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Pulmonary Infection

As the lung is a portal between the ambient environment and the internal milieu, it is the most frequent site of serious infections. A number of factors predispose to pulmonary infection, and these include distortions in lung anatomy, decreased mucociliary clearance, as well as abnormal cellular and humoral immune responses.

The optimal treatment of infection requires diagnosing its cause. As a large variety of microbes can infect the lung, and as the histopathology of noninfectious conditions frequently mimics infection, the differential diagnosis of pulmonary infection is often broad. While in many cases, the clinical history, radiographic findings, and the noninvasive sampling of secretions can establish the cause of infection, at times, a lung biopsy will be required.

THE APPROACH TO SAMPLING FOR INFECTION

The optimal approach to sampling the lung for infection depends on whether disease is localized or diffuse (Table 9.1). In immunosuppressed patients, diffuse pulmonary infiltrates due to infection are often diagnosed by sputum induction or by bronchoalveolar lavage (BAL). This is particularly the case when the microbial burden is large. However, noninvasive approaches are less sensitive than biopsy in diagnosing localized infections, and they cannot distinguish a colonizing commensal from an invasive pathogen. Lung biopsy is also often required to exclude infection and establish a noninfective diagnosis, e.g., acute lung injury due to chemotherapy.

Pathologists prefer the opportunity to examine generous samplings of lung because diagnoses based on larger biopsies are generally more accurate, yield more information with respect to the host immune response, and sometimes reveal additional potentially treatable disorders. For this reason, and based on the specific details of a case, the diagnostic pathologist should be prepared to educate clinicians with respect to the limits of minimally invasive lung sampling, thereby sparing patients the unnecessary discomforts and delays that can attend nondiagnostic procedures.

TRANSBRONCHIAL BIOPSY

The lung has roughly the surface area of a tennis court and so sampling error is an unavoidable potential pitfall in diagnostic pulmonary pathology. The transbronchial biopsy (TBB) preferentially samples peribronchiolar lung tissue, yielding tissue fragments of 1–3 mm in diameter. However, many peripherally located lung lesions cannot be accessed by this approach.

TBB is usually adequate for diagnosing diffuse pulmonary infections and peribronchiolar granulomatous diseases, such as sarcoidosis and lymphangitic spread of tumor. But at times the findings of a TBB can be nonspecific and misleading. For example, “organizing pneumonia” in a TBB may represent a nonspecific reaction adjacent to an adjacent focus of infection or malignancy, a nonspecific manifestation of chemotherapy effect, aspiration, or cryptogenic disease. For this reason, the findings gleaned from a TBB must always be thoughtfully correlated with clinical and radiographic findings.

FINE NEEDLE ASPIRATION BIOPSY

Computed tomography (CT)-guided fine needle aspiration biopsies have a high yield in the diagnosis of peripheral nodular infiltrates. Biopsies can be semiliquid, or include a 1 mm core of tissue. When performed with the assistance of a cyto-technologist, rapid diagnoses can be proffered by preparing and examining stained smears directly at the bedside. Fine needle aspirates are useful in diagnosing localized infections and cytopathologists can suggest the pattern of inflammation based on the types of inflammatory cell subsets in the sample and the presence or absence of necrosis.

TRANSBRONCHIAL NEEDLE ASPIRATION BIOPSY

Transbronchial needle aspiration biopsy of regional lymph node groups is often a low-yield procedure because nonspecific reactive regional lymphadenitis is common in the presence of pulmonary infection. The procedure is prone to artifacts that...
may present diagnostic difficulties for the surgical pathologist. However, when adopted judiciously, this approach may be adequate for the diagnosis of infection, as in one series in which ~50% of cases of tuberculous lymphadenitis were accurately diagnosed.

**VIDEO-ASSISTED AND OPEN THORACOSCOPIC BIOPSY**

Video-assisted thoracoscopic (VATS) lung biopsy has largely replaced open thoracotomy biopsy as the optimal approach for obtaining large samples of lung. The procedure is associated with modest and acceptable morbidity, has the advantage of allowing direct access to widely separated lung segments, and provides generously sized wedge biopsies of 2–3 cm. Consequently, VATS should be considered a first-line approach when a timely accurate diagnosis is essential.

**HANDLING LUNG BIOPSIES**

Appropriate handling of the lung biopsy is essential for obtaining the highest diagnostic yield (Fig. 9.1). Sampling the lung for microbiological culture should ideally take place under sterile conditions in the operating room but the pathologist processing the biopsy is ultimately responsible for ascertaining that all necessary diagnostic tests have been ordered and be prepared to harvest additional samples for testing that may have been overlooked. When preparing tissue for microbiological isolation, the lung should be minced rather than crushed, as hyphate fungi, e.g., *Zygomycoses spp.*, may fail to grow in culture following maceration. It is substandard care for a pathologist to place a lung biopsy directly into fixative, without first considering a diagnosis of infection. If questions arise as to which tests to order, or how best to transport the specimen to the laboratory, discussions with the hospital microbiology laboratory staff or a hospital infectious disease specialist will generally answer them.

The examination of touch imprints of lung tissue is a simple and rapid way of identifying pathogens. Touch imprints can be prepared from foci of pulmonary consolidation, necrosis, or suppuration, and rapidly stained for bacteria, mycobacteria, and fungi in the surgical pathology suite or the microbiology laboratory. Concomitantly biopsies may be harvested for ultrastructural analysis, polymerase chain reaction (PCR) assays, or research purposes. For large biopsies, it may be possible to inflate the lung with 5% formalin via a small (23–25) gauge needle to optimize subsequent histological examination.

**PULMONARY INJURY IN INFECTION**

**Pulmonary Host Response**

The diagnosis of infection requires both an interpretation of the morphological changes evoked by the pathogen and the identification of a pathogen in situ. The pattern of pulmonary inflammation often suggests the route of entry of an

| Table 9.1 Approach to the Isolation of Pulmonary Microorganisms |
|---------------------------------------------------------------|
| Expectorated sputum                                           |
| Induced sputum                                                |
| BAL                                                           |
| Fine-needle aspirate (1 mm)                                   |
| Bronchial biopsy (1–3 mm)                                     |
| Transbronchial biopsy (1–3 mm)                                |
| Transbronchial needle biopsy (1 mm)                           |
| Video-assisted thoracoscopic biopsy (2–3 cm)                  |
| Open-lung biopsy (2–3 cm)                                     |
| Surgical lobectomy                                            |
| Autopsy                                                       |
infectious agent and may help to narrow the diagnostic possibilities. It is necessary to be familiar with the multiplicity of response patterns evoked by infection and to recognize that these can vary depending on the route of entry, pathogen load, and the competence of host defenses. For example, although herpesvirus-1 can produce a miliary pattern of fibrinoid necrosis in an immunosuppressed patient with viremia, it can also cause ulceration of the tracheobronchial mucosa in a chronically intubated patient.

Microbes are rarely identified randomly or diffusely in infections; rather, they tend to be compartmentalized, so that substantial effort may be wasted in searching for them where they are not likely to be found. Mycobacteria and fungi are virtually always localized in areas of necrosis; Rickettsia spp. and Bartonella spp. largely target the microvasculature; viruses tend to attack the airways and so the surgical pathologist must both be acquainted with the pulmonary microanatomy and with the preferential localization of microbes in pulmonary tissues.

Pulmonary Defenses

Most microbes are small (<5 μM) and can penetrate to the distal gas-exchanging surfaces of the lung, although the majority are excluded by the defenses of the upper airways or deposit along the conducting airways to be cleared by the mucociliary escalator. Humoral factors, including IgA and defensins, released by airway cells limit microbial penetration into tissues. Airway mucosal dendritic cells trap microbial antigens and transport them to regional lymph nodes, where they are processed and present to both T and B lymphocytes, evoking adaptive immunity (Fig. 9.2).

Ulceration or thickening of the gas exchange surface limits diffusion of oxygen and carbon dioxide. For this reason, the alveolus is under normal conditions maintained sterile by resident macrophages that scavenge inhaled particulates and secrete monokines, including interleukin-10 and transforming growth factor-β, that locally suppress inflammation and promote immunotolerance.

When the alveolar lining is injured, or when the number of invading organisms exceeds the phagocytic capacities of resident macrophages, neutrophils and exudate monocytes are recruited to sites of lung infection. Even small numbers of virulent pathogens can greatly amplify inflammation via the release of chemokines, cytokines, and complement, by host immune cells. These defenses promote the clearance of infection, but can also damage the lung. Lung biopsies afford the pathologist a unique opportunity to assess these dynamic responses, directly, in addition to identifying a causative pathogen.
Patterns of Lung Injury due to Infection

A number of generic patterns of inflammation may be evoked by infection but how they are distributed is specific to the involved tissue (Table 9.2).

Clinicians and radiologists have developed classification systems that are distinct from those of pathologists with respect to pulmonary infection. For example, a variety of infectious agents yield a radiographic picture that clinicians term “atypical” interstitial pneumonia, which differentiate them from the “typical” bacterial pneumonias. However, the histopathology of an “atypical pneumonia” may be centered on the lung interstitium, small airways, or the alveolar spaces. As this text is aimed primarily at surgical pathologists, pathological schemas of classification will be adopted primarily with reference to their clinical counterparts when appropriate.

Tracheobronchitis/Bronchiolitis and Miliary Infection

Many pathogens target the conducting airways to produce tracheobronchitis and bronchiolitis. Pathologic changes range from superficial erosion of the lining respiratory epithelium, to ulceration and repair. The type of inflammation will vary from intraluminal neutrophilic exudates (Fig. 9.3) to airway cuffing by lymphocytes and histiocytes (Fig. 9.4), depending on the offending pathogen.

Diffuse Alveolar Damage

Disease of the gas-exchange alveolar surfaces can show a spectrum of changes, including acute ulceration and septal infiltration by chronic inflammatory cells. Diffuse alveolar damage (DAD) represents a global injury to the gas-exchange surfaces due to disruption of the blood–air barrier leading to exudative edema and fibrosis, resulting in severely impaired blood and tissue oxygenation (Fig. 9.5). The *sine qua non* of DAD is the *hyaline membrane* that is composed of necrotic alveolar lining.
cell debris and an extravascular fibrin coagulum apposed to an ulcerated alveolar wall, which yields a gel that entraps lung water (Fig. 9.6). Although DAD is the most frequent pathological cause of the clinical entity, the adult respiratory distress syndrome (ARDS), other diseases, including extensive bronchopneumonia and acute pulmonary hemorrhage can also lead to ARDS (Table 9.3). The pathology of the exudative phase of DAD can focally mimic acute bacterial infection and one must maintain a high threshold for making the diagnosis of acute infection in this setting (Fig. 9.7).

Viruses are the most common infectious cause of DAD, although bacteria, fungi, and parasites also produce diffuse lung injury. DAD can result from sepsis that complicates either pulmonary or extrapulmonary infection. Whenever DAD is present, the surgical pathologist must examine the lung for evidence of viral-induced cytopathic changes. These vary with the type of viral infection, and some viruses do not produce cytopathic changes, so that viral infection is always in the differential diagnosis of DAD (Table 9.4). A common pitfall in diagnosis is to mistake the hyperplastic reparative alveolar type II cells of DAD with viral infected cells, particularly when examining rapidly frozen sections, in which these changes may be especially prominent (Fig. 9.8).

**TABLE 9.2 Injury Patterns Seen in Lung Infection**

| Injury Pattern                        |
|--------------------------------------|
| Tracheobronchitis                    |
| Bronchiolitis (acute, chronic, necrotizing) |
| Bronchiectasis                       |
| Bronchopneumonia (acute, chronic, necrotizing) |
| Eosinophilic pneumonia               |
| Pulmonary hemorrhage                 |
| Pulmonary edema                      |
| Diffuse alveolar damage              |
| Pulmonary nodules and micronodules   |
| Cavitary pneumonia                   |
| Vasculitis                           |
| Capillary dissemination              |
| Lymphatic dissemination              |
| Pulmonary hypertension               |
| Pleuritis                            |

---

**FIGURE 9.3** Acute bronchiolitis showing neutrophilic exudate in the lumen of a small airway.
RNA VIRUSES

Influenza

Influenza is a rod-shaped RNA virus that can cause either bronchiolitis or DAD without cytopathic changes. Influenza infection recurs each year due to a high incidence of mutation of its hemagglutinin (H) and neuraminidase (N) antigens,
and these determine its virulence. When mutations occur concomitantly in both the H and N antigens, pandemics with potentially high degrees of morbidity due to the lack of immunity may ensue (Fig. 9.9). Currently, epidemiologists are carefully monitoring the evolution of an avian influenza in southeast Asia for evidence of spread to man.

Influenza is the most common cause of viral pneumonia, although most cases are subclinical. The virus most commonly causes a diffuse tracheobronchitis/bronchiolitis in which the normal ciliated respiratory epithelium is sloughed. But when DAD develops, it carries a high mortality even in the absence of acute bacterial superinfection (Fig. 9.10). The lungs in DAD due to influenza of patients with prolonged survival often develop prominent squamous metaplasia of bronchial-alveolar lining cells (Fig. 9.11A). Although these findings are characteristic, they are also nonspecific, so that immunostains, in situ hybridization, electron microscopy, or viral antigen detection, may be required to establish the diagnosis (Fig. 9.11B). Superinfection by pyogenic bacteria, including H. influenza, Group A Streptococcus, and Staphylococcus, is a well-recognized complication and may mask evidence of a healing influenza infection.

### Serious Acute Respiratory Syndrome

The recent epidemic of the zoonotic coronavirus infection termed serious acute respiratory syndrome (SARS) fortunately has not recurred, as the virus led to acute respiratory distress with high mortality. The lungs at autopsy showed DAD with scattered multinucleated giant cells of uncertain diagnostic significance. Otherwise, the virus otherwise produced no cytopathic changes and was essentially histologically indistinguishable from DAD due to influenza.

### Table 9.3 Causes of Diffuse Alveolar Damage

| Pulmonary Infection | Systemic infection with sepsis | Vasodilatary shock | Aspiration | Drugs | Radiation | Trauma | Accelerated phase of chronic interstitial pneumonia | Idiopathic |
|---------------------|-------------------------------|--------------------|------------|-------|-----------|--------|-------------------------------------------------|-----------|

**FIGURE 9.6** Hyaline membrane lining an alveolar duct in DAD.

**TABLE 9.3** Causes of Diffuse Alveolar Damage
Middle Eastern Respiratory Syndrome

Like SARS, middle eastern respiratory syndrome (MERS) is caused by a coronavirus. The first cases were reported in Saudi Arabia in the fall of 2012, but the first recognized cases occurred in Jordan earlier that year. All cases of MERS to date have been linked through travel to or residence in countries in and near the Arabian Peninsula. The largest known outbreak of MERS outside the Arabian Peninsula occurred in the Republic of Korea in 2015 and was associated with a traveler returning from the Arabian Peninsula. MERS-CoV spreads from ill people to others via close contact, such as caring for or living with an infected person, and patients have ranged in age from infants to nonagenarians.

Patients present with fever, cough, and dyspnea. Almost 75% of reported patients with MERS have died and most have had an underlying medical condition. Some infected people have had mild symptoms of a upper respiratory infection (URI) or even no symptoms at all, and they all recovered. Incubation time ranges from 2 days to 2 weeks. Diagnosis is confirmed by RT-PCR at the Center for Disease Control for the implicated coronavirus. The pathology of the disorder has not been established but radiographically the pictures appear to be that of a severe organizing pneumonia.

| TABLE 9.4 Changes Seen in Viral Infected Lung Cells |
|---------------------------------|---------------------------------|
| **Organism**                  | **Cytopathic Change**            |
| Influenza                     | No cytopathic change            |
| SARS (coronavirus)            | No cytopathic change            |
| Respiratory syncytial virus   | Polykaryons, inconspicuous cytoplasmic inclusions |
| Parainfluenza                 | Polykaryons, intracytoplasmic inclusions |
| Measles                       | Polykaryons, intranuclear inclusions |
| Adenovirus                    | Intranuclear inclusions (smudge cells) |
| Herpesvirus                   | Intranuclear inclusions, polykaryons |
| Cytomegalovirus               | Intranuclear and cytoplasmic inclusions |
| Varicella zoster              | Intranuclear inclusions         |
| EBV                            | No cytopathic change            |
Respiratory Syncytial Virus

Respiratory syncytial virus (RSV) causes a benign respiratory infection in older children and has been recognized as a cause of adult community-acquired pneumonia, acute bronchiolitis, and DAD in the immunosuppressed host. The infection targets the respiratory lining epithelium producing syncytial giant cells with nonprominent eosinophilic inclusions (Fig. 9.12A and B). Human metapneumovirus produces changes comparable to respiratory syncytial virus (RSV) and must be included in its differential diagnosis.

**FIGURE 9.8** Lung in reparative phase of acute lung injury showing highly atypical alveolar lining cells with changes that mimic viral infection.

**FIGURE 9.9** Neuraminidase and hemagglutinin expression of *influenza* correlates with epidemic outbreaks.
Parainfluenza

*Parainfluenza* causes a benign URI in children that rarely progresses to DAD, although severe disease may develop in the immunosuppressed host. Like RSV, parainfluenza produces bronchiolitis and DAD with syncytial giant cells and epithelial cell intracytoplasmic inclusions. However, the latter are both more frequent and larger than those seen in RSV (Fig. 9.13A and B).

Measles

Measles pneumonia is a rare and serious complication of the childhood viral exanthem. The pathology of pulmonary measles infection ranges from bronchiolitis (Fig. 9.14A) to DAD. The virus produces multikaryons with prominent glassy eosinophilic nuclear Cowdry type A inclusions (Fig. 9.12B). The differential diagnosis of giant cell pneumonia includes RSV and hard-metal pneumoconiosis; however, the giant cells in the latter disorders lack intranuclear inclusions and the giant cells in hard-metal pneumoconiosis specifically lack the exudative features of an acute infection.

![Fig. 9.10](image1.png) Lung from patient who died in the 1918 influenza epidemic showing DAD with no cytopathic changes.

![Fig. 9.11](image2.png) (A) Lung in patient with DAD due to influenza showing prominent squamous metaplasia of terminal airways; (B) immunostain confirms the presence of influenza A.
DNA VIRUSES

Adenovirus

Adenovirus primarily affects the immunosuppressed host but can produce outbreaks in healthy subjects living at close quarters, e.g., military recruits. Adenovirus typically produces (1) ulcerative bronchiolitis with karyorrhexis (Fig. 9.15A), (2) neutrophilic pneumonia (Fig. 9.15B) (3) acute intrapulmonary necrosis with hemorrhage (Fig. 9.15C), or (4) DAD. Infected cells can exhibit amphophilic intranuclear inclusions with perinuclear clearing that mimic herpesvirus infection but more characteristically produce “smudge cells” (Fig. 9.15D), showing hyperchromatic nuclei extruding beyond the confines of their nuclear membranes.

FIGURE 9.12 (A) Acute bronchiolitis in RSV; (B) multinucleated epithelial cells in RSV contain inconspicuous eosinophilic cytoplasmic inclusions (arrow).

FIGURE 9.13 (A) Bronchiolitis in parainfluenza infection; (B) epithelial cell showing eosinophilic inclusions that are both larger and more frequent than in RSV (arrow).
The appearance of “smudge cells” can be mimicked by pulmonary cytotoxic drug injury or by epithelial repair in the early proliferative phase of DAD. For this reason and because of the potential overlap with herpesvirus-induced cytopathic changes, the diagnosis of adenovirus infection should always be confirmed by immunohistochemical staining, ultrastructural examination, or viral isolation.

**Cytomegalovirus**

Cytomegalovirus occurs at the extremes of age, or as a result of immunosuppression, and it is a common infection in HIV/acquired immunodeficiency syndrome (AIDS). The number of cells showing cytopathic changes can vary considerably and parallels the severity of infection. Cytomegalovirus (CMV) primarily targets pulmonary macrophages and endothelial cells, but virtually any cell can show cytopathic features. The most common distribution is blood-borne miliary disease (Fig. 9.16) but bronchiolitis and DAD also occur. The diagnostic features of infection are (1) cytomegaly, (2) intranuclear inclusions with characteristic Cowdry Type B inclusions (Fig. 9.17A), (3) ill-defined amphophilic intracytoplasmic inclusions that are seen with hematoxylin and eosin (H&E), PAS, and GMS stains (Fig. 9.17B). In patients receiving prophylactic treatment with antivirals, CMV infection may fail to exhibit cytopathic changes. However, immunostains and in situ hybridization will continue to identify intracellular CMV antigens (Fig. 9.17C).

CMV is a frequent copathogen in the immunosuppressed patient and a cause of immunosuppression in its own right. CMV infection can be seen together with other viral infections, *Pneumocystis jirovecii*, or opportunistic fungal infections (Fig. 9.18).

**Herpesvirus**

*Herpesvirus* types 1 and 2 both infect the lung. The incidence of herpesvirus infection increases with immunosuppression and when mucosal barrier defenses have been breached, *herpesvirus* characteristically elicits a prominent neutrophilic response that mimics pyogenic bacterial infection, and foci of necrosis, cell karyorrhexis, and piled up viral infected cells with amphophilic nuclei confirm the diagnosis (Fig. 9.19). Cytopathic diagnosis includes type A or type B Cowdry nuclear inclusions showing molding of adjacent cells with multikaryon formation (Fig. 9.20). Immunosuppressed patients with *herpesvirus* viremia develop miliary foci of hemorrhagic necrosis with prominent fibrinous exudates (Fig. 9.21A and B).

*Herpesvirus* pulmonary infections also develop in patients with structural abnormalities of the airways or as complications of primary infections of the oropharynx and esophagus. Intubated patients receiving chronic ventilatory support and are at increased risk due to local barotrauma from inflated endotracheal tubes. The respiratory mucosa is the primary target (Fig. 9.22). At times, extensive necrosis of an ulcerated airway suggests the diagnosis but immunostaining for herpes viral antigen can demonstrate high background staining obscuring the diagnosis. When this is the case, examining paraffin-embedded tissues by electron microscopy can reveal diagnostic virions (Fig. 9.23A–C).
FIGURE 9.15  (A) Ulcerative bronchiolitis in adenovirus infection. (B) Neutrophilic pneumonia due to adenovirus. (C) Necrotizing hemorrhagic pneumonitis. (D) "Smudge cell" showing extrusion of nuclear contents beyond the confines of the nuclear membrane.

FIGURE 9.16  Focus of miliary infection in CMV.
Varicella Zoster

Varicella zoster pneumonia is a rare complication of the childhood chickenpox and it is more commonly encountered as the consequence of reactivated virus in the immunocompromised host. Following nonlethal pulmonary infections in childhood, the lung shows multiple calcified miliary lesions. Cases coming to biopsy or autopsy show miliary nodules of

FIGURE 9.17 (A) Alveolar type II lining cells with prominent cytomegaly, Cowdry type B inclusions, and cytoplasmic inclusions (arrow). (B) Cytoplasmic inclusions stain positive with GMS. (C) Immunostain demonstrates CMV antigen in patient treated with ganciclovir.

FIGURE 9.18 Patient with CMV infection and cryptococcal pneumonia (arrow) complicating HIV/AIDS.
hemorrhagic necrosis in lung and pleura or DAD (Fig. 9.24). Infected cells with primarily Cowdry type A inclusions may be seen at the edges of the lesion but they are harder to identify than in herpesvirus pneumonia.

**Hantavirus**

This virus produced an epidemic in the four corners region of the southwestern United States in 1993. The infection is a zoonosis transmitted by infected rodent feces. The most common radiographic presentation is diffuse pulmonary edema with pleural effusions mimicking congestive heart failure. Histologically, the lung shows pulmonary edema with scant poorly formed hyaline membranes (Fig. 9.25A) with atypical lymphocytes circulating within the pulmonary vasculature (Fig. 9.25B). Confirmation of the diagnosis requires specific immunohistochemistry, serological evidence of hantavirus-specific IgM and PCR or ultrastructural identification of the causative virions.
OTHER “ATYPICAL PNEUMONIAS”

Mycoplasma Pneumonia

Mycoplasma are the smallest (0.2–0.8 μM) free-living bacteria but they lack a true cell wall. They are facultative anaerobes, except for *Mycoplasma pneumoniae*, the most common pulmonary pathogen, which is a strict aerobe. Mycoplasma pneumonia occurs worldwide with no increased seasonal activity, but epidemics predictably occur every 4–8 years. Although primarily an infection of young adults, it can attack the elderly. The most common clinical syndrome is tracheobronchitis, with one-third of patients developing a mild but persistent pneumonia.

*Mycoplasma* pneumonia is rarely biopsied, as positive cold agglutinin and specific complement fixation antigen assays will establish the diagnosis. Biopsied cases show lymphocytic or neutrophilic bronchiolitis with alveolar wall inflammation and fibrinous exudates (Fig. 9.26). Similar changes are seen in both *Chlamydia* (Fig. 9.27) and *Coxiella* pneumonia.

![FIGURE 9.22](image)

*FIGURE 9.22* Herpetic inclusions in squamous respiratory epithelium of a chronically intubated patient.
FIGURE 9.23  (A) Ulcerated tracheal lesion showing; (B) intense immunostaining for herpesvirus-1 with diagnosis; (C) confirmed by ultrastructural examination demonstrating diagnostic virions.

FIGURE 9.24  Hemorrhagic pneumonia due to varicella zoster.
Epstein–Barr Virus

*Epstein–Barr virus* (EBV) has been implicated in disorders ranging from the mononucleosis syndrome to malignant lymphoid neoplasia. The mononucleosis syndrome includes pharyngitis, lymphadenitis, and hepatosplenomegaly. Pulmonary involvement can occur as part of the syndrome but it is unusual and rarely biopsied. EBV pneumonia shows patchy peribronchiolar and interstitial polyclonal lymphoid infiltrates with scant interstitial and intra-alveolar fibrin exudates (Fig. 9.28). The diagnosis is generally established serologically by EBV antigen titers but can be confirmed by in situ hybridization.

**Pneumocystis jirovecii**

For years, the organism formerly known as *Pneumocystic carinii* was thought to be a protozoon; however, it is now confidently classified as a fungus. Originally described as a plasma-cell interstitial pneumonia in malnourished children, it was subsequently seen in patients with hematological malignancies, and in those receiving chemotherapy, or chronic corticosteroids. In the 1980s, *Pneumocystis* pneumonia became a signal infection in establishing the diagnosis of AIDS. It was encountered in epidemic proportions, until prophylactic use of trimethoprim-sulfa (*Bactrim*) became a routine aspect of HIV/AIDS management. *P. jirovecii* is currently most often diagnosed by sputum induction, and lung biopsy is reserved for diagnostic challenges.

![FIGURE 9.25](image1) (A) Pulmonary edema in patient with *hantavirus* infection. (B) Pulmonary vessel with intraluminal atypical lymphocytes (arrow).

![FIGURE 9.26](image2) Histiocytic and fibrinous exudates in *mycoplasma* pneumonia.
Although the disease presents radiographically as an atypical “interstitial” pneumonia, interstitial inflammation is not its most striking pathological feature. In pneumocystis pneumonia, the alveoli are filled with a frothy eosinophilic exudate that mimics exudative pulmonary edema or alveolar lipoproteinosis (Fig. 9.29A). The pulmonary interstitium shows a mild plasma cell-rich pneumonitis and prominent alveolar type II cell hyperplasia.

The diagnosis is confirmed by the presence of oval, helmet, or crescentic-shaped GMS+ “cysts,” 4–6 μM in greatest dimension, within the alveolar froth (Fig. 9.29B). Pneumocystis is distinguished from GMS+ fungal yeast forms by the absence of budding, pericapsular accentuation, and a so-called intracytoplasmic “dot,” in the former. However, when these features are absent and when the organism load in the biopsy is low, it may be difficult to confidently exclude histoplasma or cryptococcus. In these cases, specific immunohistochemistry can confirm the diagnosis.

Multiple patterns of unusual host reactions to P. jiroveci have been recognized. These include DAD (Fig. 9.30A), solitary necrotizing granulomas, (Fig. 9.30B), miliary infection, lymphoid interstitial pneumonia, and regional lymphadenitis. Microcalcifications may be seen in areas of infection and thin-walled cyst formation may develop.
Bronchiectasis

Bronchiectasis is one of the major manifestations of pulmonary infection. Dilatation and anatomical distortion of conducting airways can result from acute and chronic airway injury from airway infection (wet bronchiectasis) or from adjacent parenchymal scarring ("dry" or traction bronchiectasis). A number of infections can damage the large airways and leading bronchiectasis. Reversible cylindrical bronchiectasis may appear radiographically in patients following an acute bacterial pneumonia. As this change often resolves, biopsies of suspicious bronchiectatic regions should be deferred until a period of weeks past postacute infection. As regions of chronic bronchiectasis are fed by varicose bronchial arteries that often course directly beneath the airways surface, endoscopic biopsies of bronchiectatic areas are contraindicated.
Prior to the development of childhood vaccination, viral exanthems and *Bordetella pertussis* were common causes of bronchiectasis (Fig. 9.31). Cystic fibrosis, a genetic disorder of chloride transport, is currently a leading cause of severe bronchiectasis in young adults, as advances in management have resulted in patients surviving beyond childhood (Fig. 9.32).

In bronchiectasis, the airways lose their cartilaginous support due to chronic inflammation and become dilated and prone to repeated bouts of mucoid impaction and infection. The airways develop a spectrum of gross changes ranging from cystic, varicose, to cylindrical dilatation, associated with distal peribronchiolar inflammation (Fig. 9.33A) and increasing degrees of parenchymal scarring with loss of gas-exchanging alveoli (Fig. 9.33B). Although the large airways are invariably ectatic, the distal airways in bronchiectasis are generally narrowed by constrictive bronchiolitis.

Recurrent polymicrobial infections with necrotizing bronchopneumonia and abscess formation complicate bronchiectasis. Patients are also prone to develop infections due to antibiotic-resistant mucoid forms of *Pseudomonas* and *Burkholderia spp.* (Fig. 9.33C), and *Staphylococcal spp.* Some patients with infective bronchiectasis develop allergic bronchopulmonary aspergillosis (ABPA) and superinfection with atypical mycobacteria.

**FIGURE 9.30** (A) DAD and (B) necrotizing granulomatous inflammation due to pneumocystis.

**FIGURE 9.31** Bronchiolitis secondary to *Bordetella pertussis* infection, once a common cause of bronchiectasis.
Acute Bronchopneumonia

Acute bronchopneumonia is the most common distribution of pulmonary infection. Gram-positive and Gram-negative bacteria, as well some viruses, including herpesvirus and adenovirus, elicit primarily an exudation of neutrophils, whereas the cellular responses to other viruses, fungi, mycoplasma, and chlamydia are primarily lymphohistiocytic. Bronchopneumonia generally results from microaspiration of pathogens that have colonized the oropharynx (Fig. 9.34A). At times, the aspiration of colonized food particles can carry bacteria and fungi into the lung (Fig. 9.34B). Terminal episodes of aspiration often show colonies of Gram-positive Aerococci, previously referred to as “Gaffkya,” (Fig. 9.34C) and their appearance is both common and characteristic in autopsy lungs.

Bacterial Infections

The pyogenic bacteria are distinguished by their propensity to evoke acute neutrophilic inflammation and “pus.” Pyogenic infections as well as other acute necrotizing bronchopneumonias progress to organizing pneumonia, characterized by a fibrohistiocytic response that obliterates small airways along with inflammation of the surrounding alveolar interstitium (Fig. 9.35). This reaction is nonspecific, and “organizing pneumonia” or “bronchiolitis-obliterans-organizing-pneumonia” is simply a rubric for the generic lesion that may be due to infection, noninfecive inflammatory disorders, or may be idiopathic. It is important for the surgical pathologist to convey clearly to the treating clinicians that a diagnosis of “organizing pneumonia” does not indicate a specific etiology.
Pneumococcal Pneumonia

*Streptococcal pneumonia* (pneumococcal pneumonia) is a community-acquired pneumonia that classically produces a lobar pneumonia healing by resolution, i.e., without necrosis or scarring. In some cases, pneumococcal pneumonia complicates a resolving viral tracheobronchitis or influenza. In the age of antibiotic treatment, most cases do not progress to lobar involvement and are limited to acute nonnecrotizing bronchopneumonia. A large number of serotypes of *S. pneumoniae* have been isolated, and type 3 can be virulent, producing necrotizing pneumonia, bacteremia, and death, despite prompt antibiotic treatment.

Although rarely biopsied, lobar pneumococcal pneumonia is still seen at autopsy. The early phase of the disease, the *red hepatization*, shows exudation of edema fluid with the diapedesis of red blood cells (Fig. 9.36A). The exudate spreads to fill an entire lung lobe via the pores of Kohn, interalveolar potential channels within the normal lung (Fig. 9.36B). The acute cellular response is neutrophilic, but this is followed within days by alveolar filling with exudate macrophages that ingest the infected exudate, the *gray hepatization* (Fig. 9.36C). Despite the extensive inflammatory changes, alveolar necrosis is absent—a finding best assessed by elastic stains—and the lung heals by *resolution* with minimal sequelae. The offending organisms are Gram-positive lancet-shaped cocci growing in pairs (diplococci) and in short chains, and they can be identified by both tissue Gram and GMS stains (Fig. 9.36D).
FIGURE 9.34 (A) Acute bronchiolitis due to *Staphylococcus*, (B) Lentil aspiration with colonies of Gram-positive bacteria; (C) terminal aspiration showing intraluminal colony of Gram-positive *Aerococcus* spp. (Gaffkya).

FIGURE 9.35 Organizing pneumonia showing macrophages and early fibrosis in respiratory bronchioles and alveoli.
Group A Streptococci

*Group A streptococcal* pneumonia occurs at the extremes of life or as a complication of resolving influenza infection. It produces a rapidly progressing and life-threatening pneumonia with edema, hemorrhage, abscess formation, empyema, and septicemia. *Group A streptococci* evoke a brisk increase in pulmonary capillary permeability, yielding what can be mistaken for cardiogenic pulmonary edema on low-power microscopic examination (Fig. 9.37A). But further scrutiny reveals necrotic macrophages and innumerable Gram-positive bacteria in chains (Fig. 9.37B). Pulmonary hemorrhage and abscess formation are frequently seen. Streptococci have a predilection to course along pulmonary lymphatic channels, recapitulating erysipeloid spread in the skin to produce an early empyema (Fig. 9.38).

**Staphylococcal aureus**

*Staphylococcal aureus* has emerged as frequently encountered life-threatening pulmonary pathogen. Previously seen as a community-acquired complication of influenza, staphylococcal infection is now a primary cause of nosocomial pneumonia, and its evolving drug resistance accounts for methicillin-resistant strains that are of particular concern for hospital infection control epidemiologists.

*S. aureus* spp. produce a necrotizing pyogenic pneumonia with abscess formation (Fig. 9.39A). The organisms grow in clusters as Gram-positive microcolonies (Fig. 9.39B). Infection heals by organization with scarring, and cystic
pneumatoceles may develop. Some phage-infected strains of the organism produce an exotoxin that can activate the CD3 receptor to promote the release of the T-lymphocyte’s complement of lymphokines, leading to a toxic-shock syndrome with sepsis physiology, DAD, and disseminated intravascular coagulation that leads to death if not treated promptly.

**Gram-negative Bacteria**

Most Gram-negative bacilli produce a necrotizing bronchopneumonia with hemorrhage and abscess formation. Certain virulent Gram-negative species, including *Klebsiella, Pseudomonas, Acinetobacter*, and *Burkholderia spp.*, have a propensity to infect the pulmonary microvasculature leading to necrosis, bacteremia, and septic shock. The lung shows fibrinoid necrosis with colonies of Gram-negative bacilli streaming along the vessel walls, where they create an ill-defined purplish hue in H&E-stained sections (Fig. 9.40A and B).
**Klebsiella**

*Klebsiella* pneumonia generally occurs in patients who are immunocompromised due to age, ethanol abuse, or diabetes mellitus. It is a common of ventilator-associated pneumonia. Like the pneumococcus, *Klebsiella spp.* classically produce a lobar pneumonia, with an unexplained predilection for the upper lobes (Fig. 9.41A). Infection produces hemorrhagic necrosis, microabscesses, and cavity formation. The organisms are short Gram-negative bacilli that can be demonstrated with both tissue Gram stain (Fig. 9.41B) and GMS by virtue of their capsules. Less commonly, *Klebsiella spp.* produce a chronic necrotizing pneumonia with scarring and distortion of the pulmonary anatomy (Fig. 9.41C).

**Lung Abscess due to Oropharyngeal Aspiration**

Lung abscess complicates the aspiration of polymicrobial oropharyngeal bacteria. The organisms isolated from a lung abscess include mixed Gram-positive and -negative aerobic flora, as well as anaerobes. Patients with poor oral hygiene due to dental caries, those with gingival and tonsillar disease, and those with disorders that impair either consciousness or normal swallowing, e.g., ethanolism, seizure disorder, and cerebrovascular accidents, are at increased risk for aspiration pneumonia and lung abscess. The disorder begins as a necrotizing bronchopneumonia in a dependent segment of the lung and progresses to produce a cavitary abscess communicating with a feeding adjacent airway. Most lung abscesses are diagnosed and treated noninvasively; however, failure to respond to medical treatment due to poor drainage and closure may prompt surgical excision.

Microscopically, the wall of the lung abscess is irregular with a shaggy fibrinous lining (Fig. 9.42A) that may be difficult to distinguish from a necrobiotic rheumatoid nodule or Wegener’s granulomatosis. However, palisading granulomatous inflammation is not a prominent finding in lung abscess. The area around the cavity shows acute and organizing bronchopneumonia (Fig. 9.42B). The activity of a lung abscess may be determined microscopically by examining its lining, as actively infected cavities show a squamous epithelium that indicates complete healing, and may be mistaken for a region of primary bronchiectasis.

**Actinomycosis**

*Actinomyces spp.* are Gram-positive filamentous bacteria that cause a chronic distal necrotizing pneumonia with a proclivity toward penetrating into the adjacent soft tissues of the chest wall. *Actinomyces* are aspirated from the oropharynx, where they are commonly part of the tonsillar flora in younger patients or a pathogen related to poor oral hygiene and gingivitis in the elderly. The risk factors for actinomycosis are similar to those of lung abscess. The infection extends into the pleura and then forms sinuses within the soft tissues of the chest wall that ultimately exit at the skin surface. The indurated pulmonary lesion may be mistaken clinically for an aggressive peripheral lung malignancy but its gross appearance at surgery is usually distinct (Fig. 9.43).
The histological response evoked by actinomycosis is variegate, with microabscesses, polymorphous infiltrates of lymphocytes, histiocytes, plasma cells, giant cells, and fibrosis. At times, the extent of the fibroinflammatory response can lead one to consider a diagnosis of “inflammatory pseudotumor.” The correct diagnosis is established by the presence of “sulfur granules” (Fig. 9.44A)—bright yellow specks seen with the naked eye or with the aid of a hand lens that microscopically represent colonies of tangled Gram-positive, GMS-positive, beaded filamentous bacilli (Fig. 9.44B and C), coated by an eosinophilic matrix of exudate plasma proteins termed the Splendore–Hoeppli reaction. Treatment includes long-term antibiotics and surgical resection.

The differential diagnosis of “sulfur granules” in the lung includes botryomycosis, a term used to describe a variety of infections by colonies of Gram-positive cocci, either Streptococcus or Staphylococcus that grossly appear comparable to the sulfur granules caused by Actinomyces. Distinguishing these entities depends on the morphology of the bacteria in the granules, i.e., cocci in botryomycosis versus filamentous bacteria in actinomycosis (Fig. 9.45A and B).

**Nocardia**

*Nocardia* spp. produces pneumonia primarily in the immunosuppressed host. The organism shares morphological and histochemical staining features with *Actinomyces*, but its clinical and histological responses are usually easily

![FIGURE 9.40](image-url) (A) Fibrinoid necrosis with dense bacterial growth visible in H&E sections in *Pseudomonas pneumonia*. (B) Clusters of Gram-negative bacilli are identified.
FIGURE 9.41  (A) Hemorrhagic lobar pneumonia due to *Klebsiella pneumonia*. The organism has a predilection for the upper lung lobes; (B) *Klebsiella* is a small nonmotile Gram-negative rod that also stains with GMS; (C) chronic necrotizing pneumonia due to *Klebsiella* spp. with extensive scarification of necrotic lung.
FIGURE 9.42  (A) Shaggy fibrinous exudate lining wall of lung abscess due to aspiration of oropharyngeal mixed flora; (B) necrosis and bacteria in lung abscess.

FIGURE 9.43  Subpleural nodule of actinomycosis resected for suspicion of carcinoma. Note the yellow-tan appearance that suggests inflammation rather than malignancy.

FIGURE 9.44  (A) Multiple actinomycotic sulfur granules within granulohistiocytic inflammatory response; (B) Gram stain shows irregularly beaded filaments of Actinomyces spp. that also stain with GMS. Recall that GMS stains all Gram-positive organisms and with no specificity for actinomycosis.
Nocardia produces a necrotizing pneumonia with granulohistiocytic inflammation (Fig. 9.46A) and special stains highlight tangles of Gram-positive, GMS-positive filamentous organisms showing less beading than Actinomyces (Fig. 9.46B). Sulfur granules are rarely seen in pulmonary infections. As distinct from Actinomyces, Nocardia are weakly acid fast and can be demonstrated with the Fite–Ferraco stain.

FIGURE 9.46  (A) Necrotizing pneumonia due to Nocardia asteroides shows granulohistiocytic response; (B) like Actinomyces, Nocardia is a Gram-positive filamentous bacillary actinomycetes that also stains with GMS. (C) Unlike Actinomyces, Nocardia is weakly acid-fast, and can be demonstrated with the Fite–Ferraco stain.

distinguished. Nocardia produces a necrotizing pneumonia with granulohistiocytic inflammation (Fig. 9.46A) and special stains highlight tangles of Gram-positive, GMS-positive filamentous organisms showing less beading than Actinomyces (Fig. 9.46B). Sulfur granules are rarely seen in pulmonary infections. As distinct from Actinomyces, Nocardia are weakly acid fast and can be highlighted with modified Ziehl–Neelsen stains, e.g., Fite–Ferraco (Fig. 9.46C). Nocardiosis is a
recognized complication of pulmonary alveolar lipoproteinosis and has recently been observed in patients receiving therapies that interfere with the activities of tumor necrosis factor-α.

**Legionella**

*Legionella* spp. produce pulmonary infections ranging in severity from a mild respiratory illness to life-threatening pneumonia. Patients may suffer from a modest degree of immunosuppression due to diabetes and ethanolism. The organism is water-borne, and infected water and air conditioning sources have caused point outbreaks of infection.

The diagnosis of *Legionella* infection is currently established noninvasively by immunoassays; however, the disease may be identified histologically in biopsy or autopsy tissues. The infected lung characteristically shows a fibrinohistiocytic response with alveolar filling by fibrin and histiocytes; (Fig. 9.47A), although its histology may also be indistinguishable from that of pyogenic infections. It can be mimicked by acute fibrinous organizing pneumonia (AFOP), a recently recognized noninfective pattern of pulmonary injury (Fig. 9.47B). Although *Legionella* is a Gram-negative coccobacillus, it stains weakly with Gram stains, and silver impregnation stains are required to blacken the organisms, which are often abundant in situ in the absence of prior treatment (Fig. 9.48A). *Legionella micdadei* is distinguished by its staining with modified Ziehl–Neelsen stains (Fig. 9.48B).

**FIGURE 9.47** (A) *Legionella* spp. characteristically produce a necrotizing bronchopneumonia with alveolar filling by fibrin and histiocytes; (B) This appearance must be distinguished from AFOP, in which the alveolar spaces are filled with fibrin, but this disorder is not due to infection.

**FIGURE 9.48** (A) *Legionella* spp. are Gram-negative coccobacilli but must be demonstrated by silver impregnation. (B) *Legionella micdadei*, the Pittsburgh pneumonia agent, also stains with modified acid-fast bacteria stains (arrow).
**Rhodococcus equi**

Rhodococcus pneumonia is a zoonotic infection that causes a nodular histiocytic and cavitary pneumonia in immunosuppressed patients, most commonly with HIV/AIDS (Fig. 9.49). The causative Gram-positive cocci are easily identified (Fig. 9.50A) and also stain positive with the modified Ziehl–Neelsen stain (Fig. 9.50B). The inflammatory response shows malakoplakia (Fig. 9.51A) with formation of intracellular calcific concretions termed Michaelis–Gutman bodies that although nonspecific are characteristically seen in the infection and can be highlighted by both PAS and iron stains (Fig. 9.51B).

**Tropheryma whippelii** (Whipple’s Disease)

Whipple’s disease is a rare disorder caused by the actinomycete *Tropheryma whippelii*. Whipple’s disease most commonly causes intestinal malabsorption but pulmonary and neurological disease also occur. In the lung, Whipple’s disease can present as interstitial infiltrates, pleural effusions, or as pulmonary hypertension. The characteristic change in the disorder is the accumulation of foamy macrophages that show intense staining with PAS (Fig. 9.52). In some cases, microgranulomas
that are histologically comparable to those seen in sarcoidosis may confuse the diagnosis (Fig. 9.53), together with the fact that the PAS staining in these granulomas may be equivocal. It is uncertain whether sarcoidosis is associated with Whipple’s disease or whether the sarcoidal granulomas are evidence of early infection. In these cases, a small bowel biopsy will generally establish the diagnosis. Further confirmation can be achieved via ultrastructural examination demonstrating the bacillary organisms (Fig. 9.54) or by specific PCR.

**Granulomatous Pneumonia**

Pathologists apply the term “granuloma” to a variety of histological responses, including micronodular collections of tightly knit epithelioid macrophages (tuberculoid granulomas), necrotizing histiocytic reactions (necrotizing granuloma), and diffuse polymorphic infiltrates composed of lymphocytes, histiocytes, and plasma cells (granulomatous inflammation). The organisms that evoke these cellular responses are limited, and include the actinomycetes, mycobacteria, fungi, and helminths.
Mycobacterial Infection

Pulmonary necrotizing granulomatous inflammation is most commonly caused by mycobacterial or fungal infections. Tuberculosis is an ancient disease caused by a Gram-positive soil actinomycete, and it continues to represent a major source of global morbidity and mortality, largely due to its recrudescence in the setting of HIV/AIDS. The term *tuberculosis* is properly limited to infections caused by *Mycobacterium tuberculosis* and its genetically related congener, e.g., *Mycobacterium bovis*, and is not the appropriate appellation for infections due to nontuberculous or “atypical” mycobacteria.

*M. tuberculosis* can affect the pulmonary airways, parenchyma, or pleura. Inhaled mycobacteria proliferate in the alveolar spaces and are then transported via lymphatics to regional hilar lymph nodes, from which they can enter the systemic circulation to spread to other organs. Progression of infection is limited by the acquisition of effective cell-mediated immunity. The initial pulmonary focus of infection (*Ghon focus*) subsequently heals by fibrosis and may show dystrophic calcification. This Ghon focus together with the accompanying calcified site of infection in a hilar lymph node is termed the *Ranke complex* (Fig. 9.55), and the foci of primary disseminated infection are termed *Simon’s foci*. At all sites, the cellular response to *M. tuberculosis* is characterized by nodular collections of epithelioid macrophages with multinucleated giant cells, the tuberculoid granuloma, or *tubercle*. These can undergo central necrosis due to a cell-mediated hypersensitivity response. Sites of tuberculous infection may also show neutrophilic and eosinophilic exudates but these are generally not prominent features.

*FIGURE 9.53*  Nonnecrotizing granulomas mimicking sarcoidosis in Whipple’s disease.

*FIGURE 9.54*  Ultrastructure demonstrates bacilli of *Tropheryma whippelii*. 
The mature tuberculoid granuloma is surrounded by a rim of T-lymphocytes and contained by an outer zone of fibrosis (Fig. 9.56). The presence of tuberculoid granulomas can be a distinguishing feature that differentiates tuberculosis from other forms of necrotizing granulomatous inflammation, e.g., Wegener’s granulomatosis, in which tuberculoid granulomas are infrequent.

The term caseous necrosis properly refers to the “cheesy” appearance of the necrotic lesion on gross inspection. The histological correlate is destruction of lung tissue (Fig. 9.57) with loss of the underlying reticulin stroma. But as the latter finding is not apparent in H&E-stained sections, it is best, in practice, to term tuberculous lesions as either “necrotizing” or “nonnecrotizing,” and to avoid the terms “caseating” versus “noncaseating.”

As the response to mycobacterial infection reflects a component of immune hypersensitivity, even small numbers of organism can evoke substantial lung injury, and this complicates the task of identifying mycobacteria in situ. The organisms are best identified by their red color in acid-fast bacteria (AFB)-stained sections, i.e., with the Ziehl–Neelsen stain or its modifications, e.g., Fite–Ferraco. Mycobacteria can show substantial morphologic variability. They are curvilinear,
vary in length, and exhibit a characteristic “beaded” appearance attributable to nonhomogeneous uptake of the AFB stain (Fig. 9.58A).

However, there is no reliable way to distinguish *M. tuberculosis* from “atypical” mycobacteria by histochemical staining. As mycobacteria are weakly Gram positive, they can also be demonstrated in GMS-stained sections, a finding that is nonspecific, but can at times aid in the identification of the inconspicuous bacilli (Fig. 9.58B). As nonmycobacterial organisms can also be AFB positive, differential staining and culture results at times may be required to establish an accurate diagnosis (Table 9.5).

In practice the identification of *M. tuberculosis* by Ziehl–Neelsen staining is relatively insensitive, identifying mycobacteria in roughly 60% of culture-positive cases, so that the diagnosis may depend on isolating organisms in culture. However, examining multiple AFB-stained sections can improve the chance of identifying a pathogen.

Mycobacteria grow slowly in culture, and it can take weeks before they are eventually isolated. Consequently, ancillary methods have been developed with the aim of increasing the likelihood of establishing a diagnosis in a timely fashion. Sensitive fluorescent staining techniques, including the auramine–rhodamine stain, are used routinely in some laboratories in examining smears and tissues. Polymerase chain reaction (PCR) methods have been developed that can identify

![FIGURE 9.57](image) The cheesy gross appearance of a focus of caseous necrosis.

![FIGURE 9.58](image) (A) Mycobacterial tuberculosis, the “red snapper,” is a short beaded *bacillus* that can be equally well demonstrated with either the Ziehl–Neelsen stain or its weakly acid-fast modifications. (B) Mycobacteria are apparent in GMS-stained sections, but this finding is less specific than acid-fast bacteria staining.
M. tuberculosis and distinguish them from atypical mycobacteria, both in fresh tissues and in paraffin-embedded sections. The sensitivity and specificity of the latter approach are discussed elsewhere in this text.

**Spectrum of Pulmonary Tuberculous Infection**

Tuberculosis has protean manifestations in the lung (Table 9.6). Following most exposures, the primary infection is limited by the host’s cellular immune system and the host remains asymptomatic, only showing evidence of previous limited infection via a positive tuberculin skin test. However, small numbers of mycobacteria can remain potentially viable and active infection may ensue if cell-mediated immunity is diminished by age, the use of corticosteroids, diabetes, ethanolism, or concomitant chronic infection. There is a marked increase in tuberculosis in patients with pulmonary silicosis and establishing the presence of mycobacterial infection in a patient with progressive massive fibrosis due to silicosis can be difficult.

As previously noted, histological examination of infection can provide an estimation of the adequacy of host immunity. The morphology of giant cells may be an indicator of whether host cell-mediated immunity is adequate in containing tuberculous infection. Prior to the development of effective cell-mediated immunity, many giant cells in the lesions show nuclei that have aggregated toward one pole of the multikaryon (Fig. 9.59A), whereas when infection is effectively contained, Langerhans’ giant cells with peripheral nuclei or giant cells with centrally placed nuclei predominate (Fig. 9.59B). If cell-mediated immunity is profoundly diminished, granulomas may be poorly formed or absent.

Failure to contain the primary infection leads to its progression. Primary tuberculosis may show necrotizing pneumonia (Fig. 9.60), regionally involved lymph nodes, and a granulomatous pleuritis with lymphocytic effusion. Dissemination of organisms via the bloodstream can yield miliary disease, in which innumerable foci of active infection with poorly formed granulomas are seen (Fig. 9.61A–C).

*Tuberculous acinar no-dose bronchopneumonia* results from mycobacterial infection extending along the pulmonary acinus (Fig. 9.62). Tuberculomas are defined foci of nodular tuberculous infection (Fig. 9.63). When these cavitate into an adjacent bronchus, it can lead to discharge of numerous bacilli with cough or expectoration (Fig. 9.64A). Although bacillary counts in cavitary lesions are generally high, even large cavities at times will fail to show a single identifiable organism by histochemical staining, and diagnosis must be made presumptively based on histological appearance and

| TABLE 9.5 Acid-Fast Bacteria |
|-----------------------------|
| Mycobacteria                |
| Nocardia                    |
| Rhodococcus                 |
| Legionella micdadei         |

| TABLE 9.6 Pulmonary Manifestations of Tuberculosis |
|--------------------------------------------------|
| Exposures with no disease (Ranke complex)        |
| Caseating pneumonia                              |
| Acinar-no-dose pneumonia                          |
| Nodular disease (tuberculoma)                    |
| Cavitary pneumonia                               |
| Tracheobronchitis                                |
| Miliary disease                                  |
| Lymphadenitis and calcification                   |
| Pleuritis                                        |
| Fibrothorax (late)                               |

*M. tuberculosis* and distinguish them from atypical mycobacteria, both in fresh tissues and in paraffin-embedded sections. The sensitivity and specificity of the latter approach are discussed elsewhere in this text.
empiric response to antituberculous medications. The extension of cavitary disease to involve an accompanying pulmonary artery may produce a Rasmussen’s aneurysm and risk of vascular rupture leading to fatal hemoptysis (Fig. 9.64B).

Mycobacteria can spread along the mucosal surfaces of the airways to produce ulcerated lesions in the larynx and tracheobronchial tree that can mimic Wegener’s granulomatosis (Fig. 9.65). However, as previously noted, the latter disorder rarely includes well-formed tuberculoid granulomas, and their presence favors the diagnosis of infection.

**Reactivation Tuberculosis**

In most clinically encountered cases of tuberculosis, previously asymptomatic individuals with positive cutaneous responses to purified protein derivative represent either reactivation or reinfection. Reactivation indicates an acquired defect in cell-mediated immunity. Tuberculosis tends to reactivate in the upper lobes of the lung where ventilation/perfusion ratios are high. Histologically, the lung shows necrotizing granulomas in areas of “scarring and traction bronchiectasis”
(Fig. 9.66) due to the initial mycobacterial infection. But in addition to reactivation of tuberculosis, the differential diagnosis of necrotizing granulomatous inflammation in this setting includes fungal infection and atypical mycobacterial infection, as both have a predilection to develop in areas of old pulmonary apical scarring. The distinction may be difficult in the case of atypical mycobacterial infection, as special stains cannot distinguish these possibilities, and culture or ancillary diagnostic tests are necessary.

**Atypical Mycobacteria**

A number of mycobacteria that are genetically distinct from *M. tuberculosis* can produce pulmonary infection. These organisms vary in virulence and this is often reflected in the histologic appearance of the infection (Table 9.7). *Mycobacterium avium intracellulare* or *mycobacterium–avian complex* (MAC) can attack the lung in a variety of clinical settings. Patients immunosuppressed by HIV/AIDS can develop virulent infections with features that mimic tuberculosis. When adaptive T-cell-mediated immunity is severely compromised, the host response may be limited to foamy histiocytes that have ingested large numbers of mycobacteria. MAC can be demonstrated by both AFB and PAS stains, and clinical signs of both tuberculosis and MAC disease may only be recognized following treatment with antivirals, the so-called immune reconstitution syndrome.

In the immunocompetent host, MAC tends to affect elderly women (Lady Windermere’s disease) and patients with bronchiectasis or bullous emphysema (Fig. 9.67). It is commonly seen in the right-middle lobe syndrome due to
FIGURE 9.62  Geographic infiltrates of necrotizing acinar-no-dose tuberculosis.

FIGURE 9.63  Localized tuberculoma.
bronchiectasis and chronic atelectasis. The lesions of MAC infection are detected radiographically as “tree-in-bud” opacities reflecting terminal bronchiolar infection (Fig. 9.68A), together with nodules that may be either solid or cavitary. Histologically, the pathology often shows extensive areas of nonnecrotizing epithelioid histiocytes and is highly characteristic (Fig. 9.68B). The causative mycobacteria are indistinguishable from \textit{M. tuberculosis} and only culture or PCR can accurately establish the diagnosis.

A recently described variant of MAC infection is “hot tub” lung. In these cases, the lung shows a microgranulomatous hypersensitivity pneumonitis that may be accompanied by necrotizing granulomatous inflammation. The pathology appears to represent primarily a cell-mediated hypersensitivity response to mycobacterial antigens (Fig. 9.69).

An unusual presentation of MAC infection in the immunosuppressed host is the \textit{pseudosarcomatous} nodule. This can develop in the lung or in soft tissues and hematopoietic tissues. The nodules are composed of spindle cells, and may be mistaken for a low-grade spindle-cell neoplasm (Fig. 9.70A). However, examination reveals the foamy appearance of the spindle cells that prove to be CD68$^+$ macrophages containing large numbers of ingested mycobacteria (Fig. 9.70B) and the absence of mitotic activity. Within the spectrum of unusual mesenchymal reactions seen in the immunocompromised one

\textbf{FIGURE 9.64} (A) Cavitary tuberculosis. (B) Erosion of a cavity into an adjacent pulmonary artery can produce a \textit{Rasmussen's aneurysm} and lead to fatal pulmonary hemorrhage.

\textbf{FIGURE 9.65} Tracheobronchial tuberculosis. These lesions can mimic Wegner’s granulomatosis but the presence of tuberculoid granulomas is a distinguishing diagnostic feature, as they are rarely seen in Wegener’s.
must consider inflammatory myofibroblastic tumors that may include foamy histiocytes (Fig. 9.71A) associated with *human herpesvirus*-8 infection (Fig. 9.71B).

Other mycobacteria also cause pulmonary infection. *Mycobacterium kansasii* is a virulent species of atypical mycobacteria that produces necrotizing infection indistinguishable from tuberculosis. The organism often shows a prominent pattern of “cross-linking” on mycobacterial stains in situ that is characteristic but not diagnostic (Fig. 9.72A and B). Other rapid growing mycobacteria, including *Mycobacterium abscessus*, infect preexisting areas of active bronchiectasis, particularly in cystic fibrosis (Fig. 9.73). *M. fortuitum* produces limited infection in patients with diabetes, HIV/AIDS, and chronic upper gastrointestinal disease and all of the rapid growing nontuberculous mycobacteria, including *M. smegmatis*, can complicate pneumonia due to aspiration of lipid-based substances like nose drops.

| TABLE 9.7 Classification of Mycobacteria |
|-----------------------------------------|
| **TB Complex**                          |
| *M. tuberculosis*                       |
| *M. bovis*                              |
| **Runyon Group I**                      |
| *M. kansasii*                           |
| *M. marinum*                            |
| **Runyon Group II**                     |
| *M. gordonae*                           |
| *M. scrofulaceum*                       |
| **Runyon Group III**                    |
| *M. intracellulare*                     |
| *M. avium*                              |
| *M. xenopi*                             |
| **Runyon Group IV**                     |
| *M. fortuitum*                          |
| *M. chelonei*                           |
| *M. abscessus*                          |
Melioidosis

Rarely seen outside of southeast Asia where it is endemic, chronic infections due to *Pseudomonas pseudomallei* developed in veterans of the Vietnamese War many years after they had left the region. Acute melioidosis is a systemic infection that produces widespread coalescent microabscesses but it may resolve without being recognized only to recur many years later in lung, lymph nodes, and bone. The lung shows necrotizing granulomatous lesions surrounded by a zone of fibrosis (Fig. 9.74), and regional lymph nodes show stellate necrosis that can mimic “cat-scratch” disease due to *Bartonella henselae*. The offending organism is a Gram-negative motile bacillus that shows bipolar staining that can be difficult to demonstrate in situ.

Fungal Infection due to Yeasts

Fungi produce a spectrum of changes in the lung ranging from benign colonization of airways to malignant angioinvasive infections. Some fungi grow as yeast at body temperatures, whereas others are hyphate molds (Table 9.8). Most fungal

![Image](image_url)
yeasts are soil organisms that are topographically distributed in the United States. Whereas *Histoplasma capsulatum* may be encountered virtually anywhere that soil and water coexist, most cases in the United States are endemic to the mid-Western Mississippi and Ohio valleys. *Blastomyces dermatitidis* predominantly affects individuals living in the Great Lakes regions and in the southeast United States, whereas *Coccidioides immitis* is primarily encountered in the San Joaquin valley of the southwest. But despite their usual distribution, modern air travel and a highly mobile population has resulted in the possibility of these infections presenting virtually anywhere, and pathologists must be acquainted with their characteristic histological appearances. However, it is always prudent to enquire into possible travel prior to diagnosing an “exotic” fungal infection, as substantial overlap can exist in fungal morphologies.

**Histoplasmosis**

Primary *Histoplasma* infection produces a “viral-like” illness that generally resolves spontaneously. However, if there is a defect in cell-mediated immunity, or when the yeast burden is large, progression of infection may ensue. Chronic histoplasmosis tends to develop in the lung apices in areas of bullous emphysema or bronchiectasis. Although most yeast can

![FIGURE 9.69](image1) Micronodular granulomatous inflammation in “hot-tub lung,” a hypersensitivity reaction to MAC.

![FIGURE 9.70](image2) (A) A pseudosarcomatous nodule in a patient with HIV/AIDS due to MAC. (B) Large numbers of AFB/PAS+ mycobacteria are generally seen in this response. AFB, acid-fast bacteria.
be identified in H&E-stained sections, *Histoplasma* require special histochemical staining due to their small size. GMS is the stain of choice, as PAS at times fails to decorate the yeast.

Necrotizing granulomas due to *Histoplasma spp.* show central necrosis often surrounded by regions of mummefactive necrosis in which the “ghost outlines” of the underlying framework of the lung can still be distinguished in H&E and reticulin stained sections (Fig. 9.75A and B). The lining of the necrotic granuloma includes epithelioid histiocytes and giant cells but unlike tuberculosis does not show extensive tubercle granuloma formation, and the wall of the lesion characteristically exhibits paucicellular hyalinized basket weave fibrosis (Fig. 9.76).

Although they are facultative intracellular pathogens, *Histoplasma* cluster in areas of necrosis and are often seen outside of histiocytes. The 2–4 μM yeast show tear-drop shaped forms and reproduce by single narrow neck buds whose presence is diagnostic. Despite their name, no capsule is present (Fig. 9.77A). At times, pseudohyphae may be seen and this should not dissuade the pathologist from making the correct diagnosis (Fig. 9.77B), when all other diagnostic criteria are met. The differential diagnosis includes microforms of *Cryptococcus* or *Blastomyces*, *P. jirovecii*, and *Candida glabrata*. In the former, identifying the associated larger yeast forms eliminates the possibility of *H. capsulatum* infection. *P. jirovecii* shows irregularly shaped cysts with pericapsular accentuation on GMS stain and the organisms do not bud; *C. glabrata* can closely mimic the infection in GMS-stained sections, but unlike *Histoplasma*, they also stain amphophilic with H&E and are strongly Gram positive (Fig. 9.78A and B).
However, the most common and greatest difficulties in diagnosis can arise in distinguishing small regular microcalcifications in GMS-stained sections as they can closely resemble degenerate yeast (Fig. 9.79). The presence of irregular calcifications is a clue to their actual nature but at times, ultrastructural examination may be required to exclude infection. In the immunosuppressed host, disseminated infection is primarily distributed within interstitial and alveolar macrophages (Fig. 9.80A and B).

Extension of infection from a peribronchial lymph node can produce mediastinal granuloma, a lesion characterized by dense paucicellular basket-weave hyaline fibrosis with aggregates of plasma cells (Fig. 9.81A). Organisms are rarely identified in the areas of paucicellular scarring and this form of the disease appears to be immunologically mediated. At times, necrotizing granulomatous inflammation is concomitantly present and confirms the diagnosis (Fig. 9.81B). The lesion can entrap the large vessels of the mediastinum leading to the superior vena caval syndrome and death. Surgical excision is required but not always be technically possible.

FIGURE 9.73 *Mycobacterium abscessus* complicates areas of bronchiectasis and may be exceedingly difficult to eradicate fully with antituberculosis agents.

FIGURE 9.74 *Pseudomonas pseudomallei*, the cause of melioidosis, may reactivate many years following initial exposure to produce a necrotizing granulomatous pneumonia that resembles tuberculosis.
Remotely infected calcified peribronchial lymph nodes due to histoplasmosis can erode into adjacent airways to be either expectorated or aspirated as broncholiths. Surprisingly, these may show persistently viable yeast forms and colonization by aspirated oropharyngeal bacteria (Fig. 9.82).

Old calcified granulomas are commonly encountered in surgical resection of lungs for neoplasia. Most of these are due to healed tuberculosis or histoplasmosis, depending on exposure. In the vast majority of cases no organism will be identified but occasionally nonviable degenerate histoplasma may be seen, although distinguishing them with confidence from microcalcifications can be difficult and a high threshold for the diagnosis of histoplasmosis should be maintained in this setting.

**Blastomyces**

*B. dermatitidis* shows a propensity to infect lung, skin, and bone. The spectrum of pulmonary presentations includes consolidative pneumonia, diffuse alveolar damage, and pulmonary nodules that radiographically may mimic pulmonary carcinoma (Fig. 9.83). The pulmonary lesion characteristically shows a granulohistiocytic response (Fig. 9.84A). The yeast

![TABLE 9.8 Fungal Identification in Tissue](chart)

| Organism           | Size (Width, μM) | Defining Morphology                                                                 |
|--------------------|------------------|-------------------------------------------------------------------------------------|
| *H. capsulatum*    | 2–5              | Narrow-neck bud                                                                     |
| *C. neoformans*    | 5–20             | Narrow-neck bud                                                                     |
| *B. dermatitidis*  | 15–30            | Broad-based bud                                                                     |
| *C. glabrata*      | 3–5              | Budding, no pseudohyphae                                                            |
| *Candida* spp.     | 2–3              | Yeast, pseudohyphae, hyphae                                                         |
| *Aspergillus* spp. | 3–5              | Acute-angle branching, septate, conidial head                                       |
| *Zygomycetes* spp. | 5–8              | Right-angle branching, ribbons, pauciseptate                                        |
| *Pseudoallescheria* spp. | 3–4 | Acute-angle branch, septate, terminal chlamydospore, pigmented conidia |
| *Fusarium* spp.    | 4–5              | Acute and right-angle branch, septate, narrowed branch points                       |
| *C. immitis*       | 20–200           | Endosporulation                                                                     |

![FIGURE 9.75](image) (A) Nodular pneumonia due to *H. capsulatum* often shows necrotizing granulomatous inflammation with three zones (arrows). The outer capsule encloses an area of mummificative necrosis that in turn surrounds an area of caseating necrosis findings confirmed by (B) reticulin stains.
are large (15–30 μM) and easily identified in H&E sections, where they are distinguished by their thick refractile cell wall (Fig. 9.84B). The organism is also multinucleate (Fig. 9.84C) and proliferates via single broad-based budding (Fig. 9.84D). Microforms may be present and should not be confused with coinfection by *H. capsulatum*. Giant yeast forms can also occur and may be confused with *C. immitis*.

**Cryptococcus**

*Cryptococcus neoformans* infects immunocompromised patients but can also be seen in apparently normal hosts. Meningoencephalitis is the most common clinical presentation and it represents a complication of subclinical pulmonary infection. *C. neoformans* can produce localized necrotizing cryptococcomas (Fig. 9.85A), confluent bronchopneumonia (Fig. 9.85B), granulomatous pneumonia (Fig. 9.85C and D), or a null response characterized by “yeast lakes” with minimal inflammation (Fig. 9.85E). Grossly, the infected lesions are glistening and “slimy.”

![FIGURE 9.76](image1) The wall of the necrotizing granuloma shows poorly formed granulomas and giant cells with a highly characteristic hyalinized basket-weave fibrosis.

![FIGURE 9.77](image2) (A) Narrow necked budding 2–4 μM yeast of *H. capsulatum* in GMS stained section (arrow). PAS is not reliable for demonstrating this yeast (B) *H. capsulatum* infection with irregular yeast forms and pseudohyphae (arrow).
The organism shows substantial variability in size (2–15 μM) in size and shape (Fig. 9.86A) and innumerable microforms can occasionally be seen that must be distinguished from histoplasmosis (Fig. 9.86B). The yeast proliferates via single narrow-necked buds (secrete a capsule that is optimally visualized with mucicarmine in situ; Fig. 9.87A). The organisms in fluids stain with India ink (Fig. 9.87B). With GMS, the yeast body stains gray black and the capsule is not decorated (Fig. 9.88C). In capsular-deficient organisms, the Fontana–Masson stain reacts with a melanin precursor in the yeast wall, highlighting the organisms (Fig. 9.88A), although a careful examination of the mucicarmine stain will invariably reveal a poorly developed rim of capsular staining (Fig. 9.88B).

**Coccidioides immitis**

Generally affecting patients from the southwestern United States, this organism is distinct from other yeast by virtue of its size (20–200 μM) and its endosporulating mode of reproduction. *C. immitis* produces a spectrum of changes that includes fibrocaseous granulomas (Fig. 9.89), granulomatous pneumonia, and miliary disease, often accompanied by tissue

![Figure 9.78](image1.png)

**Figure 9.78** (A) *Candida glabrata* can easily be mistaken for *H. capsulatum* on GMS stain but (B) the yeast are amphophilic in H&E-stained sections and easily differentiated on this basis.

![Figure 9.79](image2.png)

**Figure 9.79** Microcalcifications (arrow) can closely resemble *H. capsulatum*. At times ultrastructural examination may be required in order to exclude infection.
eosinophilia. The endospores are contained within a spherular capsule and both stain well with GMS (Fig. 9.90A), whereas spherules are variably stained by PAS. The cysts of *C. immitis* have a characteristic tendency to collapse after having discharged their endospores in situ (Fig. 9.90B).

In endemic areas, *C. immitis* can form fungus balls within preexisting pulmonary cavities (Fig. 9.91A). The organism is dimorphic and the presence of the infective hyphal arthroconidia should not be confused with a concomitant mold infection (Fig. 9.91B).

**Paracoccidioides**

*Paracoccidioides brasiliensis* infection is endemic in South America, where it produces a range of pulmonary findings comparable to those of blastomycosis; but cases are rare in the United States. The organism is large (10–60 μM) and replicates by multiple narrow-necked buds that produce a “ships wheel” appearance that is pathognomonic (Fig. 9.92). However, when this feature is absent, the infection can be confused with other fungi.
Candida spp.

Superficial colonization of the upper airways by Candida spp. is common in patients treated with inhaled corticosteroids or in chronically ill and diabetic patients (Fig. 9.93). Foci of aspiration pneumonia and abscess cavities may show colonization, but deep pulmonary infection is rarely seen in the absence of fungemia (Fig. 9.94A and B).

Candida can have a pleomorphic morphology that includes yeast (blastoconidia), pseudohyphae, and true hyphae, although in some cases, only yeast forms may be present. The organisms can be highlighted by either GMS or PAS and stain strongly Gram positive (Fig. 9.95A). At times, blastoconidia of Candida spp. can be large and mimic other fungal infections (Fig. 9.95B). Candida glabrata (torula glabrata) shows multiple 2–5 μM budding yeast that are amphophilic in H&E sections; they are distinct from other Candida species, as pseudohyphae and hyphae are never present.
Hyphate Fungi

Hyphate fungi or “molds” are responsible for a range of pulmonary disorders ranging from colonization of pulmonary airways to angioinvasive life-threatening infections. *Aspergillus spp.* account for the majority of pulmonary mold infections but other organisms including the Zygomyces, Pseudoallescheria, and Fusarium also produce pulmonary disease.

**Aspergillus spp.**

The hyphae of *Aspergillus spp.* range in diameter from 2.5 to 4.5 μM and show frequent septation. *Aspergillus spp.* branch progressively, primarily at acute angles of \(-45^\circ\) degree, mimicking an arborizing tree branch (Fig. 9.96A) but when cut in cross-section may be mistaken for yeast, although the absence of budding suggests the correct diagnosis. In areas of mycelial growth, organisms become tangled, bulbous, and distorted and it may be impossible to confirm the diagnosis with accuracy based on morphology (Fig. 9.96B).

The *aspergil*, a ritual implement used in the Roman Catholic mass, resembles the fruiting body, and gives the fungus its name (Fig. 9.97A–C). Fruiting bodies develop from mycelia in areas of high oxygen tension, such as lung or sinus cavities but do not develop in tissues. They are composed of a vesicle with one or two layers of phialides that produce the infective conidial spores, and the morphology of the fruiting body allows for accurate speciated in situ. In general, the specific diagnosis of “aspergillosis” should be avoided unless the aspergil is identified, as other fungi can be morphologically virtually indistinguishable in tissue. Diagnoses are therefore optimally phrased as “acute-angle branching hyphae consistent with aspergillus.”
FIGURE 9.85  (A) Nodular cryptococcoma. (B) Confluent necrotizing bronchopneumonia. (C) Histiocytic response. (D) Granulomatous response to Cryptococcus neoformans. (E) Yeast lake.
FIGURE 9.86  (A) Narrow necked budding of *Cryptococcus neoformans* showing variability in size and shapes; (B) microforms of *C. neoformans* within histiocytes must be distinguished from intracellular *H. capsulatum*.

FIGURE 9.87  (A) Mucicarmine stains capsule of *Cryptococcus neoformans*. (B) India ink preparation shows capsule of yeast. (C) Both GMS (and PAS) stain body of yeast but not its capsule.
Immune Disorders due to Aspergillus Infection

Aspergillus spp. give rise to a spectrum of disorders, some reflecting hypersensitivity responses to the organisms, whereas others are the consequence of invasive infection (Fig. 9.98). Distinguishing these is critical for the proper management of these disorders.

Allergic Bronchopulmonary Aspergillosis

Allergic bronchopulmonary aspergillosis shows a range of findings, including intractable asthma, proximal bronchiectasis, and both peripheral blood eosinophilia. It is not certain whether the fungus plays an opportunistic role in exacerbating atopic responses or is primary in its pathogenesis. Patients develop intractable bronchospasm with elevated serum IgE levels specific for Aspergillus spp. The pathology includes central cystic bronchiectasis with mucoid impaction (Fig. 9.99A). The impacted mucus is viscid and forms a cast of the airways, a disorder termed plastic bronchitis. Microscopically the mucus plugs show layers of degenerating eosinophils interspersed within the mucin (Fig. 9.99B), and the surrounding lung may show patchy eosinophilic pneumonia. The fragmented fungal hyphae can at times be difficult to
identify (Fig. 9.99C), so that silver stains should be applied routinely to the evaluation of allergic mucus plugs. Although the clinical and histologic features of this disorder are most frequently caused by hypersensitivity to Aspergillus spp., other fungi, e.g., Candida spp., can yield a comparable syndrome. A subset of patients with cystic fibrosis develops concomitant ABPA, and establishing the diagnosis in this setting requires evidence of elevated IgE in serum or BAL that is especially reactive with aspergillus antigens.

Cases of ABPA vary in severity but can be inordinately difficult to manage. Corticosteroids remain the mainstay of treatment for the asthmatic component of the disease. Flutter valves instruments (Acapella) can assist in loosening the areas of mucoid impaction. Finally, azole (itraconazole or voriconazole) treatment may reduce fungal colonization in the airways.

Bronchocentric Granulomatosis

Bronchocentric granulomatosis (BCG) appears to reflect an abnormal cell-mediated response to Aspergillus spp., in which small caliber airways develop circumferential granulomatous inflammation, loss of the normal lining respiratory epithelium, and impaction of the airway lumen by granular basophilic mucin admixed with cellular debris (Fig. 9.100A–C). The disorder may be first noted radiographically as isolated or multiple airway centered nodules. BCG may be seen as part of the spectrum of findings in ABPA, or as an isolated disorder. As in ABPA, fragmented hyphae may be difficult to identify

![Figure 9.90](image1.png)  
**FIGURE 9.90**  (A) Endospores are variably present within PAS+ cysts. (B) Cysts of C. immitis have a characteristic tendency to collapse after discharging their contents (arrows).

![Figure 9.91](image2.png)  
**FIGURE 9.91**  (A) Fungus ball due to C. immitis with (B) yeast and arthroconidia that must not be confused with a concomitant mold infection.
and surrounding areas of eosinophilic pneumonitis are common. When the disease is suspected clinically, it can be treated noninvasively with corticosteroids; however, definitive resection may be undertaken to exclude neoplasia.

**Hypersensitivity Pneumonitis**

Hypersensitivity pneumonitis reflects a combined abnormality of humoral and cell-mediated immunological responses to organic antigens. Most cases of HP are caused by thermophilic actinomycetes, but hypersensitivity to *Aspergillus spp.* is well documented. Upper lobe predominance is the rule and this can be a helpful feature in establishing the diagnosis.

The diagnosis of HP is based primarily on establishing a historical link between antigen exposures and the clinical findings but lung biopsies can establish the diagnosis. Microscopically, the lung shows bronchiolocentric lymphohistiocytic interstitial infiltrates with poorly formed microgranulomas (Fig. 9.101) and giant cells that may contain birefringent crystals and cholesterol crystals. Although CD8+ lymphocytes characteristically predominate in BAL fluid specimens,
immunostains will reveal dominance of either CD4+ or CD8+ lymphocytes in situ. In addition, other histopathologies, including, nonspecific cellular interstitial pneumonitis, organizing pneumonia, lymphoid interstitial pneumonitis, and nonnecrotizing granulomatous inflammation resembling sarcoidosis, can be caused by HP. The presence of interstitial and alveolar eosinophils is characteristically seen in HP due to *Aspergillus* antigens and is rare in the response to other antigens.

**Aspergillus bronchitis and Chronic Necrotizing Aspergillosis**

The presence of primary airway infection by *Aspergillus spp.* is a poorly recognized entity. It is generally seen in the setting of modest immunosuppression accompanying disorders like diabetes mellitus or the use of aerosolized steroids in asthmatics. In some cases, it is a precursor lesion for invasive disease. Fungal hyphae can be seen filling the lumen of airways (Fig. 9.103A), without evidence of frank tissue invasion. Elastic stains are helpful in determining whether organisms have begun to transgress normal tissue barriers (Fig. 9.102B). Centrally necrotic lesions (Fig. 9.103A) of chronic necrotizing aspergillosis can resemble those due to mycobacteria and other fungi (Fig. 9.103B). Treatment with voriconazole is indicated and if disease is localized surgical resection may be required.

**FIGURE 9.94**  (A) Necrotizing pneumonia due to *C. albicans* in fungemic patient. (B) PAS stain highlights the organism.

**FIGURE 9.95**  (A) Candida yeast are intensely Gram positive. (B) Large yeast and pseudohyphae proved to be *Candida tropicalis*. 
**Fungus Balls**

The colonization of old fibrocavitary disease, e.g., areas of bronchiectasis due to healed tuberculosis and sarcoidosis, or emphysematous bullae, by *Aspergillus spp.*, is the most common cause of a pulmonary fungus ball (Fig. 9.104A and B). The term mycetoma should not be applied to intracavitary fungal mycelial growth as it accurately applies only to soft tissue infections. Patients may be asymptomatic, or alternatively present with episodes of hemoptysis, at times massive and requiring emergent bronchial arterial embolization or definitive resection.

The morphology of the hyphae in a fungus ball is frequently distorted and it can be impossible to identify diagnostic septate acute angle branching forms. *Aspergillus* fungus balls show heterogeneous staining intensity (Fig. 9.104C), giving the impression of alternating zones of growth. The wall of the fungus ball frequently shows increased numbers of tissue eosinophils (Fig. 9.104D). The *Splendore–Hoeppli* phenomenon is invariably present and is reassuring evidence that angioinvasion is unlikely, unless there has been a recent supervening cause of immunosuppression or neutropenia. The walls of the cavity are lined with granulation tissue, granulomatous inflammation, or metaplastic squamous epithelium, depending on the activity of the disease. The occasional presence of germinative fruiting bodies of *Aspergillus spp.* with characteristic phialides and conidial forms allows definitive speciation.

The definitive treatment of fungus balls is surgical extirpation. However, the degree of underlying lung disease and adhesions to the chest wall make this form of resection technically difficult. If patients are actively hemoptysizing, coiling of a feeding bronchial artery may suffice as treatment. However, recurrent bleeding or constitutional symptoms should lead to reconsideration for surgical intervention. There is evidence that voriconazole may assist as adjuvant therapy but the thick-walled nature of these cavities limits its efficacy.

One may rarely see rapid expansion of a cavity due to vascular thrombosis induced by calcium oxalate crystal deposition, a disorder termed *chronic pulmonary oxalosis*. Oxalic acid is produced by a variety of *Aspergillus spp.* but is most commonly a feature of *Aspergillus niger* infection (Fig. 9.105A). Diffusion of oxalate into the surrounding blood vessels is prothrombotic and can lead to extensive ischemic necrosis (Fig. 9.105B and C). Oxalate crystal deposition in the renal tubules may also be seen. Emergency resection of the fungus ball is the only effective treatment.

**Angioinvasive Aspergillosis**

This life-threatening infection is seen in patients who have been chronically immunosuppressed and/or neutropenic. It is a complication of bone marrow and solid organ transplantation, as well as of antileukemic chemotherapies. Angioinvasive aspergillosis is an uncommon complication of HIV/AIDS, despite the associated profound immune deficiency. Grossly, the lung shows “targetoid” lesions showing central thrombosed vessels secondary to angioinvasion, surrounded by a rim of consolidated lung, confluent bronchopneumonia, or lobar consolidation (Fig. 9.106A) and microscopically a necrotizing pneumonia (Fig. 9.106B) at times featuring giant cells (Fig. 9.106C) may be present. Angioinvasion is identified microscopically and may be enhanced with silver and elastic stains (Fig. 9.107A and B). Rarely, foci of infarcted lung can produce an infected nonviable pulmonary sequestrum (Fig. 9.108).
The fungal hyphae tend to invade blood vessels and to “metastasize” to other organs. The presence of sunburst vasculocentric hyphal growth is diagnostic of a “metastatic” focus of infection (Fig. 9.109) and virtually any organ may be secondarily involved. Circulating *Aspergillus spp.* can also seed abnormal cardiac valves to produce endocarditis with fatal embolic hemorrhagic infarctions to brain and other vital organs.
FIGURE 9.98  Spectrum of disease due to Aspergillus spp.

FIGURE 9.99  (A) Central bronchiectasis with dense peribronchiolar scarring in patient with ABPA. (B) Expectorated “allergic” mucus plug with eosinophils and Charcot–Leyden crystals (arrow). (C) Aspergillus hyphae in mucus plug.
Other *Aspergillus* Species

*Aspergillus terreus* is an opportunistic fungus that infects patients with chronic granulomatous disease, as well as other immunocompromised hosts. Its hyphae are pyriform with orthogonal branches (Fig. 9.110A and B). Fungus balls due to *Aspergillus nidulans* have a propensity to produce pale staining Hulle cells with Maltese cross birefringence when examined under polarized light (Fig. 9.111A and B).

**FIGURE 9.100** (A) Gross appearance of BCG showing; (B) exquisite bronchocentric distribution in PAS-stained section. (C) The lining of a small airway is replaced by granulomatous inflammation and the lumen is filled with a granular basophilic exudate.

**FIGURE 9.101** The microgranulomatous hypersensitivity response to aspergillus often includes tissue eosinophils.
Other Hyphate Fungi

Although the majority of acute-angle branching septate hyphae encountered in medical practice prove to be *Aspergillus spp.*, exceptions do occur and can be difficult to distinguish in situ. Organisms that closely mimic *Aspergillus* include the *Zygomyces*, *Pseudallescheria boydii* (*Scedosporium*), and *Fusarium spp*. Pulmonary infection by *Zygomyces* is due to organisms of the order *Mucorales* (*Mucor*), including *Mucor, Rhizopus, Absidia, Rhizomucor*, and *Apophysomyces*. Infection generally occurs in immunosuppressed hosts and in patients with diabetic ketoacidosis or disorders of iron metabolism. As treatment invariably includes surgical resection, establishing an accurate diagnosis is critical.

The histologic responses to infection are comparable to those caused by angioinvasive aspergillosis. The hyphae of the *Zygomyces* are broad (5–25 μm), pauciseptate, tending to branch at right angles (Fig. 9.112A), although acute angle branching does occur and its presence should not dissuade one from the correct diagnosis. The hyphae of the *Zygomyces* are well stained by hematoxylin and they have a proclivity to produce ribbon-like structures (Fig. 9.112B) but caution in diagnosis is required as treated *Aspergillus* can assume this appearance. The fungus rapidly invades vessels, perineural lymphatics, cartilage, and tends not to respect tissue boundaries. *Zygomyces*, as well as all other hyphate fungi can rarely form noninvasive fungus balls in the lung.

![FIGURE 9.102](image1) **(A) Aspergillus bronchitis/bronchiolitis is a precursor to invasive disease; (B) elastic stains can determine whether tissue invasion has occurred (arrow).**

**FIGURE 9.103** (A) Necrotizing lesions due to aspergillus can (B) resemble mycobacterial or yeast infection.
Pseudoallescheria (Scedosporium)

The hyphae of Pseudoallescheria are smaller (2–4 μM) than those of Aspergillus spp., the fungus branches predominantly at acute angles, but unlike Aspergillus, tends to branch haphazardly rather than progressively, and terminal chlamydospores mimicking a “tennis racket” may be apparent (Fig. 9.113). Although it is a hyaline fungus, the conidia produced by Pseudoallescheria in fungus balls are ovoid and pigmented.

Fusarium

Fusarium is an opportunistic infection of lung that is seen in patients who are severely immunosuppressed. The septate hyphae of Fusarium spp. branch irregularly, and at right angles, showing constrictions at branch points (Fig. 9.114).

Differential Diagnosis

Although distinguishing hyphate fungal pathogens from one another in tissue can be exceedingly difficult, it is important, as the efficacy of available fungal antibiotics depends on the diagnosis. For example, although both Aspergillus spp. and Pseudoallescheria are sensitive to voriconazole, Pseudoallescheria are resistant to amphotericin. The sensitivity of Fusarium spp. to most antifungal antibiotics appears to be both unpredictable and limited. In all cases, culture remains the
gold standard for diagnosis. Immunohistochemical reagents that can distinguish between hyphate fungi exist but are not commercially widely available and all reagents must be carefully tested with appropriate controls. The PCR assay is presently not an effective diagnostic approach.

Serological testing can at times assist in the distinction between invasive “mucormycosis” and aspergillus infections. 2,3-Beta-glucan is generally not produced by the zygomycetes but the test is also nonspecific and positive results can be seen in other conditions and circumstances that are noninfectious. The galactomannan assay was developed as a specific marker of aspergillus infection; however, its sensitivity in part depends on the fungal burden and on whether there is tissue invasion. Results from the BAL are more sensitive but may not distinguish noninvasive colonization from angioinvasive disease. For these reasons, these tests should be used prudently based on the context of clinical and radiographic presentation.

Dematiaceous (Pigmented) Fungi

Pigmented fungi can be divided into those forming yeast (chromoblastomycosis) and those due to hyphate fungi (phaeohyphomycosis). The specific organisms producing disease cannot be diagnosed morphologically and isolation in culture is required. The Fontana–Masson stain can be applied when questions exist as to whether a fungus seen in H&E sections is pigmented. Bipolaris, Curvularia, Alternaria, and others, are pigmented hyphate fungi that cause allergic pulmonary disorders mimicking those due to Aspergillus spp. (Fig. 9.115). The correct diagnosis is suggested by the presence of pigmented hyphae within allergic mucus or within fungus balls. Chromoblastomycosis is appreciated by the

![FIGURE 9.105](image-url) (A) Fungus ball due to A. niger; (B) extensive local ischemic infarction of lung; and (C) deposition of calcium oxalate crystals are seen with polarized light.
presence of sclerotic (Medlar) bodies. These are clusters of pigmented yeast that show characteristic multiaxial septa (Fig. 9.116).

Other Fungi

Pulmonary infection due to *Penicillium marneffei* is rarely seen outside of patients from southeast Asia with HIV/AIDS, but it is a significant cause of necrotizing bronchopneumonia in this region. The organism is a small (2–5 μM) dimorphic fungus with an elongate sausage shape showing a characteristic septum. The organisms can be identified free within areas of necrosis or within foamy histiocytes (Fig. 9.117). The infection may also disseminate, commonly to involve the skin. Other fungi, including *Geotrichum* and *Sporothrix*, are rare causes of pulmonary infection.
Parasites

The lung can be host to a variety of parasitic infections. Although many are primarily seen primarily in tropical climates, others occur in temperate climes, or as the result of immunosuppression. As previously noted, the current ease of global travel has greatly increased encounters with tropical diseases.

PROTOZOA

Several species of protozoa can produce pulmonary infection. *Entamoeba histolytica* affects the lung secondary to the transdiaphragmatic extension of a hepatic amoebic abscess, or less commonly as the result of blood-borne spread from an intestinal source. A pulmonary amoebic abscess may extend to the pleura or rupture into an airway leading to

FIGURE 9.107  (A) Blood vessel invasion may be seen with H&E and to better advantage in (B) section costained with GMS and H&E.

FIGURE 9.108  Area of nonviable lung (sequestrum) due to angioinvasive aspergillosis (arrow).
intrapulmonic dissemination. The amoebic abscess shows liquefactive necrosis that grossly resembles “anchovy paste” (Fig. 9.118). The histological response in areas of necrosis primarily includes neutrophils but the margins of the lesion will show a polymorphous infiltrate of macrophages, lymphocytes, and plasma cells and tissue eosinophilia is uncommon (Fig. 9.119A). Amoeba can be distinguished from macrophages by their larger size, amphophilic bubbly cytoplasm, a sharply defined nuclear karyosome (Fig. 9.119B), and in the case of E. histolytica, by the ingestion of erythrocytes.

Free living amoebae, including Acanthamoeba, Balamuthia, and Naegleria, rarely affect the lung and primarily cause meningoencephalitis. However, in immunosuppressed patients, infection may spread beyond the confines of the nervous system to include the lung.

**Toxoplasma**

*Toxoplasma gondii* produces pneumonia in patients who are immunosuppressed most often with HIV/AIDS. Although *Toxoplasma* is a common infection of the central nervous system and retina in HIV/AIDS, pulmonary infection is rare. When present, it includes a fibrinopurulent pneumonitis with areas of necrosis (Fig. 9.120A). The organisms are obligate intracellular parasites and are identified either as engorged pseudocysts containing crescent-shaped tachyzoites and/or GMS+ and PAS+ true cysts containing bradyzoites (Fig. 9.120B).

**FIGURE 9.109** Focus of “metastatic” fungal infection showing sunburst pattern of growth out of blood vessel.

**FIGURE 9.110** (A) Aspergillus terreus infection in patient with chronic granulomatous disease showing (B) fragmented pyriform hyphae branching at right angle.
**Cryptosporidium**

*Cryptosporidium parvum* is water-borne opportunistic infection that affects patients with HIV/AIDS but has also been seen as outbreaks among children in day care centers. The disease primarily affects the small bowel leading to cholera-like watery diarrhea. In patients with HIV/AIDS, the infection can spread to the hepatobiliary tree as well as to the pulmonary airways.

The diagnosis is made by identifying the amphophilic spores (3–5 μM) of *Cryptosporidia* along the surface of infected respiratory epithelium (Fig. 9.121). Although apparently extracellular by light microscopic determination, ultrastructural analysis demonstrates that the cysts are actually intracytoplasmic and invested by apical cytoplasm. The underling mucosa shows a mild lymphocytic infiltrate. Although well seen with H&E, the cysts are also stained by GMS, modified AFB, and Giemsa. The diagnosis is obvious once considered, but can easily go unnoticed unless considered in the differential diagnosis.

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**FIGURE 9.111**  (A) Fungus ball due to *Aspergillus nidulans* with Halle cells that (B) show Maltese cross configuration when examined with polarized light.

**FIGURE 9.112**  (A) *Zygomycetes* spp. hyphae are broad, pauciseptate, and tend to branch at right angles; (B) area of necrotizing angioinvasive disease with ribbon-like hyphae that stain well with hematoxylin.
Microsporidia

Microsporidia are spore-forming protozoa that like Cryptosporidium infect immunosuppressed patients to produce a watery diarrheal illness. Extraintestinal disease, including bronchial involvement, is uncommon but has been observed. The organisms are intracytoplasmic and generally located within the apical cytoplasm. Because of their small size (1–2 μM) they may be exceedingly difficult to detect, especially when the organism load is low. Special stains, including tissue Gram stain, trichrome, Warthin—Starry, and GMS can assist in their identification (Fig. 9.122). Further speciation requires ultrastructural examination.

FIGURE 9.113  *Pseudoallescheria boydii* are slightly smaller than *Aspergillus* spp. tend to grow randomly with prominent terminal chlamydospores (arrow). Definitive diagnosis is generally not possible based solely on morphology in tissue sections.

**Microsporidia**

Microsporidia are spore-forming protozoa that like *Cryptosporidium* infect immunosuppressed patients to produce a watery diarrheal illness. Extraintestinal disease, including bronchial involvement, is uncommon but has been observed. The organisms are intracytoplasmic and generally located within the apical cytoplasm. Because of their small size (1–2 μM) they may be exceedingly difficult to detect, especially when the organism load is low. Special stains, including tissue Gram stain, trichrome, Warthin—Starry, and GMS can assist in their identification (Fig. 9.122). Further speciation requires ultrastructural examination.

**FIGURE 9.114**  *Fusarium* tend to branch at right angles with narrow branch points but definitive classification is generally not achieved in tissue sections.
NEMATODES (ROUND WORMS)

Several nematodes (round worms) have a larval developmental phase in the lung (Table 9.9). The larvae of *Ascaris*, *Necator*, *Ancylostoma*, and *Strongyloides* migrate through the airways toward the mouth where they are swallowed or expectorated. This process can evoke wheezing, migratory pneumonia, and blood eosinophilia, a complex termed Loeffler’s syndrome. The presence of track-like necrotizing granulomatous bronchitis and bronchopneumonia with prominent eosinophilic infiltrates should alert the pathologist to the presence of a migratory parasitic pulmonary infection (Fig. 9.123).

*Strongyloides stercoralis* is most often seen in the tropics, however, cases are endemic to the southeastern United States. Patients receiving high doses of corticosteroids are susceptible to infection and what is termed “hyperinfection.” In hyperinfection, filariform organisms exit the gut and migrate to the lungs. There, they cause hemorrhagic and eosinophilic pneumonia. When normal pathways of maturation are inhibited, the filariform larvae mature to egg-laying adults that give rise to rhabditiform larvae and the presence of expectorated ova indicates hyperinfection (Fig. 9.124A). Parasitemia
predisposes to Gram-negative sepsis that can lead to concomitant DAD (Fig. 9.124B). Due to the risk of activating the hyperinfection syndrome via immunosuppression, patients should either be tested prior to immunosuppressive treatment or treated empirically and prophylactically with ivermectin.

**Dirofilaria**

In temperate climates, *Dirofilaria immitis* is a zoonosis that causes canine “heartworm.” Mosquitoes transfer microfilariae into subcutaneous tissues where they mature silently and enter the systemic venous circulation. From there, they travel to the right heart, but in humans they do not mature further. Pulmonary disease reflects embolism of a nonviable helminth from the heart into the pulmonary circulation where it generally lodges in a small muscular artery to produce an area of localized rounded infarction with a chronic immunological reaction to the dead worm. The embolic event may be clinically

**FIGURE 9.117** *Penicillium marneffei* is a dimorphic fungus that is often seen within histiocytes and has a “sausage” shape with characteristic septation (arrow).

**FIGURE 9.118** Amebic abscess with “anchovy paste” gross appearance.
silent or associated with chest pain, fever, chills, hemoptysis, and peripheral blood eosinophilia. The disease is often first recognized as a solitary pulmonary nodule that is resected to exclude neoplasia.

Microscopically one sees a rounded area of pulmonary infarction (Fig. 9.125A). The diagnosis is facilitated by identifying the coiled nematode within an occluded muscular pulmonary artery. The area of surrounding necrosis is surrounded by a zone of granulomatous inflammation with lymphocytes, plasma cells, and variable degrees of tissue eosinophilia, all contained within a dense fibrous capsule. Trichrome, elastic, and reticulin stains highlight the features of the helminth and help to localize it in a vessel (Fig. 9.125B and C). 

\textit{Dirofilaria} are distinguished from other nematodes by their prominent muscular lateral cords and a striated cuticle that bulges inward in the region of the lateral cords, yielding a bat wings appearance.

\section*{Trematodes (Flukes)}

A number of trematodes produce pulmonary disease that can present as solitary pulmonary nodules, pulmonary infarctions, necrotizing granulomas, or eosinophilic pneumonia. The most frequent fluke infection in the United States is \textit{Schistosomiasis} due to its wide distribution in both the eastern and western hemispheres.

Patients who have traveled to endemic areas may develop Katayama fever 6—10 weeks following their return. This disorder consists of fever, pulmonary infiltrates, and eosinophil. It results from the antigenic response to the egg laying of the female schistosome in the bloodstream. Patients should be treated with praziquantel.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{fig119.png}
\caption{(A) Liquefactive necrosis in lung abscess due to (B) \textit{E. histolytica} showing ingestion of erythrocyte (arrow).}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{fig120.png}
\caption{(A) Necrotizing pneumonia in patient with HIV/AIDS due to \textit{T. gondii}. (B) High power demonstrates bradyzoites within macrophage.}
\end{figure}
Subsequent pulmonary involvement reflects aberrant migration of adult worms into the lung, where they are found within pulmonary vessels (Fig. 9.126A). The helminth evokes an intense granulomatous and eosinophilic response and extravascular refractile ova may be present and like the helminth can evoke granulomatous and eosinophilic reactions. The ova are large (70–170 μM) depending on the species. The ova of *Schistosomiasis mansoni*, which produces most cases of pulmonary disease, show a prominent lateral spine that can be seen with H&E and that is highlighted by modified

**TABLE 9.9 Nematodes with Pulmonary Larval Phase**

| Nematode                  |
|---------------------------|
| *Ascaris lumbricoides*    |
| *Strongyloides stercoralis* |
| *Necator americanus*     |
| *Ancylostoma duodenale*  |

Subsequent pulmonary involvement reflects aberrant migration of adult worms into the lung, where they are found within pulmonary vessels (Fig. 9.126A). The helminth evokes an intense granulomatous and eosinophilic response and extravascular refractile ova may be present and like the helminth can evoke granulomatous and eosinophilic reactions. The ova are large (70–170 μM) depending on the species. The ova of *Schistosomiasis mansoni*, which produces most cases of pulmonary disease, show a prominent lateral spine that can be seen with H&E and that is highlighted by modified

**FIGURE 9.121** *Cryptosporidium parvum* seen along the surfaces of ciliated pulmonary epithelium (arrows). The cysts are actually invested by apical cytoplasm.

**FIGURE 9.122** BAL macrophage contains *Microsporidium* spp. demonstrated by Brown–Hopps stain.
acid-fast stains, although the latter finding is inconstant (Fig. 9.126B). Other species, including *Schistosomiasis hematobium* and *Schistosomiasis japonicum*, rarely cause pulmonary disease and their ova show either a prominent or inconspicuous terminal spine, respectively.

*Schistosomiasis* can also produce a granulomatous pulmonary hypertensive arteriopathy due to the presence of either ova or migrating schistosomules within small caliber pulmonary arteries and arterioles (Fig. 9.127). The thickened vascular walls show epithelioid histiocytes and giant cells with adventitial fibrosis and eosinophils. This disorder usually arises from infection by *S. mansoni* or less commonly *S. japonicum* that has already produced pipestem hepatic fibrosis and

FIGURE 9.123  Necrotizing granulomatous and eosinophilic inflammation due to *S. mansoni*.

(Fig. 9.124) (A) Rhadbitiform larval form of *Strongyloides stercoralis* in patient with hyperinfection. (B) Patient died from DAD due to superimposed Gram-negative sepsis.
presinusoidal portal hypertension, leading to shunting of portal blood into the systemic venous circulation, with ova swept into the pulmonary arterial bed where they evoke the pathological response.

Paragonimiasis

Paragonimus, often referred to as the “lung fluke,” is a globally distributed trematode with human disease limited to endemic regions. Most cases in Asia are due to Paragonimus westermani, but other species are responsible for disease seen in Africa, Central and South America. Zoonotic forms of human infection rarely occur in North America secondary to Paragonimus kellicotti that affects rodents and cats.

The organism is a fresh water species that infects crabs and crayfish as intermediate hosts; the disease is transmitted to man via ingestion of these crustaceans, although cases may be seen that are due to ingestion of contaminated seaweed or watercress. The larvae mature in the bowel and migrate through the diaphragm to infect the lung. Patients present with pulmonary infiltrates, fever, weight loss, and malaise. Hemoptyisis is common. Pleural involvement is present in roughly half of the patients. Peripherally located cystic lesions develop in the lung, together with areas of pneumonic consolidation, and concomitant bacterial and mycobacterial infections may be present.

Grossly, Paragonimus is a large 10-mm reddish fluke. Its wall consists of a tegument with prominent spiny projections best seen on high-power examination of trichrome stained sections (Fig. 9.128A). It exhibits prominent oral and ventral suckers and a loose internal stroma. The worm evokes a cystic necrotizing granulomatous and fibrotic response with tissue...
eosinophilia. The ova of *Paragonimus* are \( \sim 80 \mu M \) and show a flattened operculum (Fig. 9.128B). They are also intensely birefringent under polarized light, and this is an important distinguishing factor with respect to schistosome ova (Fig. 9.128C).

### Cestodes (Tapeworms)

The most common cestode pathogen in the lung is *Echinococcus*, although other tapeworm larvae, including *Cystercerca* and *Sparganum* can rarely infect the lung (Fig. 9.129). The adult tapeworm lives attached to the wall of the small intestine of carnivorous canids. Intermediate hosts are the grazing ungulates, including sheep, goats, deer, and bison. In the continental United States, the disease is endemic to midwestern and western states.

Pulmonary disease is generally the result of preexisting hepatic involvement by *Echinococcus granulosus*, although other species including *Echinococcus vogeli* and *Echinococcus multilocularis* are also pathogenic. The appearance of the
disease is characteristic on chest radiographs that show single or multiple large fluid filled cysts (Fig. 9.130). These cysts can be asymptomatic or cause symptoms due to compression of the surrounding airways and lung. Rupture into an airway can lead to suppurative pneumonia, the proliferation of new cysts, and generate fatal anaphylactic reactions.

The cyst wall shows contributions from the cestode as well as from the host. The inner germinative layer of the lamellar cyst wall is the matrix for protoscolices that detach to form secondary brood capsules (Fig. 9.131A). The rostellum of the attachment apparatus of the protoscolex contains rows of hooklets that are refractile and stain with modified AFB (Fig. 9.131B). The cestode component is acellular chitinous lamellar wall that is apparent with H&E and further highlighted with GMS and within the cyst wall, detritus and hooklets give rise to so-called “hydatid sand” (Fig. 9.132).

If the disease is isolated to a single cyst, percutaneous aspiration, injection of 20% hypertonic saline and 80% ethanol, followed by reaspiration in 5–30 min (PAIR procedure) may be effective therapy especially if coupled with Albendazole therapy. Complications of this therapy, which may be coupled with subsequent resection, include rupture of the cyst wall with anaphylaxis.

**MICROBES ASSOCIATED WITH BIOTERRORISM**

Recent world events have prompted interest in biological agents that can potentially be used as weapons of mass destruction. Several of these produce pneumonia and depend on dissemination via aerosolized secretions to achieve their
ignominious goal. Although most of these infections are naturally virulent, they tend to occur under situations that are no longer commonly encountered in modern societies. Their adoption by bioterrorists may include the need to bioengineer the organisms in order to promote their attack rate.

**Anthrax**

* Bacillus anthracis, a toxin producing Gram-positive bacillus, was first isolated by Robert Koch as the cause of anthrax, a disease that has primarily involved sheep and other farm animals. However, transmission to man from infected animals has been recognized from antiquity as a complication of wool sorting (wool sorter’s disease). An epidemic of inhalational anthrax occurred in 1979 at a biofacility in Sverdlovsk, in the former U.S.S.R., and in
2001, there was a limited epidemic of anthrax due to contaminated letters sent through the US mail service by an unidentified terrorist.

Cutaneous penetration by the *bacillus* produces a necrotic eschar with rapid extension to blood vessels resulting in bacteremia, sepsis, and death. However, the most deadly form of infection is pulmonary. In these cases, the bacilli are inhaled which evokes a localized hemorrhagic pneumonia and associated pleural effusion. Organisms proliferate rapidly in the lung where they produce a localized hemorrhagic pneumonia (Fig. 9.133) and spread via the pulmonary lymphatics to the regional lymph nodes to produce hemorrhagic mediastinitis, followed by bacteremia, toxic shock, and death in a high percentage of cases. The diagnosis must be suspected and treated early in

![Figure 9.131](image1)  
**FIGURE 9.131** (A) Germinative layer of echinococcal cyst giving rise to protoscolices. (B) Rostellum and hooklets of a protoscolex stain with modified acid-fast bacteria.

![Figure 9.132](image2)  
**FIGURE 9.132** Chitinous cyst wall (left panel) and refractile hooklet of *Echinococcus granulosus* (right panel).
order to be curable. However, it has most often first been recognized at autopsy, where tissues prove to be teeming with bacteria.

**Yersinia pestis (Plague Pneumonia)**

Plague has played an important role in world history. The causative agent is *Yersinia pestis*, a Gram-negative rod that is carried by animal fleas. Infection occurs as the result of contact with infected animals via aerosol or direct contact with infected secretions. Throughout history, the black rat, *Rattus rattus*, has been most responsible worldwide for the persistence and spread of plague in urban epidemics, but any rodent can mechanically transmit infected fleas. Although *Y. pestis* has not yet been seen as a bioterrorist agent, it has received attention as a potentially weapon of mass destruction, because as few as 1–10 bacilli are sufficient to cause infection when introduced via the oral, intradermal, subcutaneous, or intravenous routes.

*Yersinia* produces a necrotizing hemorrhagic pneumonia and large numbers of extra cellular organisms that can be seen with H&E (Fig. 9.134). Pulmonary infection leads rapidly to bacteremia and to death by sepsis.
**FIGURE 9.135** Granulomatous pneumonia due to tularemia.

**FIGURE 9.136** Organizing fibrinous pleuritis due to pneumococcal pneumonia. Patient had parapneumonic effusion.

**FIGURE 9.137** (A) Empyema secondary to staphylococcal pneumonia. (B) Clusters of cocci are stained by GMS.
FIGURE 9.138  Granulomatous pleuritis in tuberculosis.

FIGURE 9.139  (A) Dense pleural adhesion transgressing diaphragm (arrow); (B) abscess cavity with granulohistiocytic inflammation; (C) Steiner stain shows filamentous bacteria in sulfur granule. Organisms were also positive with tissue Gram stain and GMS.
Francisella tularensis (Tularemia Pneumonia)

Tularemia causes a necrotizing bronchopneumonia that leads to sepsis and death. However, the Gram-negative bacillus is less virulent than either anthrax or plague, and it produces a relatively slow progression of disease, a fact that limits its potential role as an agent of bioterrorism. The histological response in the lung is polymorphic and includes an early hemorrhagic granulohistiocytic response with microabscess formation (Fig. 9.135), followed by granulomatous inflammation. When these coexist, the appearance of this infection is characteristic. The short coccobacillary forms require silver impregnation to be visualized in tissues.
Pleural Infection

Parapneumonic effusions can complicate bacterial pneumonias but they are rarely biopsied unless they lead to a restrictive rind around the lung requiring decortication (Fig. 9.136A). Both Gram-positive and Gram-negative bacteria can produce empyema, i.e., abscess in the pleural space (Fig. 9.137A and B). Mycobacteria (Fig. 9.138), actinomyces (Fig. 9.139A and B), fungi (Fig. 9.140), and parasites can all yield exudative effusions, and the presence of necrotizing granulomatous inflammation will substantially assist in narrowing the differential diagnosis, even when organisms cannot be identified. Pleural eosinophilia can be a clue to the presence of an underlying parasitic infection (Fig. 9.141) but can also be seen in fungal and mycobacterial infections, in response to pleural metastases, as well as following pneumothorax.

FURTHER READING

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