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Non-neoplastic and Proliferative Lesions

Mastitis, Breast Abscess

In inflammatory conditions such as mastitis and abscess formation, surgery can be avoided by the use of fine-needle aspiration (FNA). In conjunction with microbiologic studies of the aspirated material, FNA can provide valuable information about the etiology of an inflammatory condition of the breast (lactation, infection, or trauma). Fine-needle aspiration can also serve as a therapeutic modality when evacuating abscess material or cyst contents.

Clinical Features

- Mastitis often presents as a palpable breast lesion with varying degrees of pain and tenderness.
- Acute suppurative mastitis is typically seen in 1%–3% of lactating women in the postpartum period.
- The most common organisms are staphylococci and streptococci.
- Localized infection often results in an abscess and rarely leads to chronic mastitis with periductal inflammation, duct ectasia, fibrohistiocytic reaction, and mononuclear chronic inflammatory infiltrate.

Cytomorphologic Characteristics

- Smear cellularity is highly dependent on the clinical stage of the lesion—high cellularity in the acute/active stage and sparse cellularity in the subacute/chronic stage due to presence of varying degrees of fibrosis.
- Smears contain abundant mixed inflammatory cells (neutrophils, lymphocytes, and plasma cells), apocrine cells, and abundant macrophages often with evidence of cytophagocytosis and multinucleated giant cells.
- Isolated cells, apocrine cells, and clusters of epithelial cells with varying degrees of reactive atypia are also present (often with an appearance reminiscent of epithelial cells in repair).

Pitfalls and Differential Diagnosis

- Ductal carcinoma
- Fat necrosis with organized hematoma

Chronic Subareolar Abscess

Clinical Features

- This is considered a specific clinicopathologic entity characterized by low-grade/mild infection of the lactiferous duct or sinus leading to subsequent abscess formation and/or chronic recurrent infection and rarely fistula formation at the base of the nipple.
- Suggestion has been made that squamous metaplasia of columnar epithelial cells of the lactiferous ducts is the cause of this lesion.

Cytomorphologic Characteristics

- High cellularity
- Mixed inflammatory infiltrate, abundance of neutrophils and lymphocytes with few plasma cells, and multinucleated giant cells

- Anucleated squamous cells, parakeratotic cells, and keratinous material
- Ductal epithelium with varying degrees of reactive atypia
- Granulation tissue
- Foamy histiocytes, cholesterol crystals

Pitfalls and Differential Diagnosis

- Duct ectasia
- Ductal carcinoma with squamous differentiation, metastatic squamous cell carcinoma, and metaplastic carcinoma

Granulomatous Mastitis

Clinical Features

- Characterized by the presence of granulomatous reaction and giant cell formation
- An inflammatory lesion of either unknown etiology or the result of tuberculosis, fungal infection, epidermal inclusion cyst, or foreign body reaction such as suture and leakage from silicone implants

Cytomorphologic Characteristics

- Variable cellularity (usually high)
- Epithelioid histiocytes, singly and in loose clusters
- Mixed inflammatory cells, cellular debris
- Few to abundant foreign body-type giant cells
- Ductal epithelial fragments often with significant reactive atypia

Pitfalls and Differential Diagnosis

- Duct ectasia
- Low-grade ductal carcinoma

Fibrocystic Changes

Fibrocystic changes are the most common cause of breast lumps in women between 30 and 50 years old. These are a variety of changes in the glandular and stromal tissues of the breast. Clinically, these patients may have cysts, fibrosis, tenderness, or pain. Fibrocystic breasts may make detection of breast cancer by mammography more difficult; therefore, ultrasound may be necessary in some cases if a breast abnormality is detected in a woman with fibrocystic breasts.

Clinical Features

- Extremely common (50%–90% of all adult women), the most common cause of a clinically palpable breast lump
- Usually presents as a symptomatic lump with cyclical hormonal variation in size and symptomatology
- Young to middle aged women, peak incidence just before menopause
- Usually bilateral and multifocal
- May mimic breast cancer clinically, radiologically, and cytopathologically
- Causation not exactly known, perhaps hormonal (excess of estrogen, low progesterone, or their imbalance)
- Primarily affects the terminal duct lobular unit
- Characterized by presence of gross and microscopic cysts, apocrine metaplasia, and blunt duct adenosis
- May be accompanied by epithelial proliferation of varying degrees, which should be reported separately

Cytomorphologic Characteristics

(Figures 2.1 to 2.3)

- Smears usually hypercellular with a varying admixture of different cell types, including apocrine cells
- Usually cohesive fragments of ductal epithelium—“honeycomb fragments,” often with focal to confluent apocrine

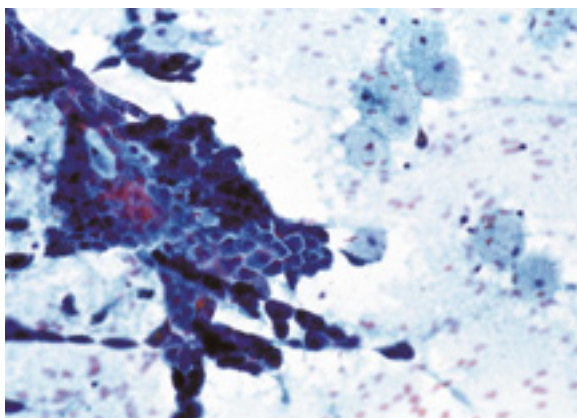


FIGURE 2.1. Fibrocystic changes. A partially folded fragment of apocrine cells seen in a background of numerous foamy macrophages and cystic debris. (Smear, Papanicolaou.)



FIGURE 2.2. Fibrocystic changes. A flat monolayered fragment of apocrine epithelium alongside a cluster of large foamy macrophages. (Smear, Papanicolaou.)

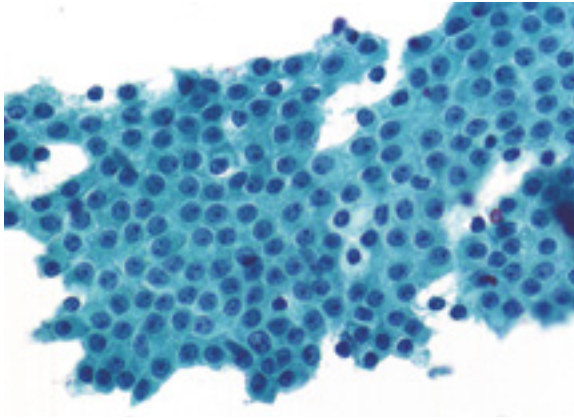


FIGURE 2.3. Fibrocystic changes. A large fragment of apocrine cells arranged in a large monolayered fashion. Cells are large and polygonal with large nuclei and prominent nucleoli with abundant granular cytoplasm. Apocrine epithelium is a fairly common finding in breast aspirates and, except for rare occasions, represents benign lesions. (Smear, Papanicolaou.)

metaplasia (large polygonal cells, abundant cytoplasm that is distinctly granular, well-defined cytoplasmic borders, often prominent nucleoli)

- Mild anisonucleosis, slight nuclear overlap
- Sometimes macrophages predominate, often with foamy cytoplasm—"foamy macrophages"
- Myoepithelial cells, fragments of stroma, adipose tissue
- Background of cystic debris
- Rarely, microcalcifications (calcified debris)

Pitfalls and Differential Diagnosis

- Atypical ductal hyperplasia
- Fibroadenoma
- Low-grade ductal carcinoma

Proliferative Breast Disease

Proliferative changes in the breast may be associated with an increased risk for breast cancer. This category is composed of epithelial hyperplasia, with or without atypia. The interobserver variability for the interpretation of this group of breast lesions (particularly when associated with atypia) is extremely high with poor cytohistologic correlation.

Clinical Features

- Mild ductal hyperplasia, adenosis, cystic changes, and apocrine metaplasia are not associated with an increased risk of cancer.
- Peripheral breast disease without atypia is associated with a slightly higher risk (1.5–2.0 times) of breast carcinoma.
- Examples of peripheral breast disease without atypia include sclerosing adenosis, moderate to florid epithelial hyperplasia, and papillomatosis.
- These lesions may be seen with or without accompanying fibrocystic changes or some other benign breast lesion.
- Peripheral breast disease with atypia, including atypical ductal hyperplasia and atypical lobular hyperplasia, are clinically significant lesions with a much higher risk for subsequent development of breast cancer (four to five times).

Cytomorphologic Characteristics

(Figures 2.4 to 2.7)

- There is moderate to high cellularity.
- Tightly cohesive ductal epithelial fragments are abundant.
- The degree of epithelial proliferation can be subdivided into mild, florid, and atypical.
- Dual cell population (epithelial/myoepithelial) is present in peripheral breast disease but only focally and minimally noted in atypical ductal hyperplasia.

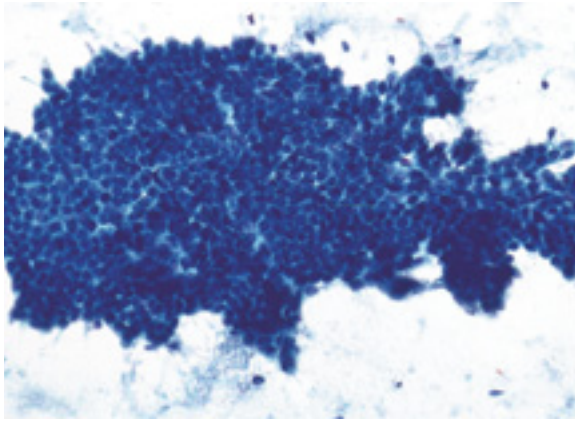


FIGURE 2.4. Usual ductal hyperplasia. A large fragment of ductal epithelium with mildly enlarged and crowded nuclei. Note the cohesive nature of the fragment and relative preservation of the flat, honeycombed architecture. A closer inspection would also reveal myoepithelial nuclei. (Smear, Papanicolaou.)

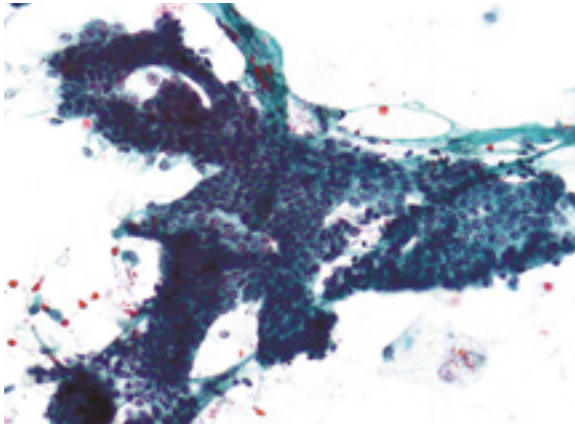


FIGURE 2.5. Atypical ductal hyperplasia. Breast epithelium displaying a more complex architecture with branching and sharply punched out spaces. Cells have enlarged and hyperchromatic nuclei. Myoepithelial cells are often appreciated in these fragments. Note the cohesive nature of the cellular fragments and the lack of individually dispersed epithelial cells in the background, a feature often seen in ductal carcinoma. (Smear, Papanicolaou.)

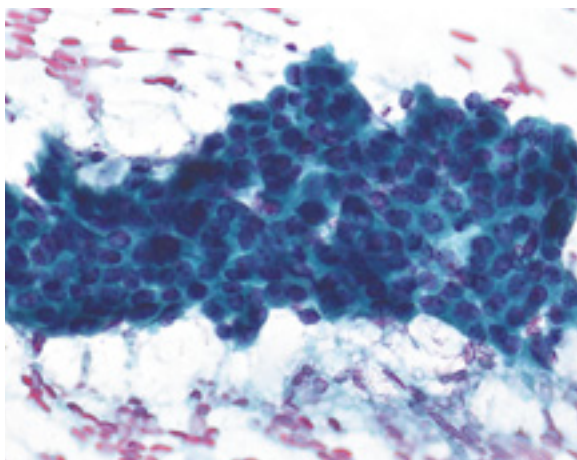


FIGURE 2.6. Atypical ductal hyperplasia. At higher magnification, this case illustrates markedly enlarged and hyperchromatic nuclei imparting a crowded look to the cellular fragment. The fragment still depicts a cohesive architecture with lack of individually dispersed epithelial cells. Although the cytologic features are worrisome, the follow-up revealed multifocal atypical ductal hyperplasia. (Smear, Papanicolaou.)

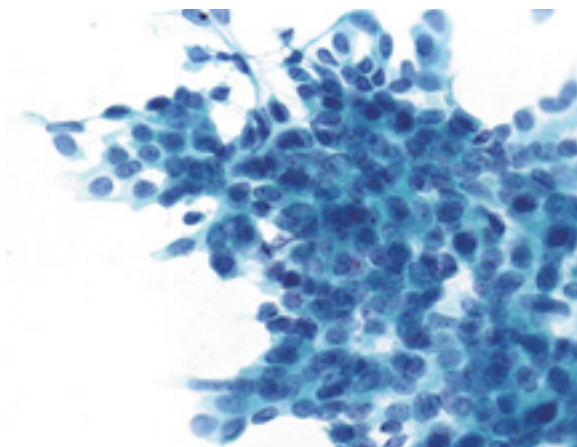


FIGURE 2.7. Atypical ductal hyperplasia. Cellular fragment displaying more pleomorphism with enlarged crowded nuclei and the beginning of a three-dimensional architecture. The cells are loosely cohesive at the fragment edges. (Smear, Papanicolaou.)

- Some associated features of fibrocystic changes may be present in peripheral breast disease but rarely in atypical ductal hyperplasia.
- Predominantly moderately crowded cellular fragments with minimal pleomorphism, lack of cellular dissociation, or single cells (peripheral breast disease). Atypical ductal hyperplasia may show a much greater degree of cellular crowding and nuclear overlap, with a varying but small number of atypical loosely cohesive cells (see Figures 2.6 and 2.7).
- Occasional papillary or, more often, pseudopapillary configurations are present.
- Cytologic atypia (lack of polarity/organization, nuclear enlargement and overlap, micronucleoli) is present in atypical ductal hyperplasia.
- Cribriformlike architecture, three-dimensional epithelial fragments with slitlike spaces/lumens, and complex infoldings of epithelial fragments are noted in atypical ductal hyperplasia.
- Myoepithelial nuclei are usually identified, often in different planes of focus in peripheral breast disease. *Florid atypical ductal hyperplasia may lack myoepithelial cells.*
- Lobular hyperplasia is characterized by an increase in the amount of intact lobular units, often with clearly visible small lumens and minimal cellular crowding. In atypical lobular hyperplasia the lumens get smaller with appreciable cellular crowding and disorganization of the epithelium.

Pitfalls and Differential Diagnosis

- Low-grade ductal carcinoma. Presence of cytologic monomorphism, high cellularity, and single cells favor ductal carcinoma
- Fibroadenoma
- Papilloma

Fine-needle aspiration reporting in peripheral breast disease.

- Proliferative breast disease (no clinical recommendation)
 - Proliferative breast disease with mild atypia (recommendation: clinical follow-up)
 - Proliferative breast disease with florid/severe atypia (recommendation: tissue biopsy)
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It is imperative to render the above interpretations in the context of the “triple test” in order to avoid a false-positive cancer diagnosis.

Cytomorphologic comparison between atypical ductal hyperplasia and ductal carcinoma in situ on fine-needle aspiration.

- The cytomorphologic distinction between atypical ductal hyperplasia and low-grade invasive ductal carcinoma in situ is often difficult and may not always be possible to make.
 - Studies have shown that, in general, cases of atypical ductal hyperplasia are most likely to be diagnosed as negative or atypical. In contrast, ductal carcinoma in situ is more likely to be interpreted as suspicious or positive.
 - Features favoring atypical ductal hyperplasia include sheetlike architecture, flat or monolayered and cohesive cells, finely granular chromatin, distinct cell borders, and presence of myoepithelial nuclei.
 - Features favoring ductal carcinoma in situ include more single dishesive atypical cells, loosely arranged epithelial fragments, prominent anisonucleosis, coarser nuclear chromatin (“clumped chromatin”), and background inflammatory cells.
 - Other cellular characteristics (nuclear size, nucleus to cytoplasm ratios, hyperchromasia, macronucleoli) show a significant overlap and are not helpful.
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The Issue of Gray Zone Cytopathology

Sometimes breast FNA cannot render an unequivocal diagnosis of a benign lesion or carcinoma. Studies have shown that the gray zone diagnoses may represent 7%–20% of all breast FNAs and are often a cause of frustration for both the cytopathologist and the clinician.

Common Reasons for Gray Zone Diagnoses

- Technical (usually the most common culprit)
 - Sparse cellularity
 - Obscuring blood, air-drying artifact

If it is unsatisfactory for evaluation, state this in the diagnosis. Do not attempt to interpret as “atypical” if the smears cannot be evaluated due to the above factors, or, worse, do not commit to a positive diagnosis.

- Interpretative, pathologist-related: lack of experience in breast FNA. The gray zone diagnosis is like a comfort zone for the interpreter. Inexperience leads to a larger comfort zone where the interpreter would not want to be definitive in his or her diagnosis. The influence of adequate training and experience cannot be overemphasized in breast cytopathology.
- Interpretative, overlapping cytomorphologic features or “true gray zone”: significant and real morphologic overlap exists between atypical/benign and atypical/malignant lesions.

Common Sources of Gray Zone Diagnoses

Benign

- Fibroadenoma (the common and the most “notorious” cause)
- Intraductal papilloma
- Atypical ductal hyperplasia
- Gynecomastia

Malignant

- Intracystic papillary carcinoma
- Infiltrating lobular carcinoma
- Apocrine carcinoma
- Tubular carcinoma

Published Accounts and Authors' Experiences of Practical Problems in Gray Zone Diagnoses

- Cellular fibroadenoma versus ductal carcinoma
- Solitary ductal papilloma versus intracystic papillary carcinoma
- Apocrine metaplasia versus well-differentiated apocrine carcinoma
- Lobular carcinoma versus benign breast lesions (lactational changes)
- Tubular carcinoma versus benign breast (or fibroadenoma)
- Atypical ductal hyperplasia versus cribriform ductal carcinoma in situ

Columnar Cell Lesions of the Breast

Columnar cell lesions are increasingly encountered in breast FNA in women between the ages of 35 and 50 years. It can be a common finding in breasts with microcalcifications or can be an incidental finding in fibroadenomas or fibrocystic changes. These peculiar lesions involve the terminal duct lobular unit and display well-formed columnar cells with apical secretory snouts, also called CAPSS or “columnar alteration with prominent apical snouts and secretions.” Columnar cell lesions represent a spectrum of proliferative epithelial change with and without significant cytologic atypia. These are often nonpalpable lesions that could be multifocal or bilateral in the breasts. Most common histologic follow-up finding is benign fibrocystic change. The clinical significance of columnar cell lesions is not well-defined; however, they can be seen in association with lobular lesions (atypia, in situ carcinoma) and tubular carcinoma.

When FNAs are performed on these lesions, the most common scenario is a palpable breast mass or a radiographic density or nodule. Cytomorphologically, moderate to abundant three-dimensional cellular fragments are seen composed of polygonal round to oval cells. There is usually a loss of polarity especially toward the center of the fragments where cellular crowding and disorganization are quite pronounced. Characteristically, the cells at the periphery display columnar morphology with prominent palisading in the long axis. Rarely flat sheets with branchings and infoldings are also seen. Secretory snouts are seen in up to half of the cases on FNA. Myoepithelial cells are almost always present intermingled with the ductal epithelium. Some cases have a significant number of single epithelial cells requiring a careful evaluation to avoid overdiagnosis, as significant atypia is rarely seen in such cells. Foamy histiocytes and apocrine metaplastic cells are rare.

Differential diagnosis of columnar cell lesions includes papilloma, fibroadenoma, low-grade ductal carcinomas, and postradiation changes.

Silicone Mastitis

Clinical Features

- Often associated with ruptured silicone tissue expanders
- Exuberant proliferative tissue reaction may result in single or multiple nodules simulating malignancy

Cytomorphologic Characteristics

(Figures 2.8 to 2.11)

- Characterized by pools or globs of liquid silicone, often surrounded by epithelioid histiocytes, foamy macrophages, or foreign body-type giant cells forming “silicone granulomata”
- Cytohistologic picture may also resemble fat necrosis
- Smears are moderately cellular

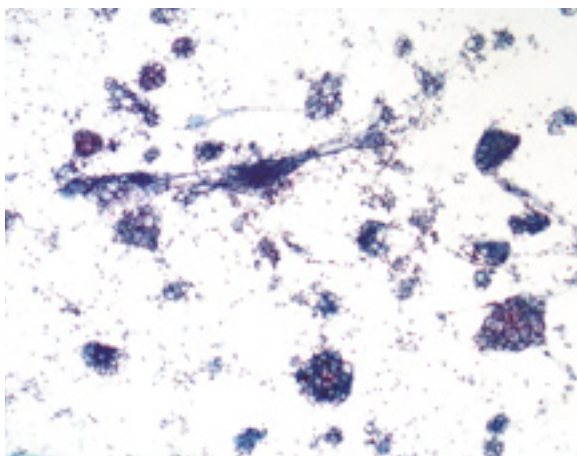


FIGURE 2.8. Silicone mastitis. A hypercellular smear displaying numerous irregular fragments of markedly distended histiocytes resembling adipose tissue fragments. Numerous inflammatory cells seen in the background. (Smear, Papanicolaou.)

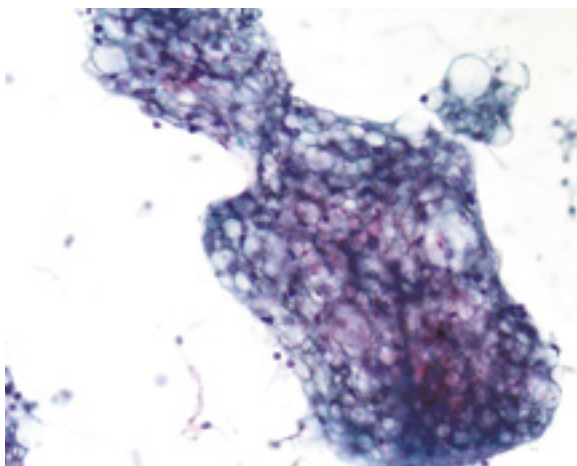


FIGURE 2.9. Silicone mastitis. A large cluster of tightly packed histiocytes. The cytoplasm appears clear and is markedly distended due to the presence of silicone material. (Smear, Papanicolaou.)

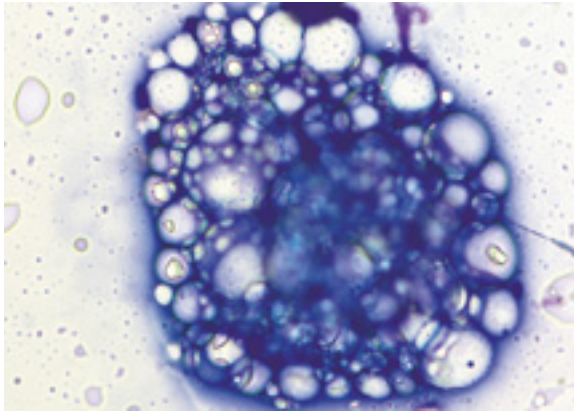


FIGURE 2.10. Silicone mastitis. Higher magnification reveals pale yellow refractile silicone material within the cytoplasm of the histiocytes. (Smear, Diff-Quik.)

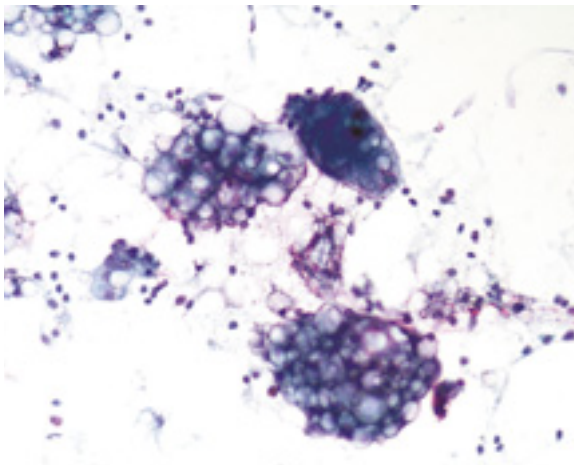


FIGURE 2.11. Silicone mastitis. Several clusters of silicone-containing histiocytes, multinucleated giant cells, and background lymphocytes representing a granulomatous reaction. (Smear, Papanicolaou.)

- Aggregates of distended macrophages, with refractile cytoplasmic globules
- Inflammatory cells, multinucleated giant cells
- Degenerated, often vacuolated, adipocytes

Pitfalls and Differential Diagnosis

- Fat necrosis
- Ductal carcinoma
- Lipoma

Fat Necrosis/Organizing Hematoma

Clinical Features

- Trauma-induced inflammatory conditions
- History of trauma may or may not be available
- Mammographically, fat necrosis with subsequent calcification may also mimic a neoplastic process
- May result in a firm, irregular, fixed, and painful breast mass
- Mimics breast cancer not only clinically and radiologically but also cytopathologically
- May create diagnostic problems if the history of injury is remote or is not recalled by the patient

Cytomorphologic Characteristics

(Figures 2.12 to 2.17)

- Scant cellularity (rarely smears appear hypercellular due to abundance of inflammatory cells, histiocytes, and endothelial proliferation)
- Abundant foamy or hemosiderin-containing macrophages, lymphocytes, plasma cells, fibroblasts, and fragments of fibrous tissue and newly formed vessels
- Degenerated/necrotic fat cells/vacuoles, often with calcified debris and dirty granular background, lipophages
- Occasional multinucleated foreign body-type giant cells

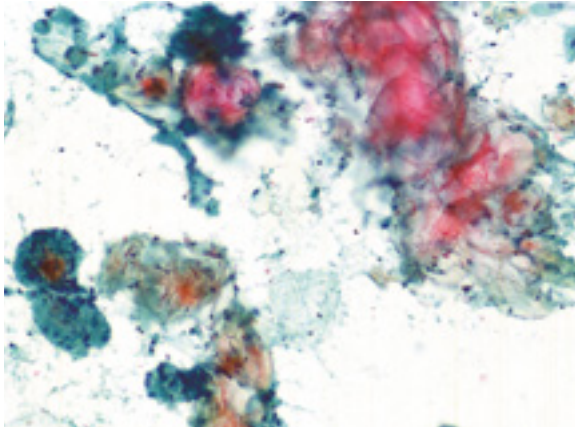


FIGURE 2.12. Fat necrosis. Degenerated fat, histiocytes, and multinucleated foreign body-type giant cells. (Smear, Papanicolaou.)

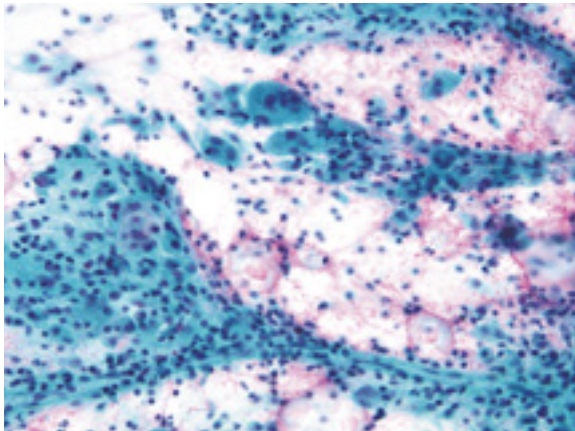


FIGURE 2.13. Fat necrosis. Hypercellular smear depicting degenerated fat, chronic inflammatory cells, and multinucleated histiocytes. Abundant fine capillary vessels represent formation of granulation tissue. (Smear, Papanicolaou.)

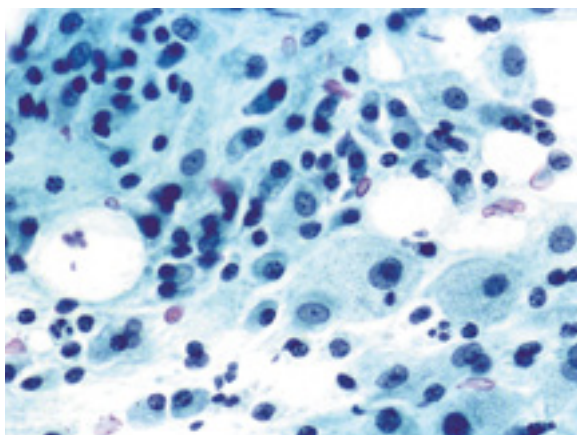


FIGURE 2.14. Fat necrosis. Higher magnification illustrating the polymorphous composition of the cellular infiltrate, that is, lymphocytes, plasma cells, endothelial cells, and foamy macrophages. (Smear, Papanicolaou.)

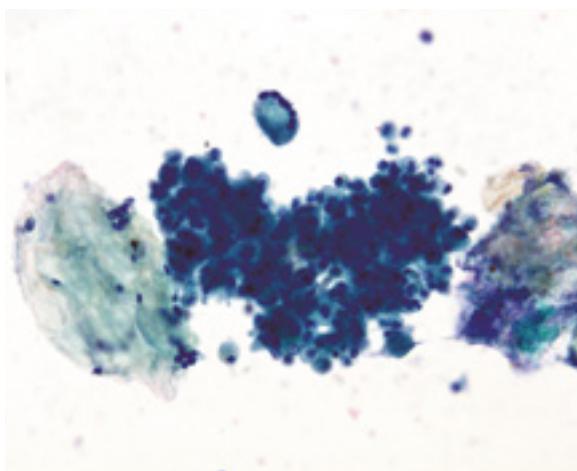


FIGURE 2.15. Fat necrosis. Higher magnification illustrates degenerated fat, a tight aggregation of inflammatory cells, and histiocytes and multinucleated giant cells. (Smear, Papanicolaou.)

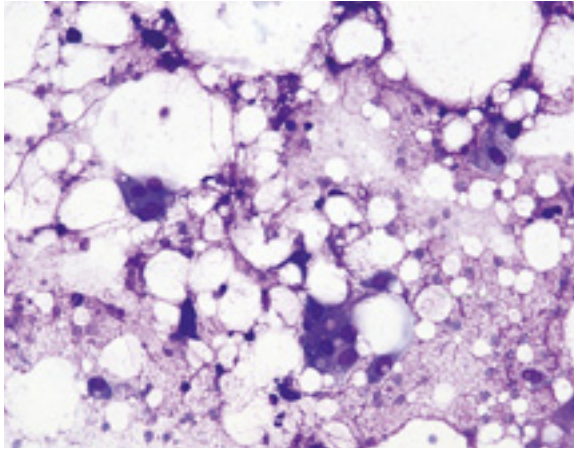


FIGURE 2.16. Fat necrosis. High magnification shows small clusters of histiocytes embedded within a degenerated, granular background. Caution should be taken not to overcall these cells as infiltrating carcinoma cells. (Smear, Diff-Quik.)

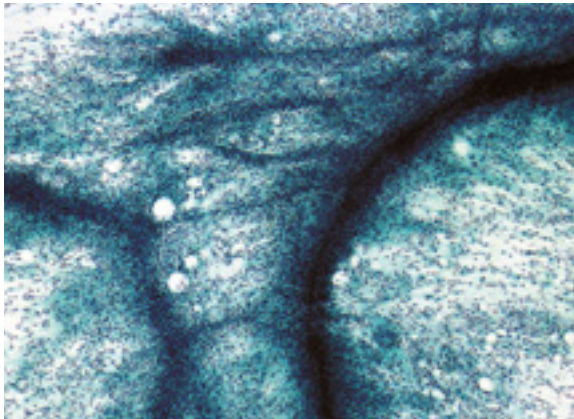


FIGURE 2.17. Fat necrosis with organizing hematoma. Hypercellular smear composed of inflammatory cells, histiocytes, and proliferating endothelial cells, which is a common accompaniment of granulation tissue formation. (Smear, Papanicolaou.)

- “Chicken-wire” or arborizing capillaries, often with proliferating fibroblasts
- Epithelioid histiocytes can be overinterpreted as malignant epithelial cells; and/or ductal epithelial fragments present in the smear are overcalled because of the significant reactive atypia present
- Reactive epithelial atypia associated with fat necrosis has resulted in false-positive diagnoses of cancer

Pitfalls and Differential Diagnosis

- Ductal carcinoma

Mucocelelike Lesion

Clinical Features

- Rare lesion often quite small, usually a diagnostic problem on FNA (differentiation from mucinous carcinoma)
- Often associated with fibrocystic changes and is thought to originate from ruptured mucinous cyst into breast stromal tissues

Cytomorphologic Characteristics

(Figures 2.18 and 2.19)

- Smears with scant cellularity
- Small epithelial fragments, monomorphic, lack of atypia
- Abundant background mucin
- Muciphages, in varying numbers
- Occasional bare myoepithelial nuclei

Pitfalls and Differential Diagnosis

- Colloid carcinoma

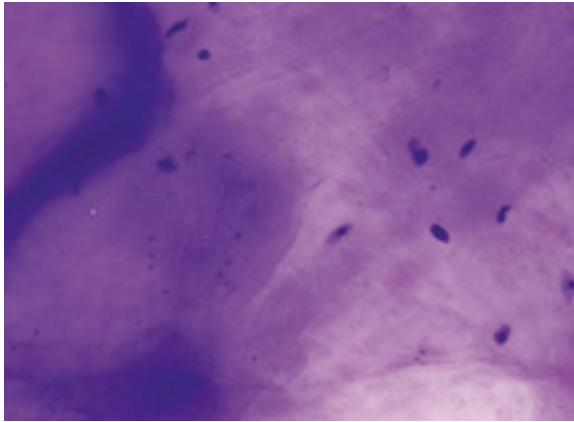


FIGURE 2.18. Mucoccele. Thick, abundant mucinous background containing rare macrophages. These lesions are devoid of ductal epithelium, a helpful finding to distinguish them from well-differentiated mucinous carcinoma. (Smear, Diff-Quik.)

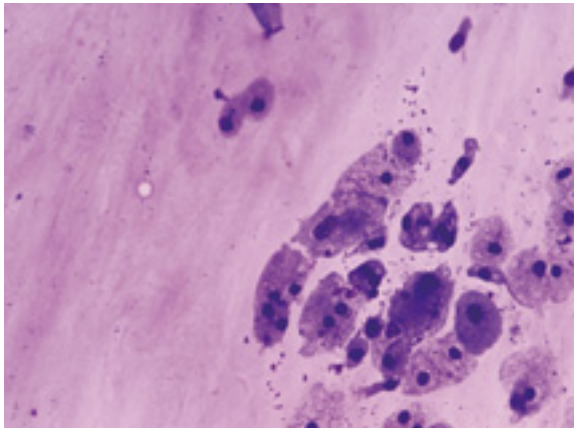


FIGURE 2.19. Mucoccele. Higher magnification shows numerous mucin-containing macrophages in a thick mucinous background. (Smear, Diff Quik.)

Radiation-Induced Changes

Clinical Features

- Radiation-induced changes are not uncommon because a larger proportion of patients are undergoing breast-conserving therapies that may include adjuvant radiation.
- The effects of radiation are noted not only in any residual carcinoma but also in the nonneoplastic mammary tissue.

Cytomorphologic Characteristics (Figure 2.20)

- Smears usually paucicellular
- Small epithelial fragments, often lobular in nature, with significant cytologic atypia (vacuolated cytoplasm, enlarged nuclei, prominent nucleoli) and degenerative changes

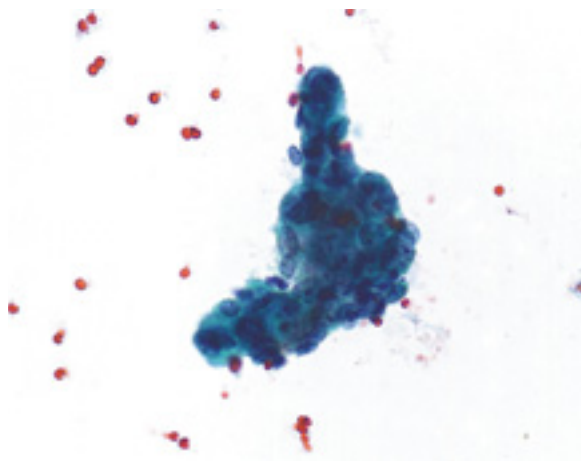


FIGURE 2.20. Radiation atypia. Partially intact breast lobule with markedly enlarged, pleomorphic nuclei displaying macronucleoli. The patient had a history of radiation treatment for ductal carcinoma. Although the morphologic changes are too bizarre to represent lobular carcinoma, such cases require a careful interpretation when patients have previously resected breast cancer. (Smear, Papanicolaou.)

- Lymphomononuclear inflammatory cells
- Rarely fat necrosis (in cases of recent surgery/biopsy)
- If significant atypia, can lead to erroneous false-positive diagnosis of cancer on aspiration

Pitfalls and Differential Diagnosis

- Atypical lobular hyperplasia
- Ductal or lobular carcinoma

Collagenous Spherulosis

Collagenous spherulosis is an uncommon lesion, first described in 1987, characterized by the presence of distinct globules of amorphous material that resemble adenoid cystic carcinoma histologically and cytologically.

Clinical Features

- Usually an incidental microscopic finding, often accompanying benign proliferative lesions of the breast such as sclerosing adenosis, radial scar, and intraductal papilloma
- Can be unifocal or multifocal

Cytomorphologic Characteristics

(Figures 2.21 to 2.25)

- Smears are moderately cellular with monolayered fragments of epithelium, often with a focal branching papillary architecture
- Metachromatic “hyaline” globules (on Diff-Quik stain), pale green and vaguely translucent (on Papanicolaou stain), usually well formed, surrounded by monomorphic ductal epithelial cells
- Higher magnification reveals fibrillar structures of the globules, which often vary in size

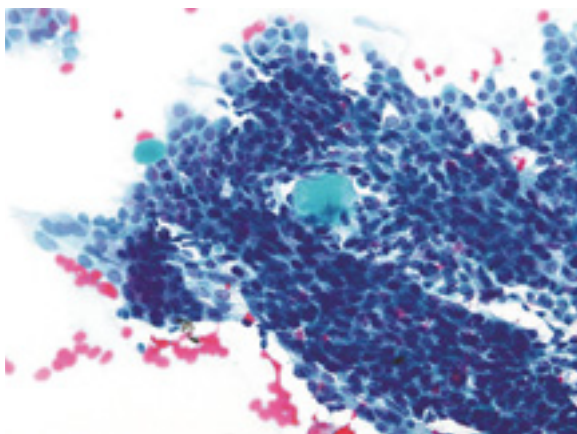


FIGURE 2.21. Collagenous spherulosis. Cellular smear with hyperchromatic and crowded ductal epithelium. Two well-defined pale green globular structures are present. (Smear, Papanicolaou.)

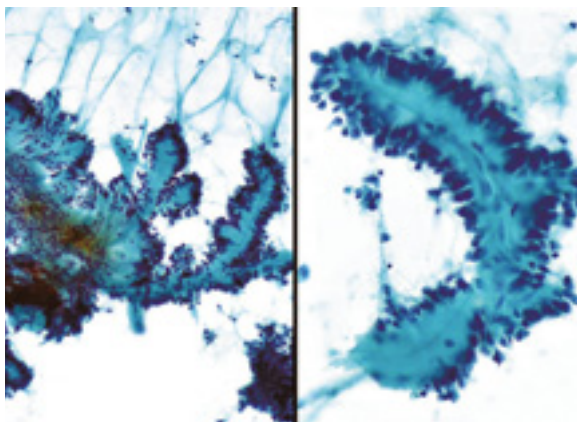


FIGURE 2.22. Collagenous spherulosis. Papillary-like branching cords of pale green cylindrical structures lined by proliferative ductal epithelium. Note the presence of stromal nuclei within the pale green substance, a feature often helpful in distinguishing collagenous spherulosis from adenoid cystic carcinoma. (Smear, Papanicolaou.)

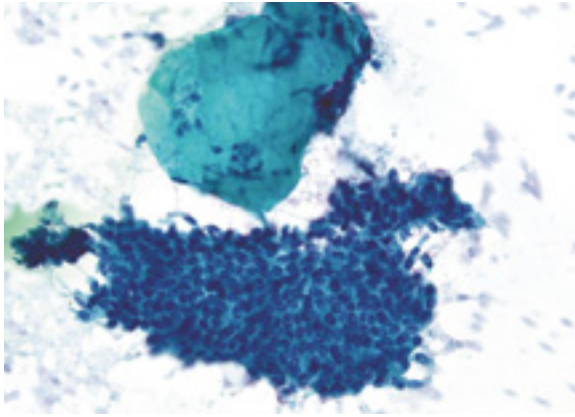


FIGURE 2.23. Collagenous spherulosis. High magnification of a hyperchromatic crowded ductal epithelial fragment and juxtaposed pale green sharply defined globular structure. A morphologic distinction from adenoid cystic carcinoma can be extremely difficult. (Smear, Papanicolaou.)

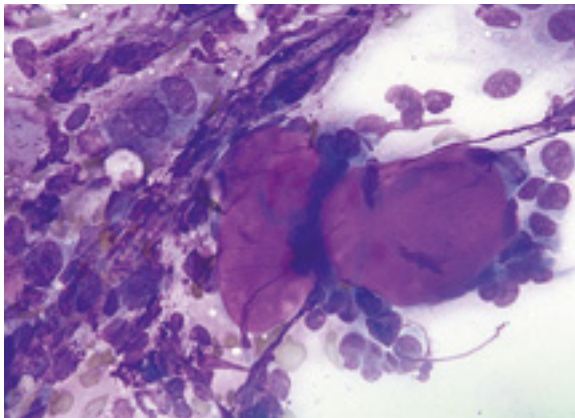


FIGURE 2.24. Collagenous spherulosis. Higher magnification of metachromatic spherules mimicking adenoid cystic carcinoma. The presence of loosely cohesive ductal epithelial cells in the background makes it an extremely treacherous cytomorphologic interpretation. The presence of other associated findings in the case (such as papillomatosis and sclerosing adenosis) are often helpful for the diagnosis of collagenous spherulosis. (Smear, Diff-Quik.)

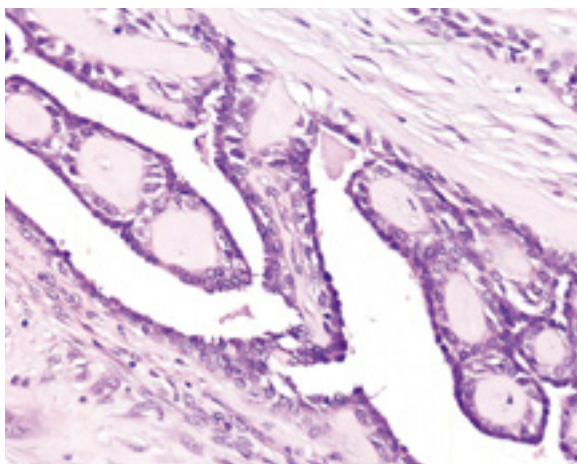


FIGURE 2.25. Collagenous spherulosis. Histologic section illustrating at high magnification the source of the amorphous globular structures seen in a fine-needle aspiration smear of this entity. Note the presence of well-defined myoepithelial cells surrounding these pale eosinophilic structures. (Histologic section, hematoxylin and eosin.)

- Lack of significant cellular atypia, lack of basaloid nature of the accompanying epithelium
- Occasional papillary ductal epithelial fragments or associated changes of a benign papilloma
- Diagnostic confusion with adenoid cystic carcinoma may lead to a false-positive diagnosis of cancer on FNA

Pitfalls and Differential Diagnosis

- Adenoid cystic carcinoma
- Ductal carcinoma in situ, cribriform type
- Adenomyoepithelioma, tubular variant

Pregnancy/Lactational Changes and Lactational Adenoma

Clinical Features

- These changes and adenomas are uncommonly encountered.
- Fine-needle aspiration distinction between lactational change and lactating adenoma is difficult (if at all possible).
- The lesions may lead to an erroneous false-positive diagnosis of carcinoma because of the atypical cytologic features. A careful clinical history of pregnancy/lactation should always be sought when rendering a diagnosis of carcinoma in a younger patient.

Cytomorphologic Characteristics

(Figures 2.26 to 2.30)

- Hypercellular smears, “yielding” FNAs
- Loosely cohesive ductal or, more often, lobular epithelial fragments
- More intact lobular fragments in lactating adenoma, often with prominent secretory changes (cytoplasmic vacuoles); prominent outer myoepithelial cell layer
- Usually larger cells, with prominent nucleoli and foamy cytoplasm; cytoplasm is extremely fragile and wispy
- Numerous round, naked nuclei in the background (epithelial cell nuclei), often with prominent nucleoli
- Numerous inflammatory cells (mostly mature polymorphous lymphocytes), few macrophages
- Proteinaceous and frothy slide background, often hemorrhagic, obscuring cellular details

Pitfalls and Differential Diagnosis

- Galactocele
- Fibroadenoma, tubular adenoma
- Atypical ductal hyperplasia, atypical lobular hyperplasia

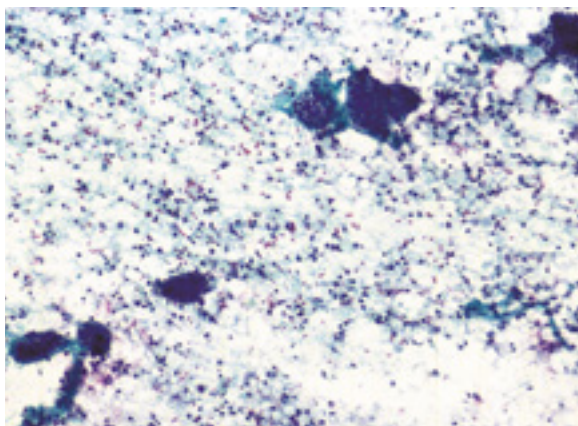


FIGURE 2.26. Lactational change. Hypercellular smear composed of distended breast lobules and abundant mixed inflammatory cells in the background. These findings may appear worrisome leading to an erroneous diagnosis of atypia or cancer. (Smear, Papanicolaou.)

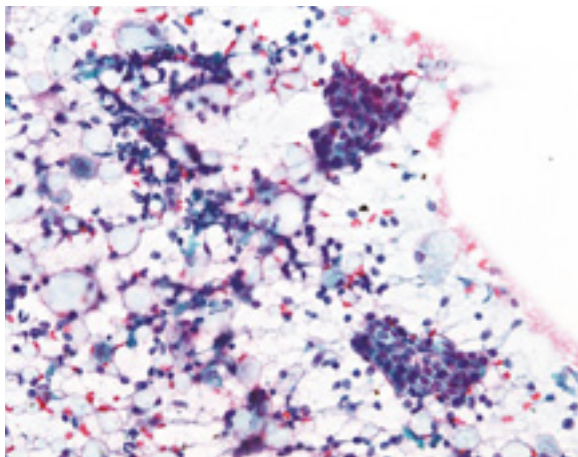


FIGURE 2.27. Lactational change. Hypercellular smear that at higher magnification reveals partially disrupted lobules with enlarged hyperchromatic nuclei. Numerous naked lobular cell nuclei are present in the background in addition to lymphocytes, histiocytes, and numerous large lipid vacuoles. (Smear, Papanicolaou.)

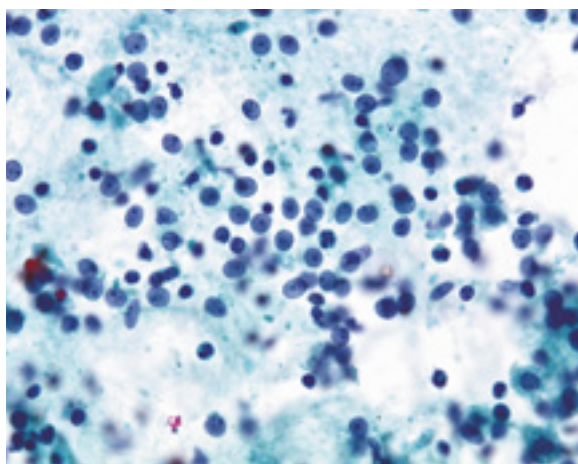


FIGURE 2.28. Lactational change. A totally dissociated population of naked nuclei of lobular cells admixed with mixed inflammatory cells is present. The presence of prominent nucleoli is unusual for lobular carcinoma. The observer should have a much higher threshold for interpreting atypia or cancer when dealing with a fine-needle aspirate from a young pregnant or lactating patient. (Smear, Papanicolaou.)

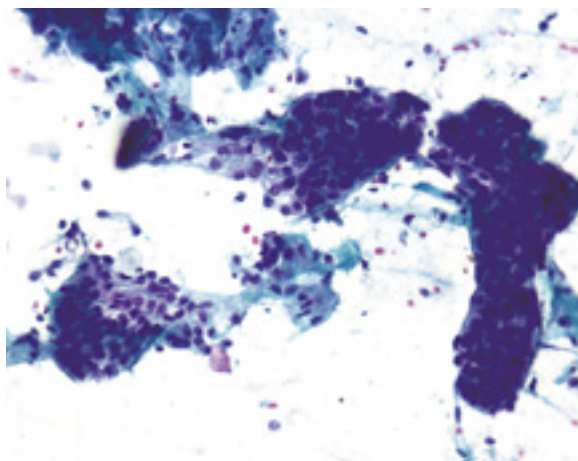


FIGURE 2.29. Lactational change. Intact breast lobules distended with enlarged and hyperchromatic epithelial cells. Note the well-defined myoepithelial cell layer around these lobular structures. A casual look at such aspirates may result in a false-positive diagnosis of lobular carcinoma. (Smear, Papanicolaou.)

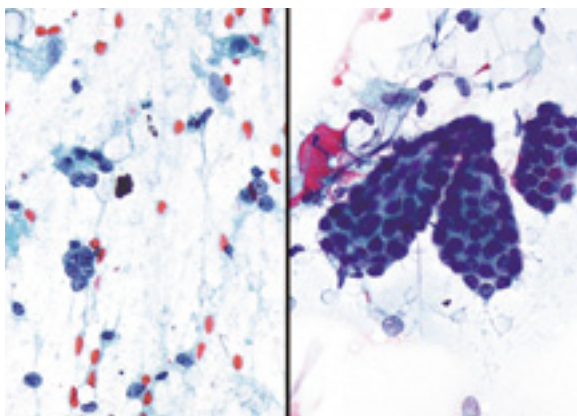


FIGURE 2.30. Lactational change. Higher magnification in the left panel illustrates cytologically atypical, dispersed lobular cells appearing as naked nuclei with prominent nucleoli. The background is granular and shows occasional lipid vacuoles. Distinction from lobular carcinoma would be extremely difficult in such cases. The case on the right shows similar cells, but they are in more intact lobules. (Smear, Papanicolaou.)

- Ductal or, more often, lobular carcinoma
- Non-Hodgkin lymphoma

Gynecomastia

Male breast masses are uncommon pathologic findings. They are rarely aspirated, resulting in limited cytopathologic experience (male breast FNAs account for 1.4%–7.3% of all breast FNAs). However, male breast FNA is considered to be a highly sensitive (95.3%) and specific (100%) diagnostic procedure. Gynecomastia is defined as male breast enlargement caused by both hypertrophy and hyperplasia of the ductal epithelial and stromal components. Although the etiologic factors may vary, the condition is

essentially caused by a relative increase in estrogenic activity, a decrease in androgenic activity, or a combination of both.

Clinical Features

- Usually located in the subareolar region
- Presents clinically as a unilateral or bilateral, tender, and often painful mass, which has a flat “discoid” appearance on palpation
- Bimodal age distribution (adolescents and adults, often in the sixth decade)
- Higher incidence recently observed in human immunodeficiency virus–positive patients receiving antiretroviral therapy

Cytomorphologic Characteristics

(Figures 2.31 to 2.34)

- Variable cellularity, most often moderate (however, cellularity can often be low because of the fibrous nature of the lesion, and the discomfort that the patient experiences at the time of aspiration is due to an often extreme tenderness)
- Large cohesive ductal epithelial fragments, often papillary-like or flat and monolayered; often a prominent cribriform architecture is seen
- Focal to confluent epithelial atypia, sometimes quite significant with cellular crowding, nuclear enlargement, and prominent nucleoli
- Small amount of scattered background myoepithelial nuclei
- Atypical single epithelial cells rarely observed (useful feature when distinguishing gynecomastia from a male breast ductal carcinoma)
- Occasional fragments of metachromatic stromal/fibrous tissue (may appear falsely biphasic resembling a fibroadenoma)

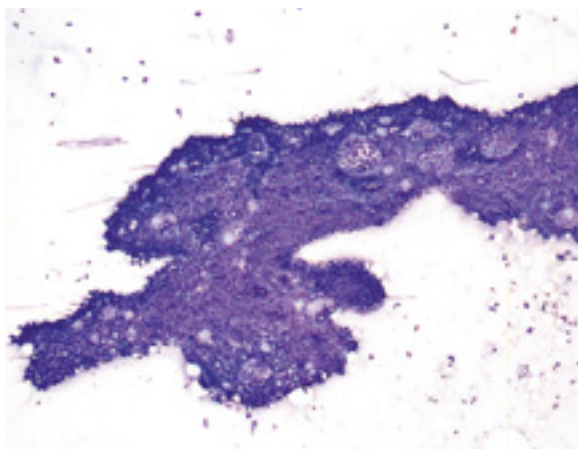


FIGURE 2.31. Gynecomastia. A large fragment of hyperplastic ductal epithelium with a vague papillary and cribriform architecture is seen. Note the presence of numerous naked myoepithelial cells in the background. (Smear, Papanicolaou.)

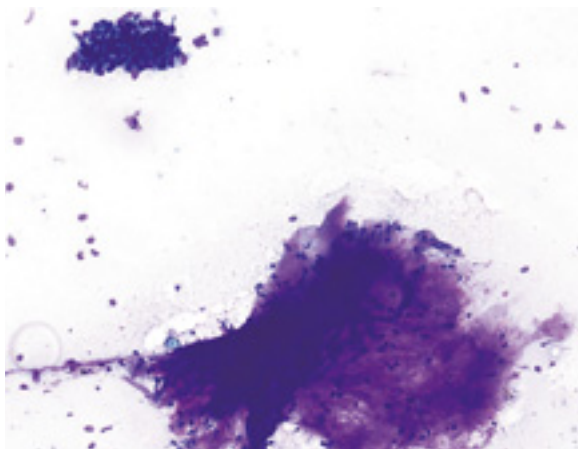


FIGURE 2.32. Gynecomastia. A biphasic architecture composed of cohesive hyperplastic ductal epithelium and myxoid stroma. Numerous myoepithelial cells are seen in the background. (Smear, Diff-Quik.)

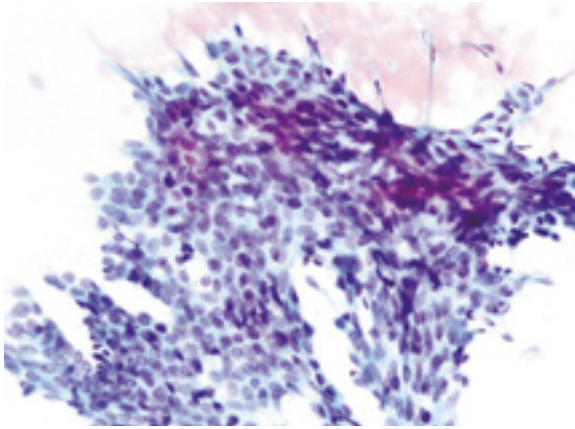


FIGURE 2.33. Gynecomastia. An atypical ductal epithelial fragment with large crowded nuclei. A total lack of individually dispersed epithelial cells helps to rule out carcinoma in these cases. (Smear, Papanicolaou.)

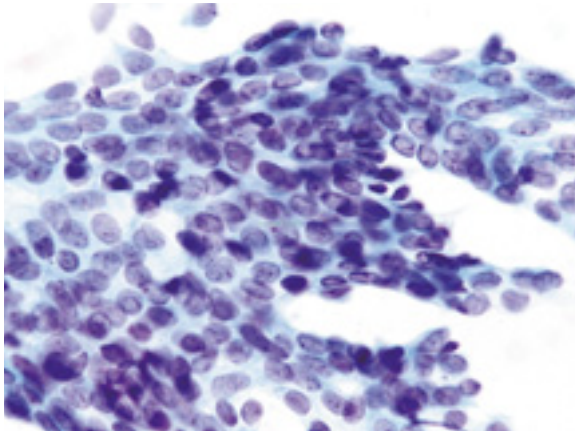


FIGURE 2.34. Gynecomastia. Higher magnification of a ductal epithelial fragment shows enlarged crowded nuclei with occasional myoepithelial cells. One should have a much higher threshold for an atypical/cancer diagnosis in a male breast aspiration because of the significant cytologic atypia in these lesions and the rarity of male breast carcinoma. (Smear, Papanicolaou.)

Pitfalls and Differential Diagnosis

- Ductal carcinoma
- Atypical ductal hyperplasia
- Metastatic tumors (most commonly, lung adenocarcinoma)
- Fibroadenoma (This possibility is uncommonly raised because of the often biphasic appearance in gynecomastia. The usual source of the loose metachromatic material often seen in Diff-Quik–stained smears of gynecomastia is the myxomatous change often noted in the periductular location of these lesions.)
- Male breast carcinoma (Because carcinoma of male breast is exceedingly rare, it should always be ruled out first; this is particularly critical because gynecomastia can harbor significant epithelial atypia. One should have a much higher threshold for a cancer diagnosis when dealing with male breast aspirates. Male breast carcinoma, which is almost always the ductal type, shows greater pleomorphism, smaller tissue fragments, more single cells, and total lack of myoepithelial cell nuclei [Figures 2.35 and 2.36].)

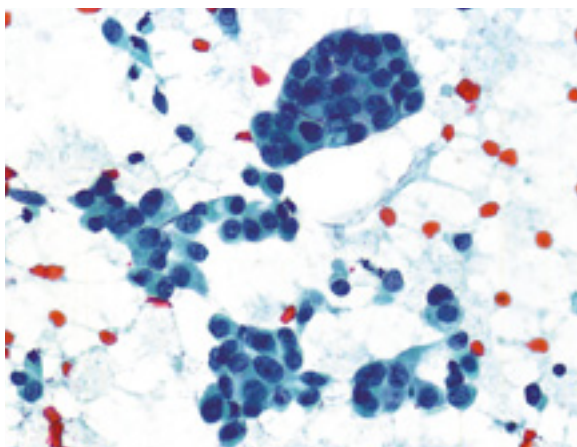


FIGURE 2.35. Ductal carcinoma in male breast. (Smear, Papanicolaou.)

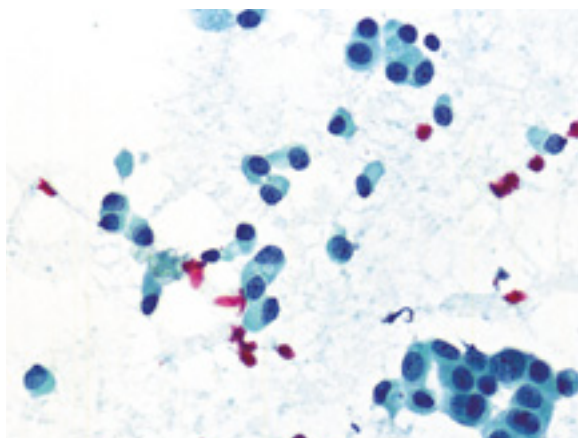


FIGURE 2.36. Ductal carcinoma in male breast. Higher magnification of the view in Figure 2.35 illustrates enlarged, pleomorphic, hyperchromatic nuclei that are eccentrically placed in the cytoplasm, imparting a plasmacytoid appearance. (Smear, Papanicolaou.)

Inflammatory Myofibroblastic Tumor

Inflammatory myofibroblastic tumor is an uncommon benign tumorlike lesion that rarely occurs in the breast. The lesion in the breast resembles its more common lung counterpart. Fine-needle aspiration experience with inflammatory myofibroblastic tumor in the breast is extremely limited.

Clinical Features

- Inflammatory myofibroblastic tumor has been observed in most human organs.
- Clinically and on radiographic studies, it may simulate a primary breast carcinoma.
- There are no systemic or constitutional symptoms of infection noted.
- This is a rare lesion with many synonyms: inflammatory pseudotumor, plasma cell granuloma, inflammatory myofibroblastic tumor, fibroxanthoma, and so forth.

- A small subset show molecular/chromosomal evidence of a neoplastic nature. However, most lesions are thought to be related to infectious etiology.
- Immunoexpression of the ALK protein as a result of chromosomal translocation involving 2p23 is seen in a number of cases.

Cytomorphologic Characteristics

- A proliferative process of myofibroblasts
- Sparsely cellular aspirates
- Characterized by benign cellular features with a polymorphous population of mostly chronic inflammatory cells, plus histiocytes and spindled fibroblasts (or myofibroblasts)
- Benign-appearing ductal epithelium may be present, as well as connective tissue fragments
- Some features may resemble fat necrosis
- Vascular-endothelial proliferation often noted
- Histiocytes and spindled cells may show well-formed intranuclear inclusions
- No granulomas

Pitfalls and Differential Diagnosis

- Granulomatous mastitis
- Fat necrosis
- Granular cell tumor
- Fibromatosis
- Metaplastic carcinoma
- Myofibroblastoma

Primary Amyloid Tumor

Clinical Features

- Primary amyloid tumors are rare nonneoplastic lesions.
- Clinically and radiologically, the findings are often indeterminate, necessitating FNA.

- Breast can be involved as an isolated organ-specific manifestation or as part of systemic amyloidosis.
- Patients often do not have clinical or pathologic evidence of amyloidosis, monoclonal gammopathy, or plasma cell dyscrasias.

Cytomorphologic Characteristics

- Sparsely cellular
- Aggregates of birefringent, dense irregular amorphous material of varying sizes, some with embedded nuclei of lymphomononuclear cells
- The waxy hyaline nature is highlighted on Papanicolaou stain when it assumes a pale green/blue hue
- Numerous background lymphocytes
- Occasional multinucleated giant cells
- Congo red reactivity with apple green birefringence is diagnostic

Pitfalls and Differential Diagnosis

- Adenoid cystic carcinoma
- Chondroid syringoma

Pseudoangiomatous Stromal Hyperplasia

Pseudoangiomatous stromal hyperplasia is a benign fibroblastic or myofibroblastic stromal lesion with well-described histologic phenotype characterized by the formation of numerous anastomosing slitlike spaces in an often densely hyalinized stroma. It shares a superficial resemblance to low-grade vascular tumor, hence the name *pseudoangiomatous*.

Clinical Features

- Pseudoangiomatous stromal hyperplasia may present as a well-defined noncalcified and homogeneous nodular mass

or, more commonly, coexist with other breast lesions (gynecomastia, hamartoma, etc.).

- Some cases are proven to be hormonally related.
- This hyperplasia is more common in premenopausal women and postmenopausal women receiving hormone replacement therapy. Some cases show size fluctuations during menses.
- Myofibroblasts in pseudoangiomatous stromal hyperplasia immunoexpress hormone receptors (particularly progesterone).
- This hyperplasia grows slowly. Rarely has rapid growth been reported in immunocompromised patients.
- Local excision is curative in most cases.
- Its exact nature is unclear; it could be related to an underlying neoplastic process, as some cases recur locally after excision.

Cytomorphologic Characteristics

- Aspirates are often extremely scant and mostly nondiagnostic (because of stromal hyalinization).
- When diagnostic, the smears are scantily cellular and display cohesive benign-appearing ductal fragments, often in flat sheets, less often as branching structures, “fibroadenomalike”
- Rare, bland-appearing spindled cells
- Numerous single bipolar naked nuclei
- Bipolar uniform spindled cells
- Hypocellular loose stromal tissue fragments or fibrillary matrix
- No cellular pleomorphism, no mitoses

Pitfalls and Differential Diagnosis

- Fibroadenoma
- Phyllodes tumor
- Myofibroblastoma
- Metaplastic carcinoma

Reactive Spindle Cell Nodules

Reactive spindle cell nodules are uncommon, benign, non-neoplastic lesions that arise following FNA procedures. The needle trauma to certain breast lesions incites a localized myofibroblastic proliferation suggesting an exuberant reactive response as a cause for reactive spindle cell nodules.

Clinical Features

- Most present as unencapsulated tiny nodules measuring up to 10mm in size.
- Interestingly, most reactive spindle cell nodules are seen in association with papillary and complex sclerosing breast lesions.

Cytomorphologic Characteristics

- Morphologically, the lesions in the breast are similar to those seen in thyroid, salivary glands, and urinary bladder.
- Smears show spindled cells with mild pleomorphism.
- Fine arborizing capillary vessels are present.
- Inflammatory cells and macrophages are present.
- Immunoexpression of smooth muscle markers is diagnostically helpful.

Pitfalls and Differential Diagnosis

- Myofibroblastoma
- Pseudoangiomatous stromal hyperplasia
- Metaplastic carcinoma

Selected Reading

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