**Preface**

The ASCP Quick Compendium of Cytopathology is the first in a New Series of ASCP Quick Compendia. It was developed to help cytology trainees, including pathology residents, cytopathology fellows, and cytotechnology students by providing them with a with a practical, high yield information resource that presented in an easy to read format.

But the New Series adds something very new: images.

As is true for each Quick Compendium volume, each chapter is organized around a detailed outline that covers key details and illustrations of common and less common entities likely to be encountered in the daily practice of cytopathology. The authors share with you not only their gems of diagnostic wisdom, but also an abundance of representative images that clearly illustrate key cytomorphologic features, results of ancillary studies, and diagnostic pitfalls. General chapters dedicated to ancillary testing in both gynecologic and nongynecologic specimens provide current information about special stains, immunostains, fluorescence in situ hybridization, flow cytometry, and molecular testing as they apply to the practice of cytopathology.

We also present up to date information gleaned from a variety of sources, beginning with the ASCP’s “gold standard,” *The Art & Science of Cytopathology, 2nd Edition* by Richard Mac DeMay.

But the authors take care to cull important information from other widely used texts, including *Cytology Diagnostic Principles & Clinical Correlates, 3rd Edition* (Cibas ES, Ducatman BS, 2009); *Comprehensive Cytopathology, 3rd Edition* (Bibbo M, Wilbur D, 2008); *Diagnostic Cytopathology and Its Histopathologic Bases, 5th Edition* (Koss LG, Melamed MR, 2006). Finally, we consulted the literature for other sources, which are cited at the end of the chapter.

The authors also bring the practical expertise derived from being actively involved in teaching cytopathology, nationally and internationally—this provides the correct perspective for a book of this kind. Our hope is that it will prove to be a helpful resource, not only for those studying for examinations in anatomic pathology/cytopathology and cytotechnology, but also for those facing daily diagnostic challenges in cytology practice.

*Wалиd E Khalbuss, Editor in Chief
Joshua Weikersheimer, ASCP Press
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**12.2 Contaminants in Lung FNA & EBUS FNA**

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<th>Contaminants in EBUS FNA F12.3-F12.4</th>
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<tbody>
<tr>
<td>Hepatocytes (particularly in right lower lobe lung aspirates)</td>
<td>Bronchial epithelial cells</td>
</tr>
<tr>
<td>Mesothelial cells</td>
<td>Mucous</td>
</tr>
<tr>
<td>Soft tissue elements from the chest wall (adipose tissue, skeletal muscle, cartilage)</td>
<td>Cartilage</td>
</tr>
</tbody>
</table>

**F12.1** Benign hepatocytes contaminating lung FNA of right lower lobe nodule (left, Diff-Quik, high magnification; right, H&E, high magnification). Hepatocytes can contaminate specimens from the right lower lobe lung, right adrenal, or right kidney. The cells are cohesive, with central round nuclei, occasional nucleoli and intranuclear inclusions, and granular to vacuolated cytoplasm with distinct cell borders.

**F12.2** Benign mesothelial cells in lung FNA (left, Pap stain, high magnification; right, Diff-Quik, high magnification). Mesothelial cells are usually seen in aspirates of pleural-based nodules, and appear as 2-dimensional sheets with clearing between the cells, small nucleoli, and a relatively uniform appearance. Some say that its appearance looks like a cobblestone road since the cells do not touch due to the microvillus border.

**F12.3** Inadequate EBUS-guided FNA specimen with contamination (left and right lower, Diff-Quik, intermediate magnification; right upper, Pap stain, intermediate magnification). This EBUS-guided has extensive contamination from the bronchial wall and lumen, including benign bronchial cells, mucous, and cartilage (arrows).

**F12.4** Benign and reactive bronchial epithelial cells (left upper, Diff-Quik, intermediate magnification; left lower, Diff-Quik, high magnification; right, Pap stain, high magnification). Benign bronchial cells have columnar morphology with terminal bars and cilia. When the cells get reactive, the nuclei can get larger and the cilia may not be seen; however, if the nuclei are similar to the ciliated cells, then they simply represent reactive bronchial cells.
12: Lung & Respiratory Cytopathology

Cytology of Normal & Benign Elements

12.2 Cytology of Normal & Benign Elements

12.2.1 Cytology of Normal Cellular Elements

12.2.1.1 Respiratory Epithelium

- Respiratory epithelial cells are columnar with terminal bars and cilia F12.4.
- Creola bodies are hyperplastic or papillary clusters of bronchial cells with occasional vacuolization and small nucleoli that can be seen with asthma, COPD, or bronchiectasis F12.5.
- Mild reactive atypia (mild nuclear enlargement and prominent nucleoli) can be seen with radiation, chemotherapy, or severe inflammation.
- Irritated bronchial epithelium, such as forcefully brushed epithelium in brushing specimens or other instrumentation, may show syncytial formation or multinucleation with small, benign appearing, similar nuclei.
- Ciliated columnar cells are most common in bronchial specimens, BALs, and as contaminants in EBUS-guided FNA, but are usually less conspicuous in CT guided FNA.

12.2.1.2 Basal or Reserve Cells

- Reserve cells are the undifferentiated cells that give rise to ciliated and goblet cells.
- Reserve cell hyperplasia can be seen with a few tightly packed clusters showing small nuclei, scant cytoplasm and occasional molding F12.6. This may mimic small cell carcinoma, but lacks the apoptotic background, necrosis, and mitotic figures seen in small cell carcinoma, and usually appears more cohesive, smaller, and less numerous than the tumor cells in small cell carcinoma.
- Other mimics of reserve cell hyperplasia include chronic inflammatory processes, lymphoma, leukemia, and other small cell tumors.
- Reserve cell hyperplasia or proliferation is more common when there is lung injury and shedding of the normal respiratory tract epithelium.

12.2.1.3 Goblet Cells

- Goblet cells are mucous-producing bronchial cells that are present in a ratio of ~1 per 6 ciliated cells F12.7.
- These cells lack cilia and have cytoplasm distended by mucus (single or multiple vacuoles).
- They are seen more commonly in bronchial specimens from smokers or patients with chronic respiratory disease (asthma, COPD, bronchiectasis).
They can mimic mucin producing or signet-ring adenocarcinoma.

12.2.1.4 Macrophages
- Macrophages have abundant foamy/vacuolated cytoplasm, oval-to-round nuclei, and occasional prominent nucleoli. The vacuolated cytoplasm may have debris or other ingested material, such as hemosiderin or anthracotic pigment F12.8.
- Lipid laden macrophages can be highlighted with an Oil Red O stain, and these cells can be elevated in patients with lipoid pneumonia, fat embolism syndrome, pulmonary aspiration, or amiodarone toxicity F12.9.
- These cells are needed for adequacy in sputum samples and BALs.

12.2.1.5 Squamous Cells
- Squamous cells are usually contamination from the upper aerodigestive tract, and are usually seen in sputum and bronchial specimens.
- These cells have small round nuclei and orangeophilic cytoplasm, or appear as anucleate squames.

- Mild reactive atypia can be seen with trauma, infection (candidiasis, near cavitary fungal lesions), pemphigus vulgaris (enlargement of nuclei and prominent macronucleoli), and injury to the lung (infarct, radiation, chemotherapy, sepsis, diffuse alveolar damage).
Malignant squamous cells can also represent a contaminant from an oropharyngeal or head and neck squamous cell carcinoma contaminating a bronchial specimen.

12.2.1.6 Neuroendocrine Cells (Kulchitsky Cells)

- These neuroendocrine cells are only identified with special stains or electron microscopy to look for dense core granules.

12.2.1.7 Type I & II Pneumocytes

- Type I pneumocytes cover 90% of alveolar surface and are long, flat cells.
- Type II pneumocytes are less numerous than type I pneumocytes and make surfactant, but are more easily seen and cuboidal-to-round with vacuolated cytoplasm with larger and clearer vacuoles than that seen in histiocytes F12.10.
- The cytologic features of type II pneumocyte hyperplasia includes small clusters of cells with nuclear enlargement, prominent nucleoli, and vacuolated cytoplasm.

Type II pneumocyte proliferation typically occurs after injury to the lung, pneumonia, sepsis, diffuse alveolar damage, infarction, chemotherapy, radiation, inhalant toxicity (e.g., oxygen toxicity), thermal injury, tuberculosis, interstitial lung disease or pulmonary fibrosis.

- In some cases, type II pneumocyte hyperplasia can mimic adenocarcinoma. Therefore, in the setting of a few atypical vacuolated cells with prominent nucleoli, it is important to avoid the overdiagnosis of malignancy. Type II pneumocytes can also mimic epithelioid histiocytes; however, the pneumocytes tend to show more clustering, larger vacuoles, and more prominent round nuclei with prominent nucleoli.

12.2.2 Cytology of Noncellular Elements

12.2.2.1 Curschmann Spirals

- The cytologic features include coiled strands or helical casts of inspissated mucus that appears darkly staining F12.11.
- This is a nonspecific finding, seen with excess mucus production (e.g., asthma).
12.2.2.2 Ferruginous Bodies
- Ferruginous bodies are iron encrusted fibers, usually dumbbell-shaped, golden yellow-brown in color and refractile F12.12.
- They stain positive for Prussian blue stain.
- They are seen in patients with asbestos exposure.

12.2.2.3 Charcot-Leyden Crystals
- Charcot-Leyden crystals are eosinophilic to orangeophilic crystals with rhomboid shape, that are the result of eosinophilic granules from degenerating eosinophils, usually in asthma and other causes of eosinophilia F12.13.
- These can be seen in allergic bronchopulmonary aspergillosis with numerous eosinophils and fungal hyphae.

12.2.2.4 Psammoma Bodies (Calcospherites)
- Psammoma bodies appear as rounded calcifications with concentric laminations.
- They are seen in papillary tumors (ovarian, thyroid, lung), and rarely, pulmonary tuberculosis and alveolar microlithiasis.

12.2.2.5 Corpora Amylacea
- Corpora amylacea are rounded, noncalcified glycoprotein structures with circular and radiating lines F12.14.
Cytology of Normal & Benign Elements > Cytology of Noncellular Elements

- These are a nonspecific finding, but thought to arise from bronchial secretions and may be more common in older patients or patients with pulmonary edema, heart failure, pulmonary infarction, and chronic bronchitis.

12.2.2.6 Vegetable or Plant Matter
- Vegetable or plant material has a characteristic thick cell wall, with a square or rectangular shape. When present in a lung specimen, they usually indicate specimen contamination or aspiration.

12.2.2.7 Ciliocytophthoria
- Ciliocytophthoria appears as detached ciliary tufts. This is associated with viral infection (adenovirus) or simply a nonspecific reaction.

12.2.2.8 Amyloid
- Amyloid appears as amorphous eosinophilic material that has a salmon-pink color on Congo red staining and shows apple-green birefringence under polarized light.

- Amyloid can be seen in the lung as part of an amyloidoma within the lung, but may also involve the lung as part of systemic amyloidosis.
12.2.2.9 Alveolar Proteinosis
- Alveolar proteinosis appears as amorphous eosinophilic material or lamellar bodies F12.18.
- Electron microscopy shows that the lamellar bodies are proteinaceous surfactant material.
- BALs can be performed in these patients for therapeutic relief.

12.2.2.10 Other
- Pollen or starch granules
  - Starch granules appear as clear and refractile cubes with maltese cross formation under polarized light.
  - Pollen appears as spherical structures that are colorful, have a thickened wall, and may have small internal bodies or a spiked border to the granule. This can mimic large fungal yeast forms or other infections, in addition to other contaminants F12.19.
- Drug particles

- Dark black carbonaceous material can appear within histiocytes in drug users, particularly crack/cocaine smokers.
- Rhomboid crystals can appear with aspiration of barium sulfate.

12.2.3 Cytology of Respiratory Infections

12.2.3.1 Bacterial Pneumonia
- Bacterial pneumonia can appear as a mass lesion in the lung and mimic malignancy.
- The cytologic features include a variable amount of inflammation, with mainly neutrophils. Bacterial cocci or rods may or may not be seen F12.20.
- Ancillary studies that can be utilized include microbial culture, and special stains (Gram stain) or immunostains.
Cytology of Normal & Benign Elements > Cytology of Respiratory Infections

- Examples of bacteria in respiratory samples:
  - **Actinomyces**
    - This is an inhabitant of the tonsillar area that is a common contaminant of sputum and bronchial specimens.
    - The cytologic features include fibrillary, "cotton-ball" like collection of filamentous bacteria that stain purple on Diff-Quik. Usually there is no acute inflammation if seen as a contaminant (consider true infection if associated with acute inflammation). These organisms can aggregate into sulfur granules, which appear yellow on gross examination.
  - **Nocardia**
    - *Nocardia* is an aerobic, filamentous bacterium that is acquired via inhalation, and usually occurs in immunocompromised patients.
    - It can cause cavitary nodules in 33% patients.
    - The cytologic features include acute inflammation with thin, filamentous, beaded organisms with right-angle branching F12.21.
  - **Legionella**
    - *Legionella* is also a bacterial pneumonia.
    - Ancillary studies demonstrate that the organisms are positive with silver stains (Steiner, Warthin-Starry, or Dieterle stains), IHC or immunofluorescent stains.

- Ancillary studies that are utilized include
  - Gram stain (gram positive organism), GMS stain (positive), acid fast stain (weakly positive with modified acid fast stain or Fite stain), and microbial cultures.

- **12.2.3.2 Viral Infections**
  - A variety of viral infections can be seen in the lung, including:
    - **Herpes simplex virus (HSV) infection**
      - Clinically may present in adults or neonates with who are immunocompromised, and may cause pharyngitis, laryngotracheitis, or pneumonia
      - HSV1 is most common subtype to involve respiratory tract.
The cytologic features include multinucleation, margination of chromatin, nuclear molding, and large eosinophilic intranuclear inclusions (Cowdry A inclusions) within the epithelial cells. Ancillary studies that can be utilized include viral culture, CMV immunocytochemical stain, or PCR.

- Supportive ancillary studies include viral culture, HSV immunostain, or in situ hybridization.

- **Cytomegalovirus (CMV) infection**
  - CMV is a common opportunistic infection in immunocompromised patients.
  - It clinically presents with fever, dyspnea, cough, and diffuse nodular interstitial infiltrates.
  - The viral cytopathic changes in CMV infections include nuclear enlargement, large basophilic intranuclear inclusions with surrounding halo ("owl eye" inclusions), occasionally small basophilic cytoplasmic inclusions, and enlarged cells (cytomegaly).
  - CMV does not only infect epithelial cells, but can also involve histiocytes, endothelial cells, or fibroblasts (infects epithelial or endothelial cells).

- **Measles virus**
  - Clinically, measles is a highly contagious, self-limited disease caused by rubeola virus.
  - It is less common today due to the widespread use of vaccination.
  - This virus can lead to pneumonia in immunocompromised children with prematurity, cystic fibrosis, malignancy, or an immune disorder.
  - The cytologic features include multinucleated cells with eosinophilic cytoplasmic and nuclear inclusions.

- **Respiratory syncytial virus (RSV) & parainfluenza**
  - RSV and parainfluenza show similar findings to that seen with measles virus.
  - These are commonly seen in pediatric patients with bronchiolitis or giant cell pneumonia.

**F12.22** BAL with herpes simplex virus infection (left, Pap stain, high magnification; right, H&E and HSV immunostain [inset], high magnification). This BAL showed large multinucleated cells with eosinophilic intranuclear inclusions, margination of the chromatin, and nuclear molding, in a background of inflammation. The cells were positive for the HSV1/2 immunocytochemical stain.

**F12.23** Lung infection with cytomegalovirus and *Pneumocystis jirovecii* (Pap stain, high magnification). This case shows the characteristic viral cytopathic effect seen with CMV infection with nuclear enlargement and large “owl eye” intranuclear inclusions. Foamy alveolar casts from infection with *Pneumocystis* are also seen in this case.
Cytology of Normal & Benign Elements > Cytology of Respiratory Infections

- The cytologic features include multinucleated cells with cytoplasmic and nuclear inclusions, basophilic cytoplasmic inclusions with halo, and occasionally a necrotic background.

  - Adenovirus
    - Clinically produces a febrile illness or severe pneumonia, but infection can be fatal in immunocompromised patients.
    - The cytologic features include ciliocytophthoria (detached ciliary tufts), F12.16, smudge cells with large intranuclear basophilic inclusions), and eosinophilic inclusions (resembling the Cowdry A inclusions seen with HSV).

12.2.3.3 Mycobacterial Infections

- Tuberculosis
  - Infection by Mycobacterium tuberculosis is one of the most common infections worldwide.
  - The cytologic features include granulomatous inflammation with multinucleated giant cells and frequently a necrotic background F12.24. The organisms may be difficult to detect because of the low number (unlike atypical mycobacterial infections, which usually have a large number of organisms visible). Ancillary studies that are helpful include acid fast stain, fluorescence microscopy with auramine O stain, culture, or PCR.

- Atypical mycobacteria
  - Infection usually occurs in immunocompromised patients, and is most commonly due to M avium intracellulare.
  - The cytologic features include histiocytic inflammation with histiocytes containing abundant cytoplasm that may appear foamy and are filled with organisms.
  - Organisms appear as a negative image because they are unstained rod shaped structures within the dark purple/blue background on Diff-Quik stained smears.
  - Ancillary studies that are helpful include acid fast stains, culture, and PCR.

12.2.3.4 Parasite Infections

- Parasitic infections are rare in the lung, but can be seen. The more common parasites in the lung include the following:
  - Strongyloides stercoralis (strongyloidiasis)
    - Respiratory infection with Strongyloides can be seen in patients on high dose corticosteroids for autoimmune diseases, renal transplant, or asthma.
    - Patients will have hemoptysis and cough up the organism in bloody sputum.
    - The cytologic features include filariform larvae (400-500 μm in length) with a notched tail that are large and seen at low power examination.

- Dirofilaria immitis
  - This is a dog heartworm that is transmitted by infected mosquitoes.
  - Usually the larvae migrate to the heart and die, then go to the pulmonary arteries and cause infarction. Thus, the prominent findings are debris due to the presence of infarction.

F12.24 Tuberculosis infection in lung (left, Diff-Quik, high magnification; right, H&E, low magnification). The touch preparation from this small, white lung nodule revealed necrotic debris with inflammatory cells and scattered Langhans-type giant cells. The corresponding histology showed necrotizing granulomas with AFB+ organisms consistent with M tuberculosis.
Toxoplasma gondii

- Toxoplasmosis is caused by an obligate intracellular protozoan that infects humans, but usually causes simply asymptomatic infection. In neonates and immunocompromised patients, the infection is severe and disseminated and can result in central nervous system abscesses, chorioretinitis, pneumonitis, myocarditis, and other organ involvement.
- Infection occurs by direct ingestion of oocytes in water or soil contaminated with cat feces, or by ingestion of raw or undercooked meat containing cysts.
- The cytologic features include an inflammatory background with crescent or banana shaped extracellular tachyzoites with a prominent central nucleus, that are seen best with a Wright-Giemsa or Romanowsky stain. Rarely, intracellular organisms can be seen within macrophages.
- Given that many laboratories use liquid based cytology for BAL processing and the organisms are only weakly stained and difficult to find, it is important to utilize alternative preparations (eg, Wright-Giemsa stained cytospins) in suspicious cases to avoid missing the diagnosis.
- An immunohistochemical stain for Toxoplasmosis is available to help in difficult cases.

Entamoeba gingivalis

- Entamoeba gingivalis is a protozoan that is usually found in the mouth and spread with oral contact. It can therefore be seen in sputum specimens, and has rarely been reported as a cause of a lung mass.
- The cytologic features include large “histiocyte-like” organisms with a dark centrosome. These organisms frequently phagocytose nuclear fragments of white blood cells, bacteria, and sometimes red blood cells into large food vacuoles.
- Actinomyces frequently is found with Entamoeba gingivalis in the same specimen, and the amoeba is sometimes best visualized at the periphery of the aggregates of actinomyces.
- Entamoeba gingivalis is similar to Entamoeba histolytica; however, Entamoeba gingivalis tends to be larger with a coarser karyosome and is more likely to have a inflammatory background with neutrophils. In addition, Entamoeba histolytica is more common as a cause of intestinal or liver infection.
- The organisms stain with PAS and fluorescein-labeled antibody.

![BAL in a heart transplant patient with toxoplasmosis](image1)

![Sputum specimen with Entamoeba gingivalis](image2)
Cytology of Normal & Benign Elements > Cytology of Respiratory Infections

- **Echinococcus granulosus**
  - *Echinococcus granulosus* is a dog tapeworm that causes hydatid disease. The eggs usually pass in the dog feces and contaminate food or drink that the human ingests, leading to infection.
  - Hydatid cysts have been reported in the liver, lung and brain as well circumscribed lesions. Symptoms can include a mass lesion or enlargement in these organs, or the patient can present after rupture of the cysts with hooklets in the sputum or evidence of anaphylactic shock. Thus, some include this rare entity as a contraindication to FNA due to the risk of rupture with resultant anaphylactic shock. However, in many cases, this diagnosis is unsuspected and FNA of these lesions has been reported.
  - The cytologic features include the characteristic refractile hooklets that look like tiny claws, and larger oval protoscoleces that contain internal refractile lines from the hooklets within **F12.27**.

### 12.2.3.5 Fungal Infections

- The common fungal infections seen in the lung are summarized below and in **T12.4**.


<table>
<thead>
<tr>
<th>Fungal Organism</th>
<th>Size &amp; Location</th>
<th>Morphology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candida</td>
<td>2-6 µm, extracellular</td>
<td>Yeast and pseudohyphae “balloon dogs” “shish kabob” edges not parallel</td>
</tr>
<tr>
<td>Aspergillus</td>
<td>3-6 µm, extracellular</td>
<td>Septated hyphae with narrow-angle (45°) branching</td>
</tr>
<tr>
<td>Zygomycetes</td>
<td>5-25 µm, extracellular</td>
<td>Broad, nonseptate hyphae with 90° branching “Ribbon like”</td>
</tr>
<tr>
<td>Histoplasma</td>
<td>2-4 µm, intracellular (within macrophages)</td>
<td>Symmetric, narrow based budding</td>
</tr>
<tr>
<td>Cryptococcus</td>
<td>5-20 µm, extracellular, occasionally intracellular</td>
<td>Asymmetric, narrow based budding, has thick mucoid capsule, few scattered forms (can be hard to find)</td>
</tr>
<tr>
<td><em>Pneumocystis jirovecii</em></td>
<td>Cyst measures 4-8 µm (about the size of a RBC), Trophozoites within cyst measure 0.5-1 µm, extracellular</td>
<td>Foamy alveolar casts with cysts that are cup shaped with a central dot, no budding &amp; no capsule</td>
</tr>
</tbody>
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**F12.27** Lung FNA in a patient with infection by *Echinococcus granulosus* (Pap stain, high magnification). Large protoscoleces are seen with internal refractile hooklets, and a few scattered refractile hooklets are seen as well (arrow).
Cryptococcus neoformans
- Cryptococcus is found in bird droppings and soil contaminated with bird droppings.
- The cytologic features include variably sized (5-20 μm) yeast forms (unlike uniform yeast forms in Candida), narrow-based asymmetric budding (tear drop shape), and a characteristic mucicarmine+ capsule (halo). The yeast forms measure 4-6 μm and are oval-to-round. There may be a background of granulomatous or histiocytic inflammation **F12.28**.
- Ancillary studies that are helpful include Grocott stain/GMS (stains positive, highlights budding), India ink (highlights capsule), mucicarmine (or PAS or alcian blue) special stain (particularly helpful for capsule-deficient Cryptococcus).
- Mimes of Cryptococcus mainly include Pneumocystis and Candida. However, unlike Candida, the yeast forms are unequal in size, have a surrounding capsule, and there are no long pseudohyphal structures. In comparison to Pneumocystis, Cryptococcus is slightly larger, with variably sized cysts, has a halo from the capsule, and does not occur in tight casts.

Histoplasma capsulatum (Histoplasmosis)
- Histoplasma is found in soil, particularly within the Ohio and Mississippi river valleys.
- Infection occurs by inhaling spores. The clinical presentation can mimic tuberculosis with nodular lung lesions and mediastinal lymphadenopathy, or it can present with disseminated, widespread disease. There are also reports of sclerosing mediastinitis associated with histoplasmosis infection.
- The cytologic features reveal small (2-4 μm), intracellular budding yeast forms that can be seen inside macrophages or neutrophils, with narrow based, equal budding. These cells look like a "polka dot" cell given the numerous yeast forms within the cytoplasm. There is often a background of granulomatous inflammation **F12.29 & F12.30**.
- Ancillary studies include Grocott stain/GMS to highlight the organisms.

Blastomyces dermatitidis (Blastomycosis)
- Blastomyces is found in wooded areas of North America, the Ohio and Mississippi River valleys, and in the southeastern USA.
- The cytologic features include broad-based budding yeast measuring 8-15 μm, thick refractile cell wall (double contour appearance), and acute suppurative or granulomatous inflammation **F12.31**.

Coccidioides (Coccidioidomycosis)
- Coccidioides is endemic in southwestern USA and Central-to-South America.
- The cytologic features include spherules (30-100 μm) and endospores (2-5 μm), with associated acute suppurative or granulomatous inflammation **F12.32**.
- Endospores may mimic Blastomyces dermatitidis, but are usually larger and do not show evidence of budding.
- Ancillary studies that can be helpful include Grocott stain/GMS, which stains spherules and endospores.
F12.29 Lung FNA with histoplasmosis (left and middle, Diff-Quik, high magnification; right, Grocott stain, high magnification). Small yeast forms are identified within macrophages with equal budding, and are highlighted on the Grocott stain (right).

F12.30 BAL with histoplasmosis (ThinPrep, Pap stain, intermediate and high magnification). This BAL showed macrophages with numerous yeast forms within the cytoplasm in a background of acute inflammation. Unlike normal alveolar macrophages, these cells have distinct dark dots from the intracellular yeast forms (“polka dot cells”).

F12.31 Sputum specimen with blastomycosis (ThinPrep, Pap stain, high magnification). This case shows abundant acute inflammation with yeast forms (arrow) that are larger than Candida and show evidence of broad based budding.

F12.32 Coccidiomycosis in Lung FNA (left, H&E, high magnification; right, Grocott stain, high magnification). Large spherules are identified in a background of debris. The Grocott stain highlights the endospores within the spherule and dispersed forms from rupture of one of the spherules.
Chapter 18

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See also DeMay RM. The Art & Science of Cytopathology, 2nd Edition.
Vol 2, Ch 14: Breast, pp 1052-1143.
18: Breast

Introduction

18.1 Introduction

- Fine needle aspiration (FNA) biopsy can be used to evaluate palpable and nonpalpable, mammographically evident breast lesions. This can be done without image-guidance for a palpable mass and with image-guidance for nonpalpable ones.

- The advantages of breast FNA include the fact that it is a rapid, simple, cost effective procedure with rare complications. Breast FNA also has high diagnostic accuracy and is useful in the management of a palpable breast mass (sensitivity 90% and specificity over 99%). Other advantages include the differentiation of benign cysts from cystic neoplasms, psychologic relief for patients with benign breast lesions, and the acquisition of material for diagnostic and prognostic testing, including FISH and other molecular tests. FNA is also an excellent tool for the detection of chest wall recurrences, distant solid organ metastases from breast primaries, and the evaluation of axillary lymph nodes. Breast FNA can occasionally be therapeutic as well as diagnostic in cases of abscess and benign breast cysts.

However, over recent decades many issues have arisen over the use of breast FNA for the initial diagnosis of breast carcinoma. This includes the need for adequate training and experience, the presence of atypical/indeterminate (“grey zone”) diagnoses which, in most cases, require tissue biopsy, the inability to evaluate for invasion, and need for sufficient tissue to perform prognostic studies such as estrogen/progesterone receptor status, cell proliferation index, and Her2neu expression. Another issue is the risk of litigation since breast FNA is one of the most common cytology specimens involved with lawsuits. This is mainly due to false positive diagnoses (eg, interpretive errors, such as overcalling a fibroadenoma), and false negative diagnoses (eg, sampling issues and interpretive errors from missing a lobular carcinoma).

- Obtaining a good clinical history prior to breast FNA biopsy is essential to determine if there is a family or personal history of malignancy. A strong family history of breast carcinoma requires adequate sampling and material for cell block for potential ancillary testing. A history of malignancy such as extra-mammary carcinoma or leukemia/lymphoma will raise the possibility of secondary involvement of the breast tissue and aid appropriate triage of the specimen during on-site evaluation. If the patient is pregnant, lactating or receiving hormonal treatment, this history is important because it will alert the cytologist to possible lactational changes, lessening the chance of over interpretation.

- In addition, the age of the patient is important. In young patients, common diagnoses include benign entities and certain malignancies, such as secretory carcinoma, basal-like carcinoma, or hematolymphoid malignancies.

- Breast implantation is a contraindication to breast FNA.

- On physical exam, the presence of nipple discharge and other characteristics of the mass lesion and overlying skin should be examined. If there is a nipple discharge, this can help in determining the differential diagnosis, and the nipple discharge can be sampled as a separate specimen for evaluation (see discussion on the nipple discharge later in the chapter).

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**T18.1 Advantages, disadvantages & complications of breast FNA**

**Advantage of breast FNA**
- Rapid and accurate diagnosis (minutes)
- Cost effective
- Can be used for palpable lesions (without US) or for nonpalpable lesion
- Minimal trauma (physically and psychologically)
- Faster management for patients with a breast mass
- Material can be collected for cell block for ancillary studies
- Avoidance of open biopsy (benign lesions, inoperable or recurrent lesions)
- Accurate and rapid assessment of tumor recurrence

**Disadvantage of breast FNA**
- Requires adequate training and experience
- Still requires open biopsy with atypical category (“gray zone” diagnoses)
- Can not reliably distinguish between in situ and invasive carcinomas
- Inability to offer specific diagnosis for some benign lesions
- Sensitivity is low in certain breast lesions: small, necrotic/cystic, hemorrhagic, desmoplastic, or deeply located tumors

**Complications of breast FNA**
- Hematoma
- Infection
- Pneumothorax
- Vasovagal reaction
- Tumor seeding
- Epithelial displacement artifacts (may cause false positive on biopsy)
**Introduction**

- Dedicated passes of aspirated breast tissue can be collected for cell block preparation. The cell block can provide tissue fragments F18.1 & F18.2 and cellular material ancillary studies in selected cases, which can confirm the diagnosis of malignancy (absence of myoepithelial markers p63, CK5/6, SMA, and calponin), subclassify the lesion, and provide prognostic and therapeutic information F18.3.

- Complications from breast FNA biopsy are extremely rare and include pain (mainly in the sub-areolar area), pneumothorax, needle tract seeding, hemorrhage (bleeding/hematoma), infection and vasovagal reaction. Displacement of epithelial cells and reactive tissue changes from the biopsy can cause alterations in the architecture and potentially lead to an erroneous diagnosis of invasive carcinoma on the subsequent excision. Therefore, some advocate performing mammography prior to FNA as changes due to aspiration may alter the mammographic findings T18.1.

- Cytologic findings should be correlated with clinical and radiologic findings (triple test). Additional sampling is indicated if there is any discordance between the FNA findings and the clinical or radiologic findings.

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**F18.1** Cell block from breast FNA of benign lesions: Upper left, breast FNA with fibrocystic change, upper right, breast FNA with benign lactational changes, lower left, breast FNA of papillary lesion/papilloma, and lower right, breast FNA with acute abscess. H&E, high magnification.

**F18.2** Cell block from breast FNA of malignant lesions. Upper left, breast FNA with ductal carcinoma, upper right, breast FNA with lobular carcinoma, pleomorphic variant, lower left, breast FNA of papillary lesion/papillary carcinoma, and lower right, breast FNA with metaplastic carcinoma. H&E, high magnification.

**F18.3** Cell block and ancillary studies in a case of ductal carcinoma of the breast (upper left, cell block, H&E; high magnification; upper middle, ER immunostain, upper right, PR immunostain; lower left, FISH testing of Her2neu with positive amplification, lower middle, Her2neu by immunostain 2+; and lower right Ki67 immunostain).
18.2 Normal Cytology & Reporting Terminology

- Adipose tissue, stroma and ductal epithelial cells are normal findings in breast FNA. A cytology specimen normally consists of fat, fibrous tissue, stromal cells and few duct or acinar cells. These epithelial cells should be regularly shaped and arranged in honeycombed sheets. Round to oval myoepithelial cells may be present as stripped nuclei or attached to epithelial sheets, but may not be obvious F18.4.

- Cytology reports should contain a statement of adequacy.

- Diagnostic categories in most laboratories include unsatisfactory for interpretation, negative for malignant cells, atypical/indeterminate, suspicious for malignancy and positive for malignant cells. Each category may have a statement explaining further findings.

- There is no standard for adequacy in breast FNA. If the lesion disappears after aspiration, it may be deemed adequate even when there is scant cellularity. However, most laboratories require a minimum of 6 clusters of epithelial cells (5-10 cells per cluster) on at least 2 slides.

- The unsatisfactory category is used for cases that lack an epithelial component (except in cystic lesions that have completely disappeared, suspected inflammatory lesions, suspected intramammary lymph nodes, or suspected lipoma cases), poorly preserved specimens, specimens significantly obscured by blood or inflammation, and markedly paucicellular specimens.

- Indications for breast FNA include the diagnoses of inflammatory diseases, primary and secondary tumors, and tumor recurrence; in addition to therapeutic drainage of simple/inflammatory cysts.

- False negative diagnoses in breast FNA have been reported due to significant desmoplasia as seen in lobular carcinoma; small carcinomas arising in a benign lesion such as a complex proliferative lesion or papilloma, well differentiated carcinomas such as tubular carcinoma, colloid carcinoma, or secretory carcinoma; rare tumor types (such as metaplastic carcinoma, apocrine carcinoma); and tumors with extensively necrotic or cystic components; and poorly prepared or inadequate smears.

- False positive diagnoses on breast FNA have been reported due to over interpretation of fibroadenomas; proliferative breast diseases with atypia; papillary lesions; pregnancy/lactational changes, fat necrosis, collagenous spherulosis, epidermal inclusion cyst and unusual benign skin adnexal tumors.

18.3 Benign Conditions

18.3.1 Breast Cystic Lesions

- Benign cysts (single or multiple) are common constituting 15% of breast FNA specimens and nearly all have a benign clinical course (>99%).

- Breast FNA in these lesions is diagnostic and therapeutic.

- The aspirate yields clear, cloudy, yellow fluid from a recent cyst or greenish fluid from an older cyst.

- This fluid may be discarded rather than processed for cytology.

- If a solid mass is appreciated after fluid drainage, then adequate sampling by FNA is required to exclude malignancy.

- The specimen is usually scant, with few clusters of ductal cells, apocrine cells and foam cells F18.5 & F18.6.

- The ductal or apocrine cells are arranged in cohesive, honeycomb sheets with a uniform appearance along with a few attached myoepithelial cells at the periphery or naked in the background.
Benign Conditions > Breast Cystic Lesions

- The differential diagnosis includes seroma (usually occurs at a prior breast surgery site and lacks ductal cells) and intracystic carcinoma (usually bloody fluid and suspicious mass by radiology).

18.3.2 Fibrocystic Change

- Fibrocystic changes of the breast are the most common breast abnormality. They are not pathologic but instead a complex of morphologic alterations consisting of any combination of cystic changes, apocrine metaplasia, fibrosis, sclerosing adenosis, ductal hyperplasia, or columnar cell changes.

- The cytologic features of fibrocystic changes are divided into nonproliferative morphology (no increased risk of malignancy) and proliferative morphology (has mild increased risk of malignancy) based on the presence or absence of significant ductal hyperplasia. When present, proliferative breast lesions can be seen without atypia (hyperplasia) or with atypia (atypical ductal or lobular hyperplasia) T18.2.

**T18.2 Cytomorphology of normal & benign noninflammatory breast lesions**

<table>
<thead>
<tr>
<th>Cytomorphology of breast FNA</th>
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<tbody>
<tr>
<td>Scant cellularity</td>
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<tr>
<td>Small clusters of benign ductal cells</td>
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<tr>
<td>Ductal cells are uniform with small nuclei &amp; cytoplasm in sheets</td>
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<tr>
<td>Myoepithelial cells—naked oval/spindle nuclei</td>
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<td>Adipose tissue fragments</td>
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<tr>
<th>Cytomorphology of nonproliferative breast disease</th>
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<tr>
<td>Low cellularity</td>
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<tr>
<td>Monolayered clusters of uniform cells with a honeycomb pattern</td>
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<tr>
<td>Mixture of apocrine cells; foam cells &amp; myoepithelial cells</td>
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<td>Stromal fragments and/or adipose tissue</td>
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<table>
<thead>
<tr>
<th>Cytomorphology of proliferative breast disease (without atypia)</th>
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<tr>
<td>Moderate to high cellularity</td>
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<tr>
<td>Marked number of large highly cohesive cell clusters</td>
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<tr>
<td>Overlapping of nuclei, nuclear enlargement &amp; occasional micronucleoli</td>
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<tr>
<td>Apocrine cells, histiocytes &amp; myoepithelial cells</td>
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<td>Mild loss of polarity</td>
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<tr>
<th>Cytomorphology of lactational changes</th>
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<tr>
<td>Cellular smears</td>
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<tr>
<td>Numerous epithelial cells in isolated, loose clusters or sheets</td>
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<tr>
<td>Background of fat droplets and cellular debris</td>
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<tr>
<td>The cells have abundant, foamy or vacuolated cytoplasm</td>
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<tr>
<td>Numerous naked nuclei due to cytoplasmic fragility</td>
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<tr>
<td>The nuclei exhibit enlargement &amp; prominent nucleoli</td>
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<tr>
<td>No irregular chromatin contours, rare bipolar naked nuclei</td>
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<tr>
<th>Cytomorphology of atypical hyperplasia</th>
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<tr>
<td>Cellular aspirate</td>
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<tr>
<td>Crowding of epithelial cells with overlapping of the nuclei</td>
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<tr>
<td>Nuclear enlargement, anisonucleosis &amp; chromatin clumping</td>
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<tr>
<td>Occasional conspicuous nuclei</td>
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<tr>
<td>Myoepithelial cells present</td>
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<tr>
<td>Rare apocrine cells &amp; macrophages</td>
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<tr>
<th>Cytomorphology of fibroadenoma</th>
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<tr>
<td>High cellularity</td>
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<tr>
<td>Biphasic (epithelial component &amp; stromal component)</td>
</tr>
<tr>
<td>Sheet of monolayered ductal epithelial cells forming “antler-horn”</td>
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<tr>
<td>Bipolar naked nuclei; apocrine metaplasia, mucinous changes</td>
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<tr>
<td>Rare multinucleated giant cells</td>
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<td>Stromal fragments, few</td>
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**F18.5** Foamy macrophages from a benign breast cyst. Scattered histiocytes with abundant vacuolated cytoplasm and small uniform nuclei are shown. Their cytoplasmic border is well defined and the background has proteinaceous material (left, Diff-Quik, and right, Pap stain, high magnification).

**F18.6** Apocrine cyst. Foamy macrophages as well as sheets of benign apocrine cells (left) and reactive epithelial cells (right) are shown in this breast FNA. Pap stain, high magnification.
Benign Conditions > Breast Cystic Lesions

- FNA in nonproliferative breast aspirates may show scant cellularity or occasional hypercellularity depending on the degree of fibrosis. The aspirate shows a mixture of any of the following morphologies: benign cysts (see above); ductal or apocrine cells in sheets or isolated, myoepithelial cells, histiocytes (foam cells), cellular debris, proteinaceous material, crystals and inflammation F18.7. The cells can show degenerative changes, apocrine metaplasia, or columnar configuration in selected cases (papillomatosis). In nonproliferative fibrocystic change, the ductal cells are uniform and arranged in 2-dimensional groups of cohesive orderly, uniform cells F18.8 & F18.9 and associated with myoepithelial cells. Myoepithelial cells are admixed into the epithelial groups or seen as naked, bipolar nuclei. Ductal cells with columnar features may be seen in the spectrum of fibrocystic changes, are usually a minor component and may be indicative of papillomatosis F18.10. Benign apocrine metaplastic cells are often arranged in 2-dimensional sheets and may show considerable pleomorphism and prominent nucleoli F18.11. Nucleoli are commonly seen in benign and malignant lesions and are not a reliable indicator of malignancy. Apocrine carcinoma is extremely rare and usually presents with high grade features, and a large number of anaplastic single cells with multiple prominent nucleoli and necrosis.

- The cytologic features of proliferative breast lesions without atypia show similar morphology, but the specimens are more cellular and the ductal epithelial cells are hyperplastic (proliferative) F18.12 displaying 3-dimensional groups or sheets with a tightly packed crowded appearance (the landmark of this entity).

**F18.8** Fibrocystic change. A large fragment of uniform ductal epithelium is shown with mildly crowded nuclei. The sheets are cohesive and exhibit a flat honeycombed architecture (cytospin; left, Diff-Quik, and right, Pap stain; high magnification).

**F18.7** Fibrocystic changes (nonproliferative breast disease) with large fragments of apocrine cells arranged in large monolayers. Pap stain, medium and high magnification.

**F18.9** Fibrocystic change (nonproliferative breast disease) in Thin Prep preparation. These cohesive sheets of ductal cells have clear chromatin and small nucleoli. Myoepithelial cell nuclei (circle, left) are present within the sheet. Pap stain, intermediate magnification, left and high magnification, right.
Benign Conditions > Breast Cystic Lesions

slightly irregular cytoplasmic borders, and small nucleoli. The presence of myoepithelial cells admixed in the clusters or nearby is quite significant, since they are absent in invasive carcinoma F18.13.

- The cytology of proliferative breast lesions with atypia will show crowded 3-dimensional cell clusters displaying moderate cellular pleomorphism and anisonucleosis, occasional chromatin clumping, micronucleoli and few myoepithelial cells T18.2 (p 389).

F18.10 Ductal cells, columnar cells, and apocrine cells with fibrocystic changes (cytospin preparation). The presence of columnar cells in this specimen suggests a papillomatosis component. Pap stain, intermediate magnification.

F18.11 Apocrine cells in a sheet from a breast FNA with fibrocystic changes (nonproliferative breast disease). The apocrine cells show reactive atypia including nuclear enlargement, pleomorphism, and prominent nucleoli. Diff-Quik, intermediate and high magnification.

F18.12 Ductal hyperplasia without atypia. The ductal cells are crowded and overlapped. There is mild nuclear enlargement and hyperchromasia. Pap stain, intermediate and high magnification.

F18.13 Ductal hyperplasia without atypia. The ductal cells are crowded and overlapped. Myoepithelial cells are best appreciated above and below the focus plane (right). Pap stain, high magnification.
18.3.3 Fibroadenoma

- Fibroadenoma is the most common benign tumor, and typically occurs in young women between the ages of 20 and 35 years.
- They are usually well circumscribed, freely mobile, solitary, firm, discrete nodules that are roughly 2-3 cm in size, and can be multiple.
- The risk of carcinoma arising from a fibroadenoma is extremely rare, but when present, is usually lobular neoplasia.
- On cytology, fibroadenomas yield highly cellular aspirates showing a characteristic biphasic appearance (epithelial and stromal tissue fragments) in a background of myoepithelial cells F18.14.
- The epithelial component will show cohesive monolayered sheets of well organized ductal-type epithelium with “papillary-like” or “stag horn” branching architecture and scattered naked bipolar myoepithelial nuclei. The stromal component appears as fibrous stromal fragments with bright metachromatic or magenta-colored stromal appearance on Diff-Quik and pale green in Pap stain F18.14-F18.16. The stromal component may show mucinous changes that create the erroneous impression of a mucinous carcinoma F18.16. Furthermore, fibroadenoma may show columnar cell morphology, apocrine cells, foam cells, and multinucleated cells.

- Fibroadenomas are the most common cause of false positive diagnoses in breast FNA, since it can have cytomorphologic overlap with atypical ductal hyperplasia, a papillary lesion (staghorn clusters can be confused with papillae), ductal carcinoma, or mucinous carcinoma.

F18.14 Fibroadenoma (conventional smear). A branching tubular structure is shown combined with a stromal matrix component (right) and myoepithelial cells. Pap stain, high magnification.

F18.16 Fibroadenoma showing myxoid change (conventional smear preparation). A combined stromal and epithelial component is present with abundant single myoepithelial cells in a myxoid background. Diff-Quik, intermediate magnification, left and high magnification, right.
18: Breast

**Benign Conditions > Fibroadenoma | Lactational Changes**

- Juvenile fibroadenomas may show a more monomorphic appearance with predominantly larger epithelial fragments of a bland uniform columnar type. A papillary architecture can also be a prominent feature.

**18.3.4 Lactational Changes**

- Lactational changes are seen in breast FNA due to hormonal changes during pregnancy or the postpartum period which may promote the formation of nonneoplastic breast lesions or highlight the presence of preexisting ones.
- Histologically, there is lobular and ductal proliferation characterized by epithelial cells with cytoplasmic vacuolization and intraluminal secretion. These lesions often show a benign course and regress after cessation of hormonal stimuli.
- These nodules are also rarely found in ectopic locations, such as the axilla or vulva.
- The cytologic features of lactational changes include numerous epithelial cells loosely clustered or isolated in a background of fat droplets and cellular debris. The cells have abundant, foamy or vacuolated cytoplasm, and due to the cytoplasmic fragility, most of the cells are present as naked nuclei. The nuclei exhibit nuclear enlargement and prominent nucleoli. However, the chromatin contours of these nuclei are regular with delicate chromatin. A scarce number of bipolar naked nuclei can also be found in these smears as well as the presence of sheets of ductal epithelial cells mixed with myoepithelial cells F18.17.
- Given the high cellularity of these specimens, with prominent nucleoli and nuclear enlargement, and numerous single cells, these aspirates can be overcalled as malignant. Therefore, it is important to recognize secretory changes as compatible with pregnancy or lactational status. These findings, along with the clinical history, help in the distinction from breast carcinomas. If a history of pregnancy/lactation is not provided, the background of fat droplets and cellular debris is a helpful clue.

**18.3.5 Mastitis**

- Patients present with a painful breast mass.
- Breast abscesses can be associated with or without lactation.

The most common cause of bacterial infection is *Staphylococcus aureus*; however, other bacteria may be involved. On very rare occasions, mycobacterial tuberculosis or nonbacterial infections such as cryptococcus, aspergillus, echinococcus, leishmaniasis, filariasis and cysticercosis may be seen.
- Aspirates that yield frank pus should be submitted for microbiologic culture which may prove very helpful for diagnosis and treatment.
- Aspirates of acute mastitis or abscess show numerous neutrophils; lymphocytes, histiocytes, necrosis and occasionally eosinophils and plasma cells. Histiocytes with ingested material may be prominent F18.18. In rare cases the causative pathogen may be noted and confirmed by Gram stain.
- Ductal cells may be present and show reparative changes with enlarged nuclei and prominent nucleoli; however, they should be cohesive and associated with myoepithelial cells in comparison to invasive ductal carcinoma.
Benign Conditions>

18.3.6 Subareolar Abscess (Zuska Disease)
- Subareolar abscess is located in the periareolar area of the breast and it is associated with squamous metaplasia of the lactiferous ducts and keratin debris. It may present as a painful breast mass, nipple retraction, discharge, and fistula.
- The aspirate shows numerous squamous cells (nucleated and anucleate), keratinized debris, and inflammatory cells including neutrophils, lymphocytes and histiocytes. Foreign-body type giant cells may be seen.
- The differential diagnosis includes epidermal inclusion cyst, especially if ruptured. Knowledge of the location of lesion is helpful as subareolar abscess is periareolar while epidermal inclusion cyst can occur anywhere in the subcutaneous tissue of the breast.

18.3.7 Granulomatous Mastitis
- Granulomatous mastitis is a specific chronic inflammatory condition of the breast that may mimic carcinoma clinically. It may be associated with hematoma. The cause in most cases is unknown; however, occasionally it can be due to mycobacterial or fungal infection.
- The aspirate shows epithelioid histiocytes in loose clusters with ill-defined cytoplasm, multinucleated giant cells, lymphocytes, plasma cells, neutrophils, necrosis, and occasionally ductal epithelial cells with reactive changes.

18.3.8 Fat Necrosis
- Fat necrosis of the breast is not an uncommon lesion, it typically presents as a firm, irregular, tender breast mass.
- It is usually secondary to trauma and may clinically and radiologically mimic carcinoma. The trauma may, in some patients, be relatively mild and be forgotten by the time the patient presents with a mass lesion.
- The cytologic findings depend on the stage of presentation with early lesions presenting with more degenerative fat and lipophages and later lesions with fibrosis.
- The specimen is often scant in cellularity with an abundance of lipid laden macrophages (lipophages), fat in various stages of degeneration, giant cells, inflammatory cells, endothelial proliferation, and fibrosis.
The background may show degenerated/necrotic fat cells, with dirty granular background. Erythrophagocytosis may also be seen if the lesion is associated with a hematoma F18.22.

Pitfalls include overcalling as carcinoma due to reactive atypia and proliferating fibroblasts F18.22. Other histiocytic lesions should be considered as well. For example, crystal storage histiocytosis has been described in the breast and is frequently associated with a lymphoproliferative disorder, which should be excluded. In crystal storage histiocytosis, there is usually a large number of plasma cells, whereas fat necrosis contains more neutrophils. Breast carcinoma may sometimes be associated with fat necrosis, therefore a woman with a cytologic diagnosis of fat necrosis should be followed until the lesion resolves.

**18.3.9 Epidermal Inclusion Cyst**

- These cysts are common and found in the subcutaneous tissue.
- They may be secondary to trauma or a dilated hair follicle.
- There can be associated pain when they are ruptured or inflamed. The keratin debris evokes an inflammatory response.
21.1.1 Sampling Techniques & Processing

- Cytologic brushings can be performed if there is a superficial lesion visualized by endoscopy. These brushes can provide smears if the brush is rolled over a slide, which can be helpful if on-site evaluation is desired. In addition, the brush can be submitted in a transport media or CytoLyt/ThinPrep vial. Small tissue fragments can be removed from the brush and submitted as a cell block and/or the remainder of the material on the brush can be removed by vortexing the brush in the transport media and preparation of cytopsin or liquid based cytology (eg, ThinPrep) preparations.
- Fine needle aspirations can be used for deeper lesions, and can provide material for smears, cell block, and liquid based cytology or other preparations. This is particularly helpful because core biopsy may not be able to target these deeper lesions accessible by FNA.

21.1.2 Accuracy

- The sensitivity generally ranges from 75-95% for malignancy; however, the sensitivity varies based on the location in the gastrointestinal tract, the sampling method used, and the type of lesion being sampled. For adenocarcinomas of the gastrointestinal tract, the sensitivity is ~75-95% and the specificity is usually >95%.
- The sensitivity and specificity are optimized with the use of biopsy with cytology. In addition, the accuracy of brushing specimens is greater if done before surgical biopsy (ie, brushing then biopsy).
- The sensitivity and specificity for detecting intestinal metaplasia is lower than that for detecting adenocarcinoma; however, in the setting of dysplasia, cytology does a better job in detection of intestinal metaplasia. In general, the sensitivity for detecting intestinal metaplasia in cytology is ~40% and the specificity is ~85%.

21.2 Esophagus

- Cytologic specimens from normal esophagus will show a predominance of mature squamous cells, occasional glandular epithelial cells from the gastroesophageal junction can also be seen.

21.2.1 Infection/Esophagitis

- Noninfectious causes of esophagitis include trauma, reflux, scleroderma or systemic sclerosis, avitaminosis, hiatal hernia, chemical esophagitis due to medication. However, the precise etiology cannot be determined by cytology and requires clinical correlation.
- Brushing specimens are usually more sensitive than biopsy specimens in the setting of infection due to the greater sampling area.
- Since oropharyngeal contamination with bacteria is common in these specimens, the presence of bacteria in frequently seen, but is usually not clinically significant. The lack of inflammation and the presence of the bacteria in association with mature squamous cells can help in identifying oropharyngeal contamination. In addition, the amount of oropharyngeal contamination is minimized by the use of a sheath to protect the brush before sampling of the lesion in the esophagus.
- Cytologic features will include reactive squamous cell and inflammatory cells, occasionally with prominent inflammatory debris. Reactive squamous cells can occasionally show pseudo-halos with a tight area of clearing around the nucleus F21.1.

- Candida will show pseudohyphae and yeast forms F21.1-F21.2.
Herpes simplex virus (HSV) infection will show the characteristic findings of multinucleation, margination of chromatin, and nuclear molding, in addition to findings seen with ulceration F21.3-F21.5.

Cytomegalovirus (CMV) infection will show more mononuclear cells than seen in HSV and will show a single large intranuclear inclusion with perinuclear halo, and occasionally intracytoplasmic inclusions F21.3.

Nonspecific inflammatory changes without an identifiable organism will be seen in the noninfectious causes of esophagitis, and thus, is essentially a diagnosis of exclusion.

IHC: immunostains are available to detect HSV 1 and 2, in addition to CMV.

Special stains: Grocott/GMS stain is helpful for confirming the presence of fungal organisms and to highlight the morphology of the yeast or hyphae for classification.

In situ hybridization and polymerase chain reaction (PCR) can also be used in the diagnosis of some infectious etiologies.

F21.2 Esophageal brushing with Candida (left, Thin Prep, intermediate magnification; right, Thin Prep, high magnification). Mature squamous cells are seen with intermixed yeast forms and pseudohyphae, compatible with Candida species.

F21.3 Esophageal brushing with cytomegalovirus (CMV) and herpes simplex virus (HSV) (left, CMV, Thin Prep, intermediate magnification; right, HSV, SurePath, high magnification). On the left, there are cells with large intranuclear inclusions in a case of CMV infection in the esophagus. On the right, mature squamous cells are seen with a rare cell showing multinucleation, margination of the chromatin (nuclear clearing with the chromatin condensed at the periphery of the nucleus), and nuclear molding, consistent with the cellular features associated with HSV infection.

F21.4 Brushing of an oral lesion in a transplant patient (left, Diff-Quik, high magnification; right, Pap stain, high magnification). The aspirates from this oral lesion reveal squamous cells with prominent margination of the chromatin and multinucleation. The margination of the chromatin is easily seen on the Pap stain. Viral changes like this can mimic malignancy, particularly keratinizing squamous cell carcinoma; however, the chromatin pattern is helpful in excluding the coarse chromatin of malignancy.
The differential diagnosis includes reactive/reparative changes in the absence of infection, and malignancy. Malignancy will usually show more obvious nuclear pleomorphism and variability in nuclei, with a lack of viral inclusions or chromatin clearing, and an absence of an acute inflammatory response.

### 21.2.2 Ulceration & Reactive/Reparative Changes

- In the setting of esophageal ulcers or other mucosal injury, the squamous epithelium can undergo reactive and reparative changes, and may be associated with granulation tissue that can mimic malignancy cytologically.
- Radiation and other treatment-related effects, such as those that occur with chemotherapy, can also mimic malignancy; however, there is usually not an elevated nuclear-to-cytoplasmic ratio, since the nuclear size and cytoplasm both increase. In addition, the 2-tone cytoplasm, cytoplasmic vacuolization, and occasional multinucleation, along with a pertinent clinical history, can help in supporting reactive or treatment-related changes.

- Other changes in the esophagus can also cause reactive changes that can mimic malignancy, including pemphigus vulgaris, where the squamous epithelial cells have bullet or bar-shaped nuclei, discohesion, and monotony. The predominance of single cells occurs due to the autoimmune destruction of intercellular junctions.
- Reactive and reparative atypia can give rise to false positive diagnoses of malignancy and lower the specificity; thus, it is important to adhere to strict criteria when evaluating these specimens to avoid an overdiagnosis.
- The cytologic features that favor a benign/reactive process over malignancy include small prominent nucleoli, fine chromatin, uniform appearing cells with streaming of the cells in a 2-dimensional sheet, and the presence of inflammation (infiltrating neutrophils or an inflammatory background) F21.6. Also, a low nuclear-to-cytoplasmic ratio, 2-tone cytoplasm, and cytoplasmic vacuolization can be a clue to the reactive nature of the changes.
21.2.3 Intestinal Metaplasia

- Barrett esophagus occurs in patients with gastroesophageal reflux when the esophageal squamous epithelium is replaced by intestinal columnar epithelium with goblet cells.
- >90% of esophageal or gastroesophageal adenocarcinomas arise from Barrett esophagus.
- Sensitivity and specificity for detecting intestinal metaplasia is less than that for detecting malignancy, due to the cytomorphologic overlap with normal gastric mucosa with features that can mimic goblet cells (e.g., pseudogoblet mucus cells). However, in the setting of dysplasia, the sensitivity for cytologic detection of intestinal metaplasia is improved.
- Cytologic features of intestinal metaplasia include the presence of goblet cells where there is a single, large vacuole within the cytoplasm of glandular cells, usually pushing and indenting the nucleus. In the setting of dysplasia, there can be crowded groups of cells with nuclear atypia that approaches the cytologic changes seen in adenocarcinoma.
- Differential diagnosis includes gastric epithelium, which usually appears as glandular cells without discrete large vacuoles. However, “pseudogoblet cells” can be seen and may be difficult to distinguish from intestinal metaplasia on Papanicolaou staining. On an H&E stained cell block, the goblet cells have more gray-pale blue staining (acid mucin) in their cytoplasm, whereas “pseudogoblet cells” have pink vacuoles (neutral mucin). In the setting of dysplasia, it is usually easier to definitively see intestinal metaplasia in the background. The differential diagnosis for dysplasia in Barrett includes reactive change and malignancy. Most cases of dysplasia will lead to indeterminate cytologic diagnoses (atypical or suspicious) with a recommendation for biopsy to exclude the possibility of invasive carcinoma, since there is cytologic overlap. In fact, high grade dysplasia and adenocarcinoma have so much morphologic overlap, that one of the only helpful features is the amount of atypia present (focal in dysplasia and more diffusely present in carcinoma) and the presence of diathesis or necrosis in the background; however, in the setting of specimens with limited cellularity, this can be difficult.

21.2.4 Benign Neoplasms

- Benign neoplasms in the esophagus include papillomas, which are similar to condyloma acuminatum, and may be associated with HPV infection. The cytology in these lesions reveals benign/reactive squamous cells with occasional koilocytic changes, and without distinctive features of malignancy, in a clean background devoid of necrotic debris. Endoscopic correlation is important to identify if a papillary or raised lesion was identified.
- In addition, rare reports of granular cell tumors and leiomyomas have also been reported in esophageal cytology specimens.

21.2.5 Malignancies

- The primary malignancies of the esophagus include adenocarcinomas of the gastroesophageal junction, and squamous cell carcinomas, including variants, such as basaloid squamous cell carcinomas.
- These primary tumors are most often sampled with biopsy, or cytologic brushings with biopsy, given that there is usually a luminal mass that is visualized and easily sampled with a biopsy.
In the setting of a periesophageal mass being sampled, it is important to ask the endoscopist if there are endoscopic findings suggestive of a luminal tumor, Barrett esophagus, or dysplasia because there are reports of FNA needle contamination from the FNA needle passing directly through a luminal tumor or atypical/dysplastic epithelium, or contamination by tumor cells within the luminal fluid from a nearby tumor. This is important because contamination involving a periesophageal lymph node EUS FNA sample could lead to a false positive diagnosis of malignancy (if the FNA is contaminated by atypical/dysplastic epithelium that is overinterpreted as malignancy), or an overdiagnosis of metastatic malignancy (if the FNA is contaminated by luminal tumor in a lymph node sample) with resultant overstaging of a patient.

21.2.5.1 Squamous Cell Carcinoma

- Most common malignancy in the esophagus, and unrelated to intestinal metaplasia or Barrett esophagus.
- Esophageal squamous cell carcinoma presents with difficulty swallowing due to mass obstruction.
- Some of these tumors can be HPV-related, and some show a strong correlation with diet (e.g., nitrosamine intake).
- The cytologic features vary depending on the differentiation of the tumor. Some tumors are well differentiated or keratinized and show abundant keratin debris with discohesive cells that have orangophilic cytoplasm, nuclear hyperchromasia, nuclear enlargement and irregular nuclear contours. Well differentiated tumors showing more single keratinized cells with orangophilic cytoplasm on Papanicolaou staining and tadpole-like shapes with long cytoplasmic tails. However, unlike benign squamous cells, there is marked nuclear atypia with hyperchromasia and irregularities. In more poorly differentiated tumors, there is scant cytoplasm with enlarged hyperchromatic nuclei that lack the single keratinized cells and tend to have more conspicuous nucleoli. Some squamous cell carcinomas may also show a small round blue cell type morphology with nuclear molding, nuclear-to-cytoplasmic ratios, palisading, crush artifact, and discohesion, which can be seen in the basaloid variant of squamous cell carcinoma.
- The differential diagnosis includes reparative/reactive changes, especially in the setting of ulceration or radiation, dysplasia, and other malignancy (poorly differentiated adenocarcinoma).

21.2.5.2 Adenocarcinoma

- The rate of adenocarcinoma of the esophagus and gastroesophageal junction has increased dramatically in the past 2 decades.
- Usually (>90%) arises in the background of intestinal metaplasia or Barrett esophagus.
- The distinction between high grade dysplasia and intramucosal or invasive adenocarcinoma may be difficult in some scenarios, and in these cases, a concurrent endoscopic biopsy can be helpful.

F21.8 Poorly differentiated squamous cell carcinoma of the esophagus (left, Diff-Quik, intermediate & high magnification; right, H&E, high magnification). The specimen reveals clusters of cells with hyperchromasia, increased nuclear-to-cytoplasmic ratios, and nuclear pleomorphism. These cells were positive for p53, and the corresponding resection showed poorly differentiated squamous cell carcinoma with basaloid features.
21: Gastrointestinal Tract & Bile Ducts

Esophagus > Malignancies

| Stomach > Infection/Gastritis |

- The cytologic features depend on the type of adenocarcinoma, but usually there is a high cellularity with tumor diathesis and a background of goblet cells. Intestinal type adenocarcinoma will show features typical of an adenocarcinoma, including disorganized cohesive clusters with nuclear enlargement, prominent nucleoli, elevated nuclear-to-cytoplasmic ratios, nuclear irregularities, and glandular formation. Signet-ring type or poorly differentiated adenocarcinomas will show more single cells and may have more vacuolated cytoplasm, which can make the diagnosis difficult, especially in cases with limited cellularity.

- IHC & special stains: mucicarmine+, variably CK7+, CK20+ & CDX2+; p63– & CK5/6–.

- The differential diagnosis includes reactive/reparative changes (less atypia, inflammatory background, does not meet all features of malignancy T21.2, dysplasia, and other poorly differentiated tumors (particularly squamous cell carcinoma).

21.2.5.3 Other Malignancies

- Other rare malignancies reported in the esophagus include salivary gland-type tumors (eg, adenoid cystic carcinoma), sarcomas, choriocarcinomas, and primary esophageal melanomas.

21.3 Stomach

- Cytologic specimens from normal stomach will show a predominance of benign glandular epithelial cells with columnar morphology, moderate amounts of cytoplasm, and centrally located round nuclei F21.9. These benign glandular cells can be seen in strips, honeycomb (2-dimensional sheets; F21.9), or tubular arrangement when cells are vigorously brushed causing the entire gland to be seen intact. Occasional squamous cells may be seen from the esophagus or oropharyngeal contamination.

21.3.1 Infection/Gastritis

- The infections in the stomach, include fungus and viral infections, as seen in the esophagus, but also Helicobacter pylori (H pylori) and atypical mycobacteria.
21.3.2 Reactive Changes

There are a myriad of cases of reactive atypia in the stomach, including, but not limited to medications (e.g., aspirin, other analgesics), granulomatous disease, infection, and vitamin deficiencies (e.g., pernicious anemia).

The cytologic features of reactive change include flat, cohesive clusters with regular, smooth nuclear membranes and without significant variability in nuclear size. Uniform, prominent, often multiple, nucleoli can also be seen. There is often a prominent inflammatory background or presence of inflammatory cells attached to the cell groups with atypia. Usually the changes in reactive atypia are seen in a few cells and exist with a spectrum of changes from benign to reactive, whereas in malignancy, the changes are seen in more of the cells in the sample, there are more single cells, and there are 2 distinct populations without a continuum.

Differential diagnosis includes chronic inflammatory process, infection-related atypia, chemoradiation effect, or other reactive process, in addition to dysplasia, intramucosal carcinoma, and invasive gastric adenocarcinoma.

21.3.3 Spindle Cell Lesions/Tumors

Spindle cell lesions can occur in the stomach can be attributed to a variety of causes, but most commonly leiomyomas, gastrointestinal stromal tumors (GISTs), or neural tumors (e.g., schwannomas). Rarely vascular neoplasms and glomus tumors can present in the stomach.

IHC findings can be critical for determining the type of spindle cell lesion.

21.3.3.1 Gastrointestinal Stromal Tumor (GIST)

Spindle cell or epithelioid neoplasms that can recapitulate differentiation towards the interstitial cells of Cajal, which are involved with coordinating gut motility.

Can show either spindle cell morphology (70%) or epithelioid morphology (30%).

These tumors can arise in a variety of locations in the gastrointestinal tract and the behavior of these tumors is related to its site, with tumors in the small bowel having the worst behavior prognosis. They are most common in the stomach, followed by the small intestine, and are rare in the colon.
Stomach>Spindle Cell Lesions/Tumors

- When in the stomach, they usually arise in the submucosa, so are not usually visualized on the mucosal surface by endoscopy, and may be missed by superficial biopsy or brushing.
- The majority of these tumors are benign, but 10-30% are malignant and represent ~1% of GI malignancies. Determination of the biologic behavior of these tumors is best analyzed upon surgical resection. Some of the features that favor malignancy include the following: size >5 cm, necrosis, hemorrhage, hyper-cellularity, nuclear atypia, and mitotic activity (mitotic count >5/50 HPF).
- Some GISTs respond to the targeted therapy, imatinib mesylate, which is also used in the treatment of chronic myelogenous leukemia.
- Local recurrences and metastases commonly develop in the abdominal cavity and liver, but are rare in the bone, soft tissue and lymph nodes.
- Cytologic features include cellular specimens with a uniform population of discohesive or loosely cohesive spindle or epithelioid cells with delicate cytoplasmic extensions and inconspicuous nuclei. These cells are seen in loose clusters or sheets. Occasional paranuclear vacuoles and stripped nuclei can also be seen. Some cases have metachromatic background material or necrosis in the background. The malignant cases tend to have more pleomorphism, more mitoses (>5/50 HPF), and may have necrosis.

IHC: c-kit/CD117+, DOG1+, and sometimes CD34+; negative for desmin and smooth muscle actin.

Molecular studies have revealed mutually exclusive mutations in KIT (60-80%) and PGFRA (5-10%) genes.

The differential diagnosis of GISTs depends on the predominant cellular morphology.

F21.11 Epithelioid gastrointestinal stromal tumor (GIST) (Diff-Quik, high magnification). Loosely cohesive epithelioid cells are seen with interlacing metachromatic stromal material. The tumor cells have occasional vacuoles in the cytoplasm, and some appear as stripped nuclei.

F21.12 Spindle cell gastrointestinal stromal tumor (GIST) (left, Diff-Quik, high magnification; right, Pap stain, high magnification). The tumor cells appear in cellular clusters and have uniform, long, cigar-shaped nuclei within a metachromatic background.

F21.13 Spindle cell gastrointestinal stromal tumor (GIST) (left, H&E, high magnification; right upper, CD117/c-kit stain; right lower, DOG1 stain). The cell block shows similar features and the immunostains confirmed positivity for CD117/c-kit (right upper) and DOG1 (right lower).
Those tumors comprised of spindle cells should be differentiated from smooth muscle tumors (e.g., leiomyoma), fibromatosis, solitary fibrous tumor, inflammatory myofibroblastic tumor and neural tumors (e.g., schwannoma). If the spindle cells show significant pleomorphism, then leiomyosarcoma, malignant fibrous histiocytoma and dedifferentiated liposarcoma, should be considered. However, the cellular features in these tumors show much more pleomorphism than in GISTs (even malignant lesions), and immunohistochemistry for CD117, CD34 and DOG1 are all negative.

GISTs comprised of epithelioid cells should be differentiated from poorly differentiated carcinoma (cytokeratin+; CD117–, CD34– and DOG1–), melanoma or clear cell sarcoma (S100+, HMB45+, and Melan-A+, while CD117–), glomus tumor (SMA+, but CD117–), ganglioneuroblastoma (neuroendocrine carcinoma (synaptophysin+, but CD117–) and benign epithelioid nerve sheath tumor like a schwannoma or neurofibroma (S100+, but CD117–).

21.3.3.2 Leiomyoma & Leiomyosarcoma

- Spindle cell tumors of smooth muscle origin that usually arises in the wall of the esophagus, stomach or colorectum. Leiomyosarcoma is exceedingly rare, as the majority of these are leiomyomas.

- Cytologic aspirates of these lesions are usually limited in cellularity or nondiagnostic. If there is material, there are usually discohesive spindle cells with plump oval nuclei and ill-defined extensions of cytoplasm. Leiomyomas tend to have lower cellularity and thick tissue fragments with abundant cytoplasm.

Leiomyosarcomas have greater cellularity and thin tissue fragments with abundant cytoplasm.

F21.14 Gastric leiomyoma (left, Diff-Quik, intermediate magnification; right, Pap stain, high magnification). The aspirates reveal dense tissue fragments with elongated spindle cell nuclei and a syncytial appearance without discrete cell borders, and dense appearing cytoplasm.

F21.15 Gastric leiomyoma (left, H&E, intermediate magnification; right, h-caldesmon stain, high magnification). The cell block shows tissue fragments of a hypocellular, bland appearing spindle cell neoplasm with abundant eosinophilic cytoplasm. The immunostain for h-caldesmon was positive (right), while the stains for cytokeratin, CD117, CD34, and S100 were all negative.

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