4
Nonneoplastic Lesions

The topic of nonneoplastic lesions of the lower respiratory tract (tracheobronchial tree and lungs) is very broad, encompassing myriads of etiologically diverse disease processes with equally diverse morphologic changes in the tissues. The morphologic evidence of tissue damage is not always reflected in the cytological specimens from the respiratory tract and, when detected, may not be evident in all types of respiratory specimens.

The subject of nonneoplastic lung disorders is so broad that many textbooks have been devoted to pulmonary diseases in general and to individual disease processes. A detailed discussion is beyond the scope of this atlas. Only those disease processes that demonstrate cellular alterations in cytological specimens from the respiratory tract will be discussed in this chapter.

SECTION I NONNEOPLASTIC EPITHELIAL CHANGES

Morphologic Alterations of Bronchial/Bronchiolar Epithelium

The epithelial lining cells of the tracheobronchial tree and alveoli exhibit a wide array of morphologic changes in response to various types of insults or injuries, such as infectious agents or mechanical trauma (e.g., instrumentation, smoking, environmental toxins, dust, immunological diseases, radiation, drugs, etc.). The resulting changes may be mild and reversible, or severe and abnormal enough as to mimic neoplasia, causing a great potential for diagnostic errors. The extent of cytomorphologic alterations is dependent on the type of cell injury or the etiologic agent, the intensity and the duration of the injury, the anatomic site, and, most important, the immune status of the host. The cellular changes can be specific and pathognomonic of the disease process or nonspecific (e.g., proliferative/hyperplastic, repair/regenerative, and degenerative with or without cell death). Overlap of such various cytopathologic features as irritation forms, hyperplastic reactions, and repair/regenerative changes in a given disease process is not unusual and is difficult to separate from each process.

Nonspecific Acute Changes (Irritation forms)

Acute nonspecific changes that involve the respiratory epithelium have been referred to as "irritation forms" (Table 4-1, Figs. 4C-1–4C-7). They are usually caused by mild infections, instrumentation, or environmental toxins, and are generally reversible. The altered epithelial cells exfoliate in such specimens as sputum, bronchial washings, and bronchoalveolar lavage (BAL) singly, in groups, or in tissue fragments of variable sizes. In abraded specimens (e.g., bronchial brushings) the epithelial tissue fragments are more numerous, frequently demonstrating ragged edges (Fig. 4C-1). The ciliated columnar epithelial cells and their nuclei are variably enlarged; however, all the cells within a given tissue fragment may not show the same degree of involvement. Their nuclei are round to oval, and they maintain a smooth nuclear membrane. The nuclear chromatin may be finely granular and evenly distributed or coarsely granular. Their nucleoli may be prominent with an increase in their numbers and size (Figs. 4C-2 and 4C-3) The cytoplasm of the reactive columnar cells may show increased secretions, appearing bubbly, vacuolated, or dense and biphasic (Figs. 4C-4 and 4C-5). With increased intensity of the injury, epithelial cells undergo degenerative changes with margination of chromatin and nuclear pyknosis (Fig. 4C-5). Their cytoplasm stains deep eosinophilic (Fig. 4C- 4). This eosinophilia, along with pyknotic nuclei, imparts an appearance of dyskeratotic squamous cells to the columnar cells (Fig. 4C-6). Bare nuclei of the degenerating columnar cells may be mistaken for small cell carcinoma. Multinucleation is a frequent feature, especially after instrumentation (Figs. 4C-7A–4C-7C). The altered columnar cells may contain two to several small, mirror image nuclei with smooth and regular nuclear membranes. At times the columnar cells lose their cilia, undergoing a process referred to as "ciliocytophthoria." The involved cell loses the distal or luminal por-

S. R. Kini, *Color Atlas of Pulmonary Cytopathology*

TABLE 4-1. Nonspecific acute changes involving bronchial epithelium (irritation forms).

• Occur due to a wide variety of insults
• Changes nonspecific; may not involve all of the epithelial cells uniformly
• Variable cell morphology within epithelial tissue fragments
• Cytokaryomegaly
• Fine to coarsely granular chromatin, smooth nuclear membrane
• Nucleoli multiple, prominent
• Loss of cilia +/−
• Ciliocytophthoria +/−
• Multinucleation with uniform mirror image nuclei
• Cytoplasm variable, pale to dense
• Mitoses rarely seen

tion bearing the cilia, which is pinched off with the formation of anucleated ciliated tufts and a separate nucleated cytoplasmic portion of the cell (Fig. 4C-7D). Ciliocytophthoria is often associated with viral infections. Single detached cilia have been reported as a potential diagnostic pitfall. In bronchoalveolar lavage fluid, the detached cilia appear as small, thin, uniform, eosinophilic, extracellular, straight, or slightly curved structures. These bacilliform pseudomicrobes may be mistaken for true microorganisms. The fragmented cilia are readily identified in Romanowsky-stained preparations. In Papanicolaou-stained smears, they are appreciated with great difficulty because they appear very pale and are easily overlooked. Detached cilia are generally seen in the vicinity of normal or degenerated bronchial epithelial cells.

Proliferative or Hyperplastic Changes

Bronchial epithelial hyperplasia occurs in several conditions such as chronic bronchitis, bronchiectasis, chronic infections (e.g. tuberculosis, viral and mycotic infections, and bronchial asthma) with involvement of ciliated columnar, goblet, and reserve cells.

Ciliated Columnar Cells

Hyperplastic or proliferative changes are characterized by the presence of a large number of columnar cells occurring either singly or in tissue fragments. The latter vary in size, sometimes reaching huge dimensions (Figs. 4C-8 and 4C-9). In exfoliated forms, they curl up acquiring papillary like configurations with smooth external contour, strongly resembling the tissue fragments of adenocarcinoma cells (see Chapter 7). Such tissue fragments are seen in large numbers in patients with asthma and are referred to as "Creola bodies" (Fig. 4C-10), which were named after the patient in whom such tissue fragments were misinterpreted as adenocarcinoma. The large epithelial fragments tend to be thick, precluding proper cytologic evaluation. Their nuclei are uniform with finely granular chromatin and micronucleoli. These hyperplastic cells lack the prominent macronucleoli of adenocarcinoma. Their cytoplasm may be abundant with increased secretions and vacuoles. Florid hyperplastic changes with coarse, deep-staining chromatin, prominent nucleoli, and altered polarity of crowded nuclei within a tissue fragment may lead to misinterpretation of malignancy. Features favoring a benign process include transition forms from normal to abnormal within a given tissue fragment and in the same smear and the presence of cilia.

Goblet Cell Hyperplasia

Hyperplasia of mucin-producing goblet cells (Fig. 4C-11) is seen most frequently in patients with chronic bronchitis, especially in chronic smokers. It is also encountered in patients with bronchial asthma. The hyperplasia may be extensive, replacing the ciliated columnar cells. Hyperplastic goblet cells are seen either singly, in aggregates, or in tissue fragments. Large mucin-filled vacuoles within the cytoplasm give an appearance of punched out holes when the tissue fragments are viewed "en face" (Fig. 4C-12). Their nuclei are slightly enlarged with finely granular chromatin and micronucleoli. Individual cells appear barrel-shaped due to distended cytoplasm. The latter must be differentiated from mucin-producing adenocarcinoma cells and foamy macrophages, which are seen in many diverse conditions.

Reserve Cell Hyperplasia and Squamous Metaplasia

Reserve cell hyperplasia occurs as a protective mechanism, in response to chronic irritants in the development of squamous metaplasia. The small primitive cells resting on the basement membrane of the bronchi proliferate histologically into several layers (Fig. 4C-13A). These cells generally do not exfoliate and are not seen in sputum samples, but they are present in such instrumented specimens as bronchial brushings, washings, and in BAL, as well as transbronchial fine needle aspiration biopsy specimens. The reserve cells are usually seen as small tissue fragments often with overlying columnar cells (Figs. 4C-13B–4C-13D). When seen "en face," the tissue fragments of reserve cells appear as sheets composed of compactly arranged small cells with insignificant cytoplasm, round nuclei with very high nuclear to cytoplasmic ratios, and deep-staining chromatin. Nucleoli are lacking and nuclear molding is inconspicuous. In the absence of attached columnar cells, the reserve cells may be misinterpreted as small cell carcinoma (see Chapter 8).

Reserve cell hyperplasia precedes the development of squamous metaplasia, which subsequently matures into stratified squamous epithelium. The small reserve or primitive cells begin to show squamous differentiation by acquiring more cytoplasm, increasing in size with lower nuclear to cytoplasmic ratios. The metaplastic cells are round, medium sized with dense cyanophilic or eosinophilic cytoplasm, with a central nucleus with thin nuclear membrane, having granular chromatin, and no nucleoli (Fig. 4C-14). They are isolated or in

TABLE 4-2. Cytopathologic features differentiating epithelial repair and carcinoma.

	Epithelial repair	Carcinoma
Presentation	Predominantly in tissue fragments; discrete cells or aggregates rare	Tissue fragments, discrete cells or aggregates +
Architecture	Flat, two-dimensional sheets with well-defined cell borders	Syncytial, well-to poorly defined cell borders; nuclei with altered polarity, crowding and overlapping
Cells	Low N/C ratios; abundant cytoplasm	Variable usually high N/C ratios; cytoplasm variable, scant to moderate
Nuclei	Round to oval; smooth crisp nuclear membranes; chromatin finely granular with micronucleoli or macronucleoli; mitoses +/−	Round to oval; smooth to irregular nuclear membranes; chromatin fine to coarsely granular; parachromatin clearing; micronucleoli/macronucleoli; mitoses +/−
Background	Inflammatory	Clear to inflammatory; necrosis +/−

two-dimensional sheets with well-defined cell borders. The metaplastic squamous cells may demonstrate abnormal shapes and varying degrees of keratinization. Atypical nuclear changes may occur as a result of chronic irritation (e.g., cigarette smoking and chronic infections). Degenerating squamous cells with eosinophilic cytoplasm and pyknotic nuclei are referred to as "Pap" cells and represent potential diagnostic pitfalls as they may be mistaken for squamous carcinoma (see Chapter 6, Fig. 6C-42).

Repair/Regenerative Changes

Cellular changes of repair/regeneration are often seen following an injury to the epithelium. Also referred as "repair atypia" by some, these changes are very similar to those seen in uterine cervical smears.

In cytologic specimens, especially in bronchial brushings and washings as well as in BAL, the repair/regenerative cells involve both squamous and columnar epithelium and are seen in large, flat, two-dimensional sheets with well-defined cell borders and abundant cytoplasm (Fig. 4C-15). Their nuclear to cytoplasmic ratios remain low. The nuclei are mildly enlarged with smooth nuclear membranes and finely granular, uniformly dispersed chromatin. Nucleoli are often multiple, prominent, pleomorphic, and at times bizarre, causing potential diagnostic pitfall. Regular mitoses are not uncommon. This type of morphologic alteration may be seen more frequently in postradiation specimens. Difficulty may be encountered in differentiating these changes from malignant neoplastic cells. Table 4-2 lists the differentiating features.

Reactive, Hyperplastic, and Hypertrophic Type II Alveolar Pneumocytes

Alveolar injuries with damage to the lining cells can result from a multitude of causes and include: infections, sepsis, shock, toxic inhalants, inspired high oxygen saturation (oxygen toxicity), thermal injury, narcotics overdose, radiation injury, drug reactions including chemotherapeutic agents, smoke inhalation, ingested toxins, chronic interstitial pneumonitis, granulomatous inflammations, pulmonary thromboembolism, industrial exposures, and pulmonary fibrosis (Table 4-3). The extent of alveolar damage is dependent on several factors (e.g., the causative agent, severity of the injury, and its duration). The response of the alveolar lining cells can be focal or diffuse. The type I cells, which are delicate, are generally destroyed. The type II cells are the progenitors of type I cells and respond to the injury in an attempt at repair/regeneration. They may undergo proliferation, hyperplasia, and hypertrophy. The reaction can be focal or diffuse. The focal response is seen around a localized lesion (e.g., granulomas, neoplasms, infarcts, localized infections, and abscess). These changes are usually seen along the perimeter of the lesions. The abnormal type II lining cells in such instances are more likely to be encountered in fine needle aspiration

TABLE 4-3. Causes of diffuse alveolar damage.

- Infections
  - Pneumocystis carinii
  - Viruses (influenza, cytomegalovirus, varicella, adenovirus)
  - Fungi (blastomycosis, aspergillosis)
  - Legionella sp.
- Toxins
  - Inhaled toxins (e.g., O_2, NO_2, household ammonia and bleach, mercury vapor)
  - Ingested toxins (e.g., parquet)
- Drugs
  - Cytotoxic: azathioprine, carmustine (BCNU) bleomycin, busulfan, romustine (LLNU) cyclophosphamide, melphalan, methotrexate, mitomycin, procarbazine, temposide, vinblastine, zinostatin
  - Nontoxic: amiodarone, amitriptyline, colchicine, gold, salts, hexamethovirum, nitrofurantion, penicillamine, streptokinase, sulfathiazole
  - Illicit: heroin
- Shock
  - Traumatic
  - Septic
  - Cardiogenic
- Radiation
- Miscellaneous
  - Acute pancreatitis

From Myersal L, Colby TV, Yousem SA. Common pathways and patterns of injury. Chapter 4. In: Dail DH, Hammar SP, editors. Pulmonary Pathology, second edition. New York: Springer-Verlag, 1993, with permission.

TABLE 4-4. Cytopathologic features of atypical type II pneumocytes in ARDS.

Presentation	Isolated, in aggregates, or in tissue fragments; generally small in size, may be three dimensional; scalloped borders frequent; open petal pattern similar to that seen in cells of bronchioloalveolar carcinoma; occasionally show small acinarlike structures with nuclei placed away from the center of the tissue fragment presenting a hobnail pattern
Cells	Pleomorphic in size; small to large; round to oval; cell borders well-defined to fuzzy; abnormal cells vary in numbers, generally few
Nucleus	Variable in size; round to oval; low to high nuclear/cytoplasmic ratios; eccentric with hobnail pattern; nuclear membrane smooth, occasionally irregular; chromatin coarsely granular may be smudgy, no parachromatin clearing; prominent nucleolus
Cytoplasm	Variable, scant to abundant; bubbly to vacuolated simulating a signet ring pattern; sometimes dense
Background	Inflammatory; neutrophils; macrophages with or without hemosiderin
Immunoprofile	Cytokeratin +; oncofetal antigen +; B72.3 +
Ultrastructure	Lamellated bodies; whorled myelin figure arrangement; numerous short surface microvilli; intercellular junctions

biopsy specimens. The alveolar reaction is florid and diffuse with damage resulting from systemic factors (e.g., sepsis, shock, or widespread exposure of lung parenchyma to toxic agents). In these cases, exfoliation of the abnormal pneumocytes may be recovered in sputum, bronchial washings, and in BAL.

The morphologic alterations in alveolar type II pneumocytes vary from mild to extremely worrisome, mimicking malignant neoplasia. Regardless of the type of injury the morphologic response is similar (Table 4-4, Figs. 4C-16–4C-23). The changes are florid with diffuse alveolar damage and therefore described in detail in the next section.

Adult Respiratory Distress Syndrome

Diffuse alveolar damage may be associated with a condition referred to as Adult Respiratory Distress Syndrome (ARDS), which is characterized by extensive necrosis of the alveolar lining cells leading to severe hypoxia, reduced lung compliance, reduced lung volume, and high mortality. Diffuse alveolar damage has been divided into two overlapping stages, acute and organizing. The acute exudative stage follows the initial insult, lasting approximately 7 days, and characterized by massive interstitial edema and hyaline membrane formation. The proliferative or organizing stage consists of interstitial inflammation and fibrosis. Alveolar hyperplasia develops 3–7 days following injury and persists through the organizing stage, eventually disappearing. The hyperplastic type II pneumocytes become enlarged with proliferation into multiple layers. They present a hobnail appearance when they protrude into the alveolar spaces with clumped chromatin and prominent macronucleoli.

The majority of the patients show rapidly progressive pulmonary dysfunction clinically, with tachypnea, dyspnea, decreased arterial oxygen tension, and variable diffuse interstitial and alveolar infiltrate on chest x-rays. Sepsis remains a common underlying cause. A differential diagnosis of malignancy is sometimes entertained with nodular or diffuse lung infiltrate. Bronchoalveolar lavage is performed to identify the infectious causes, and to rule out a malignancy.

Most conditions listed in Table 4-3 can cause ARDS; however, morphologic changes of diffuse alveolar injury may be seen in the absence of ARDS.

Cytopathologic Findings

Whether the alveolar cell response is localized or generalized, the morphologic alterations are similar. The abnormal cells that represent hyperplastic/reactive type II pneumocytes exfoliate in sputum, bronchial washings, and in bronchoalveolar lavage, but they are not encountered in direct bronchial brushings. They may also be seen in fine needle aspiration biopsy specimens from localized lung lesions.

In *sputum, bronchial washings,* and *BAL,* the altered type II pneumocytes occur singly, in groups, or in tissue fragments, generally in small numbers (Figs. 4C-16–4C-23). These cells demonstrate considerable pleomorphism in their size and shape. They may be small or large, round, oval to polyhedral, and rarely spindle shaped with poorly defined cell borders. The tissue fragments are usually small in size and do not reach the large dimensions of hyperplastic bronchial epithelium. The tissue fragments of abnormal type II pneumocytes are syncytial in nature, with ragged or knobby contour. An open petal or cartwheel arrangement is often noted (Figs. 4C-20A and 4C-21B). Although syncytial, these tissue fragments lack the extreme depth of focus that is so characteristic of bronchioloalveolar carcinoma. Their nuclei are variably enlarged and round, with smooth nuclear membranes. Binucleation and occasional multinucleation may be present. The nuclei may be central or eccentric with coarsely granular, deep-staining chromatin that sometimes appears smudgy. A single macronucleolus (Fig. 4C-22C) may be conspicuous. The nuclei in a tissue fragment with a cartwheel pattern tend to be located at the periphery away from the center (Figs. 4C-19C, 4C-20A, and 4C-20D). The nuclear to cytoplasmic ratios are variable depending on the amount of cytoplasm that ranges from scant to abundant. The cytoplasm may qualitatively stain pale to dense, bubbly, or vacuolated with distended vacuoles indenting the nucleus and producing signet ring forms. Mitotic figures are not a feature of hyperplastic/reactive type II pneumocytes. The background is often inflammatory with neutrophils and cellular debris along with hemosiderin-containing macrophages (Fig. 4C-23).

The cytomorphology is usually well preserved in *aspiration biopsy specimens.* The pneumocytes may be present in flat two-dimensional sheets, in syncytial tissue fragments, or in single file, or they may occur isolated and in groups. Their

nuclei may be very bland with uniformly distributed chromatin or present morphology similar to that seen in exfoliated cells.

Atypical hyperplastic/reactive pneumocytes are also encountered in the absence of ARDS [e.g., bronchopneumonia, granulomatous inflammation, fibrosing alveolitis, pulmonary infarcts (Fig. 4C-17), and various types of localized lesions]. Very bizarre forms of type II pneumocytes have been described in fibrosing alveolitis.

Differential Diagnoses

Atypical type II pneumocytes cause a great potential for misinterpretation because of their strong resemblance to adenocarcinoma cells. Their separation from adenocarcinoma may be extremely difficult purely on a morphological basis. Clinical history of an acute event, pulmonary dysfunction with symptoms of ARDS or history of lung injury from any cause, or respirator assistance should serve as a caution against making a malignant diagnosis. Features that favor a benign process include: (1) Clinical history of an acute event or toxic exposure; (2) Inflammatory background; (3) Sparse to moderate numbers of abnormal cells; (4) Variability in cell morphology from cell to cell or from tissue fragment to tissue fragment; (5) Nuclear chromatin coarsely granular to smudgy; (6) Tissue fragments with scalloped borders; (7) Lack of depth of focus in tissue fragments; and (8) Resolution of the acute process and disappearance of the abnormal cells after 4–6 weeks.

Great caution must be exercised in interpreting abnormal-appearing cells as malignant with a history of an acute event, or if a patient is on a respirator or has a history of toxic exposure and is in the absence of a lung mass. In such cases where a suspicious diagnosis for adenocarcinoma had been rendered, histological examination of the lungs at autopsy has failed to reveal malignancy, showing hyperplasia and reactive atypia of the alveolar type II pneumocytes. Cytologic features that distinguish atypical alveolar type II cells from adenocarcinomas will be discussed in Chapter 7 and listed in Table 7-7.

Radiation-Induced Changes

Treatment with external radiation to the lungs results in cellular injury with morphologic alterations in benign epithelial lining cells of the respiratory tract. Cellular injury may also result from radiation to chest or breast.

The cellular changes may be acute or chronic, and they are dependent on the dose of radiation as well as its duration. All types of epithelial cells (i.e., squamous, glandular, and alveolar lining cells) are involved. Radiation-induced changes are usually degenerative or may lead to cell death, and they are often associated with nonspecific changes (e.g., irritation forms and repair/regeneration) (Table 4-5).

TABLE 4-5. Radiation induced changes.

Involve squamous cells, columnar epithelial cells, and alveolar lining cells

1. Direct effects of radiation
   - A. Marked cytokaryomegaly with pleomorphic bizarre forms
   - B. Low N/C ratios, frayed cytoplasmic borders
   - C. Abundant cytoplasm with multiple vacuoles or excessive keratinization
   - D. Nuclear enlargement with pleomorphism; binucleation to multinucleation, smudgy to pyknotic nuclei with intranuclear degenerative vacuoles
   - E. Karyorrhexis, karyolysis
2. Associated changes
   - A. Irritation forms
   - B. Repair/regeneration
   - C. Squamous metaplasia with or without atypia; keratinization

The acute changes are retrogressive and include marked cytokaryomegaly with pleomorphic shapes, multinucleation, smudgy deep-staining nuclear chromatin, and ill-defined, frayed cell borders with nuclear and cytoplasmic vacuolization. Macronucleoli may be conspicuous (Figs. 4C-24–4C-27). The nuclei may also exhibit karyorrhexis and karyolysis. The nuclear to cytoplasmic ratios are usually low with cells containing abundant cytoplasm that appears bubbly with either multiple small vacuoles or a single large vacuole that does not indent the nucleus.

Associated changes include irritation forms, repair and regeneration, and squamous metaplasia with or without atypia, often with dyskeratosis.

Radiation-induced changes are potential diagnostic pitfalls because they mimic malignant neoplasia.

Drug-Induced Changes

Certain therapeutic drugs administered to patients injure the lungs via several pathways, either by direct injury, by causing hypersensitivity reactions, or by inducing systemic diseases which in turn cause lung injury. The most severe damage is produced by cytotoxic drugs used as anticancer therapy. These drugs include such alkylating agents as busulfan, cyclophosphamide, chlorambucil, bleomycin, and such antimetabolites as methotrexate and azathioprine. When used in combination, these drugs have potential to cause more damage. Of the several chemotherapeutic drugs in use, busulfan is noted for its severe effect. The clinical features and radiographic findings of drug toxicity tend to be nonspecific. Acute injury to the alveolar lining cells results in edema, congestion, hemorrhage, and hyaline membrane formation. Type I pneumocytes are destroyed and the type II pneumocytes react, proliferate, and present atypical morphology (Figs. 4C-28 and 4C-29). Degenerative changes are reflected by a loss of lamellar bodies as seen ultrastructurally.

These drugs are also toxic to the bronchial and bronchiolar epithelium. Their lining cells, exhibiting degenerative and

reparative changes, are also seen in most types of respiratory specimens.

The abnormal epithelial cells, when found in sputum, are few in numbers, but they are seen in fair numbers in bronchoscopically obtained specimens, especially BAL. Bronchial and bronchiolar epithelial cells demonstrate irritation forms and reactive and hyperplastic changes. The morphology of reactive type II pneumocytes has already been described in detail.

The cells affected by busulfan are described as large, rectangular cells with single or multiple nuclei. The latter are large, hyperchromatic, and sometimes very bizarre with macronucleoli.

Several other types of drugs cause varying degrees of lung injury. One of the antiarrhythmic drugs, amiodarone, has been described as inflicting considerable alveolar damage.

Amiodarone Toxicity

Amiodarone is a very powerful antiarrhythmic drug used in life-threatening cardiac arrhythmias. The drug causes a variety of toxic effects involving several body systems, and, in 10% or less, the drugs may cause lung injury.

Patients with resultant toxic effects present clinically with progressive dyspnea and cough. A pleural effusion may occasionally be present. Chest x-ray findings include bilateral pulmonary infiltrates that initially affect the lower lobes. The effect of the drug appears to be accumulation of phospholipids in the cytoplasm of macrophages. The latter are recovered in BAL as large foamy histiocytes (Figs. 4C-30A and 4C-30B) that are ultrastructurally proven to contain lamellated bodies within lysosomes (Fig. 4C-30C). The lung injury is seen in the form of alveolar exudate, hyaline membrane formation, organization, interstitial fibrosis, and massive accumulation of foamy histiocytes in the alveolar spaces.

Clofazimine Therapy Effects

Clofazimine is an antimycobacterial agent used most commonly in patients with leprosy. It is also recommended and used for disseminated disease by *Mycobacterium avium-intracellulare* (MAI) in AIDS patients. Clofazimine uptake occurs in fatty tissues and macrophages throughout the reticuloendothelial system. A yellowish-orange discoloration of fat and internal organs has been noted. Histiocytes containing needlelike crystals that are large, variably thick, and rhomboid have been described in sputum and in BAL. The crystals dissolve during the cytopreparation, leaving negative images seen in both Romanowsky- and Papanicolaou-stained preparations. They are similar to the negative images seen in macrophages that contain MAI bacilli (pseudo-Gaucher cells in Romanowsky-stained preparation). Because the drug clofazimine is used for MAI infections, both pseudo-Gaucher cells that contain MAI organisms and clofazimine containing histiocytes may coexist and must be differentiated from each other. The features that favor clofazimine crystals include birefringent and red-colored crystals in unstained preparation, negative images in both Romanowsky- and Papanicolaou-stained preparations (unlike MAI infected cells), and smooth outlines of negative images without beaded appearance, which is a characteristic of MAI. Clofazimine crystals are non–acid-fast.

SECTION II PULMONARY INFECTIONS

Infections that involve the lower respiratory tract, including the tracheobronchial tree and lungs, are common occurrences. Minor infections caused by bacteria and viruses are self-limiting and may or may not require specific therapy. In more severe situations, the etiologic agents are isolated in culture, identified, and confirmed with several available diagnostic modalities before specific therapy is instituted. In the last three decades or so, medicine has made great strides in the treatment of malignancies, chronic diseases, and in bone marrow and solid organ transplant recipients that cause severe immunosuppression. Compromise of the immune system in these patients has increased susceptibility of the host to many opportunistic infections, causing much morbidity and mortality. A rising incidence in active cases with acquired immunodeficiency syndrome (AIDS) or human immunodeficiency virus (HIV) infection has contributed to the increase in opportunistic infections.

Application of cytopathology in the diagnosis and management of infections in general is limited because it offers only morphological evidence of infection by detecting the microorganisms in many but not all instances. Furthermore, in nearly all types of infections, a definitive diagnosis needs to be established by confirming the causative organism prior to initiating a specific therapy. The confirming tests include isolation in culture, serological tests, histochemical stains, immunofluorescence, immunocytohistochemistry, and DNA probes. Most microorganisms are stained and visualized in routinely stained preparations (e.g., Hemoxylin and Eosin, Papanicolaou, and Romanowsky). Some are visualized in Romanowsky-stained preparations only, but not in the former two. Special stains utilized to highlight these microorganisms are listed in Table 4-6.

Cytopathologic evaluation of various types of respiratory specimens must not be discounted altogether because it often allows presumptive evidence of the infection as well as morphologic recognition of the infectious agent. This facilitates in routing the specimen for processing and appropriate confirmatory tests. In some cases, it even allows initiation of therapy, especially when the confirmatory tests are sophisticated and time consuming.

This section on pulmonary infections will focus only on a limited number of infectious disease processes involving the lower respiratory tract that can be recognized from cytological evaluation of respiratory specimens.

TABLE 4-6. Stains commonly used for demonstrating microorganisms in cytologic specimens.

Stain	
Papanicolaou	Routinely used in cytologic specimens; stains some bacteria, most fungi, and parasites; do not stain acid-fast organisms, *Legionella*, and some fungi
Hematoxylin & Eosin (H&E)	Generally used for cell blocks, tissue scrapes, and sometimes for the smears; staining reactions same as Papanicolaou
Romanowsky (Diff-Quik; Wright-Giemsa)	Stains most fungi, some types of bacteria that are not visualized by H&E or Papanicolaou stain; negative images of MAI
Gomori's Methenamine silver (GMS)	Stains most of the fungi and *Pneumocystis* organisms
Periodic acid Schiff (PAS) with diastase	Stains (1) most of the fungi, and *Pneumocystis*; (2) mucopolysaccharides of the capsules
Mucin stains	Demonstrates the mucoid capsule of the *Cryptococcus neoformans*; may stain cell walls of *Blastomyces dermatitidis*
1. Mucicarmine	
2. Alcian blue	
Modified gram stain—Brown & Brenn,	Useful for *Actinomyces*; differentiates gram-negative bacteria from gram-positive
Dieterle: Warthin-Starry, silver stain	Stains *Legionella*
Acid-fast	
Ziehl-Nielsen	Stains *Mycobacteria*, *Nocardia*
Auramine Rhodamine (fluorescent stain)	*Cryptosporidium*
Kinyoun's modified acid-fast	Michaelis-Guttmann bodies
Fite's	
Fontana-Masson	Useful for staining the cell wall of *Cryptococcus neoformans*
Modified trichrome	*Microsporidium*

Pulmonary Bacterial Infections

Cytopathologic evaluation of respiratory specimens for most common bacterial infections is not warranted. The majority of bacteria do not produce any specific cytopathologic changes. The application of cytopathology is limited, but it may be helpful in certain types of infections such as those caused by *Mycobacteria*, *Nocardia*, *Actinomyces*, *Rhodococcus equi*, and *Legionella*. Only these will be discussed.

Mycobacterial Infections

Mycobacterial infections include tuberculosis caused by *Mycobacterium tuberculosis* and those caused by nontuberculous or atypical mycobacteria.

Pulmonary tuberculosis is the most common disease caused by *Mycobacterium tuberculosis*. Although the incidence of this once very frequent infection had remained low for several years in the Western Hemisphere, it has made a comeback, especially among immunocompromised patients. The disease is still rampant in underdeveloped countries.

Mycobacteria are nonmotile, nonsporing, obligatory aerobic, weakly gram-positive rods. Their high lipid content resists decolorization by acid, once stained by the Ziehl-Nielsen method, hence they are referred to as acid-fast organisms.

Mycobacterial infection is contracted by inhaling airborne droplets containing the organisms. Infection by *Mycobacterium tuberculosis* is described as primary and secondary. The primary infection usually occurs in the early years of life, leading to a localized lesion in the lung parenchyma and the draining hilar lymph nodes. With intact body immune system, more than 90% of such lesions, both in lungs and lymph nodes, heal with fibrosis and calcification. This primary infection is referred to as *primary complex* or *Ghon's complex*. The host becomes sensitized to the tuberculous protein following the primary infection. In cases of defective immune system, the primary infection may disseminate, resulting in miliary tuberculosis with widespread multisystem involvement and death.

The secondary infection or postprimary tuberculosis occurs either as a result of reinfection or reactivation of a previously healed tuberculous infection. It is referred to as fibrocaseous tuberculosis that may result in tuberculous bronchopneumonia, lobar pneumonia, miliary tuberculosis, tuberculous empyema, and endobronchial tuberculosis. The hallmark of secondary tuberculosis is tissue destruction and necrosis, as a result of sensitization with tuberculin that developed from primary infection, leading to cavity formation.

Gross and Histologic Findings

The primary lesion grossly is localized, involves mostly the upper lobes, and is well-defined, with caseating necrosis. Secondary tuberculosis is characterized by cavitating lesions that are often in communication with bronchi. Other patterns of tuberculous involvement include multiple discrete to confluent nodules with caseous necrosis, lobar consolidation, and pleural involvement. Hematogenous spread that results in miliary tuberculosis demonstrates small tiny yellow white nodules throughout the lung parenchyma.

Both primary and secondary lesions show a granulomatous inflammation histologically, with central caseating necrosis bordered by epithelioid histiocytes, multinucleated foreign body–type giant cells, and a peripheral zone of lymphocytes and fibroblasts. The multinucleated giant cells usually have nuclei along the perimeter of the cell and are termed as *Langhans-type giant cells*. The granulomas may be discrete or confluent.

Cytopathologic Findings

Cytologic evidence of the disease may be found in sputum, bronchial brushings, and washings (with endobronchial involvement), in BAL, or in fine needle aspiration biopsy specimens.

The smears show areas of acellular amorphous debris, epithelioid cells seen singly or in aggregates forming granulomas, and Langhans-type giant cells (Figs. 4C-31–4C-34). At times, massive areas of necrotic debris are aspirated, unaccompanied by a cellular component. *Mycobacteria* are not visualized either with Papanicolaou or Hematoxylin and Eosin stain. They are demonstrated by either an acid-fast stain or a fluorescent stain (e.g., auramine-rhodanine). In acid-fast–stained preparations, *Mycobacterium tuberculosis* appears as pink, straight to slightly curved rods with a beaded appearance (Fig. 4C-35). The cytologic interpretation of tuberculous infection must always be confirmed by special stains and by isolation in culture.

Differential Diagnoses

Differential diagnoses of tuberculous lesions include disease processes that cause such granulomatous responses as sarcoidosis (see Table 4-15) and fungal infections, especially those with necrosis (e.g., Histoplasmosis). Caseous necrosis, which is typical of tuberculous granulomas, grossly and microscopically resembles necrotic keratinizing squamous cell carcinoma and must be differentiated from it (see Chapter 6).

Atypical Mycobacterial Infection

Mycobacteria other than *Mycobacterium tuberculosis* that cause diseases are called atypical or nontuberculous mycobacteria. The frequently encountered types are *Mycobacterium intracellulare* and *Mycobacterium avium*, which are collectively referred to as MAI. The infection occurs directly from the environment in contrast to the person to person transmission of *Mycobacterium tuberculosis*, and is seen more frequently in individuals with underlying lung diseases or those with decreased immunity (e.g., patients with AIDS). MAI infections cause granulomatous inflammation with caseating necrosis and cavitary lung disease, and may cause severe disseminated infection. The cavities in MAI infection are often thin walled. The granulomas are ill-formed histologically, being composed of numerous histiocytes packed with bacilli. In Hematoxylin and Eosin stain, the histiocytes have a characteristic light steel blue color and "globoid" or pseudo-Gaucher appearance.

Cytopathologic Findings

The cytologic specimens that demonstrate MAI are sputum, BAL, and aspiration biopsy specimens from the lung or hilar lymph node lesions. In Papanicolaou-stained preparations, the bacilli-containing histiocytes appear as large cells with abundant foamy cytoplasm (Figs. 4C-36A and B and 4C-37B). Despite this, negative images of MAI are not readily seen in Papanicolaou-stained smears; with abundance of bacteria, they cast pale shadows (Fig. 4C-37B). In Romanowsky-stained preparations of respiratory specimens, the distended histiocytes are filled with rodlike unstained structures that represent the negative images of the organisms (Fig. 4C-37A) and resemble Gaucher's cells; hence, the term *pseudo-Gaucher's cell*. Gaucher's cells, a characteristic finding in glycogen storage disorder, are large histiocytes with accumulation of metabolites of glycoproteins in their lysosomes. Gaucher's cells range from 20 to 100 μm in diameter, and are round to oval with abundant cytoplasm containing refractile, parallel, linear striae observed only in Romanowsky-stained preparations (Figs. 4C-38A–4C-38C). They may have single small nuclei with bland chromatin and micronucleoli. The background is generally clean. The Gaucher's cell stains strongly with Periodic acid Schiff (PAS). In contrast, pseudo-Gaucher's cells in MAI infection show linear nonrefractile images, which are also present extracellularly. They are randomly distributed within the cytoplasm, are not parallel, and are acid-fast. *Mycobacterium avium-intracellulare* are longer and thicker, more beaded, and much more curved than *Mycobacterium tuberculosis*. Special stains are necessary to confirm the diagnosis of MAI infection. The diagnosis is established by isolation of the bacteria in culture.

Differential Diagnoses

The differential diagnoses of the foamy bacilli-ridden histiocytes include lipophages from lipoid pneumonia, hyperplastic goblet cells, mucin-producing adenocarcinoma cells, reactive type II alveolar pneumocytes, and, rarely, alveolar macrophages that contain lamellar bodies in cases of drug toxicity (e.g., Amiodarone; foamy histiocytes containing clofazimine crystals, which also cast negative images; foamy macrophages from malakoplakia; muciphages; and vegetable cells). (Figs. 4C-39–4C-42).

Pulmonary Actinomycosis

Actinomycosis is caused by *Actinomyces* bacilli, an anaerobic or microaerophilic filamentous gram-positive bacteria of the order Actinomycetases. The principle agent in human infections is *Actinomyces israelii*. The organisms occur as commensals of the mouth, throat, gastrointestinal tract, and vagina. They are opportunists with the capacity to invade injured tissues. Infection by *Actinomyces* does not occur preferentially in immunosuppressed individuals and represents an endogenous infection.

Pulmonary actinomycosis usually results from aspiration of infectious material or by direct extension of a cervicofacial infection. Patients may either have only lung involvement or a combination of lung and chest wall involvement. Symptoms of thoracopulmonary actinomycosis often clinically suggest ma-

TABLE 4-7. Differential diagnosis of foamy macrophages in respiratory specimens.

Cell type and disease process	Associated conditions and specimen type	Cytopathologic features	Confirmatory tests	Fig(s).
Lipophage	Seen in cases of lipoid pneumonia; present in sputum, bronchial washings, BAL, and FNA	Round to oval, enlarged in size with giant forms; well-defined cell borders; abundant pale, foamy bubbly cytoplasm; nucleus small, central to eccentric	Special stains: oil-red O for intracytoplasmic lipid	4-39A 4C-117 7C-53E
Mycobacterium avium-intracellulare MAI) (infected cells, (pseudo-Gaucher's cells)	Infection present predominantly in HIV-infected patients; present in sputum, bronchial washings, BAL, FNA	Very large to giant forms, distended with abundant foamy cytoplasm; rod like unstained images both intracellular and in extracellular location, in air-dried Giemsa stained preparations; negative images may be seen in Papanicolaou stained smears with overwhelming infections	Special stains: acid-fast stain, positive—bacilli with beaded appearance	4C-36A 4C-36B
Foamy histiocytes containing clofazimine	Seen in AIDS patients treated with clofazimine for MAI infections, may coexist with MAI infected cells	Thick rhomboid crystals that dissolve during processing leaving negative images in both Romanowsky and Papanicolaou stained preparation; crystals stain *red* in unstained preparations and are birefringent	Acid-fast stain-negative, red-colored crystals in unstained preparation	—
Amiodarone drug toxicity	Patients with respiratory insufficiency resulting from antiarrhythmic drug toxicity; foamy alveolar histiocytes in BAL	Large foamy macrophages	US—lamellar bodies within histiocytes; history of drug therapy	4C-30
Reactive type II pneumocytes	Patients with ARDS or acute lung injury, assisted respiration, localized lesions such as infections, infarcts, benign neoplasms; abnormal cells recovered from sputum, bronchial washings, BAL ,	Foamy cells, variable in size; cell borders poorly defined, variable, sometimes abundant foamy vacuolated cytoplasm; nucleus central to eccentric; chromatin bland to granular; nucleoli +; in company of cells or tissue fragments of cells diagnostic of type II pneumocytes	Acid-fast stain-negative; history of acute lung injury or artificial ventilation; abnormal chest radiographs; surfactant protein +	4-39B 7C-52F to 7C-53H
Malakoplakia	Localized inflammatory lesion caused by *Rhodococcus equi* in patients with AIDS; present in bronchial brushings, BAL, and FNA; may be caused by other bacteria	Variably sized but generally large, round to oval uninucleated to multinucleated cells (Von Hansemann cells); abundant foamy cytoplasm containing coccobacillary organisms seen with Romanowsky-stained preparations; *Michaelis Gutmann* bodies with targetoid centers both intracellular and extracellular; inflammatory background	Special stains for coccobacilli; Brown & Brenn, Gomori's Methenamine silver, acid-fast; *Michaelis Gutmann* bodies stain positive with PAS diastase resistant and Von Cossa	4C-42
Goblet cells hyperplasia	Chronic bronchitis and asthma; present in sputum, bronchial brushings, bronchial washings, and BAL	Large round to oval cells; poorly defined cell borders; eccentric nuclei; abundant lacy, foamy, bubbly cytoplasm; nucleus central to eccentric; finely dispersed bland chromatin; micronucleoli	Mucin stains Alcian blue + PAS with diastase +	4C-12 7C-53A to 7C-53C
Mucin producing adenocarcinoma	Seen in all types of respiratory specimens	Size variable, medium to large; round to oval; poorly defined cell borders; eccentric nucleus; powdery to finely granular chromatin; nuclear membrane smooth to slightly irregular; micronucleoli/macronucleoli +	Mucin stains Alcian blue + PAS with diastase +	4C-40B
Vegetable cells	Seen in sputum contaminated with food	Very large discrete cells with voluminous foamy bubbly to reticular cytoplasm; well defined refractile cell borders; central small nuclei with compact chromatin; enormous size, very small structureless nucleus; multivacuolated cytoplasm; cytoplasmic granulations +/−		4C-41 3C-23A
Muciphage	Associated with mucin producing adenocarcinoma	Variable size; abundant bubbly cytoplasm; low N/C ratio; nuclei may be pushed to the periphery but not indented; nuclear chromatin finely granular; very difficult to differentiate from carcinoma cells with cytoplasm distended with mucin		7C-52D

lignancy and consist of fever, chills, night sweats, and weight loss. Chest radiographs reveal pulmonary consolidation, numerous opacities with cavitation, and pleural thickening.

Gross and Histologic Findings

The affected lung grossly shows multiple small to large abscesses. The lung is often adherent to the pleura with a sinus tract discharging yellow "Sulfur granules" to the skin. The abscesses, which contain actinomycotic granules (Figs. 4C-43 and 4C-44) are encapsulated histologically by granulation tissue. These granules are tangled masses of delicate filamentous bacteria with beaded appearance that are bordered by intensely eosinophilic clublike projections of Splendore-Hoeppli material (Fig. 4C- 45). This effect is a hyaline eosinophilic radiate precipitate that is variably seen around bacteria, fungi, and parasites, as well as silk sutures in tissues stained with Hematology and Eosin. The amorphous eosinophilic coating often occurs around bacterial clumps and probably represents a localized antigen–antibody reaction in a sensitized host. The epithelial lining of the bronchi containing the fungal organisms or the lining of the abscess cavity may show squamous metaplasia with atypia (see Fig. 6C-43).

Cytopathologic Findings

The cytologic specimens that may demonstrate *Actinomyces* include BAL, aspiration biopsy specimens, and smears of the sinus tract discharge. The presence of *Actinomyces* organisms in sputum or bronchoscopic specimens may not be a significant finding because they can easily contaminate these specimens from their normal habitat in the oropharynx. In Papanicolaou-stained preparations, the organisms stain similar to those seen in tissues, appearing as large, irregular basophilic masses that consist of numerous parallel thin filamentous branching structures (Fig. 4C-44B). The bacteria are delicate, 1 μm in diameter, often radially oriented, and embedded in an amorphous matrix. Branching usually occurs at right angles. The diagnosis is confirmed by special stains such as Brown and Brenn and silver stains.

Differential Diagnoses

The differential diagnoses include granules of botryomycosis or pseudomycosis, which contain gram-negative or gram-positive nonfilamentous bacteria, and granules from other mycetomas. Special stains are necessary to differentiate.

Nocardiosis

Pulmonary nocardiosis is an acute progressive or chronic bacterial infection caused by aerobic, gram-positive, filamentous spore-forming bacteria belonging to the family Nocardiaceae. Most human infections are caused by species *Nocardia asteroides*. Pulmonary infections occur by inhaling bacteria that live as saprophytes in soil in individuals with compromised immunity, especially those with AIDS or those with long-term corticosteroid therapy and in patients with underlying conditions. It has also been reported in association with patients that have alveolar proteinosis.

Nocardiosis can produce a wide spectrum of pulmonary involvement ranging from acute to subacute to chronic disease with a tendency for remissions and exacerbations. The clinical presentation is nonspecific, as are chest radiographs.

Gross and Histologic Findings

The pulmonary lesions are often suppurative with single or multiple abscesses filled with odorless thick greenish yellow pus. There may be lobar consolidation and granulomatous response. The infection can be progressive, disseminating in the body causing metastatic abscesses. Cavitation and pleural involvement with empyema are frequent complications. The organisms may be identified from the inflammatory exudate either in the tissues or in fine needle aspiration biopsy specimens as thin delicate organisms less than 1 μm in width branching at right angles. They are weakly gram-positive and weakly acid-fast, often with a characteristic beaded appearance. Multiple branching of the bacteria impart a look of Chinese characters. Fragmented forms may be present.

Cytopathologic Findings

The *Nocardia* organisms are barely visible in Hematoxylin and Eosin or Papanicolaou stained preparations and must be demonstrated by special stains such as modified Gram-stain (e.g., Brown and Brenn or silver stain) (Fig. 4C-46). *Nocardia* does not form sulfur granules, nor does it demonstrate Splendore-Hoeppli effect. The diagnosis is confirmed by isolation in culture.

Differential Diagnoses

Differential diagnoses include such other acid-fast organisms as *Mycobacteria*. The latter remain acid-fast when acid alcohol is used for decolorization, which the *Nocardia* do not.

Legionella Pneumonia

Legionella pneumophilia are aerobic gram-negative, non–spore-forming, nonencapsulated bacteria varying from short coccobacillary to long filamentous forms that cause pneumonia. The organisms are difficult to visualize on Gram-stain. The infection is contacted through contaminated water supply. Patients on chronic dialysis and transplant recipients are at a higher risk for developing the infection. Patients present with high fever. Chest radiographs reveal unilateral to bilateral widespread consolidation and sometimes cavitation. Pleural effusion may be present.

Gross and Histologic Findings

The lungs grossly are tan-white, friable in texture with abscess formation in roughly 25% of the cases. The infiltrate is microscopically neutrophilic or mononuclear, or a combination of both. Fibrin is a predominant component of the alveolar exudate. An intense lytic process in the inflammatory exudate leaves fragmented nuclear debris. *Legionella* may also cause diffuse alveolar damage.

Cytopathologic Findings

Legionella bacteria are not visualized in either Hematoxylin and Eosin, Papanicolaou, Gram-stain, or Brown and Brenn stained preparations. *Legionella* bacilli are stained with silver impregnation stains (Dieterle or Warthin-Starry) (Fig. 4C-47) and may be demonstrated in specimens such as sputum, bronchoalveolar lavage, and in aspiration biopsies of localized lesions. *Legionella* bacteria may also stain acid-fast and be misinterpreted as tuberculosis. The tuberculous infection must be confirmed by auramine-rhodamine stain. The diagnosis is also made by direct fluorescent antibody test (Fig. 4C-48) on sputum, pleural fluid, or aspirated tissue and by culture.

Rhodococcus Equi

Previously known as *Corynebacterium equi*, *Rhodococcus equi* are gram-positive weakly to partially acid-fast organisms. They are widely present in the soil causing pulmonary disease in some domestic animals. Human infections occur most commonly in immunocompromised patients.

Pulmonary infection may be slowly progressive and cavitate, mimicking tuberculosis. *Rhodococcus equi* are associated with a specific inflammatory condition referred to as *malakoplakia*, which is seen exclusively in patients with AIDS. Please refer to Chapter 10 for details (see Table 10-1, Figs. 10C-1–10C-6).

Features of the pulmonary bacterial infections just described are summarized in Table 4-8.

Pulmonary Viral Infections

Viral infections of the respiratory tract are very common occurrences, especially in the pediatric age group. The majority of these episodes are self-limiting, causing very little morbidity and extremely low mortality in healthy individuals. Some viruses, however, are opportunists and cause serious infections in immunocompromised patients that result in considerable morbidity and mortality.

The clinical presentations of viral infections vary widely and are often complicated by underlying conditions. The changes appear radiographically as a focal or diffuse infiltrate. Pulmonary involvement manifests in several different forms (e.g., necrotizing bronchitis or bronchiolitis, interstitial pneumonitis, diffuse alveolar damage with hyaline membrane formation, and focal inflammatory changes with bronchopneumonia).

Cytopathologic changes exhibit a wide spectrum. Some are nonspecific, whereas others are specific and pathognomonic. The nonspecific changes include: (1) ciliocytophthoria; (2) bronchial epithelial and alveolar lining cell hyperplasia; and (3) repair/regenerative changes involving bronchial epithelial cells. The cytopathic effects are quite often specific for a given virus.

Even when the morphologic changes strongly suggest a diagnosis of viral infection as well as the viral type, specific identification must come from the virology laboratory. The viral types are established by isolation in culture, demonstration of antigens, or nucleic acids in clinical specimens, serologic tests, and DNA probes.

The viruses that cause frequent respiratory infections include influenza, parainfluenza, adenovirus, respiratory syncytial virus, measles, Epstein-Barr virus, Herpes simplex, and cytomegalovirus. Documented cytopathologic changes are most frequently identified in infections with the Herpes family of viruses.

Herpes Simplex Virus

Herpes simplex virus (HSV) infections generally affect immunocompromised hosts or debilitated patients with lowered defense mechanisms. Patients with tracheostomies and those with endotracheal tubes are also at risk for developing the infection.

Two serologic types of HSV are defined. Either type can involve the respiratory tract. Type 1 usually affects the upper gastrointestinal tract, respiratory tract, and central nervous system. Type 2 is primarily responsible for genital infection, and it causes meningitis and disseminated neonatal infection including respiratory involvement. In most HSV infections, aspiration of oral secretions is usually the source of infection, whereas the source of infection is the maternal vagina in neonates.

Gross and Histologic Findings

The lungs grossly show patchy to diffuse areas of consolidation. The lungs are heavy, edematous, and hemorrhagic. The pulmonary involvement by HSV histologically presents several patterns (i.e., namely ulcerative tracheobronchitis, bronchiolitis, necrotizing bronchopneumonia, diffuse interstitial pneumonia with alveolar damage, and hyaline membrane formation). In ulcerative tracheobronchitis, the mucosa and the submucosa are necrotic, with the ulcer base being covered by cellular debris and inflammatory exudate. The exfoliated cells within the exudate and those at the margins of the ulcers show typical viral inclusions. Similar inflammatory changes with viral inclusions are observed in necrotizing pneumonia and interstitial pneumonitis.

Cytopathologic Findings

Cytopathologic changes involving the respiratory epithelial and alveolar lining cells in HSV infection are found in sputum, tracheobronchial aspirates, bronchial brushings, and washings, as well as in BAL. The morphological changes may be nonspecific inflammatory, repair/regenerative, or specific, with the latter characterized by multinucleation and intranuclear inclusions (Table 4-9). The repair/regenerative changes are often florid and at times difficult to differentiate from adenocarcinoma. The specific cytopathic effects of HSV (Figs. 4C-49 and 4C-50) is characterized by the presence of intranuclear inclusions involving the respiratory epithelial cells as well as alveolar lining cells. The nucleus of the affected cell initially enlarges, becoming pale and translucent with loss of the nucleolus. The chromatin marginates giving a beaded appearance to the nuclear membrane. The inclusion bodies eventually become more prominent, retract, and are surrounded by a clear halo. Multinucleation is frequent, with nuclei exhibiting the typical cytopathic effects of HSV. The background is often inflammatory.

Differential Diagnoses

The differential diagnoses of inclusion-bearing cells include cytomegalovirus and adenovirus infection. The diagnosis of HSV infection is confirmed by viral culture.

Measles

Measles, a highly contagious disease, is caused by measles virus, and is characterized by a diffuse skin rash. Although infrequent, pulmonary involvement occurs with diffuse, patchy, or nodular infiltrate with peribronchial distribution and can occasionally be hemorrhagic. The small airways and alveoli are primarily affected. The most distinctive feature is the presence of large multinucleated giant cells containing up to 50 or more nuclei, abundant cytoplasm, and eosinophilic intranuclear and intracytoplasmic inclusions (Fig. 4C-51). Similar inclusions may be found in endothelial cells. Inclusion-bearing cells may be present in sputum and in BAL. There may be associated interstitial pneumonitis and hyaline membrane formation, bronchial mucosal hyperplasia, and squamous metaplasia.

Respiratory Syncytial Virus Infection

Respiratory syncytial virus (RSV) is a well-recognized pathogen of infants and young children in whom it causes an upper airway infection that often progresses to bronchitis and bronchiolitis. The infection is associated with a very low mortality. Respiratory syncytial virus infection has been increasingly recognized as a cause of pneumonia in bone marrow transplant recipients. Although the course of RSV infection is benign in infants, the mortality rate is more than 50% in bone marrow transplant recipients. The morbidity is also high in immunocompromised patients due to prolonged shedding of the virus.

Infection with RSV occurs repeatedly throughout life, including infancy and old age. The immunity is short lived and incomplete. The clinical symptoms of RSV infection vary from mild upper respiratory tract infection to croup, bronchitis, bronchiolitis, and interstitial pneumonia. Chest x-rays show depressed diaphragm and patchy areas of atelectasis.

Gross and Histologic Findings

The lungs grossly are overexpanded. The hypertrophied alveolar lining cells histologically protrude into the lumen. The lining cells also exhibit papillary hyperplasia. There is sloughing of the lining mucosa of the airways and an inflammatory infiltrate consisting of lymphocytes and macrophages within the alveolar spaces. Interstitial pneumonitis may also be present.

Cytopathologic Findings

Bronchoalveolar lavage has become a common practice in evaluating pneumonias in immunocompromised patients. The cytologic findings include large syncytial cell aggregates that measure up to 100 μm or more in diameter. Clear halos surround pale eosinophilic inclusion bodies within their cytoplasm. The inclusions are paranuclear in location, measuring 1–2 μm in diameter, and are seen in Romanowsky- and in Papanicolaou-stained preparations (Fig. 4C-52A). The cytologic pattern resembles that of measles infection because both produce giant cells. The diagnosis is confirmed by direct immunofluorescence test.

Adenovirus

Adenovirus commonly affects the upper respiratory tract, especially in children. Some types are associated with pneumonia imparting two patterns of damage: (1) necrotizing inflammation that affects the bronchial and bronchiolar mucosa, as well as alveoli, alveolar exudate of fibrin, edema fluid, and hyaline membranes; and (2) interstitial pneumonitis.

Cytopathologic Findings

The virus-affected cells may be seen in sputum or in bronchoalveolar lavage. The affected cells cytologically exhibit two types of inclusions, where one resembles those of HSV infection with intranuclear inclusions and peripheral clearing (Fig. 4C-6). The second type is basophilic or amphophilic and it occupies the entire nucleus. It is often referred to as *smudge cells*. A very common but nonspecific feature of adenovirus infection is ciliocytophthoria (Fig. 4C-52B) involving the ciliated columnar cell epithelium. The diagnosis is established by viral culture.

TABLE 4-8. Cytopathologic features of bacterial infections involving the lower respiratory tract.

Disease organism	Geographic distribution	Clinicohistopathologic findings	Morphology	Organisms recovered from	Useful stains	Differential diagnoses	Confirmatory tests	Fig(s).
Tuberculosis *Mycobacterium tuberculosis*	Worldwide; endemic in underdeveloped countries	Occurs in both immunocompetent and immunocompromised hosts; primary infection occurs in early years of life; results in granuloma that heals with fibrosis and calcification; secondary infection occurs as reinfection or reactivation characterized by tissue destruction, cavitations; miliary spread can occur in primary or secondary infections; histologically forms caseating granulomas	Nonmotile, nonsporing, obligatory aerobic, weakly gram-positive; acid-fast organism; slender, slightly curved, beaded; granuloma present in bronchial brushings and FNA; amorphous debris	Sputum, BAL, bronchial washings, FNA, gastric contents	Not visualized in H&E or Papanicolaou; stained by acid fast; auramine-rhodamine	*Microorganisms* • MAI • *Nocardia* Caseating necrosis must be differentiated from other cavitary lesions and squamous carcinoma with necrosis; noncaseating granulomas to be differentiated from sarcoidosis	Culture	4C-31 to 4C-35
Atypical mycobacterial infections *Mycobacterium avium-intracellulare (MAI)*	Worldwide; present in soil	Occurs in immunocompromised individuals or those with some underlying lung diseases; cause cavitary lung disease, thin-walled cavities, and caseating granuloma; histiocytes filled with microorganisms appear globoid with foamy cytoplasm	Organisms slender, beaded when stained with acid fast; occur both intracellularly descending macrophage appearing as large foamy cells or extracellularly; negative images in Romanowsky stain (pseudo-Gaucher's cells)	BAL, FNA, bronchial washings, sputum	Not visualized in H&E or Papanicolaou stain, acid-fast	*Microorganisms* • *Mycobacterium tuberculosis* • *Nocardia* • clofazimine crystals *Foamy Cells* • Gaucher's cells • Amiodarone drug toxicity • Clofazimine crystals containing cells • Malakoplakia • Lipid pneumonia	Culture	4C-36 4C-37
Actinomycosis *Actinomyces israelii*	Occur as commensals in mouth, throat, gastrointestinal tract, and vagina; opportunist, invade injured tissues	An endogenous infection, results from aspiration of infectious material or direct extension of cervicofacial infection; fever, chills, night sweats, weight loss; lung reveals small abscesses; contain actinomycotic granules, "sulfur granules"—tangled masses of bacterial; Splendore-Hoeppli	Anaerobic, microaerophilic filamentous gram-positive organism; large irregular basophilic masses; numerous parallel thin filamentous branching structures, 1 μm in width, radially oriented; branching at right angles	Discharge from sinus tracts, BAL, FNA, (organisms in sputum or bronchial brushings may not be significant)	Visualized in H&E, Papanicolaou stain, Brown & Brenn, GMS	Botryomyces	Culture	4C-43 to 4C-45

		phenomenon; may cause sinus tract to chest wall; squamous metaplasia with or without atypia of lining of the cavities and bronchi						
Nocardiosis *Nocardia sp.*	Saprophyte in soils	Immunocompromised individuals, common in patient with AIDS or long-term corticosteroid therapy; may be associated with alveolar proteinosis; acute—subacute to chronic disease, abscesses; suppurative—odorless, thick greenish-yellow pus; cavitation; pleural involvement with empyema; no sulfur granules; no Splendore-Hoeppli effect	Aerobic, gram-positive filamentous spore-forming bacteria; think, delicate <1 μm wide, branching at right angles; multiple branching—look of Chinese characters; fragmented forms; neutrophilic infiltrate; necrotic background	FNA, BAL, pleural fluid with empyema	Not visualized well in H&E and Papanicolaou stain, weakly gram +, weakly acid fast, Brown & Brenn +, GMS +	*M. tuberculosis*	Culture	4C-46
Legionella pneumonia *Legionella pneumophilia*	Contaminated water supply	Patients on chronic dialysis; transplant recipients at higher risk; necrotizing pneumonia; diffuse alveolar damage	Nonspecific	Sputum, BAL, FNA	Not visualized in H&E or Papanicolaou, stained by Gram or Brown & Brenn; GMS, Fluorescent antibody, acid fast		Fluorescent antibody, GMS	4C-47 4C-48
Rhodococcus equi	Worldwide; present in soil, cause pulmonary disease in domestic animals	Infection in immunocompromised hosts, especially in AIDS; slowly progressive cavitating lesion; clinically mimics tuberculosis; cause specific inflammatory lesion of the lungs referred to as *malakoplakia*	Foamy histiocytes, coccobacilli within and outside the histiocytes (Romanowsky stain); Michaelis Gutmann bodies—diagnostic	Bronchial brushings, BAL, FNA	Not visualized in H&E or Papanicolaou, stained by Romanowsky, GMS	*Foamy histiocytes* • MAI infection • Amiodarone toxicity • Clofazimine crystals • Lipoid pneumonia		4C-42 10C-1 to 10C-

GMS = Gomori's methenamine silver

TABLE 4-9. Cytopathologic features of Herpes simplex virus infection in respiratory specimens.

- Infected cells with morphologic alterations seen in sputum, bronchial brushings, and washings, as well as in BAL
- Cells seen isolated, in loosely cohesive groups, or in tissue fragments
- Normal-sized to giant forms
- Nucleus single to multinucleation
- Nuclear chromatin ground glass; pale; margination of the chromatin with a beaded appearance of the nuclear membrane
- Nuclei within multinucleated cells show molding of apposing margin
- Intranuclear eosinophilic inclusions with periinclusion clearing
- Inflammatory background; cellular debris +/−
- Associated changes—irritation forms; repair/regenerative changes

Differential Diagnoses

The differential diagnoses of viral inclusions of adenovirus infection includes other virus infections (e.g., Herpes virus and cytomegalovirus).

Cytomegalovirus Infection

Cytomegalovirus (CMV) is an opportunist, causing pulmonary infection in immunocompromised hosts. It is encountered with a very high frequency in patients with AIDS and in transplant recipients, as well as in those patients treated with chemotherapeutic drugs. It leads to a high mortality rate.

Cytomegalovirus infection is prevalent in the general population. Most individuals become infected during childhood. Healthy (nonimmunocompromised) individuals, however, remain asymptomatic. The infection may be caused by aerosol droplets, blood transfusion, organ transplants, or by contact with semen or cervical secretion. In newborns, CMV infection can be transmitted transplacentally, via cervical secretions during labor, or via breast milk. Recurrent infections result from endogenous infection. Patients with CMV infection present clinically with fever, dyspnea, tachypnea, hypoxemia, and nonproductive cough. Chest radiographs reveal bilateral basilar shadows spreading centrally and superiorly.

Gross and Histologic Findings

The lungs grossly show areas of consolidation and may be heavy with edema and changes of diffuse alveolar damage.

Several patterns of lung involvement are noted histologically: (1) injury to the alveolar lining cells; (2) miliary multifocal lesions containing CMV infected cells with exudative response involving the air spaces and the interstitium. The inflammatory response is characterized by central necrosis, hemorrhage, accumulation of fibrin, and mixed inflammatory cells; and (3) diffuse interstitial pneumonia with edema of the interstitium, serofibrinous exudate, and hyaline membrane formation. Cytomegalovirus-infected cells are scattered diffusely throughout the lung parenchyma.

Cytopathologic Findings

Cytomegalovirus infected cells with typical morphological appearance can be seen in such cytologic samples as sputum, bronchial washings, and BAL, as well as in aspiration biopsies.

The characteristic cytopathic effect of CMV includes a large intranuclear inclusion surrounded by a clear halo and thickening of the dense staining nuclear membrane, referred to as "owl's eye" pattern (Figs. 4C-53A and 4C-53B). Some CMV-infected cells may also exhibit intracytoplasmic inclusions. The latter are rounded, granular and PAS positive, and diastase resistant. They can also be stained by Methenamine silver stain.

The CMV infected cells are considerably larger than their noninfected counterparts. The infected and diagnostic cells are usually few in numbers, often requiring a diligent search for their identification. The diagnosis of CMV infection is established by isolation in culture, which takes up to 6 weeks, immunocytochemical or immunofluorescent stains with monoclonal antibodies, and in situ hybridization.

Differential Diagnoses

The differential diagnoses include HSV infection, adenovirus infection, and reactive bronchial epithelial cells with prominent macronucleoli.

Table 4-10 lists morphologic features of previously described viral infections.

Pulmonary Fungal Infections

Pulmonary fungal infections occur as a result of inhalation of aerosolized fungal elements from environmental sources. Fungi that cause pulmonary infections are grouped into two categories: (1) primary or true pathogens; and (2) opportunistic pathogens. Primary pathogens affect immunocompetent individuals, but the incidence is very low. Opportunistic infections occur in immunocompromised patients. Although several types of fungal infections of the lung are encountered, only the most common ones will be described in this chapter. Although most fungal organisms are visualized in routine Hematoxylin and Eosin and Papanicolaou-stained preparations, special stains are often required to confirm their presence. Table 4-6 lists the commonly used stains. In mycology, certain terminology is used to describe morphological features. These are:

arthroconidium—an asexual conidium formed by mycelial disarticulation

aseptate—lacking cross walls or septations

aspergilloma—a fungus ball composed of hyphae of an aspergillus spp

bud (blastoconidium)—a variety of conidium formed by lateral outgrowth from a parent cell; buds may be single or multiple

budding—asexual reproduction process characteristic of uni-

TABLE 4-10. Cytopathologic features of viral infections involving lower respiratory tract.

Virus	Types of specimens	Immune status	Cytopathologic features	Associated features	Tissue response	Differential diagnosis	Diagnostic tests	Fig(s).
Herpes Simplex Herpes Zoster	Sputum, bronchial brushings/ washings, BAL, and tracheal aspirate	Immunocompetent; immunocompromised	Cells present isolated, in loosely cohesive groups, or in tissue fragments; no cytoplasmic inclusions; cell enlargement; cells may be normal sized; multinucleation very frequent with flat sided nuclear molding along apposing borders; nuclear chromatin pale, ground glass, structureless, chromatin marginating with beaded appearance of nuclear membrane; eosinophilic intranuclear inclusions with a halo around	Reactive/ hyperplastic epithelial changes in tracheobronchial and and bronchiolar-alveolar epithelium; necrosis	Ulcerative tracheobronchitis; interstitial pneumonitis; diffuse alveolar damage with hyaline membrane	• CMV • Adenocarcinoma	Immunocytochemical; culture	4C-49 4C-50
Cytomegalovirus (CMV)	Sputum, bronchial brushings/ washings, FNA and BAL	Immunocompromised; more common in transplant recipients often associated with Pneumocystic carinii pneumonia in patients with AIDS	Cells isolated; marked cytokaryomegaly; large basophilic intranuclear inclusions with clearing; multiple small cytoplasmic basophilic inclusions; binucleation or multinucleation absent; thickened nuclear membranes, clearing around the inclusion	No necrosis	Interstitial pneumonia; diffuse alveolar damage; hyaline membrane; hemorrhagic pneumonia	• Herpes virus • Adenocarcinoma	Culture; molecular probes; PCR; transbronchial biopsy	4C-53
Adenovirus	Sputum, bronchial washings, and BAL	Frequent in children; immunocompetent	Eosinophilic intranuclear inclusions	Ciliocytophthoria	Necrotizing broncho-pneumonia; diffuse alveolar damage; tracheobronchitis	• Herpes virus • CMV	Culture	4C-52B
Measles	Sputum, bronchial washings, and BAL	Immunocompetent; severe in immunocompromised	Large multinucleated giant cells containing up to 50 or more nuclei; abundant cytoplasm; intranuclear and intracytoplasmic inclusions		No necrosis; pneumonitis	• RSV	Serology; culture difficult	4C-51
Respiratory syncytial (RSV)	Sputum, bronchial washings, and BAL	Immunocompetent; immunocompromised, frequently bone-marrow transplant recipients; recurrent respiratory infections from infancy to childhood; incomplete immunity common	Large syncytial cell aggregates up to 100 μm or more in diameter; 1–2 μm pale eosinophilic inclusions in perinuclear locations; halo around the inclusions		Necrosis; pneumonitis	• Measles virus	Culture; direct immunofluorescence	4C-52A

cellular fungi or conidia in which a lateral outgrowth from the parent cell is pinched off to form a new cell

capsule—hyaline mucopolysaccharide coat external to the wall of a fungal cell or conidium

chlamydoconidium (chlamydospore)—a spherical, thick-walled, resistant and conidium formed by direct differentiation of the mycelium

conidium—asexual spore borne on, but easily detached from, a hypha or conidiophore

conidiophore—specialized hypha that produces and bears conidia

dichotomous branching—equal branching of hypha

dimorphic—growth as hyphae in vitro at 25°C and as budding yeastlike cells or spherules in infected tissues or in vitro at 37°C on special media

endospore—asexual spore formed within a closed structure (e.g., a spherule)

Endosporulation—process of producing endospores

fruiting body—spore- bearing organs produced by fungi

germ tube—tubelike structure, produced by germinating conidium that eventually develops into a hypha

granule (grain)—compact mass of organized mycelium that may be embedded in a cementlike substance; formed in actinomycosis

hypha (pl. hyphae)—filament that forms the body of most fungi

mycetoma—a localized, tumorous lesion caused by exogenous actinomyces or fungi that forms granules within invaded tissue

mycelium—a mass of intertwined hyphae

mycosis—disease caused by invasion of tissue by fungal elements

pseudohyphae—short, hyphalike filaments formed by successive yeast buds that elongate but fail to separate

septate—having cross walls

Spherules—closed, thick-walled, spherical structure within which asexual endospores are produced by progressive cytoplasmic cleavage

Splendore-Hoeppli phenomenon—homogeneous, eosinophilic, refractile, and often radially oriented material found around some invasive fungal elements and around granules in actinomycosis; it represents a localized antigen–antibody reaction in the sensitized host

sporangium (pl. sporangia)—a closed structure within which asexual spores (sporangiospores) are produced by cytoplasmic cleavage

yeast—spherical to oval unicellular fungus that reproduces by budding or fission, as well as sexually by the formation of ascospore

yeastlike—spherical or oval unicellular fungus that reproduces asexually by budding or fission; yeast-like cells are produced by dimorphic fungi

Data from Chandler FW, Watts JC. Pathologic Diagnosis of Fungal Infections. Chicago: American Society of Clinical Pathologists, 1987.

Pulmonary Candidiasis

Candidiasis, which is caused by yeastlike fungi of the genus *Candida*, is the most frequently encountered opportunistic infection in humans, accounting for roughly 50% of the fungal infections among immunocompromised patients and up to 75% or more of such infections in patients with solid tumors or hematologic malignancies.

Of the several species, the most common pathogen is *Candida albicans*. It is a dimorphic fungus and is a normal inhabitant of the mouth, oropharynx, upper respiratory tract, digestive tract, and vagina. It is a true endogenous pathogen and has not been isolated from the environment. The clinical and radiographic features of pulmonary candidiasis are nonspecific.

Gross and Histologic Findings

The lungs grossly show bronchopneumonia to multiple abscesses, as well as miliary nodular lesions that may be hemorrhagic. The lesions microscopially exhibit budding yeastlike cells and delicate nonseptate pseudohyphae. The cellular response is neutrophilic. The lesions may be angiocentric with hematogenous spread.

Cytopathologic Findings

Cytologic specimens (e.g., sputum, bronchial washings, BAL, and aspiration biopsies) may show *Candida* organisms; however, establishing *Candida* as a pathogen is difficult because it is found normally as a contaminant. It is not unusual to see colonization of bronchial mucosa by yeast forms and tangles of thin delicate nonseptate hyphae (Figs. 4C-54 and 4C-55). The organisms measure 2–5 μm, and they are spheroidal to oval and uniform. The presence of organisms in fine needle aspiration biopsy specimens or in histological sections of lung biopsies and histological evidence of pulmonary parenchymal invasion favor true infection. *Candida* organisms are stained by PAS and Gomori's methanamine silver (GMS) (Figs. 4C-56A and 4C-56B). Isolation and culture of *Candida albicans* from these biopsy specimens confirm the organisms as pathogens.

Histoplasmosis

Histoplasmosis, which is caused by the dimorphic fungus, *Histoplasma capsulatum*, is a respiratory disease contracted by inhaling the airborne spores. Patients with infection may be asymptomatic. Multiple lung calcifications develop in time. The symptomatic infections fall into three categories: acute pulmonary, disseminated, and chronic pulmonary with cavitation.

Acute pulmonary disease presents flulike symptoms following an incubation period of roughly 15 days. This infection may resolve or progress to fibrocaseous nodules. The organisms disseminate by way of histiocytes. Chronic histoplasmosis occurs in patients with long-standing lung disease

with clinical and radiologic features similar to pulmonary tuberculosis. The disseminated form occurs in both immunocompetent and immunosuppressed patients. Chest radiographs show a variety of patterns. The shadows may be focal or diffuse, unilateral or bilateral, or nodular with or without cavitation.

Gross and Histologic Findings

The lungs grossly show localized or diffuse lesions. Histologic findings are dependent on whether the lesion is nodular, fibrocaseous, or pneumonic with acute inflammation. The fibrocaseous form shows a histologic pattern similar to tuberculous granulomas. The necrotic lesions may become calcified. The fungus elicits an epithelioid and giant cell response. Large central zones of caseous necrosis are surrounded by a thick wall of dense collagenous connective tissue that may contain epithelioid and multinucleated giant cells.

In the disseminated form of histoplasmosis, the yeast forms replicate within mononuclear cells or histiocytes.

In tissues, the organisms are intracellular and can be easily overlooked. They are small, 2–4 μm, round to oval, and reproduce by single budding. Their basophilic cytoplasm is retracted from the rigid but thin, poorly stained cell wall, creating a clear space or halo that gives the false impression of a capsule. The cell wall may stain deeply with special stains. Special stains used to demonstrate the organisms include PAS and silver stain.

Cytopathologic Findings

The cytologic specimens useful for the diagnosis include BAL and fine needle aspirates. The organisms are not readily visualized in Papanicolaou-stained preparations, but when seen the fungal organisms appear as small dotlike structures, predominantly within histiocytes, surrounded by a clear halo (Figs. 4C-57 and 4C-58A). Macrophages that contain the histoplasma organisms are often enlarged and distended. Extracellular organisms are difficult to identify. Special stains such as GMS and PAS are necessary for morphologic confirmation (Fig. 4C-58B). The diagnosis is established by special stains, direct immunofluorescence test, and isolation in culture.

Differential Diagnoses

The differential diagnoses include yeast forms of *Candida spp.*, *Blastomyces*, and *Pneumocystis* organisms. The latter are almost always extracellular and do not reproduce by budding.

Pulmonary Blastomycosis

Pulmonary blastomycosis is a chronic granulomatous and suppurative infection caused by the dimorphic fungus *Blastomyces dermatitidis*. Most infections result from inhalation of the spores. Pulmonary involvement occurs from its inception. The infection is often confined to the lungs, may be self-limited or progressive with bilateral involvement and dissemination with high mortality, or persist as a chronic infection. Chest radiographs demonstrate patchy or nodular, solitary, bilateral infiltrate. There may be a central hilar mass that mimics lung cancer. Clinical signs and symptoms include malaise, weight loss, or low-grade fever. Skin involvement with verrucous and nodular lesions is present in 40–50% of patients.

Gross and Histologic Findings

The lesions may be localized, grossly visible as solitary nodules that may become confluent to form large areas of consolidation. The nodules may show caseous necrosis, cavitate, and be indistinguishable from tuberculous lesions. The cavities are usually thin walled and calcification is extremely rare. Pleural involvement is common.

The tissue response to infection by *Blastomyces dermatitidis* is in the form of suppuration and granulomatous reactions. Fungal organisms appear as spherical, single-budding yeast forms 8–15 μm in diameter, with thick, double-contoured walls. The broad-based budding of the fungus is very characteristic and aids in differentiating it from other yeast forms with budding. Hyphae are rarely formed.

Cytopathologic Findings

The cytologic specimens for detection of *Blastomyces* include sputum, bronchial brushings and washings, BAL, and fine needle aspiration biopsy. The organisms are seen both intra- and extracellularly often embedded and obscured by cellular and inflammatory debris. *Blastomyces* appear as spherical to oval, multinucleated yeastlike cells, 8–15 μm in diameter, having thick "double-contoured" refractile walls, and single broad-based buds (Figs. 4C-59 and 4C-60). The diagnosis is confirmed by special stains such as GMS and PAS, culture in isolation, or a direct immunofluorescence test that uses a specific conjugate directed against the cell wall polysaccharide antigen of *Blastomyces dermatitidis*.

Differential Diagnoses

Differential diagnoses include *Cryptococcus neoformans*, *Coccidioides immitis*, and pollen grains (see coccidioidomycoses for differentiating features).

Pulmonary Cryptococcosis

Cryptococcosis is a systemic infectious disease caused by the fungus *Cryptococcus neoformans* that has a strong predilection for central nervous system, although it can involve any organ or system.

The causative agent is an encapsulated organism that reproduces by budding. The fungus is a ubiquitous, worldwide

saprophyte of soil, and is most abundant in avian habitat. The respiratory tract serves as the portal of entry for aerosolized spores. *Cryptococcus neoformans* is pathogenic in apparently healthy individuals, but is more often encountered as an opportunistic infection. Patients with hematologic malignancies, on long-term corticosteroid therapy, or with HIV infection are predisposed to this fungal infection.

Patients present clinically with cough, low-grade fever, pleuritic or nonpleuritic chest pain, malaise, weight loss, and mucoid sputum. Chest x-ray reveals alveolar and interstitial infiltrates and single or multiple nodules that resemble neoplasms. There may be segmental or lobar consolidation. Hilar lymphadenopathy and pleural effusions are rare. Cavitation occurs in less than 10% of cases. Diffuse interstitial and peribronchial or miliary pneumonic infiltrates develop in profoundly immunodeficient patients.

Gross and Histologic Findings

The lesion grossly may be localized, as seen in immunocompetent individuals characterized by caseous necrosis and granulomatous inflammation. The disease tends to be diffuse in immunocompromised patients. The lungs are heavy with glistening cut surfaces and with slimy consistency. Inflammatory response may be very poor in severely immunocompromised patients. Cryptococcal organisms are seen in enormously large numbers within the alveoli as well as within the septae and in capillaries.

Cytopathologic Findings

The organisms may be identified by examining sputum, bronchial washings, BAL, and fine needle aspiration biopsy of a localized lesion. In Papanicolaou-stained preparations, *Cryptococci* appear as refractile round (Figs. 4C-61 and 4C-62), lightly eosinophilic, uninucleate, thin-walled, spherical, oval to elliptical yeast forms, 2–20 μm in diameter, surrounded by wide, clear spaces that represent unstained capsules. Single buds attached to the parent cells by narrow necks (i.e., tear drop forms) are common and characteristic. In active lesions, myriads of rapidly dividing *Cryptococci* are conspicuous. The capsules stain positively with mucin stains and often show spiked appearance due to shrinkage during tissue processing. Cryptococcal infection may coexist with Pneumocystis carinii infection. Diagnostic confirmation is by special stains (Figs. 4C-63A and 4C-63B), direct immunofluorescence, and serologic latex agglutination test for capsular polysaccharide antigen.

Differential Diagnoses

Differential diagnoses include other fungi with yeast forms such as *Blastomyces*, pollen, red cells that appear empty and devoid of hemoglobin, and Michaelis-Guttmann bodies in malakoplakia (see Chapter 10).

Pulmonary Paracoccidioidomycosis

Paracoccidioidomycosis, which is also known as South American blastomycosis, is a chronic progressive fungal infection that is largely confined to Latin America, and is caused by *Paracoccidioides brasiliensis*. The organism is a dimorphic fungus whose natural habitat is not defined. Infection is more frequent in immunocompetent adult males who are rural dwellers and have contact with soil.

Primary infection begins in the lungs and may disseminate. Patients present with cough, dyspnea, fever, weight loss, constitutional symptoms, and hemoptysis. Chest radiograph reveals a nonspecific picture of bilateral, symmetrical, interstitial, or micronodular infiltrates, consolidation, fibrosis, or cavitations.

Gross and Histologic Findings

The findings are nonspecific grossly. The lungs histologically show linear streaks of fibrosis radiating from the hilum, accompanied by emphysema and granulomas. There is initial proliferation of the pulmonary blood vessels that result in right ventricular enlargement. The lung parenchyma may show nodular lesions of granulomatous inflammation and suppuration with cavity formation. The organisms are found in intracellular locations.

Cytopathologic Findings

The organisms are detected in cytological examination of sputum, bronchoscopic specimens, or fine needle biopsy specimens. The fungal organisms range from 3 to 30 μm and can be as large as 60 μm. Larger organisms have 1 mm thick walls. The fungi display two forms of budding: large teardrop blastoconidia attached to the parent cell by a narrow neck or multiple small daughter buds that arise from the cell wall, each of which is attached by a narrow-necked base (Fig. 4C-64), a pattern described as "ships-wheel budding." The organisms can be stained with silver stains and confirmed by serologic tests and by immunofluorescence.

Pulmonary Sporotrichosis

Sporotrichosis is an infection caused by a dimorphic fungus, *Sporotrichum schenckii*. Although it commonly involves skin and subcutaneous tissues, pulmonary involvement occurs occasionally. The organisms are found worldwide as a saprophyte in soil, plants, trees, and wood timbers and are considered an occupational disease occurring in farmers, gardeners, florists, and forestry workers.

The presentation of pulmonary involvement is clinically indistinguishable from those with progressive granulomatous and cavitary lesions. X-ray findings are nonspecific with linear streaks, patchy and fibronodular infiltrates, cavitary lesions, and rarely pleural effusion.

The organisms are oval to elongated, cigar shaped single or

budding yeastlike cells 2–6 μm. Multiple budding is occasionally seen. The yeastlike cells may be coated with eosinophilic refractile radially oriented Splendore-Hoeppli material to form asteroid bodies that are usually located in microabscesses.

The diagnosis is by isolation and culture, direct immunofluorescence, and serology.

Pulmonary Coccidioidomycosis

Coccidioidomycosis is a pulmonary mycosis that is endemic in the southwestern states of the United States and is caused by a dimorphic fungus, *Coccidioides immitis*. It is widely distributed in soil. The majority of primary infections are subclinical and the individuals become seropositive to the antigen, coccidioidin. Roughly 40% of infected individuals develop a spectrum of symptoms ranging from a flulike syndrome to frank pneumonia following an incubation period of 1–4 weeks. Symptoms include cough, fever, shortness of breath, headache, chest pain, and dyspnea. About 10% of the symptomatic patients develop allergic manifestations such as erythema nodosum, erythema multiforme, and arthralgia. Chest radiographs may be normal, or they may show soft, hazy, patchy, or segmental pneumonia. The infiltrate may be in the form of solitary or multiple nodules or cavitating. Hilar lymphadenopathy and pleural effusion sometimes occur. Chronic progressive coccidioidal pneumonia occurs in less than 1% of the patients with primary coccidioidomycosis. The infection is more serious and disseminated when it occurs in immunocompromised patients. The indolent form resembles tuberculosis clinically and radiologically. Benign pulmonary lesions follow primary pulmonary infection. Coccidioidal nodules or coccidioidomas appear radiologically as solitary coin lesions 1–4 cm in diameter, usually in the upper lobes and midlung fields, and may be mistaken for a carcinoma. Coccidioidomas may cavitate or calcify. Thin-walled cavities develop within the parenchymal infiltrate resulting from necrotizing bronchitis, whereas the thick-walled cavities occur due to necrosis and drainage of residual nodules.

Gross and Histologic Findings

Pulmonary lesions of coccidioidomycosis can be grossly classified as pneumonic, cavitary, nodulocaseous, and bronchiectatic. Coccidioidomas exhibit central fibrocaseous areas histologically with peripheral granulomatous inflammation. Eosinophils may be present in large numbers in the surrounding tissues. The organisms are often present within the necrotic and granulomatous areas (see later). Splendore-Hoeppli effect may be seen surrounding the fungi.

Cytopathologic Findings

The *Coccidioides* organisms may be identified in sputum, bronchoscopic specimens (brushings, washings, and BAL), and aspiration biopsy of solitary lesions. The smears show abundant amorphous granular material and necrotic debris seen as clumps of basophilic material, as well as calcific debris. Fungal organisms may exist in the form of immature spherules, mature spherules, and endospores (Figs. 4C-65 and 4C-66). Immature spherules range from 5 to 30 μm in diameter. Their walls and granular internal contents are strongly PAS-positive (Fig. 4C-65B). The larger immature spherules endosporulate, becoming mature spherules. These range from 30 to 100 μm in diameter and occasionally may be as large as 200 μm. Their thin walls 1–2 μm in width are GMS variable but PAS-negative. The uninucleate endospores are 2–5 μm, have walls, and punctate cytoplasmic inclusions that are GMS and PAS-positive. The developmental forms can be identified by direct fluorescent antibody test. The endospores are released to produce hyphae and Arthroconidia. Mycelial elements are 1–1.5 μm, septate, and may be present along with characteristic rectangular or barrel-shaped Arthroconidia. Crushed or fractured spherules present a broken ping pong ball appearance. Calcific concretions (10–50 μm) are seen that may represent degenerated spherules with mineralization. Inflammatory cells and multinucleated giant cells may be present. Associated features include reactive and hyperplastic epithelial cells that may cause diagnostic difficulties, especially when fungal organisms are sparse and not recognized. The organisms are stained with silver and PAS stains. Diagnosis is confirmed by culture and direct immunofluorescence test, skin test, and serology.

Differential Diagnoses

Differential diagnoses include Blastomycosis, cryptococcosis, pollen grains, and vegetable matter. *Blastomyces* present broad-based budding, whereas *Cryptococci* possess capsules. Pollen grains are round and dense without budding or capsules. Vegetable cells have refractile double walls without budding or capsules.

Pulmonary Aspergillosis

Pulmonary aspergillosis presents a spectrum of pulmonary infections caused by a fungus belonging to the genus *Aspergillus*. The infection occurs in several different forms and is encountered in both immunocompetent as well as immunocompromised patients. The various forms of infection include: (1) allergic reactions in hypersensitized hosts; (2) saprophytic colonization of preexisting cavities in immunocompetent individuals; (3) noninvasive or superficially invasive necrotizing tracheobronchitis; (4) chronic progressive and destructive pulmonary infection in mildly immunocompromised patients; and (5) rapidly progressive invasive infection in severely immunocompromised patients, particularly those with leukemias. These various forms of infection may coexist or overlap.

Of the several members of the genus *Aspergillus* three species are isolated from patients with Aspergillus infection: *Aspergillus fumigatus*, *Aspergillus flavor*, and *Aspergillus niger*. Aspergillus consists of hyphae that are dichotomous and branch at a 45-degree angle. The hyphae are septate, narrow, 3–5 μm in width with parallel walls. The fruiting bodies or conidia containing the spores develop only when the fungus comes in contact with air as it grows in cavities or along the airways. The hyphae occasionally exhibit unusual features with bizarre shapes and varicose dilatations. Calcium oxalate crystals may be present with the infection. *Aspergillus Niger* infection is associated with black pigment. Chronic granulomatous lesions may be surrounded by Splendore-Hoeppli material. The hyphae stain blue-green or golden brown with Papanicolaou stain; however, the morphology is highlighted by the silver and PAS stains (see Figs. 4C-69 and 4C-70). Other stains used are Toluidine blue, Gram stain, and Giemsa stain.

Allergic bronchopulmonary aspergillosis occurs in hypersensitized patients who present with symptoms of asthma and tissue eosinophilia or mucoid impaction of the airways, especially the second to fourth order of bronchial segments. The mucoid plugs greatly dilate the bronchi. They are tenacious, inspissated, gray to green-yellow, or rusty brown, round, oval, or elongated, rubbery, up to 2.5 cm thick, and up to 6 cm long. They may be coughed up or removed by bronchoscopy. Fungal hyphae can be demonstrated in these mucus plugs.

Intracavitary aspergilloma is formed by saprophytic colonization of the fungus within preexisting cavities. It is a compact spherical conglomerate of hyphae that grow in cavities such as those caused by chronic abscess, tuberculosis, or in patients with cystic fibrosis. Aspergillomas may also be associated with cavitary malignant neoplasms. Most such cavities are sharply demarcated, ranging from 1 to 7 cm or more in diameter. The walls of the cavities may be thick, gray-white, and fibrous, with either a smooth or shaggy lining. The adjacent pleura are thickened and fibrous. The fungus ball is microscopically composed of concentric or convoluted layers of radially arranged and intertwined branching hyphae. Fruiting bodies or conidia may be present.

Necrotizing tracheobronchitis involves the tracheobronchial tree in patients who had tracheostomies or endobronchial intubation. It represents a superficial form of infection and may involve peribronchial lung parenchyma. The eroded mucosa is replaced by a granular brown adherent pseudomembrane composed of inflammatory exudate, mucus, and fungal hyphae that may occlude the subsegmental bronchi. The infection is generally limited to the bronchi.

Chronic necrotizing pulmonary aspergillosis (CPNA) occupies an intermediate position in the spectrum of bronchopulmonary aspergillosis. It is a chronic progressive and destructive process that resembles pulmonary tuberculosis and is characterized by large cavities that contain amorphous granular aggregates or balls of hyphae. There is some degree of invasion and destruction of the surrounding tissue with abscess formation and chronic inflammation with fibrosis, which may represent a preexisting condition.

Invasive pulmonary aspergillosis (IPA) is a fulminant, rapidly progressive infection. The clinical symptoms are often non-specific. Patients develop fever, are not responsive to broad spectrum antibiotics, and demonstrate new or changing pulmonary infiltrates in the setting of neutropenia or corticosteroid therapy. They may develop pleuritic chest pain and hemoptysis. Chest radiographs show patchy, multifocal, or diffuse bilateral areas of consolidation, which are peripheral, wedge-shaped, pleural-based infiltrates resembling infarcts. These may cavitate. There may be multiple nodular densities. The involved lungs histologically show large wedge-shaped pleural-based hemorrhagic infarcts, often involving most of the lobe, and associated with thrombosis of a major artery branch caused by hyphal invasion from an adjacent bronchus. The infarcts may be multiple and small. Cavities resulting from necrotic infarcts may harbor fungus balls. Abundant hyphae are seen in bronchial, vascular, and parenchymal lesions, often radiating outwards from the center of the lesions and extending through the tissue planes. A granulomatous response is present in noncompromised patients and those patients treated with antifungal therapy.

Cytopathologic Findings

Aspergillus spp. are generally found in all types of respiratory specimens in infected patients. Slender, septate hyphae with parallel walls and dichotomous branching allow easy recognition (Fig. 4C-67). The background in cytologic specimens is often necrotic and the hyphae are embedded within the debris. Hyphae stain light blue in Papanicolaou stain (Figs. 4C-67 and 4C-68). Fruiting bodies or conidia may be identified (Fig. 4C-68A). Varicose dilatations and bizarre forms are occasionally seen (Fig. 4C-68B). Hyphae are highlighted by special stains (Figs. 4C-69 and 4C-70). Calcium oxalate crystals are frequently present and can be appreciated under polarized light (Fig. 4C-71). In long-standing cavitary lesions with aspergillomas, the lining epithelium undergoes squamous metaplasia with atypical changes. Exfoliated tissue fragments of atypical squamous epithelium are a potential diagnostic pitfall (see Chapter 6, Figs. 6C-44–6C-46). The diagnosis is established by special stains (Figs. 4C-69 and 4C-70) and culture.

Differential Diagnoses

The differential diagnoses of aspergillosis include hyphae of *Mucor* and *Candida*. *Mucor* is wider, irregular, pauciseptate, and flat, with branching at right angles. *Candida* hyphae are more slim, nonseptate, and are associated with yeast forms. Elastin fibers in an abscess with tissue necrosis may resemble hyphae of *Aspergillus* (Fig. 4C-72). The elastin fibers are not septate.

Pulmonary Mucormycosis

Mucormycosis is caused by fungi belonging to the genus Zygomycetes, also known as *Phycomycetes*. These organisms are saprophytic, present in soil, and have worldwide distribution. The most fulminant and invasive form of infection occurs in patients with diabetic ketoacidosis and patients with lymphomas and leukemia.

Patients present with fever, new or progressive lung infiltrates, and are unresponsive to antibiotic therapy. The organisms have a strong propensity to invade blood vessels and cause arterial thrombi. Patients may develop massive hemoptysis or present signs and symptoms of pulmonary infarct. Chest radiographs reveal solitary or multiple areas of consolidation and patchy nonhemorrhagic infiltrates. There may occasionally be no radiographic abnormalities. Cavitation is unusual.

Gross and Histologic Findings

The lungs grossly show hemorrhagic infarcts and suppurative inflammation. Fungal hyphae are scattered haphazardly throughout the lesions and are also seen invading the walls of blood vessels. The hyphae are pleomorphic, broad, flat, and 10–25 μm in width, with delicate thin walls. They are paucicseptate, often twisted, folded, and wrinkled with uneven contour. The hyphae branch irregularly at right angles. Transected hyphae are frequently present in the tissues, and appear as round or oval structures, with optically clear centers. Hyphae exposed to air may form chlamydoconidia, which may be mistaken for yeastlike cells or sporangia when detached. The thick-walled chlamydoconidia are 15–30 μm in diameter, densely basophilic, and PAS positive.

Cytopathologic Findings

The organisms may be identified in sputum, bronchial brushings and washings, BAL, or in aspiration biopsy specimens. Their appearance in cytologic preparation is similar to that seen in tissues. The fungal hyphae are pale, flat, ribbonlike, and may be overlooked (Figs. 4C-73–4C-75). The diagnosis is confirmed by special stains and culture.

Differential Diagnoses

Differential diagnoses include aspergillus. The aspergillus hyphae are septate and more uniform in thickness, with regular dichotomous branching at 45 degrees.

The salient clinicopathologic features, cytologic findings, confirmatory tests, and differential diagnoses of fungal infections described earlier are summarized in Table 4-11.

Pulmonary Parasitic Infections

Parasitic infections in general are uncommon in the Western world; however, they are frequent occurrences in underdeveloped countries. Pulmonary involvement is still rare. Several types of parasites may cause pulmonary disease [e.g., protozoa (amebic pneumonitis and abscess), nematodes (roundworms) trematodes (schistosomes), and cestodes (tapeworms)]. Most of these parasites involve human beings only accidentally. Furthermore, they are only rarely encountered in cytological specimens.

Strongyloidosis

Strongyloides stercoralis is a nematode that is known to cause hemorrhagic pneumonia, as reported in patients receiving high-dose steroid therapy for such conditions as rheumatoid arthritis, renal transplantation, and severe asthmatic bronchitis, as well as in patients who are severely immunosuppressed (e.g., with AIDS).

Pulmonary infection is produced by filiform larvae that migrate through the intestinal walls into the bloodstream, making their way to the alveolar spaces, and resulting in hemorrhagic pneumonia. The larvae can be coughed up in the sputum (Figs. 4C-76 and 4C-77). The larvae are 400–500 μm in length and curved with a blunt and slightly notched tail.

Pulmonary Ascariasis

Ascariasis lumbricoides is a nematode or a roundworm that is extremely prevalent in underdeveloped countries, causing infestation of the gastrointestinal tract. They rarely cause pulmonary disease in spite of their high prevalence and the usual migratory route of the larvae from the lungs to their final destination in small intestine. Roundworm larvae may be coughed up in the sputum on extremely rare occasions (Fig. 4C-78).

Pulmonary Dirofilariasis

Pulmonary dirofilariasis is caused by a dog tapeworm, *Dirofilaria immitis*. The lesion involving the lung is described radiologically as a coin lesion about 2–3 cm in diameter, usually located at the periphery, and fixed to the pleura. The lesion consists histologically of a central area of coagulative necrosis, surrounded by epithelioid cells, Langhans-type giant cells, lymphocytes, and plasma cells. The necrotic area may show intact or degenerating ova lodged in remnants of a pulmonary arteriole (Fig. 4C-79). Similar findings have been described in aspiration biopsies.

Pulmonary Echinococcosis

Echinococcosis, which is also referred to as Hydatid disease, is caused by an adult tapeworm, *Echinococcus granulosis*. Animals such as dogs, sheep, and some carnivorous animals are definitive hosts, and human beings are accidentally infected. The primary or the definitive host passes the ova via feces. Humans become infected via contamination by the exc-

TABLE 4-11. Pulmonary mycotic infections.

Disease organism	Geographic distribution	Clinicohistopathologic findings	Morphology
Aspergillosis *Aspergillus fumigatus* *Aspergillus niger* *Aspergillus flavus*	Worldwide; common household mold; saprophytic in soil	Predominantly affect immunocompromised host; can affect immunocompetent hosts by colonizing preexistent cavities; present a spectrum of pulmonary infections: (1) perivascular and peribronchial suppurative infection; (2) chronic granulomatous or chronic necrotizing aspergillosis; (3) invasive aspergillosis involving arteries and veins resulting in thrombosis, tissue infarction and systemic dissemination; (4) allergic bronchopulmonary aspergillosis; (5) asymptomatic colonization of cavitary lesions, (e.g., tuberculosis, infarcts, bronchiectasis, and cavitary carcinomas); may induce squamous metaplasia with atypia	Organisms present as septate hyphae 3–6 μm in width, parallel walls; characteristic dichotomous branching at 45 degrees; often present as tangled mass of hyphae; mycelial growth in preformed cavities forming fungus ball or aspergilloma; when in contact with air form fruiting bodies or conidia; may exhibit irregular bizarre shapes and varicose dilatations; black pigment with infection by aspergillus niger; calcium oxalate crystals present in association with fungi
Blastomycosis *Blastomyces dermatitides*	North America; a soil saprophyte; dimorphic fungus	Infection results for inhaling the spores; may cause acute or chronic granulomatous and suppurative infection of the lung; affect both immunocompetent and immunocompromised hosts; Splendore-Hoeppli phenomenon in the granulomatous lesions; clinically, signs and symptoms resemble those of neoplasia, blood-streaked sputum, or hemoptysis; cough, chest pain, fever, weight loss; bilateral dense irregular shadows on chest radiographs	Yeast forms 8–15 μm in diameter; spherical, single, budding with a broad base; sharply defined thick refractile walls
Histoplasmosis *Histoplasma capsulatum*	Americas, especially Ohio and Mississippi valleys; dimorphic fungus present in soil, in areas with large amounts of bird droppings	May affect both immunocompetent and immunocompromised hosts; infection results from inhaling airborne infectious spores; may result in asymptomatic infections, leading to multiple calcified nodules over time; can cause acute pulmonary infection or chronic pulmonary granulomatosis or cavitary lesions; infection may be disseminated; clinically, radiologically resemble tuberculosis	Yeast forms, small budding 2–4 μm; intracellular within macrophages; organism have rigid cell walls; retraction of the cytoplasm creates a clear space or halo giving a false impression of capsule
Sporotrichosis *Sporothrix schenckii*	Worldwide; saprophyte in soil, plants, trees, wood, timbers; a dimorphic fungus	Considered an occupational disease involving farmers, forestry workers, gardeners, florists; commonly involves skin and subcutaneous tissues, occasionally involves lungs; affects immunocompetent hosts; pulmonary lesions consist of large, often confluent necrotizing and non-necrotizing granulomas containing the organisms	Spherical, oval to elongated, cigar shaped, single or budding; may be associated with Splendore-Hoeppli effect in micro abscesses
Candidiasis *Candida albicans* *Candida tropicalis* *Candida glabrata*	Worldwide; normal inhabitant of mouth; oropharynx, upper respiratory tract, digestive tract, vagina; a dimorphic fungus	Most frequently encountered opportunistic infections, especially frequent in patients with hematologic malignancies and solid tumors; affecting immunocompromised hosts; nonspecific clinical, radiologic features; also affect patients with diabetes, with recent surgery, or severe burns; infection follows aspiration of organisms into lungs or via hematogenous dissemination resulting in bronchopneumonia, miliary, abscesses, pulmonary infarcts.	Budding yeast forms; size 2–4 μm; delicate nonseptate branching hyphae; 2–4 μm in width; chains of yeast forming pseudohyphae
Paracoccidiomycosis *Paracoccidio braziliense*	Central and South Americas natural habitat undefined; dimorphic fungus present in soil	In severely compromised patients, also affects immunocompetent hosts; considered to be an occupational disease in rural dwellers; causes a chronic progressive disease; clinically presents with cough, dyspnea, fever, hemoptysis, and weight loss; radiologic features nonspecific—bilateral symmetrical interstitial or micronodular infiltrates; consolidation, cavities, or fibrosis; histology—linear streaks of fibrosis radiating from the hilum, emphysema, suppuration, cavities, granulomatous inflammation; intimal proliferation of the blood vessels causing right ventricular enlargement and cor pulmonale	Yeast forms; size 3–30 μm, large as 60 μm; thick cell walls up to 1 μm; multiple budding; daughter cell remains attached around the parent cell; appearance of a steering wheel

Organisms recovered from	Useful stains	Differential diagnoses	Confirmatory tests	Fig(s).
Sputum bronchial brushings/ washings bronchoalveolar lavage fine needle aspiration biopsy	Papanicolaou H&E PAS GMS Gram Giemsa Toluidine blue	1. *Mucor*—septate hyphae, but very broad ribbon like, irregular, branching at right angles 2. *Candida spp.*, thin nonseptate hyphae, often associated with yeast forms 3. Elastin fibers	1. Culture 2. Fluorescent antibody	4C-67 to 5C-71
All types of respiratory specimens	Papanicolaou H&E PAS GMS	1. *Cryptococcosis* 2. *Histoplasmosis* 3. *Coccidioidomycosis*	1. Culture	4C-59 4C-60
Fine needle aspiration biopsy	H&E GMS PAS—negative Mucicarmine negative	1. *Blastomycosis* 2. *Cryptococcosis* 3. *Coccidioidomycosis*	1. Culture 2. Serology	4C-57 4C-58
			1. Culture 2. Dirct immuno-fluorescence 3. Serology	—
Sputum bronchial washings and lavage fine needle aspiration biopsy (since candida organisms are often contaminants, diagnosis as a pathogen must be made with caution and in clinical context)	Papanicolaou (pale pink) Romanowsky inconspicuous GMS PAS	1. *Cryptococcosis* 2. *Coccidioidomycosis* for yeast forms 3. *Aspergillosis* for hyphae	1. Culture 2. Latex agglutination	4C-54 to 4C-56
Sputum bronchial washings and lavage fine needle aspiration biopsy	GMS	—	1. Immunofluorescence	4C-64

(*Continued on next page*)

TABLE 4-11. Pulmonary mycotic infections. (*Continued*)

Disease organism	Geographic distribution	Clinicohistopathologic findings	Morphology
Cryptococcosis *Cryptococcus neoformans*	Worldwide; saprophytic in soil, most abundant in avian habitat; unimorphic	Commonly affect immunocompromised patients but may be seen in immunocompetent hosts, often coexistent with Pneumocystis infection; marked predilection for cerebromeningeal dissemination; portal of entry is lungs; clinical presentation includes cough, low grade fever, pleuritic or nonpleuritic chest pain, malaise, weight loss, mucoid sputum; chest x-ray alveolar and/or interstitial infiltrate in single or multiple nodules resembling neoplasia, segmental or lobar consolidation; histology granulomatous response; intense local inflammatory reaction with suppuration; diffuse interstitial or miliary infiltrate, host response absent in severely immunocompromised patients	Yeast forms 4–15 μm; budding with narrow base—teardrop forms; round to oval, thick mucopolysaccharide capsule; thin cell wall, extracellular
Phycomycosis *Zygomycosis* *Mucor Rhizopus*	Worldwide; saprophytic in soil	Most fulminant and invasive form occurs in patients with diabetic ketoacidosis; progressive pulmonary infiltrate; signs and symptoms of pulmonary infarct, propensity of organisms to involve pulmonary vasculature, arterial thrombosis; x-ray solitary or multiple areas of consolidation, patchy nonhemhorragic infiltrate; histology—hemorrhagic infarct; suppurative pneumonitis, haphazard distribution of hyphae throughout the lesions and the walls of the blood vessels	Hyphae up to 100–30 μm in width, broad ribbon like, irregular shapes; branching at right angles (90 degrees); delicate; pauciseptate; often twisted, folded, wrinkled, uneven contours due to variation in width
Coccidioidomycosis *Coccidioides immitis*	North American deserts; dimorphic fungus; widely distributed in soil	Pulmonary mycosis; dissemination rare; affects both immunocompetent and immunosuppressed hosts; endemic in the western hemisphere; majority of the cases clinically inapparent silent and resolve; non-specific symptoms; radiologic features may suggest acute pneumonia, inflammation and suppuration, rarely cavitation; granulomatous inflammation	Nonbudding, encapsulated spherules 15–100 μm; thick, refractile walls, contains numerous small endospores 2–5 μm; stains basophilic

reta. The ingested ova are hatched in the intestine. The embryo penetrates the intestinal wall and reaches the liver via blood vessels. It may develop into hydatid cysts. Some embryos may find their way to the lungs. More than 70% of hydatid cysts are found in the liver, and the lung is the next most common organ to be infected. The cysts can reach large dimensions, up to 20 cm in diameter (Fig. 4C-80). They have an outer laminated elastic layer and an inner germinal layer from which develop Brood's capsules containing scoleces (Figs. 4C-81 and 4C-82). The cyst fluid is usually slightly turbid to clear and contains scoleces and free hooklets. Pleural involvement may be diagnosed by finding scoleces and free hooklets in pleural fluid (Fig. 4C-81B).

Pulmonary Filariasis

Filariasis is a common parasitic infestation in tropical countries, caused by *Wuchereria bancrofti*. The infection is endemic in India and is transmitted by mosquitoes. The microfilaria or the larvae enter the blood stream of the host following a mosquito bite and lodge in the lymph nodes, where they mature into adult worms. Lymphadenitis and lymphangitis develop, followed by lymphadenopathy and lymphatic obstruction. The microfilaria laid by the adult worm in the lymph nodes travel via blood to virtually any body site and may be encountered in a variety of cytological specimens.

Pulmonary involvement by microfilaria is referred to as *tropical eosinophilia* and is characterized by dry hacking cough, fever, and spasmodic bronchial asthma. Chest radiographs show generalized ill-defined mottling with small nodules. A high blood eosinophil count, high levels of IgG, and positive filarial complement test suggest the diagnosis. Microfilaria rarely may be identified in bronchial brushings (Fig. 4C-83) or in fine needle aspiration biopsy specimens of lung masses. Microfilaria are seen as sheathed, curved, linear structures with discrete nuclei.

Pulmonary Paragonimiasis

Pulmonary paragonimiasis is an endemic lung disease in West Africa, the Orient, and certain regions of Central and South America caused by lung flukes, *Paragonimus westermani*.

Organisms recovered from	Useful stains	Differential diagnoses	Confirmatory tests	Fig(s).
Sputum bronchial washings and lavage fine needle aspiration biopsy	Papanicolaou H&E India ink PAS—stain the wall GMS Alcian blue Mucicarmine Immuno	1. *Blastomycosis* 2. *Histoplasmosis* 3. *Coccidioidomycosis*	1. Culture	4C-61 to 4C-63
Sputum bronchial brushings/washings bronchoalveolar lavage fine needle aspiration biopsy	Papanicolaou H&E GMS	*Aspergillosis*		4C-73 4C-74
Sputum bronchial washings and lavage fine needle aspiration biopsy	Papanicolaou H&E PAS—negative GMS	1. Pollen grains 2. Vegetable cells 3. *Cryptococcosis* 4. *Blastomycosis*	1. Culture 2. Direct immunofluorescence 3. Latex agglutination to capsular polysaccharide antigen 4. Complement fixation	4C-65 4C-66

These flukes belong to the class of Trematoda, are flat, measuring 8–16 mm × 4–8 mm, spoon shaped with one end contracted and the other elongated, and possess an anterior and a ventral sucker.

Humans develop infection following ingestion of poorly cooked crab meat or crayfish containing encysted metacercariae, which hatch in the duodenum. The released larvae penetrate the duodenal wall, transmigrate to the diaphragm into the pleural space, and bore into peripheral lung tissue where maturation to the adult worm takes place. The adult fluke resides in a pseudocyst, which may rupture into the bronchiole/bronchi and be coughed up in the sputum. Patients may develop hemoptysis. During the migratory phase, patients may complain of chills and fever, and may develop blood eosinophilia. The flukes cause chronic disease with cavitary lesions, abscess, and pulmonary fibrosis.

Cytopathologic Findings

The adult flukes as well as their eggs have been reported in sputum, bronchial washings, and in fine needle aspiration biopsy specimens from lung lesions. The eggs are also detected in stools. The ova appear dark yellow-brown with a thick and smooth shell (Fig. 4C-84). They have a prominent shouldered operculum and measures 49 μm × 85 μm. There may be necrosis in the background, along with eosinophils and Charcot-Leyden crystals.

Pneumocystis Carinii Pneumonia

Pneumocystis carinii pneumonia (PCP) is caused by the organism *Pneumocystis carinii*, which is considered to be a protozoan; however, it possesses certain properties that some believe puts Pneumocystis in the family of fungi.

Pneumocystis carinii organisms are ubiquitous, affecting 75% of children by the age of 4 years. The infection is acquired via the respiratory tract, remaining latent and asymptomatic in healthy or immunocompetent individuals. It may be reactivated in immunocompromised patients. *Pneumocystis carinii* infection has become life threatening in immunocompromised patients, especially those with AIDS.

The clinical presentation of PCP varies. Symptoms are of-

TABLE 4-12. Cytopathologic characteristics of foamy alveolar casts in pneumocystitis carinii pneumonia in respiratory specimens.

- Well-demarcated, three-dimensional extracellular structures
- Globular shape
- Size, range of typical or distended lung alveoli 80–340 μm in longest dimension
- Pale eosinophilic to cyanophilic with negative imaging as multiple round clear spaces due to nonstaining of cysts in Papanicolaou stains
- Special stains required to confirm the presence of organisms

Data from Stanley ME, Henry-Stanley MJ, Iber C. Bronchoalveolar Lavage: Cytology and Clinical Application. New York: Igaku-Shoin, 1991.

ten nonspecific (e.g., fever, malaise, and weight loss), or the patient could be acutely ill, running a fulminant course with respiratory failure. Chest x-rays show bilateral, symmetrical, interstitial infiltrates in the majority of cases. Other patterns include unilateral infiltrates, nodules, and cavities.

Gross and Histologic Findings

Gross appearance of Pneumocystis pneumonia is not diagnostic and may resemble bacterial pneumonia or diffuse alveolar damage. Histological manifestations of PCP are highly variable. The most frequent pattern is pneumonia with alveoli filled with foamy eosinophilic casts accompanied by variable degrees of lymphoplasmacytic interstitial infiltrate. There may be alveolar damage with hemorrhage and hyaline membrane formation. Unusual presentations include abscesslike lesions, epithelioid granulomas that affect lung parenchyma and hilar lymph nodes, and cavitary lesions with or without pleural effusion. The fluffy alveolar casts demonstrate multiple small clear spaces within them, a pattern also characteristic of PCP infection, which represents the cysts of the organisms. The latter are not stained by either Hematoxylin and Eosin stain or Papanicolaou stain. With silver stain, the cyst walls are stained black. The cysts themselves appear round, cup shaped, or crescent shaped, measuring 5–7 μm in diameter. The frothy material itself does not stain with silver. Within the cysts are five to eight sporozoites, each measuring 1–2 μm, and which are not stained by silver but are instead visualized in Romanowsky-stained preparations. The cysts demonstrate auto fluorescence in Papanicolaou-stained smears. Other useful stains include toluidine blue, Gram-Weigert, and PAS.

Cytopathologic Findings

Cytologic samples for identification of *Pneumocystis* organisms include induced sputum (i.e., because the cough in AIDS patients is often nonproductive), bronchial washings, BAL, aspiration biopsies, and imprints of bronchial or transbronchial tissue biopsies. Bronchoalveolar lavage is by far the best type of respiratory specimen, offering a high diagnostic yield. The eosinophilic fluffy exudate, with round negative images of the trophozoites and cysts, is characteristic enough to be identified in Papanicolaou-stained smears (Table 4-12, Fig. 4C-85). Characteristics of *Pneumocystis* organisms with different stains are listed in Table 4-13 and illustrated in Figs. 4C-86A–4C-86C. Monoclonal antibodies have been used for confirming the diagnosis of PCP. The organisms have not been isolated by culture.

Differential Diagnoses

Differential diagnoses include conditions that are characterized by the presence of eosinophilic fluffy exudates (e.g., pulmonary alveolar proteinosis, amyloidosis, and lysed red blood cells) (see Table 4-20, Figs. 4C-114–4C-116).

Toxoplasmosis

Toxoplasmosis is caused by a sporozoan, *Toxoplasma gondii*. The organism has a worldwide distribution and is a soil contaminant. Humans are indefinite hosts and acquire infection via contamination by excreta of cats, which are definitive hosts. The organisms are intracellular protozoans. Up to 70% of the population is seropositive. Reactivation occurs in a small percentage of people. The infection can be disseminated in immunocompromised patients with a high risk for meningoencephalitis and pulmonary involvement. Patients present with dyspnea, tachypnea, and fever. Chest radiographs reveal diffuse alveolar and interstitial infiltrates.

Gross and Histologic Findings

The lungs grossly are heavy, congested with petechiae, consolidation, coagulative necrosis, and fibrinous exudate

TABLE 4-13. Characterization of *Pneumocystis carinii* under various methods of staining and visualization.

	Routine stains (Pap stain, H&E)	Trophozoitic stains (Giemsa, MGG, Diff-Quik®)	Capsular stains (GMS, PAS, G-W)
Foamy material	Visible as alveolar casts	Appear as woolly blue blobs	Invisible with GMS and PAS; partially visible with G-W
Cysts	Pale outline, variable by Pap stain under UV light	Pale outline with multiple intracystic bodies	Distinct cell walls with external dots
Trophozoites	Not visible with Pap stain	Visible, intensity varies	Not visible with GMS or PAS; visible with G-W

Pap = Papanicolaou; UV = ultraviolet; GMS = Gomori's Metamine silver; G-W = Gram-Weigert; MGG = May-Grünwald Giemsa; H&E = Hematoxylin & Eosin; PAS = Periodic Acid Schiff

From Bedrossian CWM, Mason MR, Gupta, PK. Rapid cytologic diagnosis of *Pneumocystis*: a comparison of effective techniques. Semin Diagn Pathol 1989; 6(3):245–261, with permission.

within the alveoli, which may contain cells packed with tachyzoites. The infected cells from the host are referred to as *pseudocysts.* True cysts are not present in human beings. Tachyzoites are proliferating forms seen in infections. They are crescentic and subtly pyriform, 4–8 μm in size, but appear half that size in tissues (Fig. 4C-87). Toxoplasma are visualized in routine Hematoxylin and Eosin and with such special stains as PAS or silver stain. Diagnosis is confirmed with serologic tests, fluorescent antibody staining, and immunostains.

Cytopathologic Findings

Toxoplasma gondii have been identified in respiratory specimens such as BAL or fine needle aspiration biopsies. The organisms are not visualized in Papanicolaou stain. They are identified in Romanowsky-stained preparation as crescent shaped structures, 4–5 μm in length with light blue cytoplasm and a reddish-violet round to oval nucleus present in intra- and extracellular locations (Fig. 4C-88).

Cryptosporidiosis

Cryptosporidiosis is caused by a protozoan belonging to *Cryptosporidium* species. The infection is seen in both immunocompromised patients and in immunocompetent individuals, especially children. The clinical course in these two groups of patients is different, distinctive with different prevalence.

The infection usually involves the gastrointestinal tract and is contracted by ingesting the mature oocysts, which release the sporozoites in the intestine. The sporozoites invade the host cells by asexual multiplication, followed by the sexual cycle leading to production of the oocyst. Pulmonary infection may be caused by aspiration of the gastrointestinal contents. The oocysts are found in sputum, bronchial brushings, tracheal aspirate, and in BAL appearing as oval, basophilic structures with Hematoxylin and Eosin stain and are acid-fast with modified Kinyoun acid-fast stain (Fig. 4C-89). Cryptosporidium also stain positively with PAS and GMS. The oocysts measure 4–5 μm with one dark granule in a large vesicle, surrounded by numerous small granules. *Cryptosporidia* must be differentiated from *Candida* organisms, which are non–acid-fast and show budding.

Microsporidiosis

Microsporidiosis is an opportunistic infection caused by *Microsporidium*, which is an obligatory intracellular protozoan ambiguously present in nature. The human infection is caused by organisms that belong to *Enterocytozoon spp.* and is seen in patients with acquired immunodeficiency syndrome. The source and transmission of the infection is unknown. Although the protozoan predominately causes a gastrointestinal infection with severe diarrhea and weight loss, pulmonary involvement is seen increasingly in immunocompromised hosts. Patients develop nonproductive cough, fever, bronchiolitis, pneumonitis, and respiratory distress. *Microsporidia* are identified in respiratory specimens such as sputum, bronchoscopic brushings, and biopsy, as well as in bronchoalveolar lavage. The organisms are stained by Wright-Giemsa or modified trichrome stain appearing as rounded structures, measuring 1.5–2 μm (Fig. 4C-90), sometimes showing a central bar. The organisms are seen within the macrophages and epithelial cells, as well as extracellularly. They are not visualized in Papanicolaou-stained preparations. Diagnostic confirmation is made by serology, immunofluorescent antibody staining, ultrastructural examination, and tissue culture.

SECTION III ALLERGIC AND IMMUNOLOGIC DISORDERS

The lungs are susceptible to many immunologically mediated disorders. Some of the more commonly described conditions include bronchial asthma, hypersensitivity pneumonitis or extrinsic allergic alveolitis, eosinophilic pneumonia, bronchopulmonary aspergillosis, and Goodpasture's syndrome. Although cytopathology is not a medium for the diagnosis of immunologic lung disorders, certain features of the disease processes may be reflected in cytologic preparations and help to rule out a neoplastic condition and also indirectly support the clinical diagnosis under proper circumstances.

Bronchial Asthma

Bronchial asthma is a condition in which acute diffuse reversible narrowing of the airways occurs as a result of allergic response to an allergen. The condition is "extrinsic" when a specific offending allergen is identifiable, and "intrinsic" when no such antigen is found.

The acute episodes are characterized by sloughing of bronchial mucosal fragments. There is bronchial and bronchiolar mucosal hyperplasia. Goblet cell hyperplasia can be marked, replacing the ciliated columnar cells of the bronchioles. The mucus secretions thicken and obstruct the distal airways, with formation of bronchiolar casts including Curschmann's spirals. The bronchial walls become edematous. The bronchiolar smooth muscles become hypertrophic, and their lumina are filled with fibrin and inflammatory cells. Large numbers of mast cells are found within the respiratory mucosa.

Cytopathologic Findings

Respiratory epithelial cells are mainly seen in sputum samples (Table 4-14). They consist of large numbers of columnar cells in tissue fragments that often bear a strong resemblance to cells of adenocarcinoma and are termed as "Creola bodies" (Fig. 4C-91). These large tissue fragments of columnar epithelium tend to curl upon themselves, have a smooth

TABLE 4-14. Cytopathologic findings in respiratory specimens from patients with bronchial asthma.

- Hyperplasia of ciliated columnar epithelium
- Goblet cell hyperplasia in bronchioles
- Shedding of large numbers of ciliated columnar cells, isolated and in tissue fragments in sputum
- Papillary like architecture of mucosal tissue fragments (Creola bodies)
- Curschmann's spirals
- Eosinophils and Charcot-Leyden crystals
- Clean background

external contour, and are often thick and difficult to evaluate. The presence of cilia when present suggest their benign nature. Findings include large numbers of hyperplastic goblet cells (Fig. 4C-12), Curschmann's spirals, eosinophils, Creola bodies (Fig. 4C-91C), and Charcot-Leyden crystals (see Chapter 3, Fig. 3–17).

Goodpasture's Syndrome

Goodpasture's syndrome is a disorder characterized by hemorrhagic pneumonitis usually associated with a rapidly progressive crescentic-type glomerulonephritis. The disease most commonly affects young men 20–30 years of age. The most frequent pulmonary sign is hemoptysis, which occurs prior to or simultaneously with the onset of renal disease. Pulmonary signs and symptoms have also been described without renal involvement. Exposure to hydrocarbons, infections with influenza A2 virus, and treatment with penicillamine have been implicated as etiologic factors.

The lungs morphologically show alveolar damage with intraalveolar hemorrhage and nodular areas of myxomatous fibrosis. Patients with Goodpasture's syndrome have high titers of antibasement membrane antibodies in their serum. Transbronchial biopsy demonstrates linear IgG protein by indirect immunofluorescence.

Cytopathologic Findings

Although there are no characteristic cytologic findings in Goodpasture's syndrome, the sputum or bronchoscopic specimens may show hemosiderin-containing macrophages or siderophages (Fig. 4C-92A) with positive iron stain (Fig. 4C-92B)

Allergic Bronchopulmonary Aspergillosis

Allergic bronchopulmonary aspergillosis is common in Great Britain. The syndrome consists of mucus impaction causing marked dilatation of the proximal bronchi by thick tenacious material, often associated with bronchocentric granulomas, and necrotic reaction centered on more distal bronchiolar walls. There is variable tissue eosinophilia. The impacted mucus may be removed through a bronchoscope. Fungal organisms can be identified within the impacted mucus.

Extrinsic Allergic Alveolitis

Extrinsic allergic alveolitis, which is also known as hypersensitivity pneumonitis, is characterized by an acute or chronic inflammation of the bronchioles and alveolar septa that results from sensitization to a variety of inhaled organic antigens. The clinical forms range from an acute illness characterized by fever, cough, dyspnea, and pulmonary infiltrates that occur 4–6 hours after exposure to a more chronic form that is similar to idiopathic fibrosing alveolitis. Farmer's lung is the prototype of the chronic form, resulting from a hypersensitivity reaction to moldy hay contaminated with thermophilic actinomyces. Most cases of extrinsic allergic alveolitis currently occur from exposure to "contaminated" air conditioning systems.

The pathologic findings may be nonspecific. There is a chronic interstitial inflammatory infiltrate with varying degrees of interstitial fibrosis and focal small intraalveolar granulomas with a tendency toward peribronchial distribution. Bronchiolitis obliterans and occasionally pleural fibrosis occur. The giant cells of the granulomas contain birefringent material of uncertain origin. The changes appear similar to those seen in sarcoidosis.

Eosinophilic Pneumonia

Eosinophilic pneumonia is referred to as a condition associated with flooding of alveoli with eosinophils and macrophages. It can occur due to drugs and infections especially due to parasites.

SECTION IV MISCELLANEOUS

This section includes miscellaneous nonneoplastic disease processes that are not categorized in any particular groups. The majority are infrequently encountered in the routine practice of cytopathology. All have documented cytopathologic features in at least in one type of respiratory specimen.

Granulomatous Inflammation

Several disease processes that affect the lungs provoke a granulomatous response. Most are of infectious origin (i.e., bacterial or fungal infections), with tuberculosis being the most common. The rest include granulomas secondary to foreign body, occupational exposure, and idiopathic lung diseases. A partial list is presented in Table 4-15. The inflammatory response may result in localized nodular lesions or cause diffuse parenchymal and interstitial involvement. Chest radiographic patterns vary accordingly. Granulomatous inflammation in general is characterized by aggregates of epithelioid cells (Fig. 4C-93), multinucleated giant cells, lymphocytes, plasma cells, and fibroblasts. Epithelioid cells are altered macrophages that present pleomorphic shapes ranging from

TABLE 4-15. Pulmonary granulomatous inflammation.

Infectious
Bacterial
Fungal
Parasitic
Idiopathic and Immunologic Disorders
Sarcoidosis
Rheumatoid disease
Wegener's granulomatosis
Allergic angiitis and granulomatosis
Occupational Exposure
Asbestosis
Psittacosis
Heavy metals
Organic dusts
Miscellaneous
Drug toxicity
Radiation
Oxygen therapy
Foreign body reaction
Tumor-related granulomas

round, elongated to oblong forms with variable pale to foamy cytoplasm devoid of such tingible ingested material as carbon particles. They are seen isolated or in aggregates. The epithelioid cell nuclei are very pleomorphic in shape and size. They can be round, elongated, spindle-shaped, comma-shaped, boomerang-shaped, or deeply indented and clefted, producing footprint shapes. Multinucleated giant cells within the granulomas present different morphologic patterns as to the arrangement of their component nuclei (Figs. 4C-94–4C-96). Some multinucleated giant cells are specialized and are associated with specific types of inflammations, whereas others are nonspecific. The giant cells may contain microorganisms, foreign bodies, keratin, or collagen. The morphology of various types of multinucleated giant cells encountered in respiratory specimens is summarized in Table 4-16 and illustrated in Figs. 4C-97–4C-99. Granulomas may show necrosis. In cases of tuberculous granulomas, the necrotic material appears yellow, greasy, and is referred to as caseation (cheese-like). Granulomas may be discrete or confluent, walled off by fibrosis, and calcified. Cellular constituents of granulomas are only rarely identi-fied in sputum. The granulomas can be brushed only if they involve the bronchi and extend through the mucosa. They may be encountered in bronchial washings and BAL. Granulomas that cause localized lesions and appear as a solitary nodule often enter the differential diagnosis of neoplasia and are subjected to fine needle aspiration biopsies. The morphology of granulomas is often well demonstrated in cell block preparations.

Sarcoidosis

Sarcoidosis is a granulomatous disease of unknown etiology with multisystem involvement that affects mostly young or middle-aged patients, especially women. Pulmonary involvement is extremely common and is associated with hilar lymphadenopathy.

Gross and Histologic Findings

The lungs initially exhibit lymphocytic interstitial pneumonitis followed by formation of noncaseating granulomas. The latter are also seen in submucosal locations in bronchi and bronchioles, as well as in hilar lymph nodes. The granulomas may be discrete or confluent, noncaseating, composed of aggregates of epithelioid cells with elongated nuclei and Langhans-type multinucleated giant cells that lack phagocytized debris and possess dense cytoplasm with nuclei arranged peripherally or clustered at one pole. Multinucleated giant cells may contain Schaumann bodies or asteroid bodies within their cytoplasm.

Cytopathologic Findings

The cytopathologic findings of sarcoidosis are only infrequently documented in respiratory specimens, especially in sputum and bronchoscopic specimens. These findings include the presence of multinucleated giant cells and aggregates of epithelioid cells in a clean background that lacks necrotic and cellular debris (Table 4-17). The giant cells are large, 50–500 μm in size, round, oval, or elongated, containing dense cyanophilic cytoplasm, with poor to sharply defined cell borders (Figs. 4C-100 and 4C-101). They are often sticky and seen in aggregates in mucus streaks in sputum. Their nuclei vary in numbers and may be as high as 200, either distributed randomly within the cytoplasm or clustered at one pole or arranged along the perimeter. The cytoplasm of these cells does not contain phagocytized debris and may house asteroid or Schaumann bodies. The epithelioid cells are round, oval, polygonal, or spindle shaped, occurring singly or in aggregates, and containing pale to dense cytoplasm (Fig. 4C-102). Their nuclei display a great variation in their shapes, consisting of oval, oblong elongate, curved, carrot, boomerang, and kidney, as well as some with multiple indentations that resemble footprints and twisted forms. This variation in nuclear shapes and haphazard arrangement of nuclei within the cytoplasm is what is so characteristic of epithelioid cells. Lymphocytes may be present in large numbers, especially in BAL specimens. In fact, a differential count of inflammatory cells in BAL has been used to support the diagnosis of sarcoidosis as well as in monitoring the response of drug therapy (see Chapter 2, section on BAL).

Lesions of sarcoidosis are more likely to be encountered in fine needle aspirates, particularly the transbronchial ones, rather than in sputum or bronchoscopic specimens.

Differential Diagnoses

The differential diagnoses include other granulomatous diseases of which tuberculosis strongly resembles the lesions of

TABLE 4-16. Morphologic features of various types of multinucleated cells in respiratory specimens.

Multinucleated cell type	Associated conditions	Cytomorphology	Fig(s).
Foreign body–type	Most commonly encountered type, formed by the fusion of phagocytic histiocytes or macrophages in order to eliminate the foreign body (e.g., histiocytes containing anthracotic pigment, keratin in keratinizing squamous cell carcinomas, talc granuloma, ferruginous bodies)	Size variable, medium, large to giant forms; round, oval to polygonal; number of nuclei vary; round, oval to kidney shaped; randomly distributed nuclear membrane thin, smooth, and crisp; chromatin finely granular and evenly dispersed; micronucleoli; cytoplasm cyanophilic, dirty, granular, may contain foreign body, some foreign bodies may polarize	4C-94
Langhans' type	A specialized type of foreign body–type multinucleated giant cell, predominantly seen in tuberculous granulomas, also seen in fungal granulomas, sarcoidosis	Variable size, but large; nuclei vary in numbers; arranged along the perimeter like a garland or clustered at one pole or both poles; abundant cytoplasm; no phagocytic material	4C-95
Touton type	Encountered in pseudotumor, Wegener's granulomatosis, fibrous histiocytic tumors associated with phagocytized lipid and hemosiderin	Nuclei arranged in the center around a small island of nonfoamy cytoplasm and surrounded by foamy cytoplasm	—
Multinucleated columnar cells	Nonspecific reaction of respiratory epithelium	Enlarged in size, columnar shape maintained with terminal bar; nuclei clustered at the base, small in size; mirror image of one another; no nuclear molding	4C-7A to 4C-7C
Viral infection	Common prototype seen in Herpes simplex virus infection; also seen in RSV and measles	Nuclei round, overlapped, molded, structureless, dark, surrounded by clear halo; viral intranuclear inclusions	4C-49 4C-50 4C-98
Multinucleated giant cells with asteroid bodies	Seen most frequently in granulomas associated with sarcoidosis	Stellate inclusions, refractile; single or multiple	4C-96B 3C-21A
Multinucleated cells with Schumann bodies	Often seen in sarcoid granulomas, but not a specific feature	Large giant cells containing laminated crystalline inclusions	4C-96A 3C-21A
Tumor giant cell	Present in various types of malignancies	Size variable, can reach huge dimensions; nuclei pleomorphic in size, randomly distributed; obvious malignant criteria; cytoplasm variable, scant to moderate; may demonstrate emperipolesis	4C-99
Osteoclast type	Normally found in bone marrow; involved in bone absorption; present in bone tumors; cells morphologically resembling osteoclasts seen in some poorly differentiated carcinomas	Large multinucleated cells with giant forms; pale blue cytoplasm (Romanowsky stain); contain many azurophilic (purple-red) granules; individual nuclei are round, uniform, contain a single prominent nucleolus	4C-97A
Megakaryocytes	Infrequently seen in bronchial brushings, bronchoalveolar lavage; fine needle aspirates, and pulmonary arterial sample	Size large; do not reach huge dimensions; nuclei *multilobulated*; dense chromatin	4C-97C 3C-8
Radiation-induced changes	Predominantly seen in squamous epithelial cells secondary to external radiation to the lungs	Variable size, may reach huge dimensions; nuclei bland to atypical with deep-staining chromatin, sometimes structureless, degenerative changes within the nucleus and the cytoplasm; low N/C ratios	4C-24A 4C-24B 4C-25

sarcoidosis. Their cytologic differences are listed in Table 4-18. The diagnosis of sarcoidosis is made only after excluding the causes for other granulomatous disease processes by special stains and microbiologic studies to rule out acid-fast organisms, fungi, or any other organisms.

Rheumatoid Lung and Pleural Nodules

Parenchymal lung and pleural involvement in patients with rheumatoid disease is uncommon. It can manifest as nodules within the lung parenchyma or in endobronchial location and as pleural nodules with pleural effusion. Pulmonary involvement occurs predominantly in males with an advanced seropositive rheumatoid arthritis and who have subcutaneous nodules. In some cases, however, the pulmonary involvement can precede the onset of rheumatoid arthritis. The parenchymal lung nodules clinically and radiologically mimic neoplasia. The rheumatoid lesions may cavitate and be mistaken for tuberculosis. Endobronchial lesions may also mimic neoplasia.

Histologic Findings

The rheumatoid lesions histologically are characterized by necrotizing granulomas with central fibrinoid necrosis, bordered by radially arranged elongated, spindle-shaped macrophages, multinucleated foreign body–type giant cells, fibroblasts, and variable numbers of inflammatory cells (Fig. 4C-103).

TABLE 4-17. Cytopathologic findings in sarcoidosis.

- Background clean, no necrosis; little mucus or inflammation (in sputum); rare Curschmann spirals (in sputum)
- Variable numbers of epithelioid cells, occurring singly or in aggregates, forming granuloma; oval, polyhedral, or elongated with abundant cyanophilic, finely vacuolated cytoplasm; indistinct cell borders; nuclei round, cigar shaped, or carrot shaped or drawn out, indented, with footprint shape; granular chromatin; phagocytosis rare
- Multinucleated giant cells scattered individually, occurring in streaks or in aggregates; 50–500 μm in diameter; round, oval to elongated; sharply outlined with sticky borders; cells adherent to each other; cytoplasm abundant, cyanophilic, denser than the carbon-bearing multinucleated giant cells; nuclei round to oval; uniform, granular chromatin and micronucleoli; vary in numbers up to 200; often crowded centrally or distributed peripherally or randomly throughout the cytoplasm; no ingested material or phagocytosis; Schumann or asteroid bodies +/−
- Lymphocytes, plasma cells
- Stromal tissue fragments (in FNA specimens)

Cytopathologic Findings

Cytologic findings of rheumatoid inflammation can be appreciated in effusion fluid, bronchial brushings in cases of endobronchial lesions, and in fine needle aspiration biopsy specimens of localized parenchymal lesions (Figs. 4C-104 and 4C-105). The smears of the effusion fluid consist of a polymorphic cell population of spindle-shaped macrophages in variable numbers, round multinucleated giant cells, and mixed inflammatory cells that consist of neutrophils, lymphocytes, and small mononuclear macrophages. There is generally abundant fluffy, granular material in the background. The spindle-shaped cells measure up to 160 μm long, are fairly uniform in width except at their pointed ends, and contain one or more round to elongate nuclei with bland chromatin. Their cytoplasm is dense and the cell borders are well defined. Multinucleation of the spindle cells is occasionally observed (Fig. 4C-105C). The large, round, multinucleated cells are distinct from the elongated cells and contain as many as 20 or more uniform, round to oval nuclei (Fig. 4C-105D). The most striking and characteristic feature of rheumatoid granulomas is the presence of granular acellular precipitate that can take different hues in Papanicolaou-stained smears (Fig. 4C-104). Cholesterol crystals are often seen in the cell block preparation. The cytologic features described earlier are pathognomonic for rheumatoid granulomas; however, all the features may not be present in a specimen from every case of rheumatoid nodule or pleural effusion. It is not uncommon to have only the granular precipitate or to lack spindle-shaped cells. Squamous metaplasia of the bronchi and bronchioles has been described in the vicinity of the granulomas. In fine needle aspirates, extensive necrosis and the elongated cells have been reported as suspicious for malignancy.

TABLE 4-18. Cytopathologic differences between tuberculous granuloma and sarcoid granuloma.

	Granulomatous lesions in tuberculosis	Granulomatous lesions in sarcoidosis
Gross characteristics of aspirate	Yellow cheesy	0
Cellularity	Variable; sometimes acellular	Variable
Amorphous debris	Variable amounts, sometime extensive	Not present
Clean background	+/−	Clean
Well-formed granulomas under low power	+	+
Epithelioid cells	+	+
Multinucleated giant cells of Langhans' type	+	+
Lymphocytes	+	+
Asteroid bodies	0	+
Schumann bodies	0	+
Calcific debris	+/−	+/−
Acid-fast organisms (special stains required)	+	0
Culture	+	0

Talc Granuloma

Talc is a mineral chemically consisting of hydrous magnesium silicate that sometimes contains aluminum ciliate. Talc granulomas develop when talc is inhaled or used as a base for intravenous injection of certain narcotics. Talc gets trapped in pulmonary vessels, inciting both intravascular and extravascular granulomatous response that leads to diffuse or focal nodular lesions that are seen radiographically. Microscopic circulation may be compromised, resulting in angiothrombotic pulmonary hypertension. Talc particles cause an irreversible damage. Patients may complain of chronic dyspnea and cough.

Gross and Histologic Findings

Talc granulomatosis may be seen grossly as small miliary nodules. Granulomas histologically may be discrete or confluent and are noncaseating (Fig. 4C-106). Multinucleated giant cells within these granulomas contain birefringent crystals (Fig. 4C-107).

Cytopathologic Findings

Cytologic examination of sputum or bronchial washings is not helpful in identifying the talc granulomas. Fine needle aspiration biopsies of the nodular lesions are characterized by an inflammatory response with the presence of uni- and multinucleated macrophages, fibroblasts, and lymphocytes. Under polarized light, numerous closely packed, strongly birefringent, platelike crystals are seen within and outside the macrophages, ranging from 2 to 100 μm with an average of 20 μm. The background shows granular debris.

Pulmonary Alveolar Proteinosis

Pulmonary alveolar proteinosis (PAP) is a rare condition characterized by filling of the alveoli by PAS-positive, diastase-resistant proteinaceous material rich in lipids.

Pulmonary alveolar proteinosis occurs in association with such various situations as exposure to dust or toxic chemicals, pulmonary infections, immunodeficiency states, hematologic abnormalities, or in patients receiving chemotherapy. The disease also occurs in newborns. Patients with PAP usually present with progressive dyspnea, low-grade fever, dry cough, hemoptysis, and pleuritic chest pain. Chest radiographs demonstrate fine diffuse feathery to vaguely nodular bilateral infiltrates with fluffy appearance.

Gross and Histologic Findings

The lungs grossly are extremely heavy and solid. Viscid, white, milky fluid exudes from their cut surfaces, which show multiple firm yellow-tan to gray-white nodules that range from a few millimeters to 2 cm.

The most dominant feature histologically is filling and distension of the alveoli with eosinophilic, fluffy, granular, acellular material. The alveoli remain intact. The intraalveolar material is PAS positive, diastase resistant (Fig. 4C-108), and negative for mucin. The intraalveolar material is rich in lipid, stains positively with oil red O, and occasionally contains cholesterol crystals. The alveoli peripherally show hyperplasia of lining cells.

Cytopathologic Findings

Bronchoalveolar lavage has been successful as a therapeutic procedure in patients with PAP. The lavage fluid presents very characteristic gross, cytologic, histochemical, and ultrastructural findings, offering an accurate diagnosis (Table 4-19).

The lavage fluid is grossly opaque, milky-white to gray with granular white sediment (Fig. 4C-109). The smears show sparsely cellular, fluffy to amorphous granular debris, containing a few mononuclear cells (Figs. 4C-110 and 4C-111). The latter probably represent alveolar histiocytes, occurring singly or in aggregates. A tissue fragment of alveolar lining cells is rarely present. The amorphous material stains eosinophilic or cyanophilic with Papanicolaou stain. Another characteristic feature is the presence of varying-sized dense eosinophilic globules within the granular material (Figs. 4C-112A and 112B). Cholesterol crystals have been identified.

Ultrastructural Findings

The fluid sediment ultrastructurally shows a large number of multilamellated bodies within the amorphous material (Fig. 4C-113).

Differential Diagnoses

The differential diagnoses of the fluffy, eosinophilic, acellular material in the Papanicolaou-stained smear include alveolar casts seen in PCP, pulmonary amyloidosis, and lysed red blood cells in aggregates (Figs. 4C-114–4C-116). The differentiating features are listed in Table 4-20.

TABLE 4-19. Cytopathologic features of pulmonary alveolar proteinosis in bronchoalveolar lavage.

Gross	Lavage fluid opaque, milky white to gray; sediment granular to sandy
Microscopic	Amorphous, fluffy to granular debris staining eosinophilic or cyanophilic with Papanicolaou stain and basophilic with Romanowsky stains; sparsely cellular with alveolar macrophages; multinucleated giant cells and reactive alveolar type II pneumocytes; dense eosinophilic globules of varying sizes; cholesterol crystals +/−
Histochemistry	Granular material PAS +, diastase resistant; alcian blue and mucicarmine −; oil red O +
Ultrastructure	Large numbers of multilamillated bodies in extracellular location

Lipoid Pneumonia

Lipoid pneumonia is an uncommon condition, characterized by alveoli filled with lipid-containing macrophages. Two forms are recognized: endogenous and exogenous. The endogenous variety results from aspiration of gastrointestinal contents. The exogenous variety is associated with chronic users of oil-based nasal drops or mineral oil laxatives. These oils are phagocytized by pulmonary alveolar macrophages and incite an inflammatory response within the lung parenchyma, causing radiological abnormalities. Most patients remain asymptomatic and are investigated for incidental findings of abnormal chest x-rays to rule out a malignant process. The diagnosis may be established by cytologic examination of sputum, bronchoalveolar lavage, or by lung biopsy. The smears prepared from sputum or BAL show normal to very large macrophages with abundant pale bubbly vacuolated cytoplasm (Fig. 4C-117A). The presence of fat may be confirmed with such special stains as oil red O (Fig. 4C-117B).

Differential Diagnoses

Foamy histiocytes containing lipid substance must be differentiated from MAI-infected cells (Table 4-7), goblet cells, mucin-producing adenocarcinoma cells, and mucophages. Large, pale macrophages have also been described in rare cases of drug toxicity due to Amiodarone (Figs. 4C-39–4C-42). Such cells stain negative for lipid and contain lamellated bodies on ultrastructural studies. Foamy alveolar lining cells are also encountered in BAL specimens from patients with ARDS (Figs. 4C-20D and 4C-28D) and in patients receiving clofazimine for MAI infections. Vegetable cells in sputum may also mimic foamy histiocytes.

Pulmonary Thromboembolism and Infarct

Cytopathologic changes in pulmonary thromboembolic disease involve reactive/proliferative changes in bronchial and bronchioloalveolar lining epithelial cells. The changes are independent of whether or not actual infarction of the lung

TABLE 4-20. Differential diagnoses of fluffy, granular, or amorphous acellular material in respiratory specimens.

Diagnostic entity	Cytopathologic features	Fig(s).
Pneumocystis carinii pneumonia	Fluffy, granular, eosinophilic precipitate; round, small "ghost" shadows of cysts; silver stain shows cyst 8–10 μm, either spherical, crescent shaped, or crinkled; trophozoites within the cysts 0.5–1 μm appear as dots	4C-85 4C-86 4C-114
Alveolar proteinosis	Fluffy granular eosinophilic precipitate, almost acellular; PAS positive with or without diastase; mucin stain negative; silver stain negative; ultrastructural exam—lamellated bodies	4C-115
Pulmonary amyloidosis	Amorphous, fluffy, granular to dense eosinophilic or cyanophilic acellular material; may be associated with giant cell reaction; plasma cells when associated with plasmacytoma or multiple myeloma	10C-7 to 10C-10
Alveolar hemorrhage with lysed red blood cells	Eosinophilic granular precipitate with rounded "ghost" shadows of lysed red blood cells; pale center, darker borders; negative with silver stains	4C-116

Modified from Kini SR. Color Atlas of Differential Diagnosis in Exfoliative and Aspiration Cytopathology. Baltimore: Williams and Wilkins, 1999, with permission.

parenchyma has occurred. When infarction occurs, it may present as a solitary lesion on chest radiograph, mimicking cancer. The epithelial reaction usually occurs around the perimeter of the infarct. Patients may develop blood-streaked sputum or frank hemoptysis.

The abnormal cells may be present in sputum, bronchial washings, BAL, or in fine needle aspiration biopsy. The smears show a bloody background with hemosiderin-containing macrophages. Tissue fragments of hyperplastic and metaplastic epithelial cells with nuclear atypia may be misinterpreted as malignant (Fig. 4C-17).

The epithelial changes are transient in nature and disappear in few weeks. Lack of single cells should also serve as a caution against making a malignant diagnosis.

The incidence of pulmonary thromboembolic disease with or without infarction exhibiting such remarkable epithelial changes is quite low.

Pulmonary Complications of Drug Abuse, Including "Crack" Cocaine Use

Intravenous (IV) drug abusers are at high risk for HIV infections and all of the attendant opportunistic infections and complications (see Chapter 15). The most common pulmonary infectious complication among IV drug abusers is community acquired pneumonia. Pulmonary tuberculosis is especially common regardless of HIV infection. The incidence of atypical presentation and disseminated disease is increased among drug abusers. Septic pulmonary emboli and hematogenously acquired pneumonia are also common. The common offenders are *Staphylococcus aureus* and *Staphylococcus alba*, with the source being the skin at the site of injection as well as the infected cardiac valves from endocarditis.

Bacterial pneumonias are necrotizing, causing septicemia. Fungal infections with *Candida spp* and *Aspergillus spp* are not uncommon. Drug toxicity and overdose may cause diffuse alveolar damage and sudden death.

Drug abusers who inject material intended for oral use develop talc granulomas in the lungs.

Pulmonary changes that result from abuse of inhaled drugs are different. The most common of these are marijuana and cocaine. The pulmonary changes are described as acute and chronic. The acute changes include pneumomediastinum, pneumothorax, diffuse alveolar hemorrhage, noncardiogenic pulmonary edema, organizing pneumonia, and bronchiolitis obliterans, pulmonary infiltrate with eosinophilia, and thermal injuries to the airways.

Chronic smokers develop changes similar to tobacco users (e.g., basal cell hyperplasia, goblet cell hyperplasia, cellular disorganization, and basement membrane thickening).

In individuals smoking "crack" cocaine, the alveolar macrophages accumulate large quantities of carbonaceous material. This material is also present extracellular, imparting black discoloration to sputum and bronchoalveolar lavage specimens. The specimens are described as turbid, gray or black, exceeding the blackness seen in heavy tobacco smokers. The carbonaceous residue in cocaine users probably comes from inhalation of nonvolatilized impurities that occur when crack and its tarry residue are smoked.

Cytopathologic Findings

Sputum or BAL smears show a large number of macrophages distended with finely granular to large aggregates of black carbonaceous material ranging from 1 to 5 μm in diameter. Large fragments of the material with similar appearance are seen extracellularly (Fig. 4C-118), giving a dirty appearance. Birefringent material not associated with the carbonaceous material is also present in the background. This pigment sometimes finds its way to the pleural fluid, which can be discolored black.

Idiopathic Pulmonary Fibrosis

Idiopathic pulmonary fibrosis is a chronic progressive pulmonary syndrome that usually occurs in middle-aged men and women. It is known by a variety of names (e.g., usual interstitial pneumonitis or fibrosing alveolitis) and may be associated with collagen vascular diseases or be a consequence of viral pneumonitis. Idiopathic pulmonary fibrosis represents the end result of several different disease processes. In many

cases, no etiologic factors can be demonstrated. It can begin as an acute episode or have insidious onset with gradual progression. The disease is usually progressive, leading to respiratory insufficiency and death.

The lungs histologically show a variegated pattern of fibrosis, inflammation, alveolar lining cell hypertrophy, and hyperplasia, as well as thickening of small pulmonary vessels. Fibrosis of the lung develops either within alveolar spaces following active inflammation, resulting in alveolar fibrosis, or in the alveolar walls leading to interstitial fibrosis. Both processes may occur simultaneously. Long-standing pulmonary fibrosis is frequently associated with abnormalities of bronchial and alveolar epithelial cells irrespective of underlying cause. As in the other cases of alveolar injury, type I cells are destroyed, and the type II cells enlarge with hyperplasia and hypertrophy. The nuclear abnormalities may be striking, with giant cell formation.

Cytopathologic Findings

Bronchoalveolar lavage has been considered to be a useful diagnostic technique in evaluating cases of idiopathic pulmonary fibrosis. The ratio of lymphocytes versus neutrophils is an important indicator in its differentiation from sarcoidosis, where the lymphocyte count is higher. Smears prepared from lavage as well as from bronchial washings may show alveolar lining cells with marked atypia and multinucleation and may lead to misinterpretation of malignancy (refer to the section on type II pneumocytes).

Wegener's Granulomatosis

Wegener's granulomatosis is a distinct clinicopathologic entity characterized by necrotizing and granulomatous inflammation, as well as vasculitis involving the upper and lower respiratory tracts and kidneys. The etiology is unclear, but immunopathogenic mechanisms have been implicated.

The disease most commonly involves the head and neck region, followed by lung, kidney, and eye. Respiratory manifestations include cough, hemoptysis, and pleuritis. Head and neck involvement presents with sinusitis, nasal disease, otitis media, hearing loss subglottic stenosis, and ear pain. Patients may develop arthralgia, fever, weight loss, and skin lesions. Chest radiographs show an infiltrate or nodular densities.

Gross and Histologic Findings

The pulmonary lesions of Wegener's granulomatosis usually consist of multiple bilateral white nodules, measuring from a few millimeters to several centimeters. They are sharply circumscribed, and cavitation occurs in 50% of the cases. There is extensive liquefaction necrosis histologically at the center of the lesions (Fig. 4C-119). The necrotic foci enlarge and coalesce, taking on geographic appearances that often blend with areas of organizing pneumonia rich in proliferating fibroblasts, histiocytes, and multinucleated giant cells (e.g., Touton, Langhans', and foreign body type) (Fig. 4C-120). Palisading of the histiocytes and multinucleated cells is noted around and along the walls of the necrotic foci. Eosinophils around the necrotic blood vessels can be abundant. Lymphocytes and plasma cells are present in much smaller numbers.

TABLE 4-21. Cytopathologic findings in Wegener's granulomatosis of lung.

- Fragments of necrotic basophilic debris with entrapment of intact neutrophils
- Scattered histiocytic giant cells; multinucleated foreign body type; Touton type or Langhans' type; lymphocytes; eosinophils
- Stromal tissue fragments
- Reactive type II pneumocytes
- Vasculitis in cell block preparation

Cytopathologic Findings

The cytopathologic findings of Wegener's granulomatosis have been reported in various types of respiratory specimens. Although the findings by themselves are not pathognomonic (Table 4-21, Figs. 4C-121–4C-123), they are helpful in excluding malignancy, and in some cases may support the clinical and radiologic findings of Wegener's granulomatosis. The smears usually depict an inflammatory and necrotic background with neutrophilic debris. Irregular fragments of eosinophilic or cyanophilic (Fig. 4C-121B), granular, necrotic collagen are present, permeated by neutrophils and a few lymphocytes. Mononuclear cells with epithelioid appearance and multinucleated giant cells are seen in varying proportions. The nuclei of the giant cells are crowded, overlapped, and located centrally (Figs. 4C-123A and 123B). They may be isolated or be associated with mononuclear histiocytes and necrotic collagen. Large tissue fragments of reactive bronchial and bronchiolar-alveolar epithelial cells are often present (Fig. 4C-123C). Hemosiderin-containing histiocytes are also present.

The cell block, if available, may show vasculitis and granulomatous inflammation, which supports the diagnosis.

The diagnosis is usually that of exclusion. Cultures are negative for bacteria and fungi; special stains do not reveal any organisms. Elevated titers of antineutrophil cytoplasmic antibody with a cytoplasmic pattern support the diagnosis.

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