilloma" by some authors. The morphology and cytopathology of these lesions overlap with those of large radial scars. Classical radial scar produces architectural distortion detected on mammogram. It may form masses with speculated margins suspicious of malignancy, and may have a central lucent zone. Sometimes the mass has a wellcircumscribed margin consistent with a benign process. These lesions, especially when they are large, show very florid ductal hyperplasia of usual type, and have an increased risk for superimposed atypical epithelial proliferations including in-situ lobular neoplasia types LIN1 (so-called "Atypical Lobular Hyperplasia") and LIN2 (socalled "Lobular carcinoma in-situ" or LCIS) and ductal intra-epithelial neoplasia types DIN1a (so-called "Flat Epithelial Atypia"), DIN1b (so-called "Atypical Ductal Hyperplasia") and DIN1c (low-grade ductal carcinoma in-situ). There is also an increased risk of invasive low-grade carcinoma often of tubular type adjacent to these lesions, especially when the lesion is large >1cm.

FNA from nodular sclerosing adenosis, sclerosing papilloma and radial scar often exhibits atypical features including hypercellular crowded groups of cells, loss of cohesion, and moderate cytological atypia (Fig. 4.20). Indeed the atypia may be more extreme than that encountered in most papillary carcinomas. Considerable atypia can be seen in samples from atypical apocrine adenosis. The FNA results must be interpreted in conjunction with clinical and diagnostic imaging findings (Triple test) to avoid diagnostic errors. Furthermore, these lesions should be further evaluated histologically by core biopsy or excision biopsy.

















Fig. 4.20: FNA from a retro-areolar mass in a 42-year-old woman. The Giemsa stains show cohesive groups of benign ductal cells with myoepithelial cells and histiocytes (A) with a separate population of atypical ductal cells arranged in crowded poorly-cohesive groups and dispersed as single cells (B-F). The two cells

types are shown in G. The Papanicolaou-stained ThinPrep from the rinse is illustrated in H-K with pseudo-papillary clusters showing atypia. The histology of the benign sclerosing papilloma is shown in L-N. The atypical cells are illustrated in O and features of usual hyperplasia with many intranuclear helioid bodies are shown in P (H&E stains). This FNA was diagnosed as "suspicious for malignancy".

12. Radiation changes

In recent years with the increased use of lumpectomy and radiation therapy for small breast cancers, breast lumps at the previous site of surgery may be suspected to be a recurrent cancer and are targets for FNA examination. Mammary cells with radiation effects show cellular and nuclear enlargements with preserved nuclear: cytoplasmic ratio as seen in other anatomic sites. These cells may show slightly hyperchromatic nuclei, conspicuous nucleoli and cytoplasmic vacuoles that may contain some polymorphonuclear leukocytes. Usually, the nuclei are pale, contain vacuoles and the cells have a two-tone (green and pink) staining colour on Papanicolaou stained slides. The atypical ductal cells are often associated with the changes of fat necrosis (Peterse 1989).

13. Keratinous cyst (Epidermal cyst)

Occasionally, cysts derived from the overlying cutaneous adnexal structures are thought to be arising within the breast. These may be sampled by FNA technique. Most commonly encountered is the epidermal inclusion cyst. These are characterized by a superficial location. The FNA yields loosely cohesive sheets of keratinized squamous cells most of which have lost their nuclei. The cells have a blue or greenish-blue hue in Giemsa-stained preparations and have orangeophilic cells on Papanicolaou preparations (Figure 4.21). Squamous cells with "ghost" nuclei are also encountered in pilomatrixoma, which is uncommon in the breast. Here, the cells form compact aggregates and are often associated with cohesive groups of basaloid matrix cells and multinucleate histiocytic giant cells.





4.21D

Figure 4.21: FNA of a benign keratinous cyst (Epidermal inclusion cyst) of the breast of a 79 year-old woman submitted as contents of a breast cyst. Poorly cohesive sheets of mainly anucleate squamous cells are seen (A-C Giemsa). These have orangeophilic cytoplasm in Papanicolaou stains (D)

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Chapter 5

FIBROADENOMA AND PHYLLODES TUMOUR

A. FIBROADENOMA

Fibroadenoma is one of the most common benign lesions misdiagnosed as carcinoma because it may occur in women over 50 years of age. It occurs in a wide age range but is uncommon in children. The imaging features of a smooth hypoechoic mass are usually characteristic (Fig. 2.1). On ultrasound examination, fibroadenomas typically appear as an elliptical mass with smooth borders orientated parallel to the chest wall (Fig 5.1A & B) and exhibit acoustic hypoechogenicity. These imaging features reflect the gross morphology of the lesion (Figure 5.2). It is the most common solid mass in the breast that is sampled by FNA.



Fig 5.1 Ultrasound of a fibroadenoma showing a smooth elliptical mass orientated parallel to the skin surface.



Fig. 5.1B Ultrasound of a fibroadenoma undergoing needle biopsy.



Fig. 5.2: Gross morphology of a fibroadenoma showing a circumscribed homogeneous mass with smooth borders. (Photograph provided by Dr. D. Filipenko, S. Paul's Hospital, Vancouver).

Histologically, a fibroadenoma is composed of ducts surrounded and compressed by proliferated stromal tissue that forms nodules and club-shaped formations. The ducts within a fibroadenoma are always lined by a dual layer of inner luminal and outer myoepithelial cells and can show varying degrees of epithelial hyperplasia. In some tumours a florid proliferation of epithelial cells is observed. (Fig.5.3)



Fig.5.3. A. Histology a fibroadenoma showing a predominance of stroma forming lobulated masses compressing breast ducts. Some ducts show hyperplasia. B. Fibroadenoma with florid ductal hyperplasia. (H&E stain).

Cytological findings:

- Highly cellular aspirate (Figs.5.4-5.6)
- Many cohesive groups of ductal cells with sharply demarcated borders with branching glove-like or "antler-horn" shapes
- Flat or folded sheets of ductal cells with evenly spaced nuclei imparting a "honeycomb pattern".
- Some crowded poorly cohesive groups of ductal cells often present
- Myoepithelial nuclei within and at the periphery of epithelial cell groups
- Many stripped nuclei (ductal, myoepithelial and fibroblastic in origin)
- Stromal fragments some with a sharp club-shaped or clover-leaf appearance may be present and are diagnostic (Fig 5.5)
- Uncommon features of fibroadenoma aspirates include the presence of apocrine cells (Fig. 5.6), histiocytes, histiocytic giant cells (Fig. 5.8), and mucin (Fig 5.9).
- Mildly atypical ductal cells are often present (Fig. 5.10)
- Atypical stromal cells are usually not seen in the smear background

RULE: Never make a quick diagnosis of malignancy when in the presence of many stripped nuclei – think again!

Epithelial atypia may be observed in cell samples from a fibroadenoma. The distinction between a FA and a low-grade ductal carcinoma is usually not problematic but may be more challenging in ThinPrep samples than on standard smears (Ly 2011; Jing 2013). In some fibroadenomas isolated atypical epithelial cells are present, mimicking those of a low-grade ductal carcinoma. If one applies the triple test rule, such lesions will not be misdiagnosed as malignant. A core needle biopsy is necessary to solve this diagnostic dilemma.





Fig. 5.4. Breast fibroadenoma showing in FNA: A. Hypercellular aspirate featuring cohesive sheets of ductal cells with sharp borders and branching finger-like or antler horn shapes

B. Apposition of a group of uniform ductal cells with a stromal fragment

C. Many stripped nuclei of varying shapes and sizes, many representing myoepithelial cells (MGG stain).





Fig. 5.5. A large club-shaped, shamrock or cloverleaf metachromatic stromal fragment (A) and a smaller club-shaped stromal fragment (B). (Giemsa stain). Cellblock showing club-shaped stromal fragments in a fibroadenoma (C). (H&E stain).









Fig 5.6. Ultrasound-directed FNA biopsy of a lobulated mass from the breast of a 48 year-old woman. The SurePath preparation shows large cohesive sheets of uniform ductal cells with sharp borders with projections resembling the fingers of a glove and branching fragments resembling antler horns. A few dispersed cells are also present. Immunostains of the SurePath slides show positive staining of the nuclei of the myoepithelial cells for p63 (5.6D) and scattered epithelial cells within the fragments staining for CK5/6 (5.6C). The overall morphology and immunoprofile are those of a fibroadenoma which was confirmed on excision (5.6E). (Case contributed by Dr. Koen van de Viyver, NKI, Amsterdam)



Fig.5.7. Fibroadenoma with apocrine cellular change showing in FNA cohesive sheets of uniform apocrine cells in addition to other cellular elements of the tumour (MGG stain)



Fig. 5.8. A multinucleate histiocytic giant cell and a sheet of ductal epithelial cells. (MGG stain)





5.9C

Fig. 5.9. Fibroadenoma with myxoid stromaA. Histology of the tumour (H&E)B, C. Mucinous stromal material that is weakly metachromatic on Giemsa stain and

irregular sheet of ductal epithelial cells admixed with scattered myoepithelial cells





5.10B

Fig. 5.10. Atypical epithelial cells from fibroadenoma: A. A fragment of benign ductal epithelium from a fibroadenoma showing superimposed darkly stained spindle nuclei of myoepithelial cells. A mild degree of nuclear atypia is noted.

B. Loss of cell cohesion and mild cellular atypia together with many stripped nuclei. (MGG stain)

Fibroadenoma with myxomatous stroma.

This histologic variant of fibroadenoma is occasionally associated with Carney's multiple myxoma syndrome.

The tumour shows in FNA metachromatic myxoid material and irregular fragments of hyperplastic ductal epithelium as well as scattered naked nuclei of myoepithelial cells (Yamaguchi 2012). (Fig.5.9)

"Juvenile" or Cellular fibroadenoma (Figs. 5.11 & 5.12)

FNA yields a highly cellular aspirate with sharply demarcated epithelial cells groups and large fragments of cellular stroma, uniform epithelial cells groups, many stripped "naked" nuclei and some club-shaped stromal fragments. The stromal tissue fragments usually lack cellular atypia but may appear hypercellular. Abundant bipolar nuclei of myoepithelial cells are present, and sheets of apocrine cells may be observed. In a woman aged more than 40 years such cellular stroma is more often an indication of a phyllodes tumour.



Fig. 5.11 Juvenile fibroadenoma showing in FNA: Highly cellular aspirate with sharply demarcated epithelial cells groups and large fragments of cellular stroma







Fig.5.12. Juvenile fibroadenoma showing in FNA:

- A. Uniform epithelial cells groups and many stripped "naked" nuclei
- B. Many stripped nuclei and some club-shaped stromal fragments
- C. Sharply demarcated ductal epithelial cell fragments, sheets of apocrine cells and stripped nuclei (Pap stain)

B. PHYLLODES TUMOUR

Phyllodes tumour is less common than fibroadenoma and accounts for less than 1% of all breast tumours. It occurs in women between 30 and 70 years of age and can be large, 5 cm in greatest dimension in average, and it can mimic a breast cancer clinically. On imaging studies it may have a focally irregular margin and can be partly cystic. A clinical history of an enlarging mass is common. It is formed as the result of a neoplastic proliferation of stromal elements derived from the specialised periductal/lobular stroma and a non-neoplastic proliferation of ductal epithelial cells. Grossly, it can be identical to a fibroadenoma but may be softer in consistency, less circumscribed, exhibit a leaf-like pattern, or show cystic areas (Fig. 5.13). The tumour can be low-grade (WHO "Benign") intermediate-grade (WHO "Borderline") or high-grade (WHO "malignant").



Fig. 5.13: Gross morphology of a Phyllodes tumour showing the leaf-like pattern. (Photograph supplied by Dr. Bruce Youngson, UHN, Toronto, ON.)

Histologically, the stroma indents the ductal epithelium to form a "leaf-like pattern". The stroma is hypercellular and show spindle-shaped stromal cells that may show mitoses and express smooth muscle actin. (Fig.5.17). A malignant phyllodes tumour is characterized by the sarcomatous nature of its stroma, stromal overgrowth, more extreme atypia, necrosis, heterologous metaplasia and frequently local invasion. Phyllodes tumours are treated by local excision without lymph node dissection. Malignant tumours often recur after wide local excision and may develop late metastases (15%), mostly to lung.


Fig.5.14. Histology of phyllodes tumour. The typical leaf-like architecture, hypercellular stroma and entrapment of fat are demonstrated. (H&E stain).

Cytological findings: Figs. 5.15 - 5.18.

- Abundant groups of ductal epithelial cells and myoepithelial cells
- Hypercellular stromal fragments.
- Free-laying atypical spindle stromal cells
- Stripped nuclei sometimes atypical

Differential diagnosis between a fibroadenoma and a phyllodes tumour is difficult by FNA. The presence of hypercellular stromal fragments favors a phyllodes tumour. However, similar stromal cell fragments can be seen in fibroadenomas, especially in young women. The grading of a phyllodes tumour cannot be ready performed on FNA sampling. Stromal hypercellularity, stromal cell atypia and free-lying atypical stromal cells with mitoses and necrosis favor malignancy but histologic confirmation is necessary. Usually, the combination of clinical, imaging and cytological findings enable one to render a cytological diagnosis of "suspicious for phyllodes tumour".





5.15C

- **Fig. 5.15**. Phyllodes tumour showing in FNA (MGG stain): A. Sharply-demarcated sheets of uniform ductal and myoepithelial cells B. Cohesive groups of benign ductal cells and a hypercellular stromal fragment
- C. Cellular stromal fragments and dissociated spindle cells in the background.





5.15C

Fig.5.16. Phyllodes tumour showing in FNA:

- A. Cellular stromal fragments
- B. Detached atypical spindle cells and stripped spindle-shaped nuclei
- C. Dissociated atypical spindle cells, mast cells and histiocytes (MGG stain)



Fig. 5.17. Immunostain for smooth muscle actin showing labeling of the atypical spindle cells.





Fig. 5.18 A&B. Low-grade phyllodes tumour showing atypical spindle stromal cells in cell block preparation (H&E stain)

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Chapter 6

PAPILLARY NEOPLASMS

A. INTRADUCTAL PAPILLOMA

Intraductal papilloma is usually solitary and subareolar. It is seen most commonly in women less than 40 years of age but may occur in postmenopausal women. On imaging studies the lesion is circumscribed with a smooth border and may contain calcifications. Grossly, the circumscribed border is evident and the lesion lies within a dilated duct that is evident on histological examination (Fig. 6.1). The patients usually present with a unilateral bloodstained discharge, which constitutes the most common sample to be evaluated. It shows erythrocytes, hemosiderin-laden histological small present with a present of benign ductal epithelial cells (Fig. 6.2). The ductal cells may show nuclear atypia due to degenerative changes.





Fig.6.1 A&B: Gross appearance and histology of intraductal papilloma lying within a dilated duct with a fibrous wall. A dual layer of small ductal cells and underlying myoepithelial cells lines broad sclerotic papillae. (H&E stain). The gross image was provided by Dr. D. Filipenko, St. Paul's Hospital, Vancouver.



Fig. 6.2. Intraductal papilloma showing in nipple discharge pseudo-papillary cluster of ductal epithelial cells. (MGG Stain)









Fig 6.3. Nipple fluid cytology from a 39 year-old woman who had a clear yellowish discharge. The SurePath preparation shows cohesive clusters of ductal cells are seen some containing stromal cores indicative of true papillary fragments. Tissue biopsy confirmed a benign intraductal papilloma. (Case contributed by Dr. Koen van de Viyver, NKI Amsterdam)

Some papillomas contain psammomatous calcifications, which add to the clinical suspicion of malignancy. Needle aspirates from papillomas may show many cellular features in common with those from papillary carcinomas. The cell samples are usually highly cellular and show a loss of cellular cohesion. Epithelial cell atypia secondary to degenerative changes may be observed. Some authors have demonstrated that image analysis of nipple discharge may be helpful in separating ductal papilloma from papillary carcinoma. Awareness of the central sub-areolar location of the mass can be helpful in minimizing interpretive errors. Immunostaining of the cellblock preparation for P63/Heavy chain myosin and S-100 protein staining may be used to demonstrate myoepithelial cells. Typically myoepithelial cells are absent in papillary carcinoma. Papillomas are prone to infarction, especially after FNA biopsy. This may induce necrosis, reactive atypia and squamous metaplasia.

FNA Cytology of papilloma: Figs 6.4 - 6.5

- Cellular smears
- 3-dimensional papillary tissue fragments
- Papillary stromal fragments
- Flat sheets and pseudo-papillary clusters of epithelial cells and myoepithelial cells
- The epithelial cells can be small, cuboidal or columnar in configuration with oval nuclei with finely granular chromatin and conspicuous nucleoli
- Stripped nuclei of myoepithelial, stromal and epithelial origin
- Histiocytes and hemosiderin laden macrophages
- Atypical ductal epithelial cells and apocrine cells may be seen
- Immunostaining of the cell block for myoepithelial markers, highmolecular weight keratins and estrogen receptors may be helpful.





Fig.6.4. Intraductal papilloma showing in FNA thick and large papillary clusters of tumour cells (A and B), two small clusters of tumour cells and several foamy histiocytes in C. (Pap stain)











Fig. 6.5: FNA of a papilloma showing the true papillary fragments with stromal cores (A) and pseudo-papillary clusters of ductal and myoepithelial cells (B-E). Immunostains for Smooth muscle heavy chain myosin (F) and p63 (G) on the cellblock sample show a myoepithelial cell layer in the papillary processes and CK5/6 stains the sheets of hyperplastic epithelium on the surface (H). The stain for estrogen receptors shows the weak, patchy variable staining pattern typical of hyperplasia (I).

B. PAPILLARY CARCINOMA

Papillary carcinoma represents 1-2% of all breast cancers and is defined histologically by the presence of a papillary growth pattern accounting for at least 90% of the tumour. Papillary Carcinoma is seen more commonly in women over the age of 40. Invasive papillary carcinoma is uncommon apart from the encapsulated papillary variant. Papillary DCIS can be graded as a low- or high-grade according to the degree of cytological atypia. A low-grade tumour is composed of columnar epithelial cells with oval nuclei showing mild atypia. A high-grade neoplasm is composed of pleomorphic malignant cells. (Fig.6.6). Clinically papillary DCIS often presents as a unilateral bloodstained discharge from a single duct in a woman >40 years of age. The nipple discharge may contain small groups and pseudo-papillary clusters of malignant glandular cells. (Fig.6.7). This cytological finding or pattern is not reliable for the specific diagnosis of papillary carcinoma because in most cases an intraductal carcinoma (NOS) is identified histologically.



Fig. 6.6. Histology of two intraductal papillary carcinomasA. Low-grade tumour showing uniform, oval and relatively bland nucleiB. High-grade tumour displaying more pleomorphic nuclei and conspicuous nucleoli (H&E stain)

Nipple discharge cytology of Papillary DCIS:

- Erythrocytes, hemosiderin-laden histiocytes (indicative of prior bleeding)
- Pseudopapillary clusters and groups of neoplastic glandular cells
- These tumour cells may show malignant features or marked nuclear atypia
- Histologic confirmation is mandatory prior to radical therapy





Fig. 6.7. A-C. Nipple discharge from an intraductal papillary carcinoma showing many pseudopapillary groups of malignant epithelial cells, numerous erythrocytes, and siderophages. Nuclear molding is present in C. (MGG stain).

FNA cytology of intraductal papillary carcinoma:

- Hypercellular aspirate showing crowded groups of epithelial tumour cells with some groups having papillary cores of stromal tissue
- Many papillary groups are "super-crowded" with "feathered" edges and some groups have a pseudopapillary globular shape
- Loss of cohesion with many dissociated epithelial cells, frequently columnar in shape and some columnar cells are arranged in rows, seen more commonly in low-grade tumour (Fig.6.8)
- Myoepithelial cells are absent or difficult to identify (Fig. 6.9)
- Mild nuclear atypia in low-grade tumours and pleomorphic malignant nuclei in high-grade tumours (Fig. 6.10)
- Foamy histiocytes and hemosiderin laden macrophages often present
- An identical pattern is seen in encapsulated papillary carcinoma (EPC) but in our experience the apocrine variant of EPC is invariably interpreted as benign on FNA cytology samples.













Fig. 6.8 FNAs from Papillary carcinoma in-situ, low-grade showing: Crowded groups of tumour cells showing loss of cohesion (A & B) and some fragments with a true papillary architecture (C&D). Note the columnar shape of many of the cells with super-crowded papillary and pseudo-papillary groups with "feathered" edges and cells in rows resembling that seen in Papanicolaou smears of a cervical adenocarcinoma in situ. (MGG stains A-I and Papanicolaou stain J).









Fig. 6.9: H&E-stained cell block from FNA of encapsulated papillary carcinoma showing papillary structures with some cribriform growth on the surface (A), crowding of hyperchromatic columnar cells (B) and dissociated cribriform fragments (C&D). There is absence of myoepithelial cells (immunostains for Heavy Chain Myosin and p63) (E&F) and strong positive immunostaining for estrogen receptors (G).



Fig.6.10. Papillary carcinoma, high-grade: The FNA shows pleomorphic malignant cells in large pseudopapillary clusters and in small groups with nuclear molding. No tumour cells with columnar configuration are observed in this cell sample. (DiffQuik)

Differential diagnosis of Papillary carcinoma:

- 1) Sclerosing papilloma (complex sclerosing lesion/radial scar)
- Papillary hyperplasia
 Fibroadenoma with pseudo-papillary structures
 Nodular hidradenoma see Fig. 6.11














Fig. 6.11: FNA of a nodular hidradenoma of the breast. Papillary clusters are seen (A&B). The epithelial cells are seen associated with metachromatic matrix material (C-E). The cells are one-cell type, uniform in size with round nuclei and abundant greenish-blue cytoplasm suggesting squamous differentiation (F & G). The cellblock shows a papillary architecture, a hyaline stroma and cells with clear cytoplasm. Immunostains for p63 (J) and CK5/6 (K) are strongly positive throughout and the stain for estrogen receptors is negative (L).

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Chapter 7

PRIMARY BREAST CARCINOMAS

Breast cancer is the most common cancer in women in the United States. About 1 in 9 women will develop breast cancer at some point in their lives. Clinical and pathological features of breast carcinoma include:

Age: The likelihood of a breast lesion being malignant increases with the age of the patient. Most invasive breast carcinomas occur in the >50 year age group but carcinoma can occur at all ages including childhood.

Sex: Although carcinoma of the breast is usually seen in females, it is occasionally encountered in males where there is an association with gynecomastia, Klinefelter's syndrome, cirrhosis of the liver and prostate cancer. Male breast cancer may be associated with the BRCA-2 hereditary syndrome.

Presentation: Today, most breast cancers are asymptomatic and are detected by routine mammographic screening. In-situ ductal carcinoma (DCIS) typically presents as abnormal calcifications. In-situ lobular carcinoma (LCIS) is usually not detectable on imaging studies but some cases are also associated with calcifications. Invasive carcinomas may be detected by the presence of abnormal clustered calcifications, architectural distortion, or mass lesions. When the mass is large enough, it may be palpated clinically. Both invasive and in-situ carcinoma can present as a bloodstained nipple discharge. Other clinical presentations include nipple inversion, excoriation of the nipple (Paget's disease), skin tethering, erythematous skin rash with or without oedema of the skin (*peau d'orange*), and skin ulceration in cases of advanced disease.

Sampling methods: DCIS may present as a bloody nipple discharge that may show malignant tumour cells. A palpable mass can be sampled by direct fine needle aspiration using one hand to fix the mass and the other to operate the needle. Non-palpable masses can be sampled with the aid of ultrasound, mammography or MRI to direct the needle to the correct target. In cases of invasive carcinoma, sampling of enlarged axillary lymph nodes can be undertaken to assess spread of the cancer to the nodes. For the investigation of abnormal calcifications in the absence of a mass, we recommend image-directed core biopsy for histological diagnosis rather than FNA cytology.

Types of breast carcinoma: Breast carcinomas may be in-situ or invasive. Most cases fall into the broad group of ductal carcinoma, which may include special sub-

types with challenging cytological features. About 20% are lobular in type and frequently pose difficulty in diagnosis. In a screened population about 25% of cancers are in-situ or non-invasive at the time of detection. Usually, invasive cancers are associated with a mass but some in-situ lesions can be palpable.

Cytological features of breast carcinomas: The cytological manifestations of breast carcinomas vary depending upon the type of sample and grade of the carcinoma. However, the FNA biopsies from most carcinomas exhibit several features in common. Typically, aspirates from breast carcinomas contain many groups of cells. The groups are crowded, show overlapping of nuclei and have irregular margins. The cells are poorly cohesive resulting in the presence of many small clusters of cells and many free lying dissociated epithelial cells that have intact cytoplasm. The cells of most carcinomas lack apocrine features, except in the rare instance of apocrine carcinoma. The cell groups lack a component of myoepithelial cells, a feature that can be shown on immunohistochemistry performed on cellblock or ThinPrep samples. The dissociated cells show atypia including displacement of the nucleus to one pole of the cell often imparting a "plasmacytoid" appearance, increased nuclear:cytoplasmic ratio, irregularity of nuclear margins, and variation in size, shape, and intensity of nuclear staining. High-grade carcinomas may be associated with necrotic material. Calcifications may be seen in the smears. In lowgrade breast carcinomas the degree of cytological atypia can be minimal and extremely subtle. Indeed, more atypia can be encountered in some benign lesions such as fibroadenomas than is seen in some low-grade carcinomas. The FNA from some low-grade carcinomas is often deceptively bland while cells from a high-grade carcinoma are clearly malignant by standard cytological criteria. Often, FNA smears from lobular carcinomas are hypocellular and the malignant cells are interspersed between groups of benign cells. The scattered small non-cohesive cells with eccentric nuclei, some containing a vacuole of mucin in the cytoplasm are the key to the recognition of this type of cancer. Some authors have advocated using image analysis and neural networks to assist with the diagnosis (Dey 2013) Invasive carcinoma cannot be separated reliably from in-situ carcinoma based on fine needle aspirates. The presence of a mass lesion, malignant cells within stromal fragments and absence of myoepithelial cells in the cellblock material favour an invasive process (Guo 2013).

Summary of cytological criteria required for a diagnosis of Carcinoma of the breast on FNA.

- 1) Hypercellular aspirate crowded groups with nuclear overlapping.
- 2) Loss of cellular cohesion dissociated epithelia cells
- 3) Absence of myoepithelial cells
- 4) Atypia of the epithelial cell component.

A. DUCTAL CARCINOMA WITH NIPPLE DISCHARGE-CYTOLOGICAL FINDINGS:

- Malignant epithelial cells singly and in clusters (Fig.7.1)
- Nuclear moulding in some tumour cell clusters
- Erythrocytes, hemosiderin-laden macrophages and necrotic debris



Fig. 7.1. Nipple discharge from a patient with Low-grade ductal carcinoma in situ showing poorly cohesive malignant epithelial cells with eccentric nuclei in a background of blood (MGG stain)

B. FNA CYTOLOGY FINDINGS:

1i) Invasive ductal carcinoma – low grade, (NOS)

- Hypercellular aspirate showing single and clustered oval cells
- Single tumour cells showing plasmacytoid configuration (Fig. 7.2)
- Oval, hyperchromatic nuclei with conspicuous or inconspicuous nucleoli
- Crowded cell groups with overlapping of nuclei and irregular outlines
- Nuclear atypia can be minimal, subtle and cells are often deceptively bland
- Absence of myoepithelial cells (the smears contain one cell type)



Fig. 7.2 A, B. Invasive ductal carcinoma – low grade, NOS showing in FNA: A hypercellular aspirate containing many dyshesive cells with fairly monomorphic nuclei displaying nuclear crowding and overlapping, irregular borders to groups, poor cohesion and absence of myoepithelial cells. (MGG stain)

1ii) High-grade ductal carcinoma, NOS

- Hypercellular aspirate showing crowded groups malignant epithelial cells with irregular borders (Fig.7.3)
- Many dissociated cells with retained cytoplasm, high nuclear:cytoplasmic ratio, markedly irregularity in nuclear contours, pleomorphic enlarged and eccentrically located nuclei with prominent nucleoli
- Stripped malignant nuclei
- Absence of myoepithelial cells











Fig. 7.3. High-grade ductal carcinomas, NOS showing in FNA: A. Crowded groups and dyshesive malignant epithelial cells

B, C. Tumour cells showing pleomorphic nuclei and prominent nucleoli. D-G An example showing only cohesive groups of highly pleomorphic ductal cells. (MGG stain)

2. Invasive Lobular Carcinoma

This tumour comprises about 20% of all invasive mammary carcinomas in women. Histologically an invasive lobular carcinoma with classic pattern is characterized by tumour infiltrating in cords of one cell thickness without evidence of duct formation. The malignant cells are small and have uniform nuclei lacking overt malignant nuclear features. The cords of cells are often arranged concentrically around preexisting benign breast ducts. Often, the tumour cells contain a single vacuole of mucin in the cytoplasm and are typically e-cadherin negative on immunostaining (Fig.7.4). Other histological variants of the tumour are rare and include alveolar, signet ring, solid, tubulolobular, histiocytoid and pleomorphic lobular carcinomas.





7.4B

Fig.7.4. Histology of lobular carcinoma, classical type. (H&E stain)

Cytological findings in lobular carcinoma, classical type:

- Needle aspirates are often hypocellular (Figs. 7.5 and 7.6)
- Scattered small non-cohesive tumour cells have eccentric nuclei
- Some cells showing intracytoplasmic vacuoles containing mucin with a central dot imparting a "targetoid" configuration
- Mildly atypical nuclei
- Admixed benign breast elements are frequently present.

Pleomorphic lobular carcinoma:

In FNA, the pleomorphic variant maintains the isolated single cell pattern and cytoplasmic vacuoles seen in classical lobular carcinoma but exhibits larger cells with more nuclear pleomorphism, prominent nucleoli and abundant cytoplasm with apocrine features.



Fig. 7.5. A,B. Lobular carcinoma showing in FNA dispersed small cells with eccentric nuclei and mucin-containing cytoplasmic vacuoles (MGG stain)



Fig. 7.6. A,B. Lobular carcinoma showing in FNA scattered single tumour cells with eccentric nuclei in a liquid-based preparation. An intracytoplasmic vacuole containing a mucinous globule is noted in some cells. (Pap stain)

3. Mucinous Carcinoma

This tumour accounts for about 2% of all breast cancers. It usually presents as a circumscribed solid mass - resembling a fibroadenoma and has abundant extracellular mucin in the stroma. Since >90% of the tumour has to demonstrate mucinous features to qualify for the term mucinous carcinoma, such a diagnosis cannot be made reliably on FNA biopsy and we prefer the term "carcinoma with mucinous features" (Fig.7.7). Mucinous carcinoma usually has low-grade nuclei and a good prognosis. Axillary node metastases are uncommon and its tumour cells are strongly positive for ER and negative for Her2-neu. The cytological features of one case mucinous cystadenocarcinoma of the breast has been described but the cytomorphology is not separable from usual mucinous carcinoma (Sentani 2012).





Fig. 7.7. Histology of mucinous carcinoma: A. Tumour with less cellularity and abundant mucus

B. Tumour with more cellularity (H&E stain)

Cytological findings:

- Pools of mucinous material showing cohesive groups of tumour cells with low-grade nuclei, often arranged in ball-like clusters (Figs. 7.8-7.11)
- Focal loss of cohesion occurs in most cases
- The mucin is typically blue on Giemsa stain whereas the mucin found in myxoid fibroadenoma is metachromatic
- Occasionally calcifications are seen



Fig. 7.8. Mucinous carcinoma showing in FNA thick mucous material and tridimensional clusters of tumour cells (Pap stain)





Fig. 7.9. A,B: Mucinous carcinoma showing in FNA thick mucous material and rare tri-dimensional clusters of tumour cells (MGG stain)





Fig. 7.10. A,B: Mucinous carcinoma showing in FNA thick mucus, cohesive, 3dimensional ball-like clusters and loose groups of malignant epithelial cells and a few psammoma bodies. (Pap stain)









Fig 7.11 A-F: A 69 year-old woman presented with a palpable breast mass. Ultrasound examination showed a multilobulated rounded mass. FNA shows cohesive aggregates of mildly atypical ductal cells lying within pools of mucin. Immunostaining of the SurePath slides shows staining of all nuclei for estrogen receptors and positive staining for synaptophysin confirming a mucinous carcinoma of endocrine type (Case contributed by Dr. Koen van de Vijver, NKI, Amsterdam).

4. Adenoid Cystic Carcinoma (ACC)

This is a low-grade epithelial-myoepithelial cancer of the breast resembling its counterpart in salivary glands. The tumour is rare and accounts for <1% of all breast cancers. It is a slow-growing neoplasm - often clinically circumscribed and late lung and other distant metastases may occur. It has a very low incidence of axillary lymph node metastases. Histologically, the tumour consists of 3 histologic patterns: cribriform, tubular and solid. The cribriform pattern is most common. ACC is characterized by basaloid cells with little cytoplasm forming solid sheets and sieve-like aggregates of cells with tubular differentiation. Basophilic and slightly eosinophilic material within cell masses is present. Mucinous, squamous and sebaceous differentiation can be seen and high-grade variants occur. (Fig.7.12). In contrast to most low-grade ductal carcinomas, the tumour cells are either ER/PR weakly positive or negative. It has a characteristic MYB-NFIB translocation.



Fig. 7.12. Histology of adenoid cystic carcinoma, cribriform subtype. (H&E stain)

Cytological findings in adenoid cystic carcinoma:

- Cellular aspirate showing crowded groups of small cancer/basaloid cells with scanty cytoplasm forming characteristic spherical globules of matrix material – metachromatic on Giemsa stain (Figs. 7.13).
- Poor cellular cohesion
- Nucleoli usually present





7.13C

Fig. 7. 13. (A+B) Adenoid cystic carcinoma, cribriform subtype showing in FNA crowded poorly cohesive groups of small cancer cells with scanty cytoplasm and globular masses of metachromatic material

C. A small mass of tumour cells showing metachromatic globular core (MGG stain)

5. Tubular Carcinoma

The tumour accounts for <5% of all breast cancers and it has a stellate configuration on mammogram.

Histologically the tumour has an infiltrative pattern on scanning power and consists of crowded tubules with open lumens and pointed ends making >90% tubular structures. The tubules are lined by columnar cells with low-grade nuclei, maintained polarity and scanty mitoses. No myoepithelial layer is present. (Fig. 7.14)



Fig. 7.14. Histology of tubular carcinoma (H&E stain)

Cytological findings:

- Cellular aspirate showing cohesive tumour cell groups with many having long tubular formations (Fig. 7. 15)
- Clustered and dissociated uniform small tumour cells with scant cytoplasm and low-grade nuclei
- Rare stripped "naked" nuclei are present
- Myoepithelial cells and club-shaped stromal fragments are absent





Fig. 7.15. Tubular carcinoma showing in FNA: A. Many cohesive groups of uniform evenly spaced ductal epithelial cells and no myoepithelial cells

B, C. Tumour cells forming long tubular and tortuous structures (MGG stain)

6. Low-grade Neuroendocrine Carcinoma

This is a rare tumour occurring mainly in elderly patients >60 years of age. It often presents in the in-situ phase with a bloodstained nipple discharge and it has a good prognosis if it has a low grade by Nottingham. The solid papillary variant of this tumour shows a solid growth pattern with tumour nests containing subtle remnants of stromal papillary cores. The nodules have "pushing" borders. The tumour cell nuclei are low grade, uniform, round, oval or spindle-shaped and contain small nucleoli. The cytoplasm is granular and strongly eosinophilic and reacts positively with neuroendocrine antibodies. (Fig. 7.16)





7.16C

Fig. 7.16. Histology of low-grade neuroendocrine carcinoma of solid papillary type showing solid masses of tumour cells with low-grade nuclei and eosinophilic cytoplasm that stains positively with chromogranin antibody. (A, B: H&E stain; C: Synaptophysin).

Cytological findings: (Kawanishi 2011)

- Many crowded groups of malignant epithelial cells with loss of cohesion of eccentric low-grade nuclei (Fig. 7.17)
- Metachromatic granules may be prominent in the tumour cell cytoplasm
- Some tumour cell clusters have a true papillary architecture with stromal cores
- Myoepithelial cells difficult to identify and mucin may be present in the smear background



Fig. 7.17. Low-grade neuroendocrine carcinoma showing in FNA dissociated lowgrade tumour cells with intracytoplasmic metachromatic granules (MGG stain).

7. Medullary Carcinoma

This is a relatively uncommon variant of ductal carcinoma, accounting for 5-7% of all breast cancers. Its diagnostic criteria are subjective and have been shown to be poorly reproducible even amongst expert breast pathologists. Recent gene expression analysis showed that medullary carcinoma has the molecular profile of a high-grade invasive ductal carcinoma, falling into the molecular basal-type group. There is an association with the BCRA1 genotype.

Histologically it has a well-circumscribed "pushing" margin with a dense continuous cuff of lymphocytes and plasma cells. The neoplasm has a syncytial sheet-like growth pattern (>75%) with grade 3 nuclei, ill-defined cytoplasm and minimal fibrosis within the lesion. (Fig. 7.18). It is typically ER/PR negative, Her2-neu negative, has a high Mib-1 index and is p53 strongly positive.




7.18B

Fig. 7.18. Histology of medullary carcinoma showing well circumscribed margin, syncytial arrangement of highly atypical ductal cells and dense cuff of lymphocytes, histiocytes and plasma cells. (H&E stain)

Cytological findings:

- Hypercellular aspirate (Fig. 7.19)
- Dyshesive malignant cells with high-grade nuclei admixed with many lymphocytes and some plasma cells
- Apart from the tendency for cell clusters to be more cohesive, it is difficult to differentiate between medullary carcinoma and lymphoepithelioma-like carcinoma of the breast on cytological findings (Trihia 2012).
- In our opinion, a specific diagnosis of medullary carcinoma is not possible on cytology and these cases are best diagnosed as malignant with a comment that "grade 3 nuclei and numerous lymphocytes are present suggesting a medullary-like carcinoma". In fact, studies of FNA of basaltype carcinoma describe many cytological features identical to those of medullary carcinoma (Akashi 2013).



Fig. 7.19. Medullary carcinoma showing in FNA poorly cohesive and dispersed malignant cells with scant cytoplasm, pleomorphic nuclei and scattered lymphocytes, histiocytes and plasma cells (Pap stain)

8. Secretory Carcinoma

This tumour occurs most commonly in prepubescent children but it may occur in adult females and in males. Clinically it often presents as a slow growing, occasionally large circumscribed ball-like or multilobulated mass. The tumour is composed of cells with typically low-grade nuclei, dense, vacuolated cytoplasm. Necrosis is unusual and mitoses are rarely observed. (Fig.7.20). It may have a considerable in-situ component and it is ER negative in >60% cases. Nodal metastases occur but distant metastases unusual. It has a good prognosis but may recur late. An abnormal gene fusion ETV6-NTRK3 has been described in secretory carcinoma but it has been found as a sporadic abnormality in a small percentage of ductal carcinoma NOS.



Fig. 7.20. Histology of a secretory carcinoma of the breast. (H&E stain)

Cytological findings:

- Hypercellular aspirate. (Fig. 7.21)
- Single and loosely cohesive clustered malignant cells with foamy cytoplasm.
- Slightly pleomorphic nuclei with conspicuous nucleoli.
- Distinction from metastatic clear-cell carcinoma of kidney, lipid-rich and glycogen-rich carcinomas of breast is not possible based on the cytomorphology alone.

• This neoplasm has a specific translocation ETV-6/NKTR3 that can be identified on FISH analysis in FNA material.



Fig. 7.21. Secretory carcinoma of the breast showing in FNA: A. Abundant polygonal epithelial cells singly and in clusters B. A cluster of tumour cells showing vacuolated cytoplasm and monomorphic oval nuclei with inconspicuous nucleoli (DiffQuik stain).

9. Apocrine Carcinoma

This is a rare variant of ductal carcinoma accounting for less than 1% of all breast cancers. FNA yields a cellular aspirate showing a marked loss of cellular cohesion. The tumour cells are seen predominantly in cohesive clusters and show abundant vacuolated or dense cytoplasm, large nuclei and strikingly prominent macronucleoli. Nuclear pleomorphism is typically marked except in low-grade apocrine carcinoma, which is almost impossible to diagnose with confidence on FNA.

It is important to note that some benign lesions such as intraductal papilloma, sclerosing papilloma, atypical apocrine adenosis and reactive changes in apocrine cysts can show marked atypia of apocrine cells. Therefore, the diagnosis of apocrine carcinoma by FNA should be made with extreme caution and a core needle biopsy may be needed for histological assessment.

Cytological findings:

- Cellular aspirate (Fig. 7.22)
- Large polygonal tumour cells with granular cytoplasm present singly and in loose clusters
- Striking loss of cohesion contrasting with the sheet-like pattern encountered in most benign apocrine lesions.
- Eccentrically located high-grade nuclei with conspicuous macronucleoli



7.22A



7.22B

Fig. 7.22. A,B: Apocrine carcinoma showing in FNA loose aggregates of large apocrine cells with eccentric oval nuclei with conspicuous nucleoli. (MGG stain)

10. Cribriform Carcinoma

This is an invasive carcinoma growing as sheets of cells with a sieve-like arrangement and tubular formations. Cribriform ductal carcinoma in situ and focal calcification is commonly present. The tumour cells are relatively monomorphic with granular cytoplasm and low-grade nuclei. (Fig.7.23)



Fig. 7.23. Histology of cribriform carcinoma (H&E stain)

The tumour shows in FNA cytological features similar to those of a low-grade ductal carcinoma of non-specified type. Some authors have described a cribriform architecture in the cytology preparations but in our experience such a pattern is rarely encountered.

- Loosely clustered monomorphic tumour cells with mild nuclear atypia
- Rare stripped "naked" nuclei (Fig. 7.24)
- Absence of myoepithelial cells



Fig. 7.24. A,B: Cribriform carcinoma showing in FNA poorly cohesive groups of monomorphic epithelial cells with slightly atypical nuclei. No myoepithelial cells are noted. (MGG stain)

11. Carcinoma with Osteoclastic Giant Cells

This is a rare morphologic variant of ductal carcinoma of the breast. It usually presents clinically as a circumscribed brown or haemorrhagic mass lesion. Histologically, it displays features of a low-grade ductal carcinoma, most often with a cribriform pattern. The stroma is cellular and shows extravasated erythrocytes, abundant lymphocytes, histiocytes, plasma cells, hemosiderin pigment granules and many osteoclast-like giant cells – often hugging the clusters of carcinoma cells. (Fig. 7.25)





7.25 B

Fig. 7.25. A,B: Histology of carcinoma with osteoclastic giant cells: Cribriform carcinoma with hypercellular stroma containing osteoclastic giant cells, extravasated erythrocytes and hemosiderin pigment granules. (H&E stain)

Cytological findings:

- Cytological findings of a low-grade ductal carcinoma
- Many osteoclast-like giant cells (Fig. 7.26)
- Scattered lymphocytes and hemosiderin-laden macrophages



Fig. 7.26. A, B. Carcinoma with osteoclastic giant cells showing in FNA poorly cohesive clusters of polygonal tumour cells admixed with osteoclast-like giant cells and hemosiderin laden macrophages. (MGG stain)

12. Pleomorphic Carcinoma

This is a rare variant of high-grade ductal carcinoma, NOS characterized by a proliferation of pleomorphic and bizarre giant cells comprising > 50% of the tumour cells in a background of adenocarcinoma with spindle or squamous differentiation (Fig. 7.27). Patients with this tumour have a median age of 51 years, and in 12% of cases metastasis is present at initial clinical presentations.



Fig. 7.27. Histology of pleomorphic carcinoma (H&E stain)

The tumour shows in FNA single and clustered malignant pleomorphic giant cells with many displaying multiple nuclei. (Fig. 7.28)





Fig. 7.28. Pleomorphic carcinoma of the breast showing in FNA bizarre tumour giant cells with some cells showing multiple nuclei. (A, B: MGG stain; C, D: H&E stain)

13. Metaplastic Carcinoma

Metaplastic carcinoma accounts for less than 5% of all breast cancers. It is a ductal carcinoma with extensive mesenchymal or squamous differentiation. Metaplastic carcinoma can be classified as low-grade or high-grade. The wide range in the histomorphological spectrum of metaplastic carcinomas is reflected in their cytological features. High-grade sarcomatoid metaplastic carcinomas can be mistaken for sarcomas.

13.1. Low-grade metaplastic carcinoma is rarely encountered in cytopathology and is seen most often in women aged >60 years (Figs. 7.29 and 7.30). It has a nodular pattern with irregular margins on low power view. The tumour may extend around adjacent benign ducts and entrapped ducts within the lesion may show focal carcinoma in situ. The spindle cells may display mild cytological atypia and scanty mitoses. A component of low-grade invasive squamous carcinoma or complex sclerosing lesion may be seen. It often shows myoepithelial features by immunohistochemistry. The tumour is prone to local recurrence and axillary nodal metastasis is uncommon. Some cases are composed entirely of low-grade spindle cells and resemble nodular fasciitis or a fibromatosis. Others show squamous differentiation.

FNA often shows a hypercellular aspirate reflecting the presence of an underlying complex sclerosing lesion or sclerosing papilloma. Some cases of LGAS yield a hypocellular aspirate. In either case, scanty atypical squamous cells and/or spindle cells and elongated tubular structures representing eccrine-type ducts are also present. These may be difficult to detect in the smears (Fig 7.31). A firm diagnosis of the tumour is made by histologic examination of tumour tissue sampled by core needle biopsy.





Fig. 7.29. Histology of low-grade metaplastic carcinoma
A, B: Spindle cell component showing minimal cytological atypia.
C. Epithelial cells with spindle configuration showing positive reaction with pan cytokeratin antibody
(A&B: H&E stain; C: Immunostain for pankeratin)



Fig. 7.30. A, B: Histology of low-grade adenosquamous carcinoma (H&E stain)







Fig. 7.31: Low-grade adenosquamous carcinoma associated with a sclerosing papilloma. A: Benign papillary fragments. B: Long tubules of eccrine-type ducts, C-F: Atypical squamous cells with spindled shapes. MGG stain.

13.*ii.* A high-grade metaplastic carcinoma or mixed epithelial/mesenchymal metaplastic carcinoma consists of a wide variety of tumour. Some are matrix producing carcinomas or carcinosarcomas. The heterologous epithelial elements are most commonly squamous in type (Fig 32). The heterologous mesenchymal elements range from bland chondroid and osseous differentiation to frank sarcoma (chondrosarcoma, osteogenic sarcoma, rhabdomyosarcoma, leiomyosarcoma, liposarcoma). When the mesenchymal component is malignant the designation of carcinosarcoma is used. A high-grade metaplastic carcinoma with chondroid matrix displays in FNA clusters of malignant cells and irregular fragments of metachromatic chondroid material that are easily visualized by MGG stain. (Figs. 7.33 & 7.34). A metaplastic carcinoma with leiomyosarcomatous component may yield in needle aspirates malignant glandular cells and abundant spindle cells with elongated or oval nuclei, similar to those of a low-grade fibrosarcoma or leiomyosarcoma. (Fig. 7.35).







7.32C



Fig 7.32. A 35 year-old woman presented with a 4 month history of an enlarging breast mass in the 11 o'clock position of the breast. Ultrasound examination showed a mass with mixed cystic and solid components. FNA showed poorly cohesive crowded groups of atypical squamous cells and atypical spindle cells associated with necrotic debris. Tissue biopsy confirmed a high grade metaplastic carcinoma with squamous differentiation. (Case contributed by Dr. Koen van de Viyver, NKI Amsterdam)









7.33H

Fig 7.33: FNA of a High-grade metaplastic carcinoma with a chondrosarcomatous component. Poorly cohesive malignant ductal cells are seen in a background of myxochondroid matrix seen best as metachromatic material with the MGG stain A-E and grayish lobulated material with the Papanicolaou stain F-H.



Fig. 7.34. Metaplastic breast carcinoma with chondroid matrix showing in FNA single and clustered tumour cells with high-grade nuclei, prominent nucleoli and fragments of metachromatic chondroid material. (MGG stain)



Fig. 7.35. A carcinosarcoma with leiomyosarcomatous component showing in FNA abundant isolated spindle malignant smooth muscle cells with elongated, blunt-end nuclei, in addition to malignant glandular cells. (Pap stain)

14. Paget's disease of the Nipple

It is defined by the presence of malignant glandular cells within the squamous epithelium of the nipple. It is almost always associated with an intraductal carcinoma, usually involving more than one lactiferous duct with or without infiltration of the breast. Paget disease of the nipple without an underlying ductal carcinoma is very rare. Scrapping from the nipple usually reveals malignant glandular cells admixed with inflammatory exudates (Fig. 7.34). Reactive squamous cells associated with the lesion may cause diagnostic confusion with squamous carcinoma of the skin (Vohra 2012).









Fig. 7.34. Paget's disease in a 57 year-old woman – nipple scrape smear showing atypical squamous cells in a background of acute inflammation (A-D) and globular clusters of malignant glandular cells (E-G).

15. Syringomatous Adenoma of the Nipple

This rare tumour is confined to the stroma of the nipple and it shows overlapping histologic features with those of a low-grade adenosquamous carcinoma. Small tubules resembling eccrine ducts with teardrop shaped configuration, solid cord of tumour cells, islands of well-differentiated squamous epithelium and marked desmoplastic reaction are observed. Cysts containing keratin – sometimes associated with calcifications are present. The tumour cells display mild nuclear atypia. (Fig. 7.34). If the tumour is cytologically low-grade and confined to nipple stroma, it will behave in a benign fashion. Rarely the tumour metastasizes to axillary lymph nodes – usually after repeated local recurrences due to inadequate excision. The tumour FNA is usually scanty in cellularity and shows a small number of mildly atypical squamous cells. Biopsy of the tumour for histologic confirmation is needed for final diagnosis.



Fig. 7.34. Histology of syringomatous adenoma of the nipple (H&E)
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Chapter 8

OTHER NEOPLASMS

A. BENIGN NEOPLASMS

1. Adenomyoepithelioma

This is a very rare tumour occurring most commonly in adult women. The neoplasm appears as a solitary breast mass that is well circumscribed, usually multilobulated and incompletely surrounded by a thin fibrous capsule. It consists of nests of proliferated myoepithelial cells around tubular glandular structures that can be inconspicuous. (Fig. 8.1). The neoplastic cells have a variable, ill-defined or clear cytoplasm and round or oval nuclei, and the nests of tumour cells are separated from each other by a variable amount of matrix consisting of amorphous, fibrillary material that stains positively with periodic acid-Schiff with and without prior diastase digestion. The cytoplasm of the myoepithelial component expresses S-100 protein, high molecular weight keratins (CK5/6,CK14) and is variably positive with immunostains for CD10, smooth muscle actin, calponin and smooth muscle heavy chain myosin. The nuclei of these cells stain for p63. In contrast, the luminal cells stain for low molecular keratins CK7, CK8, CK18 and Cam 5.2.Focal squamous and sebaceous metaplasia are frequently encountered in the luminal component.

An adenomyoepithelioma with inconspicuous glandular spaces or tubular structures and abundant matrix yields in FNA irregular and tight bundles of spindle myoepithelial cells arranged in 3-dimensional, lobulated clusters with strong cellular cohesiveness. Scattered bipolar, naked nuclei of myoepithelial cells and myoepithelial cells with ill-defined, granular cytoplasm are present in the smear background (Fig. 8.2). Intranuclear inclusions may be encountered (Saad 2014).



8.1B

Fig. 8.1 A,B: Histology of breast adenomyoepithelioma: nests of tumour cells with clear or granular cytoplasm and round or spindle nuclei surrounded by large amount of amorphous basement membrane-like material. The glandular spaces and tubular structures are inconspicuous or vague in this case. (H&E stain)





Fig. 8.2. Adenomyoepithelioma with inconspicuous tubular structures showing in FNA:

A. Irregular, thick, 3-dimensional clusters of myoepithelial cells with lobulated configuration and strong cellular cohesiveness

B. Cluster of spindle tumour cells with granular or fibrillary cytoplasm and round or oval monomorphic nuclei

C. Scattered myoepithelial cells and their naked nuclei (Pap stain)

Fig. 8.2B is reproduced with permission from "Nguyen et al. Aspiration biopsy

cytology of mammary myoepithelioma. Diagn Cytopathology. 1987;3:335-338".

A mammary **adenomyoepithelioma** with more obvious glandular spaces or tubular variant yields in FNA globular masses of amorphous, granular, basement membrane-like material containing cellular cores consisting of small cells with dark nuclei and scant cytoplasm. Small aggregates of tumour cells without surrounding amorphous granular material are also seen. (Figs. 8.3 and 8.4). This interesting cytological pattern/finding in FNA of adenomyoepithelioma resembles to some extent that of an adenoid cystic carcinoma. The key difference is that the cellular aggregates or cores are located within the globular masses of granular material in the former and outside of these globular structures in the latter. Furthermore, the luminal cell component is more prominent than in ACC, the cells have more cytoplasm and show cohesion in contrast to the small poorly cohesive cytoplasmpoor cells of ACC. A core needle biopsy of the lesion is necessary for further confirmation.





Fig. 8.3. Histology of adenomyoepitheliomas showing myoepithelial cells forming glandular spaces surrounded by a thick basement membrane (A&B), sebaceous metaplasia (C).and Clear cytoplasm (D) (H&E stain)





8.4C A:

Fig. 8.4. Adenomyoepithelioma, tubular variant showing in FNA: A, B. Globular structures of amorphous, granular, basement membrane-like material with cellular cores

C. An aggregate of tumour cells with scant cytoplasm located adjacent to a globular structure (MGG stain)

Malignant adenomyoepithelioma may occur de novo or as a high-grade transformation of a low-grade AME. The malignant component often resembles metaplastic carcinoma and frequently shows heterologous differentiation to form cartilage, bone and spindle-shaped squamous cells. The myoepithelial component is prominent and atypical with crowding and overlapping of nuclei, and loss of cohesion. A metachromatic matrix is often seen that is often the clue to the diagnosis (Fig. 8.5).



Fig 8.5. Malignant adenomyoepithelioma showing atypical myoepithelial cells clustered around central metachromatic matrix material. On histological examination. other areas showed sarcomatoid metaplastic carcinoma.

2. Myofibroblastoma

This is a rare and benign mesenchymal tumour occurring predominantly in adult males and females in their seventh decades of life. It is the most common stromal neoplasm of the male breast. Myofibroblastoma is subdivided into 6 histologic subtypes: classic, fibrous, epithelioid, cellular, myxomatous and infiltrative variants. The fibrous variant is characterized by intersecting bundles of slender, bipolar and uniform tumour cells separated by a variable amount of hyalinized collagen, often with a wire-like appearance. A more epithelioid cell population may be present focally. The tumour cell cytoplasm stains negatively with S-100 protein, pancytokeratin and positively with vimentin, desmin, BCL-2 and CD34 antibodies. (Fig. 8.6). Myofibroblastoma, fibrous type yields in FNA abundant randomly arranged monomorphic benign spindle cells with oval or spindle nuclei with finely granular chromatin and no nucleoli. (Fig. 8.7). A myofibroblastoma, epithelioid type displays in FNA single and loosely cohesive clustered oval tumour cells with granular cytoplasm and oval, bland nuclei. Nuclear pleomorphism and binucleation can be seen. Nuclear grooves and intranuclear pseudo-inclusions are helpful diagnostic clues (Alvarez-Rodriguez 2012; Landeyro 2012). These tumour cells display the above-mentioned immunocytochemical features.



Fig. 8.6. Histology of myofibroblastoma, fibrous type (H&E stain)



Fig. 8.7. Myofibroblastoma, fibrous type showing in FNA randomly arranged single, benign spindle fibroblastic cells with scant cytoplasm and bland, elongated or oval nuclei with inconspicuous nucleoli (Pap stain)

3. Pseudoangiomatous stromal hyperplasia (PASH)

PASH is a benign proliferative lesion of the specialized periductal and lobular stromal cells that may present as palpable masses or as irregular mass lesions identified on imaging studies. It is most commonly diagnosed on histological examination of core biopsies or excision specimens. The lesion is characterized by a nodular circumferential stromal proliferation surrounding medium-sized ducts. The spindleshaped stromal cells are arranged in linear chords often simulating a vascular proliferation. They have bland oval and elongated nuclei and pale cytoplasm. They exhibit positive immunostaining for CD34 but not other vascular markers (Fli-1, CD31). Our experience with the fine needle aspiration cytology of PASH is that all cases were interpreted as other benign disorders including fibroadenoma, and fibrocystic changes. The study by Vicandi et al. (1998) showed many overlapping features with fibroadenoma including moderate cellularity, a predominance of medium-sized and small groups of ductal cells, stripped oval and spindle-shaped nuclei and stromal fragments. Most cases were interpreted as fibroadenoma. The cytological findings were deemed to be non-specific by Aron et al. (2005). The smears show cohesive sheets of uniform benign ductal cells with interspersed myoepithelial cells, dissociated stripped myoepithelial nuclei and irregular stromal fragments that are metachromatic on the Giemsa stain. The stromal fragments lack

the club shape seen in fibroadenoma. They resemble the stromal fragments seen in gynecomastia (Fig 8.8).







Fig 8.8. FNA of a case of Pseudoangiomatous hyperplasia (PASH) showing cohesive sheets of benign ductal and myoepithelial cells and irregular fragments of metachromatic stroma containing a few bland spindle shaped nuclei (Giemsa stain).













8.9K

Fig 8.9 FNA cytology of cases of PASH showing cohesive groups of benign ductal and myoepithelial cells, dissociated myoepithelial stripped nuclei (A-D), fragments resembling fibroadenoma (E) and benign epithelial cells adjacent to irregular fragments of metachromatic stroma (F-H) with corresponding histology (I-K).

4. Benign Nerve Sheath Tumours

Schwannoma, neurofibroma and perineurioma rarely arise in the breast. Schwannoma may show cystic change mimicking an epithelial cyst on imaging. FNA of the lesion may cause radiated pain. Aspirated tumour cells may occur in bundles with buckled nuclei having pointed ends arranged in palisades, similar to those seen in tissue sections. Metachromatic matrix material is often present associated with the spindle cells is best seen in the Giemsa preparation. A single case of schwannoma with extensive cystic change in our files showed in FNA single and clustered benign spindle cells with scant cytoplasm and foamy histiocytes. (Figs. 8.10 and 8.11). The cells are strongly positive for S-100 protein. Histological confirmation is required to exclude the spindle cell variant of melanoma.



Fig. 8.10. A, B. Histology of a schwannoma of the breast with extensive cystic change. Spindle tumour cells exfoliating in cystic cavity is seen in B. (H&E stain)



Fig. 8.11. FNA of schwannoma showing foamy histiocytes, single and clustered benign spindle cells with elongated, slender nuclei and scant, ill-defined cytoplasm. (Pap stain)

5. Granular Cell Tumour

The tumour is thought to be of Schwann cell origin and rarely arises in the breast. It occurs more commonly in females than in men with a wide age range from 17 to 75 years. The neoplasm may mimic a breast cancer clinically, radiologically and grossly. Histologically, it is composed of cells with ill-defined, granular cytoplasm and oval, bland nuclei (Fig. 8.12). The granular cytoplasm is due to the presence of numerous intracytoplasmic lysosomes. The tumour cell cytoplasm reacts positively with periodic acid Schiff with prior diastase digestion and S-100 protein antibody.

A few cases of mammary granular cell tumour with cytological evaluation by FNA have recently been reported. The aspirated tumour cells have a granular, ill-defined cytoplasm and bland, oval nuclei. They are seen in sheets and clusters, and are indistinguishable from histiocytes with granular cell metaplasia. As both types of cells express CD68 (KP1), a lysosomal marker, but histiocytes are usually negative for S-100 protein which can suggest the diagnosis of granular cell tumour if cell block material is available for immunostaining. Cells from breast carcinoma may also be positive for S-100 protein but they co-express keratin unlike the cells of GCT. However, core biopsy of the lesion is needed for histologic confirmation. The single case we have encountered on FNA cytology yielded crowded poorly cohesive clusters of polygonal cells that were erroneously interpreted as being of epithelial origin and was diagnosed as being suspicious for malignancy (Fig. 8.13).





8.12B

Fig. 8.12: Histology of a Granular cell tumour showing the oval aggregates of cells (A) that have abundant eosinophilic granular cytoplasm and bland nuclei (B). (H&E stain)





Fig 8.13A-C: A 45 year old woman followed up for invasive ductal carcinoma of the right breast developed an irregular mass in the left breast sampled by FNA. Irregular poorly cohesive clusters of polygonal epithelioid cells with nuclear overlapping. Irregular nuclear outlines and variation in size and shape of nuclei were noted. The smear was interpreted as "suspicious" for malignancy. Subsequent excision showed a benign granular cell tumour. (MGG stain)

6. Tubular adenoma

Tubular adenoma is a benign fibroepithelial lesion closely related to fibroadenoma. It presents as a palpable breast mass or a circumscribed smooth-bordered, solid nodule on imaging studies. On histological examination, it has a well-circumscribed border. The epithelial cells predominate over the stroma and are arranged in structures resembling branching terminal ducts or as lobular units. There is a dual epithelial-myoepithelial cell layer around the tubules. Occasionally, the myoepithelial cells may be prominent and may have clear cytoplasm simulating the tubular variant of adenomyoepithelioma. The stroma is loose and edematous and lacks hypercellularity or atypia.

An FNA biopsy shows stromal, tubular and myoepithelial components. In contrast to fibroadenoma, the stromal fragments are not club-shaped. Many of the ductal epithelial elements are arranged to form long cohesive tubular structures similar to those encountered in FNA's from tubular carcinoma (Fig. 8.14). In contrast to tubular carcinoma there is no loss of cohesion of the epithelial cells and myoepithelial cells are seen attached to the clusters and also as free-lying stripped oval nuclei. However, distinction from tubular carcinoma is also based on the imaging features.









8.14H








Fig. 8.14. Tubular adenoma: 49F with "benign" mass on imaging - FNA showing stromal, epithelial and myoepithelial elements (A, B, C), myoepithelial nuclei sticking to the edge of the stromal fragments (D) and cohesive groups of small uniform

ductal cells with interesting shapes including tubules, branching tubules, and small sheets with evenly spaced nuclei (E-J). Interspersed stripped nuclei of myoepithelial cells are also evident. Tubules and stromal fragments containing ducts and myoepithelial cells are present in the cellblock preparation (K-M). A core biopsy confirms features of tubular adenoma (N-P).

7. Other Benign Tumours and reactive lesions.

Other benign neoplasms of the breast such as **lipoma**, **vascular tumours** and **hamartoma** may be targets of FNA. The benign cytological findings in these cases should be interpreted in conjunction with clinical and diagnostic imaging findings (Triple test) to avoid possible diagnostic errors. FNA may also be useful in the diagnosis of inflammatory lesions such as tuberculosis, filariasis, schistosomiasis, and myospherulosis.

B. MALIGNANT NON-EPITHELIAL NEOPLASMS

All types of soft tissue sarcoma may arise in the breast and the most common one is angiosarcoma. Other types of soft tissue sarcoma are extremely rare. Correlation with the clinical history and imaging findings is essential and when only smear preparations are available, distinction from metaplastic carcinoma and malignant phyllodes tumour is not possible.

1. Angiosarcoma

Angiosarcoma of the breast is a rare neoplasm accounting for less than 1% of all breast cancers. The tumour occurs most commonly in adult women in the 6th and 7th decades of life but primary angiosarcoma of the breast is occasionally seen in younger patients. Risk factors for secondary angiosarcoma include chronic lymphedema and a prior history of radiotherapy for breast cancer. Angiosarcoma presents clinically as one or more irregular ill-defined ecchymotic masses. Histological features include irregular vascular spaces lined by crowded atypical neoplastic endothelial cells (Fig. 8.15) together with a variable component of solid areas. The degree of nuclear atypia varies from mild to extreme but the prognosis is poor regardless of the degree of atypia or the architectural picture. Clinical and imaging correlation is key in its distinction from benign vascular lesions that tend to be small and well circumscribed.

FNA biopsy of angiosarcoma yields in a large amount of blood containing poorly cohesive groups of spindle cells and polygonal cells with atypia ranging from mild to marked. The solid areas yield pleomorphic nuclei and tumour giant cells. Hemosiderin-laden histiocytes are also commonly seen. Some cells have cytoplasmic vacuoles. Nucleoli are prominent in some of the cells, especially the polygonal cell population. The cytological features vary depending upon the grade of the area of the lesion that is sampled (Figs. 8.16). Where cellblock material is available, confirmatory immunohistochemical staining for endothelial antigens listed below is essential in differentiating the lesion from metaplastic carcinoma or malignant phyllodes tumor. The tumour cells express CD31, Fli-1, ERG, CD34 and Factor VIII-related antigen on immunostaining. Angiosarcoma following radiation to the breast or secondary to chronic lymphedema usually shows amplification of c-MYC gene that can be demonstrated by immunostaining for keratin and result in an erroneous diagnosis of carcinoma.





Fig. 8.15. Histology of mammary high-grade angiosarcoma. (H&E stain)



Fig. 8.16. A and B. High-grade mammary angiosarcoma showing in FNA loosely cohesive clusters of pleomorphic malignant spindle cells with focal ill-defined acinar arrangement. (Pap stain)





8.16F

Fig. 8.16. C-F. High-grade mammary angiosarcoma showing in FNA cohesive clusters of pleomorphic malignant spindle cells with a trabecular arrangement (MGG stain)

2. Osteogenic Sarcoma

Primary osteogenic sarcoma of the breast is a very rare neoplasm. A few cases with cytological examination by FNA have been reported. Exclusion of metaplastic carcinoma and malignant phyllodes tumour with osteosarcomatous features is not possible by cytology alone and requires a thorough histological examination. In the majority of cases the FNA reveals a variable number of malignant spindle cells present singly and in loose aggregates. Rarely irregular fragments of eosinophilic and granular material representing osteoid fragments are identified. These are best seen in cellblock fragments (Figs. 8.17 and 8.18)



Fig.8.17. Histology of breast osteogenic sarcoma (H&E stain)





Fig. 8.18. Breast osteogenic sarcoma showing in FNA:A, B. A loose aggregate of malignant spindle cells with scant cytoplasmC. Osteoid with a few attached spindle tumour cellsD. A benign multinucleated osteoclast-like giant cell(Pap stain)

3. Lymphoma

Any type of lymphoma may occur in the breast involving either the breast parenchyma directly or indirectly through spread from an intra-mammary lymph node. Non-Hodgkin's lymphomas are more common than Hodgkin's lymphoma (Park 2010; Arora 2013) and Burkitt's lymphoma is seen especially in endemic areas. In our practice B-cell lymphomas outnumber T-cell lymphomas by far. Most breast lymphomas fall into the following categories:

- Small lymphocytic lymphoma/Chronic lymphocytic leukaemia (Fig 8.19)
- Extranodal marginal zone lymphoma (Maltoma)
- Follicular lymphoma
- Diffuse large B-cell lymphoma
- Anaplastic large cell lymphoma (T-cell) associated with breast prosthesis (Fig 8.20).

FNA of breast non-Hodgkin's lymphoma is usually cellular and reveals some common cytological features listed below. Flow cytometry is helpful to show monoclonality and provides lymphocyte subtyping. Tissue biopsy is usually required for confirmation of the tumour and its subtype.

FNA cytology:

- Abundant monotonous atypical lymphoid cells showing no cellular cohesion typifies the low-grade B-cell lymphomas.
- A mixed population of small and large atypical lymphoid cells is seen in the higher-grade lymphomas of follicle centre cell type.
- Distinction between follicular and diffuse growth patterns cannot be assessed on FNA cytology.
- Nuclear indentation and protrusion may be present especially in diffuse large B-cell lymphoma
- Lymphoglandular bodies may be seen





Fig. 8.19. A-C: FNA of a small lymphocytic lymphoma showing numerous monotonous small lymphocytes with round and uniform nuclei. Nuclear indentation and protrusion are noted in some cells. (MGG stain)

The prosthesis-associated anaplastic T-cell lymphoma has a distinct clinical presentation as a cystic mass surrounding or adjacent to a breast prosthesis that is most often of silicone type. The aspirate yields non-cohesive highly pleomorphic cells which may not be recognised as lymphoid (Fig. 8.20). The cells have irregular often polylobated nuclei containing prominent nucleoli and have abundant dense cytoplasm imparting a histiocytoid appearance. The typical "hallmark" cells contain polylobated nuclei with a horseshoe shape. Mitoses are numerous and a background of necrosis is common. Knowledge of the entity allows confirmatory immunostaining of cellblock material for T-cell antigens (CD2, CD4), CD30, EMA, and cytotoxic activation markers. In contrast to most systemic ALCLs, ALK-1 is typically negative in these neoplasms.





Fig 8.20. FNA of an implant-related anaplastic large cell lymphoma in a 50 year-old woman. A & B: Large pleomorphic lymphoid cells with polylobated nuclei and mitoses. C: Immunostain for CD30.

C. METASTATIC CANCERS

Metastatic cancers to the breast account for 0.5 to 6% of all breast cancers and women are affected about 5 times more than men, according to some studies. Cancers arising in any other body sites can metastasize to the breast and on rare occasions the primary tumour is clinically occult and the metastatic tumour is the initial clinical manifestation. The appropriate clinical history is import to facilitate the diagnosis (Rodriguez-Gil 2012). Metastatic cancers that we encounter most often are cutaneous melanoma, prostatic carcinoma, ovarian carcinoma, lung carcinoma, colonic carcinoma, renal cell carcinoma, multiple myeloma (Kelten 2010), rhabdomyosarcoma and leiomyosarcoma. Some examples of metastatic cancers to the breast are illustrated below in Figs. 8.21 to Fig. 8.27.



Fig. 8.21. Metastatic amelanotic cutaneous melanoma to the breast showing in FNA dissociated pleomorphic malignant cells with macronucleoli. (MGG stain)







Fig 8.22. A 27 y/o woman with a 2cm subareolar rmass. The FNA shows crowded poorly cohesive groups of atypical polypgonal and spindle cells that have tails of feathery cytoplasm. Some nuclei contain pseudo-incusions. Some cells contain intracytoplasmic melanin pigment. The immunostain fror HMB-45 performed on the Surepath slide is positive in the malignanct cells. Histology of the excised mass confirmed the diagnosis of metastatic melanoma. (Case contributed by Dr. Koen van de Viyver, NKI Amsterdam).







8.23E

Fig 8.23. A 69 y/o woman presented with a 2cm subcutaneous mass in the lower outer quadrant of the right breast. Imaging studies suggested fat necrosis or a malignancy. FNA yielded cohesive groups of malignant glandular cells. The cells showed positive immunostaining for Napsin A (8.23D). A clinical history lung carcinoma and subsequent immunohistochemical work-up of the tissue biopsy confirmed metastatic pulmonary adenocarcinoma. (Case contributed by Dr. Koen van de Viyver, NKI Amsterdam).



Fig. 8.24 A & B. Metastatic colonic adenocarcinoma to the breast showing in FNA irregular clusters of mucus secreting malignant glandular cells with cytoplasmic vacuoles containing mucinous material (MGG stain).



Fig. 8.25. Metastatic renal cell carcinoma to the breast showing in FNA cohesive sheets of malignant glandular cells with clear, granular cytoplasm and pleomorphic nuclei with conspicuous nucleoli (Pap stain).



Fig. 8.26. Metastatic multiple myeloma to the breast showing in FNA single and loosely clustered neoplastic plasma cells with eccentrically located nuclei and juxtanuclear clear spaces (MGG stain)



Fig. 8.27. Isolated pleomorphic malignant cells in FNA of a metastatic poorly differentiated leiomyosarcoma to the breast. Tumour typing was made by extensive immunohistochemical studies of the biopsied tissue (Pap stain).

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