Infectious diseases are one of the main causes of morbidity and mortality worldwide. With new pathogens continuously emerging, known infectious diseases reemerging, increasing microbial resistance to antimicrobial agents, global environmental change, ease of world travel, and an increasing immunosuppressed population, recognition of infectious diseases plays an ever-important role in surgical pathology [1–6]. This becomes particularly significant in cases where infectious disease is not suspected clinically and the initial diagnostic workup fails to include samples for culture. As such, it is not uncommon that a lung biopsy becomes the only material available in the diagnostic process of an infectious disease [7]. Once the infectious nature of the pathological process is established, careful search for the causative agent is advised. This can often be achieved by examination of the hematoxylin and eosin-stained sections alone as many organisms or their cytopathic effects are visible on routine staining. However, ancillary studies such as histochemical stains, immunohistochemistry, in situ hybridization, or molecular techniques may be needed to identify the organism in tissue sections or for further characterization, such as speciation [8–10]. In addition, examination of histological or cytological material provides a means for rapid diagnosis by frozen-section analysis or fine needle aspiration cytology, respectively, in cases where urgent patient care is required. On the other hand, the findings of histopathological assessment should always be evaluated in the context of the clinical presentation and the results of microbiologic or molecular results in order to arrive at the final diagnosis. Consequently, close interaction of the surgical pathologist with clinical and laboratory colleagues is essential in the diagnosis and treatment of infectious diseases.

1.1 Bacterial Pneumonias

Bacterial pneumonias are among the most common infectious diseases worldwide. They are caused by a variety of microorganisms that can elicit a spectrum of symptoms ranging from asymptomatic or mild illness to severe disease with high mortality [11]. The common bacterial pneumonias, such as those caused by *Streptococcus pneumonia*, *Haemophilus influenzae*, and *Klebsiella* species, among others, are clinically diagnosed by a combination of clinical history, physical findings, radiographic imaging, and microbiological cultures and rarely require invasive surgical techniques for diagnostic purposes. On the other hand, there are a small number of bacterial pneumonias that clinically and radiologically closely mimic fungal disease, aptly named “pseudomycoses.” Because these often raise a clinical suspicion of a primary lung cancer, surgical resection may be performed for pathological examination and definitive diagnosis. Among the pseudomycoses, three bronchopulmonary infections (actinomycosis, nocardiosis, and botryomycosis) have the potential to be mistaken for primary bronchogenic carcinoma and are more likely to be encountered by the surgical pathologist. The most important findings of these entities are summarized in Table 1.1.

1.1.1 Pulmonary Actinomycosis

The word actinomycosis is derived from the Greek terms “aktino” and “mykos,” referring to the radiating appearance of a sulfur granule and the assumption that the condition was a mycotic disease, respectively. Initially recognized as a disease affecting cattle, the first description of human actinomycosis was published in 1878 by Israel [12]. *Actinomyces* and the closely related *Nocardia* species were initially believed to be fungi because of their branching filamentous nature but were subsequently reclassified as bacteria due to recognition that they replicate through bacterial fission rather than by budding, that they lack sterols in their cell walls, that they are resistant to polyene antifungal agents, and that they are sensitive to standard antibacterial agents such as penicillin [13]. *Nocardia* species are morphologically indistinguishable from *Actinomyces* species on Gram staining and also clinically resemble *Actinomyces* in that they produce chronic infections of the lung and central nervous system. However, *Nocardia* species are aerobic in growth, and some strains
Pulmonary actinomycosis is a rare infection causing disease in about 300,000 people a year. Individuals of all ages may be affected with a peak in the mid-decades and a male to female ratio of 3:1 [18]. Actinomycosis usually occurs in immunocompetent persons but may occur in persons with diminished host defenses, such as patients with chronic pulmonary disease, alcoholism, poor oral hygiene, and dental disease. The clinical picture of thoracic actinomycosis often mimics that of tuberculosis or malignancy, with findings of cough, low-grade fever, sputum, or chest pain. While chest pain can be a prominent symptom and may act as a pointer to actinomycosis, symptoms are typically quite non-specific and similar to those of other chronic suppurative chest diseases and malignancy. In a patient known to have pulmonary actinomycosis, marked weight loss, malaise, and high fever may be more suggestive of disseminated disease [19, 20]. The radiological signs of actinomycosis are non-specific and may mimic primary or metastatic malignancy or other infections, especially tuberculosis. Chest radiographs may reveal infiltrates suggestive of aspiration pneumonia, fibronodular or cavitary parenchymal lesions, or the presence of a lung mass. Actinomycosis can be radiologically suspected if pulmonary lesions extend to the chest wall and show bone destruction. In these cases, pleural effusion, pleural thickening, and empyema are often associated [18]. Penetrating chest infection with a chest wall mass and draining sinus used to be among the classic presentations [21]. Once a diagnosis of actinomycosis is established, intravenous followed by oral penicillin over a course of 6–12 months is the preferred treatment. Surgery is usually reserved for patients with hemothysis or those who fail to respond to medical therapy [22]. Untreated actinomycosis is ultimately fatal, while early treatment can result in cure rates of more than 90% [18]. In general, the prognosis of the pulmonary actinomycosis may be less favorable compared with the other commoner forms, such as oropharyngeal or abdominogenital disease [19]. This may be due to the difficulties associated with the diagnosis of the condition and greater incidence of disseminated disease in the thoracic form. On the other hand, if the infection is recognized early and treated appropriately, pulmonary actinomycosis has an excellent prognosis with a very low mortality [23].

### Table 1.1 Pertinent characteristics of selected bacterial pulmonary infections

| Infectious agent | Actinomyces israelii | Nocardia asteroides | Staphylococcus aureus, Escherichia coli and Pseudomonas aeruginosa |
|------------------|----------------------|--------------------|---------------------------------------------------------------|
| Distribution     | Commensal of oropharynx, gastrointestinal and female genital tracts | Soil worldwide | Worldwide |
| Predisposing condition | Chronic pulmonary disease, alcoholism, poor oral hygiene | Immunosuppression | Immunosuppression |
| Histological pattern | Abscess formation with sulfur granules and Splendore-Hoeppli phenomenon | Necrotizing abscess formation | Eosinophilic granules with suppurative abscesses and Splendore-Hoeppli phenomenon |
| Special stains   | Gram stain +, acid-fast stain – | Gram stain +, acid-fast stain + | Gram stain depending on underlying agent |
| Morphology       | Slender, beaded, and branched filamentous bacteria | Slender, beaded, and branched filamentous bacteria | Bacterial cocci or bacilli depending on underlying agent |
| Ancillary testing| Tissue culture, RNA sequencing | Tissue culture, RNA sequencing | Tissue culture |
| Treatment        | Antibiotics +/- surgery | Antibiotics +/- surgery | Antibiotics and surgery |

RNA ribonucleic acid
disease, the airways contain a chronic inflammatory cell infiltrate and/or foamy macrophages. The lumen contains characteristic sulfur granules with peripheral eosinophilic clubbing containing slender branching Gram-positive filamentous bacilli embedded in a matrix (Splendore-Hoeppli phenomenon) (Fig. 1.1a, b). Sulfur granules are the pathological hallmark of the disease; although they are usually highly suggestive of actinomycosis, they are not diagnostic on their own but can also be seen in nocardiosis, chromomycosis, eumycetoma, and botryomycosis, albeit rarely [25]. If the pulmonary parenchyma is involved, the bronchi will often show bronchiectasis, with the typical granules in the bronchial lumina associated with a mixed inflammatory cell infiltrate, bronchial squamous metaplasia, ulcerations of the bronchial epithelium, and a granulomatous reaction with epithelioid-type macrophages [16, 18] (Fig. 1.2). Most of the literature classifies the tissue response as granulomatous or “granulomatoid-like,” although giant cells and granulomata are rarely seen [26]. The surrounding pulmonary parenchyma can contain microabscesses (Fig. 1.3). In cases, in which tumorlike masses or more diffuse parenchymal patterns are identified, the granules are often identified within parenchymal abscesses or cavitations and are surrounded by fibrous inflammation. Alveolitis, fibrin, macrophages, neutrophils, foci of necrosis, and vasculitis can be associated features [16] (Fig. 1.4). Once established, the initial acute inflammation is followed by the characteristic chronic, indolent phase that generates local necrosis and fibrosis and commonly cavitates [26].

1.1.1.3 Laboratory Diagnosis and Histochemical Stains

Members of the genus Actinomyces are Gram-positive, nonspore-forming, predominantly anaerobic prokaryotic bacteria belonging to the family Actinomycetaceae.
Actinomyces are fastidious bacteria that are difficult to culture. Bacterial confirmation of a clinicopathological diagnosis is usually obtained in <50% of cases due to inadequate culturing technique, previous antibiotic therapy, and bacterial overgrowth, even when the clinical suspicion is high [13]. Furthermore, *Actinomyces* species are difficult to identify on sputum or bronchial excretions because these specimens are not cultured anaerobically. This means that in many cases, the diagnosis is only made on histologic material derived from surgical resections after suspected malignancy [18]. In tissue, *Actinomyces* present as Gram-positive beaded, branched filamentous bacteria that will be highlighted on Gomori methenamine silver or the Brown and Brenn modification of the Gram stain [27]. Contrary to *Nocardia* species, *Actinomyces* are not acid-fast and cannot be stained with acid-fast stains [18]. Serological methods of detection are not reliable.

### 1.1.1.4 Differential Diagnosis

Although clinically and radiologically, actinomycosis raises the suspicion of malignancy, histological examination will help to reveal the inflammatory nature of the lesion and exclude a neoplastic proliferation. In tissue sections, it may be difficult to distinguish between actinomycosis, nocardiosis, and botryomycosis and the use of histochemical stains such as Gram and acid-fast stains may be needed to identify the causative agent; *Actinomyces* and *Nocardia* are slender filamentous Gram-positive bacteria, but only *Nocardia* is positive with acid-fast stains. On the contrary, botryomycosis shows the presence of Gram-positive/negative and acid-fast-negative cocci or rods depending on the underlying organism.

### 1.1.2 Pulmonary Nocardiosis

In 1888, French veterinarian Edmond Nocard discovered the genus of bacteria that now bear his name – *Nocardia* [28]. These bacteria are the cause of nocardiosis, a disease which manifests itself mainly in animals, but may also cause disease in humans, particularly in immunocompromised patients. Although first considered a fungus because of its branching filaments that can easily be mistaken for fungal hyphae, the composition of its cell wall components including envelope lipids and peptidoglycans mandated reclassification, and the organism is now considered an anaerobic, filamentous, Gram-positive bacterium. *Nocardia* are acid-fast which allows distinction from the morphologically very similar *Actinomyces* species. Among the *Nocardia* species, *Nocardia asteroides* is the major pathogen in both immunocompromised and immunocompetent patients and is an important opportunistic pathogen especially in patients with organ transplants or AIDS [29]. *Nocardia* are soilborne bacteria that are ubiquitous organisms and are commonly found in soil, organic material, freshwater and saltwater, dust, compost vegetation, and other environmental sources. Inoculation of the bacteria into the skin or inhalation can lead to cutane-
ous syndromes or systemic disease. Pulmonary infection is perhaps the most significant presentation of nocardiosis, but hematogenous spread to a wide range of organs may also occur, especially to the brain [18, 30–32].

### 1.1.2.1 Clinical Features

Pulmonary nocardiosis is an uncommon occurrence in humans with a low incidence of 500–1000 new cases each year in the United States [33] and primarily affects patients with impaired local pulmonary defenses or systemic immunosuppression. Patients with lymphoproliferative diseases, AIDS or those requiring chemotherapy or steroids are at particular risk. The disease can occur in patients of all ages, and men are more commonly affected than women. Pulmonary nocardiosis may be a self-limiting or subclinical event or progress to an acute, subacute, or chronic suppurative infection with episodes of remissions and exacerbations often mimicking tuberculous or mycotic infections or even malignancy [32]. The symptoms of pulmonary nocardiosis are highly variable and by no means specific and include fever, cough, sputum production, dyspnea, chest pain, and constitutional symptoms. Hemoptysis from large cavities or abdominal pain is less frequently reported [18, 30–32]. Non-segmental air space consolidation, fluffy infiltrates, and irregular pulmonary nodules are the most common abnormalities on chest imaging. Lesions frequently stud the pleural surfaces and can occasionally extend to the chest wall. Thick-walled cavities and endobronchial lesions are also frequent findings and may be confused with a malignant process. Pleural effusions are seen in up to a third of the patients [30, 31]. Antibiotic therapy with sulfa-containing regimens such as trimethoprim-sulfamethoxazole is the standard of care for pulmonary nocardiosis. This therapy should be continued for a minimum of 6 months in immunocompetent patients and 12 months in immunocompromised individuals. The need for surgical intervention is less common for nocardiosis than for actinomycosis but may be required in complicated disease [22]. The overall mortality rate for pulmonary nocardiosis lies in the range of 15–30% [18].

### 1.1.2.2 Pathological Features

On macroscopic examination, there can be fibrous or fibrinous pleural adhesions. Cut section of the lung parenchyma will show yellowish white necrotizing abscesses simulating miliary tuberculosis. A fibrous exudate may exude from the affected areas. Cavitation is also a common finding. In acute nocardiosis, necrotizing abscesses involve the alveoli (Fig. 1.5). These contain basophilic granular debris as well as degenerate mixed inflammatory cells including neutrophils, plasma cell, lymphocytes, and macrophages (Fig. 1.6a). Cavitation or sinus formation may develop in the course of the disease. Chronic nocardiosis is characterized by dense fibrosis, lymphohistiocytic inflammation, and giant cell infiltration with a granulomatous response. Multiple small abscesses may also be seen in chronic infection. Nocardia may occasionally produce a mycetoma when the bacteria populate pre-existing cavities. Direct extension of the infectious process often involves the blood vessels, pleura, and chest wall which can result in vasculitis, empyema, or bronchopleural fistula. The adjacent lung parenchyma can show alveolitis, diffuse alveolar damage, or chronic organizing pneumonia. The filamentous and beaded bacteria may or may not be apparent in tissue sections (Fig. 1.6b). Contrary to actinomycosis, the formation of sulfur granules is infrequent in nocardiosis and mainly restricted to immunocompetent patients; in addition, the peripheral clubbing typically observed in the granules of Actinomyces infection is not a feature recognized in nocardiosis [15, 16, 18, 30, 32, 34].

### 1.1.2.3 Laboratory Diagnosis and Histochemical Stains

Nocardioises are not fastidious and grow aerobically within 48 hours to several weeks on routine laboratory media. In addition, they may be rapidly diagnosed by examination of sputum, bronchial lavage fluid, pleural fluid, or direct tissue examination using Gram and modified acid-fast stains. On Gram stain alone, the filamentous, beaded bacteria of Nocardia are indistinguishable from Actinomyces species;
however, modified acid-fast stains (such as Fite stain) will usually highlight \textit{Nocardia} but not \textit{Actinomyces} [18, 30, 35]. Species identification can be performed by RNA sequencing techniques if necessary [30].

1.1.2.4 Differential Diagnosis

Nocardiosis can easily be mistaken for other bacterial infections, tuberculosis, fungal pneumonia, or malignancy based on the clinical presentation and radiological appearance. While malignancy, tuberculosis, and fungal infections should be easily distinguished from nocardiosis on a histological level, separation from actinomycosis may require the use of special stains. Of greatest help in this context will be the use of a modified acid-fast stain, which will stain \textit{Nocardia} but not \textit{Actinomyces}. Should these fail, RNA sequencing techniques may be used to differentiate \textit{Nocardia} from other related species.

1.1.3 Pulmonary Botryomycosis

Pulmonary botryomycosis is an uncommon suppurative bacterial pseudomycosis of the lung that clinically and histologically closely mimics fungal infection, tuberculosis, or a primary lung neoplasm [36–38]. Initially described as a fungal disease in horses in 1870 [39], its name was coined by Rivolta alluding to its grape-like granules (\textit{botryo} = grapes) and the mistakenly implied fungal etiology (\textit{mykes} = fungus) [40]. However, its bacterial etiology was ultimately revealed by Magrou in 1919 who managed to isolate \textit{Staphylococcus aureus} from an equine lesion and reproduced the disease in guinea pigs [41]. Since then, few human cases have been described in the literature, 75\% of these primarily involving the skin. Primary pulmonary botryomycosis is a rare phenomenon with less than 20 reported cases [36]. The pathogenesis of pulmonary botryomycosis remains uncertain and may be related to an abnormal immune response in the host [42] which is supported by the overwhelming occurrence in patients with cystic fibrosis, AIDS, chronic granulomatous disease, and diabetes mellitus [42–45]. Several bacterial agents can be responsible for the disease, the most common being \textit{Staphylococcus aureus}, \textit{Escherichia coli}, and \textit{Pseudomonas aeruginosa} [36]. The histological hallmark of pulmonary botryomycosis is the presence of eosinophilic material that surrounds organisms associated with a suppurative focus closely resembling the sulfur granules seen in actinomycosis [46].

1.1.3.1 Clinical Features

Contrary to actinomycosis, immune deficiency seems to predispose patients to botryomycosis. In fact, many of the patients reported in the literature had underlying immunologic abnormalities [47] to a degree, whereby it was recommended that any patient with visceral botryomycosis should be evaluated for the presence of an underlying immune disorder possibly implying a breakdown in local defenses [45]. Among the reported cases with pulmonary botryomycosis, there was a slight male predilection and an age range from 9 months to 69 years [37]. The clinical manifestations are
often non-specific and sometimes difficult to distinguish from the underlying disease especially in patients with cystic fibrosis. Chronic cough, dyspnea, hemoptysis, and pleuritic chest pain have all been reported [37]. Similar to the clinical presentation, no classical radiological appearance exists for pulmonary botryomycosis. The disease may form a discrete parenchymal mass, cavitory lesions, and areas of consolidation or present as a diffuse infiltrating process [42]. Positron emission tomography (PET) may show positive uptake in the region of interest and may thus not be able to rule out malignancy [36]. Treatment of botryomycosis remains empirical and consists of a combination of antibiotic (amoxicillin/clavulanate, erythromycin, gentamicin, and tetracycline) and surgical therapy; in fact most patients require surgical intervention in order to confirm the diagnosis [38].

1.1.3.2 Pathological Features
Histologically, pulmonary botryomycosis is defined by the presence of eosinophilic granules of variable size and shape surrounding suppurative bacterial colonies, known as the Splendore-Hoeppli phenomenon. Unlike in actinomycosis, the granules of botryomycosis are often more variable in size and shape and can reach up to 500 μm in diameter [48]. Extensive consolidation with microabscess formation, intense inflammation, and fibrosis of the surrounding pulmonary parenchyma are further, more non-specific morphological changes (Fig. 1.7a, b). In some cases, the process arises in a pre-existing cavity, often due to former tuberculosis, characterized by thick fibrous walls with or without the presence of squamous metaplasia [38].

1.1.3.3 Laboratory Diagnosis and Histochemical Stains
The diagnosis of pulmonary botryomycosis heavily relies on histological and microbiological analysis, and most patients require surgical excision of the lesion for definitive diagnosis. Gram stains and cultures of lung tissue and/or cytological preparations may identify the causative bacterial agent [36–38]. The characteristic granules can be highlighted in tissue sections using Brown-Benn, Grocott-Gomori, or Giemsa stains if necessary [48] (Fig. 1.8).

1.1.3.4 Differential Diagnosis
On a histological level, a neoplastic process is easily excluded due to the presence of a suppurative inflammatory process and absence of a malignant epithelial proliferation. Actinomycosis and nocardiosis may show similar histological findings as those seen in botryomycosis; however, in actinomycosis and nocardiosis, the bacteria are slender and filamentous and surrounded by large, oval or horseshoe-shaped sulfur granules, while botryomycosis shows the presence of cocci or bacilli associated with the granular material. Tissue cultures are indicated in equivocal cases.

![Fig. 1.7](image1.png)  (a) A case of pulmonary botryomycosis with ulceration of the airways and florid inflammatory changes of the surrounding lung parenchyma; (b) high power magnification reveals the presence of eosinophilic granules consistent with botryomycosis. (Courtesy of Dr. C Moran, Houston, USA)
1.2 Mycobacterial Pneumonias

Mycobacteria are classically divided into two clinically important groups: *Mycobacterium tuberculosis* complex and non-tuberculous mycobacteria (NTM). The former includes *Mycobacterium tuberculosis*, *Mycobacterium bovis*, *Mycobacterium africanum*, and *Mycobacterium microti*, while NTM encompass a group of more than 90 species, the most prevalent of which include *Mycobacterium avium-intracellulare* (MAI) complex and *Mycobacterium kansasii*. Lung disease can also be caused by a range of other NTM which vary markedly in terms of geographic distribution and play a less important role in the US. Interestingly, there appears to be an inverse relationship between the incidence of tuberculosis (TB) and disease caused by NTM: many parts of the world have seen a reduction of tuberculosis rates, while NTM infections are on the rise [49]. The surgical pathologist will most likely encounter mycobacterial infections in the form of lung biopsies or rarely lung resections as a form of last resort diagnostic approaches when laboratory tests or culture have failed to provide a definitive diagnosis or the disease is refractory to medical treatment. The two most likely forms of mycobacterial infection – those that are caused by *M. tuberculosis* and MAI, respectively – will be discussed here. The most important findings of pulmonary mycobacterial infection are summarized in Table 1.2.

1.2.1 Pulmonary Tuberculosis

Tuberculosis is a lung infection caused by inhalation of *M. tuberculosis*, the most virulent of the mycobacterial species. Approximately 1/3 of the world’s population is infected with TB; the prevalence of active disease is estimated at 13.7 million people [50]. The incidence of active TB is highest in African and Asian countries and Eastern Europe contrary to low rates in the United States, Canada, Australia, and Western Europe [51]. Although the prevalence of TB is on a downward trend, drug resistance, HIV infection, and global poverty have prevented a significant breakthrough in the fight of this disease [50]. Tuberculosis presents in two forms: primary TB and post-primary TB (Fig. 1.9). Primary TB occurs in patients with no previous exposure or loss of acquired immunity.

Table 1.2 Pertinent features of pulmonary tuberculous and non-tuberculous mycobacterial infections

| Etiologic agent | *Mycobacterium tuberculosis* | *Mycobacterium avium-intracellulare/kansasii* |
|-----------------|-----------------------------|--------------------------------------------|
| Geographic distribution | Africa, Asia, Eastern Europe > USA, Canada, Western Europe, Australia | Worldwide |
| Predisposing condition | Debilitation, immunosuppression | Structural lung disease, immunosuppression, hot tub use |
| Transmission | Aerosolized droplet transmission from patients with active lung disease | Aerosolized droplet transmission from environment |
| Histological pattern | Granulomatous inflammation characterized by necrotizing palisading epithelioid granulomas | Necrotizing or non-necrotizing granulomatous inflammation with or without bronchiectasis, organizing pneumonia or proliferation of foamy histiocytes |
| Special stains | Acid fast stains (Ziehl-Neelsen, Kinyoun, Fite) | Acid fast stains (Ziehl-Neelsen, Fite) |
| Morphology of etiologic agent | Non-motile beaded rods, 2–4 μm | Thick beaded rods, up to 20 μm |
| Ancillary testing | Sputum or tissue cultures, immunohistochemistry, tuberculin skin test, interferon-γ release assay, PCR | Sputum or tissue culture, PCR |
| Treatment | Isoniazid, rifampin, ethambutol, and pyrazinamide | Macrolide in combination with second or third antimycobacterial agent |

*PCR* polymerase chain reaction
immunity. Symptoms are generally mild, and the majority of patients actually remain asymptomatic. Primary TB can be followed by progressive primary TB in cases where the primary foci fail to involute and progress to disseminated cavitary lesions, especially in patients with impaired cellular immunity. Approximately 90% of adult TB cases can be attributed to post-primary TB (also called “secondary” or “reactivation” TB) in patients who have previously been exposed to the organism. Fulminant infection with dissemination of mycobacteria via the bloodstream can lead to miliary TB with involvement of other organ systems in any of these forms. Transmission of tuberculous bacteria occurs through droplet aerosolization from patients with active lung disease. The highest risk of transmission emanates from patients with cavitary disease or those with positive direct smears [52]. Patients with immunosuppression due to HIV, malignancies, and other debilitating diseases or on immunosuppressive drugs are at highest risk for contracting primary TB or progression to active disease [53].

1.2.1.1 Clinical Features
Symptomatic TB is often a disease of the debilitated and immunosuppressed and is major cause of death in patients with HIV. Primary pulmonary TB usually presents with very mild symptoms that can include low-grade fever, however many patients remain entirely asymptomatic [54]. Symptoms in reactivation TB have an insidious onset and are characterized by cough, fatigue, weight loss, and night sweats. Chest
pain, dyspnea, and hemoptysis are less common findings. Chest radiographs in primary TB most commonly demonstrate focal airspace consolidation associated with hilar lymphadenopathy or more rarely pulmonary infiltrates in the mid and lower lung fields. A solitary cavitary infiltrate may be apparent in approximately 10% of patients [55]. Pleural effusions can occur in up to 10% of new TB infection [56]. Post-primary TB shows infiltrates primarily in the upper lobes, lobular and peribronchial consolidation, cavities with air-fluid levels, and intraparenchymal nodules [55]. On CT scanning, mediastinal lymphadenopathy characteristically displays low-density centers and peripheral rim enhancement [57]. Lobar consolidation may be accompanied by variably sized cavities, the walls of which may appear thick or thin, smooth or irregular; air-fluid levels are common. A calcified scar – the “Ghon focus” – is seen in 15–17% of the patients and together with calcified hilar or mediastinal lymph nodes constitutes the “Ghon or Ranke complex” [58]. Centrilobular nodular opacities associated with branching opacities may impart a “tree-in-bud” appearance, a characteristic but nonspecific finding in TB. The centrilobular distribution of nodules reflects a bronchiocentric process and is suggestive of intrabronchial spread [55]. Numerous small nodules (1–2 mm) associated with diffuse reticulation are typical for miliary spread [55]. Patients with active TB should be treated with multiple agents to achieve bacterial clearance, to reduce the risk of transmission, and to prevent the emergence of drug resistance. First-line drugs are isoniazid, rifampin, pyrazinamide, and ethambutol. Second-line drugs include the aminoglycosides streptomycin, kanamycin, and amikacin, the polypeptide capreomycin, p-amino salicylic acid, cycloserine, the thioamides ethionamide, and prothionamide as well as several fluoroquinolones. To guard against drug resistance and to ensure maximal effectiveness, the initial phase of treatment should include four drugs. The minimum duration of treatment for culture-positive TB should be 6 months. Treatment for latent TB is recommended for individuals who are deemed to be at high risk of developing active TB and should be initiated only after active TB has been excluded by clinical and radiographic evaluations. For most such patients, treatment with isoniazid for 9 months is the preferred management. Persons at risk of new infection include contacts of patients with active pulmonary TB, employees at facilities with a high risk of exposure, and those who have recently immigrated from endemic regions. Persons at highest risk of reactivation include those taking immunosuppressive medications (including tumor necrosis factor alpha-blockers) and those with HIV infection, malignancy, silicosis, and dialysis-dependent renal failure [50].

1.2.1.2 Pathological Features

The gross findings of pulmonary TB often show a consolidation pattern similar to bacterial pneumonia, albeit with areas of caseous or cheese-like necrosis. Cavitating lesions develop as the infection progresses, and these are most commonly located in the upper lobes and can reach large dimensions (up to 10 cm). Erosion into bronchial structures not uncommonly leads to intrabronchial spread. Nodules or mass-like lesions (“tuberculoma”) are another gross finding in TB; these may present with fibrosis, calcification, or central necrosis. Pleural involvement manifests itself as a thickened pleura studded with small granulomas or pleural effusion. Numerous small nodules in diffuse distribution are typical for miliary TB.

- **Primary TB**: The most characteristic lesion of TB infection is the necrotizing granuloma in which a central area of caseous necrosis is surrounded by a peripheral rim of epithelioid histiocytes, Langerhans giant cells, and lymphocytes (Fig. 1.10a–d). These lesions may enlarge and progress to form cavities which can reach large dimensions (up to 10 cm). Some granulomas undergo central calcification and heal with fibrosis or scarring. Histiocytes containing the bacilli can travel and involve the hilar lymph nodes. Indeed, the typical first infection TB heals to form the classical “Ghon complex,” consisting of a calcified granuloma in the lung and associated involved hilar lymph nodes [59].

- **Post-primary TB**: Post-primary TB is typically limited to the apices of the upper lobes of the lungs. The process begins with the accumulation of foamy histiocytes in the alveoli. Approximately 90% of these lesions heal with the formation of small fibrous scars in the apices. If the lesions fail to heal, they will eventually undergo caseous necrosis and can progress to the formation of cavities. These cavities can either mature and fibrose to form a thick capsule or the caseous material contained within can heal with fibrosis and granuloma formation. Solitary pulmonary nodules (“tuberculoma”) or endobronchial involvement are other presentation patterns. Miliary spread to the lungs and extrathoracic organs can complicate post-primary TB. In immunosuppressed patients, the disease is often more generalized, not restricted to the upper lobes of the lung and less cavitating than in immunocompetent patients. In addition, granulomas will often contain fewer lymphocytes and lack epithelioid histiocytes. The marked heterogeneity of the lesions typical for immunocompetent patients is replaced by a more homogeneous disease process [59].

1.2.1.3 Laboratory Diagnosis and Histochemical Stains

The diagnosis of active TB is based on a combination of epidemiological, clinical, radiological, microbiological, and histological investigations. Sputum or bronchoalveolar lavage can be used for direct smears or culture [60]. New molecular
techniques such as nucleic acid amplification test using PCR or DNA probes can dramatically reduce the diagnostic process [61, 62]. Detection of mycobacteria in tissue sections or cytological preparations can be accomplished using Ziehl-Neelsen, Kinyoun, or Fite acid-fast stains: *M. tuberculosis* are non-motile beaded rods with a high mycolic acid content and stain bright red using these stains (Fig. 1.11a, b). They range in length from 2 to 4 μm and have a width of 0.2 to 0.5 μm. Despite the wide availability of these special stains, their sensitivity and specificity have limitations [63]. More recently, better sensitivity and specificity has been shown with by mycobacterial antigen detection using immunohistochemical stains [63] although this technique has not been found wide application in surgical pathology at the present time. The diagnosis of latent TB on the other hand can be diagnosed by a tuberculin skin test (Mantoux test) that measures cell-mediated immunity to a mixture of antigens of several mycobacterial species [64]. Another method, the interferon-γ

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Fig. 1.10  (a) Pulmonary tuberculosis infection with necrotizing granulomatous inflammation; (b) the granuloma is demarcated from the surrounding lung parenchyma by a rim of epithelioid histiocytes and giant cells; (c) high power view demonstrating the typical epithelioid histiocytes bordering the necrotic center of the granuloma; (d) high power view of a Langerhans giant cell in pulmonary tuberculosis
release assay (IGRA) has the advantage of being able to differentiate *M. tuberculosis* from other non-tuberculous mycobacteria and from previous Bacille Calmette-Guérin (BCG) vaccination [65].

### 1.2.1.4 Differential Diagnosis

Mycobacteria and fungi are the main causes of pulmonary granulomatous infections. While many of the fungi that cause granulomatous lung disease can be confidently identified by histological examination, in mycobacterial disease, *M. tuberculosis* cannot be reliably differentiated from NTM on morphological grounds alone. In this context, microbiologic cultures or PCR-based molecular methods should be used to speciate the mycobacteria.

### 1.2.2 Pulmonary Atypical Mycobacterial Infection

Non-tuberculous mycobacteria are widely distributed organisms and are frequently isolated from soil, tap water, and dust [66]. Contrary to *M. tuberculosis*, NTM do not transmit from person-to-person but are contracted from the environment. *M. avium-intracellulare (MAI)* complex followed by *M. kansasii* is the most frequent NTM causing pulmonary disease in the United States. Pulmonary infection with NTM has been an increasingly recognized phenomenon over the last 25 years, and the number of NTM isolates by far exceeds the number of *M. tuberculosis* isolates these days [67]. In the literature, four distinct types of pulmonary MAI disease have been described, each with different epidemiologic, clinical, radiological, and pathological presentations [68]: fibrocavitary MAI in patients with underlying structural lung disease; MAI in association with immunodeficiency; the reticulonodular bronchiectatic type in patients with Lady Windermere or right middle lobe syndromes; and the so-called “hot tub” lung disease due to inhalation of aerosolized MAI.

#### 1.2.2.1 Clinical Features

- **Fibrocavitary MAI.** This type of NTM infection is a disease of older patients with a slight predilection for males and an association with structural lung disease such as chronic obstructive pulmonary disease (COPD), pulmonary fibrosis, rheumatoid lung disease, prior TB, industrial lung disease, or lung cancer [67, 69, 70]. Also affected may be children and young adults with cystic fibrosis whose airways are often colonized by MAI. Presenting symptoms are often attributed to worsening of the underlying lung disease. Bilateral cavitary or fibrocavitary disease with reticulonodular infiltrates with or without pleural thickening are characteristic findings on radiographic imaging [69].

- **MAI with immunodeficiency.** MAI infection may be associated with immune deficiency due to HIV infection, leukemia/lymphoma, solid organ transplants, steroid use, or severe combined immunodeficiency [71–73]. Patients often have severe and disseminated disease and pulmonary involvement presents with aggressive and cavitary disease (Fig. 1.12).
**Reticulonodular bronchiectatic MAI.** Nodular bronchiectatic NTM usually affects the right middle lobe of the lung or left lingular segment of middle-aged or elderly non-smoking women without prior underlying lung disease [74]. This form of NTM is often associated with idiopathic cylindrical bronchiectasis (Lady Windermere syndrome) [75]. The onset of the disease is usually slow and indolent, and radiographically, multiple small pulmonary nodules are described, classically associated with bronchiectasis, tree-in-bud pattern, and ground glass opacities affecting the right middle lobe, lingula, or dependent areas of the lungs [76]. Progression to consolidation and cavitation is possible.

**Hot tub lung.** A relatively new form of NTM is the so-called hot tub lung disease [77, 78]. Infection develops after inhalation of aerosolized MAI after significant (months to years) exposure to contaminated hot tubs. These patients are usually young and immunocompetent with an average age around 40 years. Presenting symptoms include cough, dyspnea, chest pain, and fatigue with slow progression over months before diagnosis [79]. Radiographic investigations reveal diffuse interstitial or nodular pulmonary infiltrates [80]. On CT scanning, ground glass opacities and nodules are commonly seen and mosaic attenuation pattern representing bronchiolitis is well documented. Of note, contrary to the other forms of NTM infection, cavitary lung disease is not a feature of hot tub lung.

Treatment of NTM pulmonary infection can be difficult and involves prolonged courses of multiple antimycobacterial agents. The approach to treatment and the choice of medication varies according to the NTM species isolated. For MAI infection, current recommendations are for a minimum of three drugs. The backbone of any regimen should be a macrolide, either clarithromycin or azithromycin, which are the most effective agents for MAI infection, combined with a second or third agent to prevent the emergence of macrolide resistance. As a general rule, most patients treated with a macrolide-based regimen should improve within 3–6 months and convert their sputum to culture negative within 12 months. The role of surgical therapy is limited as MAI pulmonary disease tends to be a multifocal process but may be important for select individuals [81].

### 1.2.2.2 Pathological Features

- **Histological examination of fibrocavitary MAI infection** can demonstrate findings strikingly similar to TB. This includes primarily ill-defined and extensively caseating granulomas and well-formed fibrotic cavities [82]. A florid histiocytic reaction and varying degrees of bronchiectasis may accompany the granulomas [83].

- **MAI associated with immunodeficiency** is also characterized by extensive necrotizing granulomatous inflammation at the microscopic level (Fig. 1.13). A massive proliferation of foamy histiocytes many of which contain the bacilli is another common finding. Cavitating lung disease is a common occurrence in this type of NTM infection.

- **Reticulonodular bronchiectatic MAI** shows a combination of histological features including the presence of bronchiectasis, peribronchial chronic inflammation, and numerous small non-caseating (sarcoidal) granulomas [83] (Fig. 1.14).
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1.2.2.3 Laboratory Diagnosis and Histochemical Stains

Cultures of sputum, lung biopsy specimens, and hot tub water are the most critical diagnostic tools in any suspected NTM infection. However, NTM grow very slowly and cultures require special media and prolonged incubation. Newer methods of detection include PCR-based techniques that can more rapidly and reliably identify the exact mycobacterial species [81]. In tissue sections, NTM can be made visible using acid-fast stains (Ziehl-Neelsen) or modified acid-fast stains (Fite) (Fig. 1.15). The bacilli are described as thick beaded rods, up to 20 \( \mu \text{m} \) in length that are S-shaped and often curled up into heaps [85]. In practice, these organisms are difficult to distinguish from TB microscopically, and culture or PCR methods are still the gold standard for speciation.

1.2.2.4 Differential Diagnosis

The diagnosis of NTM lung disease requires appropriate symptomatology, radiographic evidence of pulmonary involvement, positive cultures or suggestive histological findings, and exclusion of other diagnoses. Based on the pathological patterns, tuberculosis and sarcoidosis and other disease processes causing bronchiectatic lung disease should be considered in the differential diagnosis. Tuberculosis cannot be excluded based on the histological appearance of the mycobacteria alone, and epidemiologic, clinical, radiographic, and cultures results are ultimately necessary to confirm the diagnosis. Similarly, sarcoidosis will have to be excluded primarily based on the clinical presentation and laboratory values, especially in cases in which acid fast bacilli are not identified in cytology or biopsy specimens or in culture-negative cases. Patients with bronchiectasis need to be worked up to exclude common underlying diseases such as cystic fibrosis or primary ciliary dyskinesia as these conditions are inextricably linked with NTM infection.

1.3 Fungal Pneumonias

A growing number of immunocompromised patients due to malignancy, hematologic disease, and HIV and those receiving immunosuppressive medication after organ transplantation have resulted in an increase in the incidence of pulmonary fungal infections. Although such infections may also occur in immunocompetent patients, their frequency in this population is rare. The diagnosis of pulmonary fungal infections is facilitated by recent advances in serologic and molecular testing although standard techniques such as culture and microscopic examination remain the mainstay of diagnosis. In a similar manner, the introduction of new antifungal agents has expanded the treatment option for physi-
Histoplasmosis is a deep seated mycosis caused by the dimorphic fungus Histoplasma capsulatum. It was first described by Darling while working in Panama who described a case of the disseminated form of the disease [86]. The fungus is highly prevalent in the Central and Southern United States and Central America where it lives as a mold in moist soil. Soil rich in bird or bat guano supports growth of the mold. Histoplasmosis is primarily a pulmonary disease, and airborne transmission via inhalation of spores can lead to a variety of clinical features including asymptomatic infection, acute pulmonary histoplasmosis, chronic cavitary pulmonary histoplasmosis mimicking tuberculosis, or a disseminated form in patients with immunosuppression. Most infections, however, will remain asymptomatic or subclinical (>90%) [87–89].

### 1.3.1 Pulmonary Histoplasmosis

Histoplasmosis is primarily a pulmonary disease, and air–borne transmission via inhalation of spores can lead to a variety of clinical features including asymptomatic infection, acute pulmonary histoplasmosis, chronic cavitary pulmonary histoplasmosis mimicking tuberculosis, or a disseminated form in patients with immunosuppression. Most infections, however, will remain asymptomatic or subclinical (>90%) [87–89].

### 1.3.1.1 Clinical Features

An acute self-limited form of histoplasmosis occurs primarily in children who are exposed to the fungus for the first time causing symptoms such as fever, malaise, headache, cough, and chest pain followed by rapid improvement. Severe acute pulmonary infection can occur after inhalation of a large amount of fungus and lead to fever, chills, malaise, dyspnea, chest pain, and cough and may culminate in acute respiratory distress syndrome [87]. Chronic cavitary pulmonary infection is unique among the fungal infections in that it commonly affects older individuals or patients with pre-existing lung

### Table 1.3 Pertinent characteristics of pulmonary fungal infection

| Infectious agent | Histoplasmosis | Cryptococcosis | Coccidioidomycosis | Blastomycosis | Paracoccidioidomycosis |
|------------------|----------------|--------------|-------------------|---------------|-----------------------|
| Distribution     | Soil of Central and Southern US and Central America | Soil worldwide | Arid soil of Southwestern US, Mexico, Central and South America | Soil worldwide (in US in Ohio, Mississippi and St Lawrence river valleys, Great Lakes, Southeast) | Soil of tropics and subtropics (South America) |
| Predisposing condition | Disseminated disease in immunosuppression | Immunosuppression | Individuals exposed to soil in endemic areas, immunosuppression | Disseminated disease in immunosuppression | Farm workers |
| Histological pattern | Necrotizing granulomatous inflammation with lamellar pattern | Nodular granulomatous reaction | Epithelioid granulomatous reaction with eosinophilic infiltrate | Necrotizing supplicative palisading granulomas | Pneumonic form: acute alveolitis Granulomatous form: well-formed epithelioid granulomas Pulmonary fibrosis |
| Special stains | GMS +, PAS + (weak) | GMS +, PAS +, mucicarmine + | GMS +, PAS + | GMS +, PAS + | KOH wet mount, GMS +, PAS + |
| Morphology of etiologic agent | Round to ovoid narrow-based budding yeasts, 2–4 μm | Narrow-based budding yeast with mucoid capsule, 5–20 μm | Large round to oval spherules with endospores, 20–80 μm | Oval, broad-based budding yeasts with thick refractile double wall and central nuclei, 8–15 μm | Large globose cells surrounded by narrow-necked budding yeasts (pilot’s wheel), 4–30 μm |
| Ancillary testing | Urine or serum antigen, antibody tests, tissue culture, PCR | Serum antigen detection, tissue culture, PCR | Sputum and tissue culture, serologic and urine antigen tests, PCR | Sputum and tissue culture | Sputum and tissue culture, serologic antigen test |
| Treatment | Antifungals | Antifungals | Antifungals | Antifungals | Antifungals |

*GMS* Grocott methenamine silver stain, *PAS* periodic acid-Schiff, *US* United States, *PCR* polymerase chain reaction, *KOH* potassium hydroxide
with mild to moderate pulmonary histoplasmosis. Among the compounds is recommended as first-line therapy for patients with acute histoplasmosis. Progressive infiltrates are seen in patients undergoing investigations for unrelated reasons that may eventually calcify in a characteristic laminated pattern. The cavity is a common finding. Solitary (“histoplasmoma”) or multiple nodules with laminated calcification are another presentation of chronic pulmonary histoplasmosis and are often mistaken for bronchogenic carcinoma or metastatic disease [87, 89, 90]. Treatment of histoplasmosis is not usually needed for patients with the acute form of the disease, while chronic histoplasmosis and severe acute histoplasmosis require medical attention. Antifungal treatment with azole compounds is recommended as first-line therapy for patients with mild to moderate pulmonary histoplasmosis. Among these, itraconazole is the drug of choice and can also be used for patients with cavitary disease. Amphotericin B is still recommended for patients with severe infection or those who are immunocompromised [87, 91].

### 1.3.1.2 Pathological Features

The histological characteristics of acute histoplasmosis are incompletely described as this disease form is rarely biopsied. Within these limits, several reports have noted the presence of nodular parenchymal inflammatory infiltrates composed of lymphocytes and histiocytes filling alveolar spaces and expanding the adjacent interstitium [92]. These changes can be accompanied by areas of parenchymal necrosis and foci of vasculitis resulting in a resemblance to lymphomatoid granulomatosis (LYG). A more characteristic finding is small necrotizing granulomas scattered within the lymphohistiocytic infiltrate, isolated histiocyte aggregates, or few multinucleated giant cells [92]. In contrast, chronic pulmonary histoplasmosis is characterized by progression of the disease process over several months. A so-called histoplasmoma represents the walled-off residuum of prior pulmonary histoplasmosis and is usually encountered as a solitary pulmonary nodule in patients undergoing investigations for unrelated reasons (Fig. 1.16). Both histoplasmoma and chronic histoplasmosis are composed of well-formed necrotizing granulomas that may eventually calcify in a characteristic laminated pattern.
manner (Fig. 1.17). Disseminated histoplasmosis in immunocompromised individuals has a wide variety of clinical manifestations and is characterized histologically by sheets of histiocytes filled with large numbers of fungal yeasts without the typical well-formed granulomas [92]. More unusual histopathological findings in pulmonary histoplasmosis are patterns of disease mimicking bronchocentric granulomatosis, diffuse alveolar damage, pulmonary alveolar proteinosis, tuberculosis, and even formation of a spindle cell tumor-like lesion [93, 94].

1.3.1.3 Laboratory Diagnosis and Histochemical Stains
At 37 °C, *H. capsulatum* converts to the yeast phase and forms tiny smooth round to ovoid narrow-based budding structures 2–4 μm in diameter. The yeasts may be found inside and outside of macrophages and can be highlighted in tissue sections using methenamine silver or periodic acid-Schiff stains (Fig. 1.18). Further methods of detection include culture of tissue or body fluids, antigen detection in urine or serum, antibody tests, or PCR-based assays [87].

1.3.1.4 Differential Diagnosis
Histopathologically, pulmonary histoplasmosis can be confused with various other fungi when studying tissue sections. Small variants of *Blastomyces dermatitidis*, capsule-deficient cryptococci, endospores of *Coccidioides* species, and *Pneumocystis jirovecii* may morphologically mimic *H. capsulatum*. In cases of blastomycosis, the presence of broad-based budding and identification of occasional larger forms may confirm the diagnosis. A mucicarmine positive capsule may provide evidence in support for cryptococcosis, while remnants of a ruptured spherule or intact spherules support a diagnosis of coccidioidomycosis. Lastly, lack of budding and intracystic foci favor a diagnosis of *Pneumocystis* infection. If
definitive diagnosis cannot be performed, culture or alternative testing should be considered.

1.3.2 Pulmonary Cryptococcosis

Cryptococcosis ("European blastomycosis") is an invasive mycosis associated with significant morbidity and mortality worldwide caused by fungi of the genus Cryptococcus. The two main species are Cryptococcus neoformans and Cryptococcus gattii which are ubiquitous encapsulated fungi that occur in a global distribution. They are inhabitants of soil, particularly soil contaminated by pigeon droppings [95, 96]. The fungi are budding yeasts that are characterized by a thick polysaccharide mucoid capsule that forms a discrete halo on India ink smears. Pulmonary cryptococcosis is caused by inhalation of the organism and rarely affects immunocompetent individuals; on the contrary, the majority of cases are found in immunocompromised patients, and cryptococcosis is one of the most relevant opportunistic infections in patients with HIV [89, 97]. Clinically, the disease can range from self-limited asymptomatic infection to severe pneumonia in cases of immunosuppression or massive inoculation of the fungus [98]. The disease may remain limited to the lungs or undergo hematogenous dissemination to involve the central nervous system, bones, and skin depending on the host immune status.

1.3.2.1 Clinical Features

Cryptococcosis typically occurs in immunocompromised patients such as those with HIV/AIDS in whom the infection is associated with high mortality although the disease may also rarely affect immunocompetent individuals. In general, males are more frequently infected than females. The clinical picture ranges from asymptomatic infection, especially in immunocompetent patients, to symptoms of fever, productive cough, chest pain, weight loss, hemoptysis, and night sweats in cases of acute pneumonia. Systemic spread to the central nervous system will lead to cerebral or meningeal involvement, and skin and bone lesions may also become apparent in such patients [99]. The radiographic appearance of pulmonary cryptococcosis can show a spectrum of abnormalities. The disease can manifest as a discrete pulmonary mass, multiple nodules, segmental or lobar consolidation, or diffuse bilateral pulmonary nodules in an interstitial pattern. Cavitation, lymphadenopathy, and pleural effusion may be accompanying findings [90] (Fig. 1.19). Cases with a solitary mass-like lesion are easily mistaken for a neoplastic process. Antifungal drug regimens for management of cryptococcosis are some of the best-characterized for invasive fungal diseases, and fluconazole has become the treatment of choice both for immunocompromised and immunocompetent patients with mild to moderate forms of the disease [91]. Treatment of the underlying immunosuppressive disease, such as antiretroviral therapy in patients with HIV/AIDS, has lowered the incidence of cryptococcosis in medically developed countries, but incidence and mortality of this infection remain extremely high in areas where uncontrolled HIV disease persists [100].

1.3.2.2 Pathological Features

In accordance with the radiological features, the histological findings in pulmonary cryptococcosis can show several distinct patterns. Peripheral solitary or multiple granulomas with or without rupture of the granulomatous wall and proliferation of organisms in the surrounding lung parenchyma correspond to the nodular or mass-like presentation on chest radiographs (Fig. 1.20). A second histological pattern shows abundant fungal organisms within alveolar spaces and airways in a bronchopneumonia-like distribution. The organisms elicit a range of inflammatory reactions which may culminate in a diffuse granulomatous response (granulomatous pneumonia) with organisms confined to histiocytes and multinucleate giant cells (Fig. 1.21a, b). Colonization of interstitial tissues by the organism with concurrent inflammation and granulomatous response is another pattern of pulmonary cryptococcosis and may be mistaken for interstitial lung disease on imaging studies [101].

1.3.2.3 Laboratory Diagnosis and Histochemical Stains

The diagnosis of pulmonary cryptococcosis can be established by culture from bronchial washings, bronchoalveolar lavage, or transthoracic needle core biopsy. Cultures from sputum material may not suffice as colonization of the tracheobronchial tree is a common occurrence. Cryptococcus antigen detection in body fluids or serum is useful for the diagnosis, but high false-negative rates have been reported [102]. Therefore, the diagnosis often requires direct visual-
ization of the organisms in cytological preparations or tissue sections or PCR-based methods. As mentioned above, in tissue sections, the organism is a narrow-based budding yeast usually measuring 5–20 μm in diameter although occasional cases may contain larger forms labeled “titan cells” that can measure up to 100 μm [103, 104]. The typical mucoid capsule can be highlighted using methenamine silver or mucicarmine stains (Fig. 1.22a, b). In the unusual event of a capsule-deficient form, a Fontana-Masson stain will render the fungal melanin reddish brown which may be useful to confirm the diagnosis [89, 105].

1.3.2.4 Differential Diagnosis

In tissue sections, a correct diagnosis of cryptococcosis may be difficult especially when dealing with unencapsulated forms that are negative for mucicarmine stains. In this context, cryptococcosis can show a striking resemblance to blastomycosis or histoplasmosis. Tissue culture may be needed for definitive diagnosis and is mandatory in all cases of suspected fungal infection.

1.3.3 Pulmonary Coccidioidomycosis

Coccidioidomycosis (“San Joaquin valley fever”) is an infectious disease caused by the dimorphic fungi Coccidioides immitis and Coccidioides posadasii and is considered one of the most virulent primary fungal infections. Coccidioides species are soil-dwelling fungi that are endemic in arid and semi-arid regions of the Southwestern United States, Mexico, and parts of Central and South America [106]. They cause mainly pulmonary infection although many other organs can be affected. The organism survives dormant in the soil during long dry spells but develops into a mold with
long filaments that break off into airborne spores during rain. The spores, also known as arthroconidia, can be released into the air by disruption of the soil during construction, farm work, or windstorms causing outbreaks even in non-endemic areas [107, 108]. The incidence of coccidioidomycosis has risen in recent years due to population growth and increasing travel to endemic areas, and cases are now diagnosed worldwide [109]. The lungs are the port of entry after inhalation of the fungal organisms, and pulmonary infection is the most common clinical manifestation, although the majority of infections will remain subclinical [110]. Complications and sequelae of coccidioidomycosis include acute pneumonia, granulomatous inflammation, caseous nodules, cavitary disease, pleural involvement, and eosinophilic infiltrates [110–116]. Three to five percent of patients with acute coccidioidomycosis will not recover from the infection and progress to chronic fibrocavitary pulmonary coccidioidomycosis or disseminated disease [117]. Disseminated disease usually results from hematogenous spread of a primary lung infection and can involve many organs such as the skin, bones, joints, nervous system, and meninges. Of note, direct inoculation of the fungus into the skin – although uncommon – can lead to primary cutaneous coccidioidomycosis which is characterized by ulcerated nodules and plaques [118].

1.3.3.1 Clinical Features
Coccidioidomycosis primarily affects individuals exposed to aerosolized soil in endemic areas such as construction or agricultural workers, archeologists, or excavators [119, 120]. In addition, immunosuppressed patients, patients with diabetes mellitus, pregnant women, and certain ethnic groups (Filipino and African American) are at an increased risk of acquiring the infection [121]. Most symptomatic patients develop a flu-like syndrome including high fever, headache and chills, dry non-productive cough, pleuritic chest pain, and arthralgias (“Valley Fever of San Joaquin”) [122]. The skin is affected in up to 50% of cases in the acute infection, most commonly in the form of a non-pruritic ocular rash, erythema nodosum, and erythema multiforme [123]. Interestingly, skin lesions including erythema nodosum and an erythema multiforme-like exanthema during the acute illness seem to indicate a favorable immunologic response to the infection [124, 125]. Radiographically, coccidioidomycosis may show features similar to other forms of pneumonia, such as pulmonary alveolar infiltrates, pulmonary nodules, bilateral hilar adenopathy, and thin- or thick-walled cavitations which are common findings on chest radiograph or CT scanning. The presence of pleural effusions, pneumothorax, or pleural thickening is highly suggestive of pleural involvement in coccidioidomycosis. Pulmonary nodules may be solitary (“coin lesion”) or bilateral often mimicking a neoplastic process and prompting biopsy for suspicion of a malignant process [126] (Fig. 1.23). In immunocompromised patients the disease can disseminate and cause a miliary pattern with multiple reticulonodular opacities. Pulmonary coccidioidomycosis is often self-limited, and if patients are immunocompetent, treatment may not be needed. Symptomatic patients, however, should receive antifungal therapy in order to reduce the risk of dissemination. Azole compounds, especially flu-
conazole, are the preferred treatment, while amphotericin B is reserved for patients with refractory disease or severe manifestations of the infection. Long-term treatment and follow-up are warranted in most cases of pulmonary coccidioidomycosis [91, 116].

1.3.3.2 Pathological Features

Once inhaled, the fungus develops into thin-walled spherules that may rupture and release numerous endospores eliciting a granulomatous tissue response in the lung (Fig. 1.24). This inflammatory response initially consists of an infiltrate rich in epithelioid histiocytes, giant cells, plasma cells, lymphocytes, eosinophils, and neutrophils. Eventually epithelioid granulomas will develop that may or may not contain central necrosis. These granulomatous nodules can either be loose or well-formed but are usually sharply demarcated from the surrounding lung parenchyma (Fig. 1.25). On progression of the disease, the necrotizing nodules may enlarge and form a cavitory lesion with thin or thick fibrous walls [110]. These cavities may be in communication with the airways or rupture into the pleura causing pleural fibrosis, granulomatous response, and pleural effusion [113]. The tissue adjacent to the lesions can show marked bronchitis or bronchiolitis and can contain an inflammatory infiltrate rich in eosinophils [127]. Primary pleural coccidioidomycosis without any significant parenchymal disease — albeit rare — has also been described [113].

1.3.3.3 Laboratory Diagnosis and Histochemical Stains

The diagnosis of coccidioidomycosis requires a high degree of suspicion on clinical grounds, residence or travel history, serologic testing, microbiological cultures, and histopathological demonstration of the agent in tissue sections. *Coccidioides* species may be present in the form of either hyphae or spherules. The latter are considered pathognomonic for coccidioidomycosis and consist of spherules, 20–80 μm in diameter, containing numerous endospores (Fig. 1.26a, b). The spherules may rupture and drain their contents into the surrounding tissue leaving behind an empty spherule (Fig. 1.27). Hyphal forms are more
commonly present in cavitary disease and may easily be confused with other fungi, especially *Aspergillus* species [112]. Fungal tissue stains such as Grocott-Gomori methenamine silver or periodic acid-Schiff (PAS) stains can be used to confirm the presence of *Coccidioides* elements in tissue sections [110] (Fig. 1.28). In addition, sputum culture, serologic tests such as enzyme-linked immunoassays, immunodiffusion, or complement fixation tests remain very specific tests for the disease. More recently, coccidioidal
1.3 Fungal Pneumonias

1.3.3.4 Differential Diagnosis

On a histological level, coccidioidomycosis can show considerable overlap with other granulomatous diseases. Thus, when coccidioidomycosis is suspected, it is important to look for spherules; endospores outside spherules or young spherules without endospores can be confused with Blastomyces, Histoplasma, Candida and Pneumocystis species. In cases where spherules are not identified, close clinical, radiographic, laboratory, and histological correlation is required to confirm the diagnosis. It should also be noted that in immunosuppressed patients, more than one infection may coexist; thus, in endemic areas, Pneumocystis and Coccidioides could be found in the same specimen.

1.3.4 Pulmonary Blastomycosis

Blastomycosis, also called “North American blastomycosis,” is a systemic pyogranulomatous disease caused by the thermally dimorphic fungus Blastomyces dermatitidis. In the United States, the disease is endemic along the Ohio, Mississippi, and St Lawrence river valleys as well as the Great Lakes region and the Southeast [130, 131]. Initially the disease was regarded a dermatologic infection, however, later it was proven to be a primary pulmonary infection [132]. Pulmonary disease is caused by inhalation of aerosolized spores from the soil or from rotting wood [131, 133] although primary cutaneous blastomycosis has infrequently been reported after dog bites and accidental inoculation in the laboratory. The clinical spectrum of blastomycosis is varied and includes asymptomatic infection, acute or chronic pneumonia, and disseminated disease. Extrapulmonary disease has been described in as many as two thirds of patients with chronic blastomycosis and most frequently involves the skin, bones, and genitourinary system [134, 135]. Acute pulmonary blastomycosis mimics influenza or bacterial pneumonia and occurs after inhalation of Blastomyces spores. These transform into yeast form at normal body temperature and give rise to the pulmonary infection which may in some instances remain subclinical but in others can be symptomatic and even disseminate hematogenously. Most infections with Blastomyces will occur in immunocompetent individuals and due to greater exposure predominantly in male patients [131]. Infections in immunocompromised people are more common in diabetic patients or patients using long-term steroid or cytotoxic medication; these patients are more likely to develop aggressive or disseminated disease. Blastomycosis is only uncommonly seen in patients with HIV [130]. The clinicopathological manifestation of the disease is wide and ranges from an asymptomatic pneumonia to an acute community-acquired pneumonia-type picture to a lung mass suspicious for malignancy. In cases of hematogenous spread of the organism, metastatic disease is often suspected initially before culture or direct visualization of tissue reveals the presence of the fungal organism [136, 137].

1.3.4.1 Clinical Features

The clinical presentation may show either an indolent picture that includes cough, chest pain, weight loss, or night sweats or more acute symptoms such as fever, shortness of breath, and purulent sputum. Extrapulmonary manifestations result from dissemination of the organism via the bloodstream. The skin and bone are the most frequent sites of extrapulmonary involvement; skin lesions present as ulcerated or verrucous papules draining large amounts of purulent material. Ulcerating lesions or fungating masses are typical for bone and soft tissue involvement [138]. Imaging findings in blastomycosis include patchy or confluent airspace consolidation which may be accompanied by cavitation [139]. Nodules or masses, either solitary or multiple, are another common finding and often mimic a neoplastic process or metastatic disease [140]. Pleural effusions and hilar lymphadenopathy are less common findings [139]. Miliary forms are a sign of dissemination. Although blastomycosis is an infection with great potential for clinical morbidity, it is rarely a fatal illness. Treatment consists of itraconazole for the mild to moderate forms of the disease, while amphotericin B remains the initial treatment for severe or life-threatening disease [91, 136].

1.3.4.2 Pathological Features

Autopsy cases have shown that the lungs in blastomycosis are heavy and are often covered by fibrinous adhesions. Yellow plaques and hemorrhagic discoloration can also be found. The cut surface may show confluent necrotic nodules some of which can have cavitary changes [141]. Microscopically, granulomas, necrotizing or non-necrotizing, are typically seen. Of note, the necrotic centers in the necrotizing lesions have a suppurative quality being composed of numerous neutrophils [142, 143] (Fig. 1.29a, b).

1.3.4.3 Laboratory Diagnosis and Histochemical Stains

Definitive diagnosis of blastomycosis requires the growth of B. dermatitidis from clinical specimens. Visualization of the characteristic budding yeast form in clinical specimens supports a presumptive diagnosis of blastomycosis and may, in the appropriate clinical setting, prompt the initiation of antifungal therapy. B. dermatitidis are yeast forms with an average diameter of 8–15 μm. On occasion, the size of the fungi can vary and mimic histoplasmosis or cryptococcosis at one end and coccidioidomycosis on the other end of the spectrum [141, 144, 145]. The cell walls are thick, refractile, and double-walled and enclose a central core containing
8–12 nuclei [133]. Daughter cells typically approach the size of the mother cell before detachment resulting in the characteristic broad-based budding. The morphologic diagnosis can be facilitated by the use of special stains such as GMS and PAS (Fig. 1.30). Similar to cryptococcosis, the cell wall of *B. dermatitidis* can take up a mucicarmine stain; however the staining will be thin and incomplete contrary to the staining pattern seen in cryptococcosis [143]. Diagnosis by culture of respiratory specimens is still the gold standard for confirmation of the disease but results may be delayed for up to 4 weeks making morphologic assessment vital for clinical management and initiation of therapy [143, 146]. More recently, commercially available urine antigen assays or serum antigen techniques have become available although they have proven insensitive and are not suited for diagnostic screening [146].

### 1.3.4.4 Differential Diagnosis

After identification of the organisms, the differential diagnosis for blastomycosis primarily includes cryptococcosis and coccidioidomycosis. As outlined above, close attention to the morphological and histochemical properties will normally help differentiate the organisms. A mucicarmine stain can be used to distinguish *B. dermatitidis* (thin and incomplete staining of the cell wall) from *C. neoformans* which shows strong staining of its true pericellular capsule. In order to separate the multinucleated cells of *B. dermatitidis* from the endospores of *C. immitis*, a GMS stain may be helpful: while coccidial endospores are GMS-positive, the nuclei of *B. dermatitidis* are GMS-negative [141].

### 1.3.5 Pulmonary Paracoccidioidomycosis

Paracoccidioidomycosis is the most common systemic mycosis throughout the South American continent.
Formerly known as “South American blastomycosis,” paracoccidioidomycosis is an endemic disease caused by *Paracoccidioides brasilensis*, a thermomorph fungus found in the soil of tropical and subtropical humid areas, particularly in countries like Brazil, Colombia, Venezuela, and Argentina [147]. Although an estimated ten million people are infected with the fungus, only 1–2% will actually develop clinical disease [147, 148]. The disease is acquired via inhalation of the infectious particles. After inhalation, the fungus usually causes a transient and self-limited pulmonary infection [149]. In a small minority of patients, the infection may progress to cause systemic disease and evolve in two ways: an acute or subacute form (juvenile type) or a chronic form (adult type) [147, 148, 150–152]. The acute form of paracoccidioidomycosis primarily affects children and young adults and represents only 3–5% of all cases. It runs a more rapid and severe course and is characterized by marked involvement of the reticuloendothelial system, the gastrointestinal tract, and the bones. Lung involvement in this type of paracoccidioidomycosis is rare. On the other hand, the chronic form accounts for the large majority of cases (>90%) most commonly resulting from reactivation of quiescent lung disease or reinfection. It primarily affects adult men, and although the lung is the most frequently affected organ in chronic paracoccidioidomycosis, the infection can disseminate to involve numerous other tissues including the mucous membranes, lymph nodes, skin, adrenal glands, central nervous system, and other organs. Almost 60% of patients with chronic paracoccidioidomycosis will develop sequelae of the infection resulting in pulmonary fibrosis which remains a significant factor for morbidity and mortality [147, 148, 150–152].

### 1.3.5.1 Clinical Features

Acute or juvenile paracoccidioidomycosis accounts for 3–5% of all cases and affects children, adolescents, and young adults. The most common clinical manifestations of this type of paracoccidioidomycosis are fever, weight loss, lymphadenopathy, osteolytic lesions, hepatosplenomegaly, and intestinal or bone marrow involvement and infrequent pulmonary disease [147, 148, 150–152]. Juvenile paracoccidioidomycosis develops within weeks or months and is usually more severe than the adult form with significantly higher rates of mortality [153]. On the other hand, chronic paracoccidioidomycosis (>90% of cases) predominantly affects men aged between 30 and 60 years who work in rural areas such as farm workers, due to exposure to the fungus habitat [148, 154, 155]. Chronic paracoccidioidomycosis results from reactivation of quiescent lung lesions and has an insidious onset of disease. The lungs are the most frequently involved organs leading to pulmonary symptoms such as cough, expectoration, dyspnea, chest pain, hemoptysis, fever, malaise, and weight loss [156, 157]. The lungs may be affected in isolation or in combination with other organs. In particular, oropharyngeal mucous membrane lesions occur in about 50% of cases with chronic paracoccidioidomycosis and are often the reason that patients come to medical attention [148, 158]. The insidious onset and silent course of chronic paracoccidioidomycosis often results in steady progression of the disease with resulting pulmonary damage. Many of the radiological findings of paracoccidioidomycosis are non-specific. Although an initial lesion resembling the primary complex of tuberculosis can sometimes be noted with the acute form, this finding is rarely observed. Chronic paracoccidioidomycosis can cause linear reticular opacities, nodular lesions, airspace consolidation, and cavitation on chest radiographs. Computed tomography scanning will reveal ground glass areas of enhancement, areas of consolidation, nodules of varying size, interlobar septal thickening, fibrotic lesions, and cavitation. The disease distribution is described as bilateral and symmetric and contrary to tuberculosis appears to primarily affect the middle zones [159]. *P. brasiliensis* is a very sensitive organism when exposed to antifungal drugs. The standard treatment for mild or moderate clinical forms of paracoccidioidomycosis is itraconazole, while for severe or disseminated disease, intravenous preparations of amphotericin B are indicated. Despite this, paracoccidioidomycosis has a high incidence and high rate of mortality in South America, and the clinical course is characterized by a high frequency of relapse and sequelae such as pulmonary fibrosis [160].

### 1.3.5.2 Pathological Features

The histopathological features of paracoccidioidomycosis can be divided into three patterns: pneumonic, granulomatous, and fibrotic forms [161]. The pneumonic form is characterized by an acute alveolitis in which the inflammatory infiltrate is predominantly composed of histiocytes and giant cells containing the fungal organisms (Fig. 1.31a). The fungus can also be identified extracellularly and produce an exudative or productive granulomatous interstitial infiltrate (Fig. 1.31b). In the extreme forms of purulent inflammation, destruction of the lung tissue can lead to abscess formation. The granulomatous pattern consists of well-defined epithelioid granulomas containing giant cells often located in the interstitium. These granulomas may engulf the organisms and may coalesce to cause consolidation and bronchopneumonia. Abscess formation and cavitation may ensue in the process, and miliary nodules can be detected in other organs after hematogenous spread. Ultimately, the lung will undergo fibrotic thickening of the interlobar and alveolar septa due to proliferation of collagen fibers. The fibrosis may involve large areas and is commonly prominent in the hilar regions. Bullous and panacinar emphysema is another common finding [161].
1.3.5.3 Laboratory Diagnosis and Histochemical Stains

Suspicion of paracoccidioidomycosis relies on clinical and epidemiological circumstances and detection of the fungal organisms in clinical specimens or tissues. The yeast phase of *P. brasiliensis* will demonstrate large globose cells (4–30 μm) surrounded by multiple narrow-necked budding yeasts resembling a pilot’s wheel. The fungus has a well-developed thick refractile cell wall which can be visualized using potassium hydroxide (KOH) wet mounts, methenamine silver (Grocott-Gomori), Gridley’s fungus (GF), or periodic acid-Schiff (PAS) stains (Fig. 1.32). Direct examination can be complemented by microbial cultures that usually take 20–30 days to grow. Faster diagnosis can be achieved with specific serologic testing such as immunodiffusion tests, immunoenzymatic assays, or counterimmunoelectrophoresis [159, 161].

1.3.5.4 Differential Diagnosis

The diagnosis of pulmonary paracoccidiomycosis is often delayed because it can mimic many other conditions, including bacterial pneumonia, other fungal infections, tuberculosis, or malignancy. Definitive diagnosis should be based on a combination of direct visualization of the typical budding yeast structures of *P. brasiliensis* in clinical specimens or biopsy material, microbiological culture, and/or specific serologic tests.

1.3.6 Pulmonary Pneumocystosis

*Pneumocystis jirovecii* (formerly *carinii*) is a well-recognized pathogen that causes pulmonary infection in patients with immunodeficiency or immunosuppression. An increased incidence in the last half of the twentieth century is attributed to the widespread use of modern aggressive chemotherapy, greater rate of organ transplantation, and the AIDS epidemic [162–164]. The organism was first described by Chagas in 1909 who believed that *Pneumocystis* was a morphologic form in the life cycle of *Trypanosoma cruzi*.
has more recently led to proposal of a name change from Trypanosoma was disproved [167]. Although for a long time believed to be a protozoan, ultrastructural and molecular studies have since confirmed that Pneumocystis is a type of fungus [168]. Recognition of the functional and genetic distinctness of the organism in humans as opposed to mammals was disproved [167]. Although for a long time believed to be a protozoan, ultrastructural and molecular studies have since confirmed that Pneumocystis is a type of fungus [168]. Recognition of the functional and genetic distinctness of the organism in humans as opposed to mammals was disproved [167]. Although for a long time believed to be a protozoan, ultrastructural and molecular studies have since confirmed that Pneumocystis is a type of fungus [168]. Recognition of the functional and genetic distinctness of the organism in humans as opposed to mammals was disproved [167]. Although for a long time believed to be a protozoan, ultrastructural and molecular studies have since confirmed that Pneumocystis is a type of fungus [168]. Recognition of the functional and genetic distinctness of the organism in humans as opposed to mammals has more recently led to proposal of a name change from P. carinii to P. jirovecii in honor of the Czech parasitologist Otto Jirovec, who is credited with describing the organism in humans [169, 170]. It is believed that P. jirovecii resides in the environment and is transmitted via inhalation of air. It is usually absent in healthy humans or present only in very low levels. Nevertheless, reactivation of latent disease or reinfection via asymptomatic carriers is associated with acquiring the infection [171]. In the immunocompromised host, the number of organisms usually correlates with the degree of immunosuppression [169]. Despite chemoprophylaxis and rigorous antibiotic treatment, Pneumocystis pneumonia remains a serious and life-threatening complication for patients with immunosuppression.

1.3.6.1 Clinical Features
Patients susceptible to Pneumocystis pneumonia usually have an underlying disease associated with a defective immune response or require treatment with steroids or cytotoxic drugs such as patients with chronic inflammatory conditions, patients after organ transplant, or individuals with malignancies, especially hematologic malignancies. In general, the onset of clinical symptoms is insidious, with initial non-specific symptoms, including cough, dyspnea, low-grade fever, cyanosis, wheezing, loss of appetite, and possible weight loss. Tachypnea, due to impaired gas exchange, shortness of breath, and fatigue are also common [172]. The diagnosis of Pneumocystis pneumonia can be suspected on the basis of the radiological appearance. The disease presents as bilateral diffuse alveolar and interstitial parenchymal infiltrates, often in a perihilar distribution [173, 174]. Atypical presentations are well described and may include cysts (30%), lymphadenopathy (10%), small or large nodules (5%), and rarely consolidations or spontaneous pneumothorax [175, 176] (Fig. 1.33). Treatment for Pneumocystis infection should occur when symptomatology and diagnostic evidence conclude that P. jirovecii is likely the causative pathogen. Trimethoprim-sulfamethoxazole is the first-line agent for the treatment of mild to severe Pneumocystis pneumonia. Steroids may be used adjunctively with trimethoprim-sulfamethoxazole to reduce the likelihood of respiratory failure and death, while clindamycin-primaquine is the salvage regimen of choice for those patients who fail standard therapy with trimethoprim-sulfamethoxazole. Factors associated with risk of death are increasing patient age, prior receipt of Pneumocystis prophylaxis, poor oxygenation at hospitalization, low hemoglobin, presence of medical comorbidity, and the need for mechanical ventilation, among others [177].

1.3.6.2 Pathological Features
Gross findings of Pneumocystis pneumonia observed in autopsy series have revealed an increased firmness of the lungs, stasis, and edema, a mottled appearance due to foci of white/grey or red/brown discoloration and decreased air content. Such changes can have a wide and diffuse distribution with no particular subpleural or perihilar distribution [178]. Microscopic examination typically shows foamy or frothy eosinophilic intraalveolar exudates composed of the organisms admixed with fibrin (Fig. 1.34a, b). This exudate is usually devoid of inflammatory cells contrary to the interstitial spaces which may be variably infiltrated by an inflammatory cell infiltrate including lymphocytes, plasma cells and histiocytes. In some cases, organization of the exudates results in its partial or complete replacement by proliferating fibroblasts. Alveolar septal edema and type II pneumocyte hyperplasia are other common findings. Other features less commonly identified and hence termed “atypical” include an absence of the frothy eosinophilic alveolar infiltrate, granulomatous inflammation, interstitial or intraluminal fibrosis, prominent alveolar macrophages, hyaline membranes, parenchymal cavities, microcalcifications, or vascular invasion and vasculitis [179–181].

1.3.6.3 Laboratory Diagnosis and Histochemical Stains
Pneumocystis pneumonia can often be suspected by the typical clinical and radiological findings. The diagnosis can then be confirmed by identification of the causative agent in sputum or bronchoalveolar lavage specimens making open lung biopsy rarely necessary. Molecular analysis by PCR-based methods is a more recent mode of
detection. Cyst forms of *P. jirovecii* can be identified in any of cytologic or tissue specimens using methenamine silver (GMS) or Giemsa stains (Fig. 1.35a, b). The cysts are small measuring 4–6 μm in maximum dimension. They are ovoid, spherical, or cup-shaped and have thin black walls and grey homogenous centers. A characteristic finding is the presence of discrete single or paired foci of dark staining (so called dark bodies or darkly staining foci) within the cyst wall that have an oval or comma-shaped configuration [182].

1.3.6.4 Differential Diagnosis

The cysts of *P. jirovecii* can cause confusion with other yeast forms of pathogens of similar size, more specifically *H. capsulatum*, *Candida* species, and *C. neoformans*. In this context, *P. jirovecii* can be distinguished based on the presence of the char-
acteristic dark staining foci which are absent in *Histoplasma* organisms. *Candida* is usually accompanied by the presence of hyphae or pseudohyphae, and *C. neoformans* contains a thick mucoid capsule which is lacking in *P. jirovecii* [182].

### 1.3.7 Pulmonary Candidiasis

In the last few decades, a steep increase in the number of immunocompromised patients has resulted in a high incidence of opportunistic fungal infections. Fungi of the genus *Candida* are ubiquitous human saprophytes, of which *Candida albicans* is the most common type to cause human disease. Pulmonary candidiasis can be acquired through aspiration of organisms from the oropharyngeal tract or through hematogenous dissemination from an extrapulmonary source such as infected intravenous catheters. The criteria for the diagnosis of pulmonary candidiasis, however, are still controversial since the isolation of candida from sputum, bronchoscopic samples, transthoracic needle aspirations, or lung biopsies may merely represent colonization of the tracheobronchial tree. Thus, the frequency of pulmonary candidiasis has not been well established. The diagnosis is further hampered as there are no specific clinical and radiological findings that could raise the suspicion for this disease. In addition, coinfection with other pathogens is not uncommon. Definitive diagnosis of the disease currently rests on histological evidence of the fungus in lung tissue with an associated inflammatory response [183–186].

#### 1.3.7.1 Clinical Features

Most patients with pulmonary candidiasis are chronically ill, transplant recipients, or immunocompromised individuals. Another contributing factor includes the liberal use of wide-spectrum antibiotics in modern patient care which promotes fungal overgrowth and vessel invasion in the gastrointestinal tract. Candidiasis can cause a severe, often life-threatening pneumonia. The clinical presentation of the disease is non-specific and commonly consists of prolonged fever, cough, and hemoptysis [183–186]. The radiologic manifestations of pulmonary candidiasis are equally non-specific and include patchy air-space consolidation with preferential lower lobe distribution or an interstitial pattern of disease. In cases of hematogenous spread to the lung, a macro- or micronodular pattern of disease may be evident. Pleural effusions are seen in up to a fourth of cases, while cavitating lesions or lymphadenopathy are only rarely observed [185, 186] (Fig. 1.36). Echinocandins are indicated as first-line treatment of candidiasis because of good fungicidal activity, activity against fluconazole-resistant strains, favorable safety profile, and low propensity for drug-drug interactions rendering them superior to fluconazole. In critically ill patients and those with candidemia, liposomal amphotericin B is considered the standard of care [187].

#### 1.3.7.2 Pathological Features

Endobronchial candidiasis caused by aspiration of the organisms results in asymmetric macroscopic lesions involving the airways of the lower lobes. Parenchymal disease is usually limited to the alveoli immediately adjacent to the airways in the absence of candidiasis in extrapulmonary sites. Hematogenous dissemination of the pathogen results in a symmetrical distribution of nodular lesions throughout both lungs and small subpleural nodules (Fig. 1.37). This type of the disease is usually accompanied by involvement of extrapulmonary organs. Microscopically, aspiration pulmonary candidiasis shows clusters of pseudohyphae and/or yeast forms arranged around the bronchioles and an associated purulent bronchopneumonia and abscess formation [183, 186]. Histological examination of hematogenous pulmonary candidiasis reveals small miliary nodules (usually 2–4 mm in size) randomly distributed throughout the lungs. These nodules are characterized by central necrosis with clusters of pseudohyphae and budding yeasts and an acute inflammatory cell reaction (Figs. 1.38, 1.39, and 1.40).

#### 1.3.7.3 Laboratory Diagnosis and Histochemical Stains

The criteria for the diagnosis of pulmonary candidiasis are yet to be defined fully. Although the diagnosis has always relied on the detection of candida in sputum or bronchoscopic cultures, these methods are unreliable because the pathogen frequently colonizes the upper airways and definitive diagnosis still heavily relies on the demonstration of the fungus in lung tissue with an associated inflammatory reaction [183–186].

Fig. 1.36 Diffuse consolidative ground glass opacities on the lung windows of a computed tomography scan in a patient with pulmonary candidiasis. Note the extensive pleural effusion in the left lung.
C. albicans is a diploid fungus that grows in yeast-like (blastoconidia) or elongated pseudohyphal forms. The budding yeasts are ovoid or spherical in shape and measure 2–7 μm in size, while the pseudohyphae are arranged in chains that resemble sausage links. Both forms can easily be identified in tissue sections using PAS or GMS special stains (Fig. 1.41a, b).

1.3.7.4 Differential Diagnosis

Candida species are yeasts that can produce pseudohyphae. Hence, they require differentiation from other yeasts and molds that produce true hyphae in tissue. The most frequent differential diagnosis is with Aspergillus species. Elongated Candida pseudohyphae can appear to be branching but are
differentiated because pseudohyphae are slender and do not have septations. *Histoplasma* is also in the differential diagnosis but can be separated from *Candida* by the absence of hyphal forms.

### 1.3.8 Pulmonary Aspergillosis

*Aspergillus* species are ubiquitous soil fungi of worldwide distribution. After contact, the fungus can affect any organ but most commonly involves the lungs. Species with virulence against humans include primarily *A. fumigatus*, *A. flavus*, and *A. niger* and rarely other species. The manifestations of pulmonary aspergillosis are determined by the degree of fungal exposure, the host immune status, and the presence of underlying structural lung disease. Thus, the spectrum of disease can be subdivided into five categories: (a) saprophytic aspergillosis (aspergilloma), (b) hypersensitivity reaction [allergic bronchopulmonary aspergillosis (ABPA)], (c) chronic necrotizing pulmonary aspergillosis (CNPA), (d) airway-invasive aspergillosis (acute tracheobronchitis, bronchiolitis, bronchopneumonia, obstructing bronchopulmonary aspergillosis), and (e) angioinvasive aspergillosis [188, 189].

#### 1.3.8.1 Clinical Features

The clinical spectrum of pulmonary aspergillosis correlates with the degree of tissue involvement and invasion. *Saprophytic aspergillosis* is characterized by aspergillus infection without tissue invasion and shows accumulation of fungal hyphae in a pre-existing cavity or ectatic bronchus (so-called fungus ball, aspergilloma, or mycetoma) [89, 188, 189]. Patients with structural lung disease, such as tuberculosis, sarcoidosis, bronchogenic cysts, or pulmonary sequestration are most commonly affected. Although most of these patients remain asymptomatic, the most frequent symptom is hemoptysis. *Allergic bronchopulmonary aspergillosis* (ABPA) occurs in patients with long-standing bronchial asthma and is caused by a complex hypersensitivity reaction to *Aspergillus* antigens. The fungus proliferates in the airway leading to excessive mucus production with bronchial wall damage and bronchiectasis. Recurrent wheezing, malaise, fever, cough, sputum production, chest pain, and recurrent pneumonia are typical symptoms. *Chronic necrotizing pulmonary aspergillosis* (CNPA) or “semi-invasive” aspergillosis occurs in patients with chronic debilitating diseases, prolonged steroid use, or chronic obstructive pulmonary disease (COPD) and leads to granulomatous inflammation associated with tissue necrosis. The clinical symptoms often have an insidious onset and include cough, sputum production, fever, or rarely hemoptysis. *Airway-invasive aspergillosis* encompasses acute tracheobronchitis, bronchiolitis, bronchopneumonia, and obstructing bronchopulmonary aspergillosis due to the presence of aspergillus fungus deep to the basement membrane of airways. Immunocompromised neutropenic patients or patients with AIDS are most commonly affected. Clinically, this form of aspergillosis presents with the signs and symptoms of acute tracheobronchitis, bronchi-
olitis, and bronchopneumonia. Angioinvasive aspergillosis is the most severe form of the infection and almost exclusively occurs in immunocompromised patients with severe neutropenia, especially those receiving chemotherapy for solid tumors or lymphoma/leukemia. The disease typically presents with rapidly progressive respiratory symptoms such as cough, chest pain, and hemoptysis and is associated with a high mortality [89, 188–190]. On imaging studies, saprophytic aspergillosis or aspergillomas radiologically impress as solid round or oval masses with soft tissue opacity within a lung cavity. This mass is separated from the surrounding parenchyma by an airspace resulting in the characteristic “air crescent” sign (Fig. 1.42). When the patient changes position, the aspergilloma typically moves. The wall of the cavity may show thickening, and the overlying pleura may also be affected. Interestingly, approximately 10% of aspergillomas may resolve spontaneously. Radiologic changes in ABPA include homogenous tubular finger-in-glove areas of increased opacity in a bronchial distribution, usually affecting the upper lobes. Further findings include lobar or segmental atelectasis or mucoid impaction and bronchiectasis in the bronchi of the upper lobes. Unilateral or bilateral segmental areas of consolidation, cavitation, or multiple nodular areas of opacity are seen in CNPA. Typically, these lesions progress slowly over months or years. Acute tracheobronchitis in airway-invasive aspergillosis usually shows normal radiological findings or mild tracheal or bronchial wall thickening. Bronchiolitis is characterized by centrilobular nodules and branching linear or nodular areas of increased attenuation with a “tree-in-bud” appearance. Bronchopneumonia results in peribronchial or lobar areas of consolidation. Pleural-based, wedge-shaped areas of consolidation or nodules surrounded by a halo of ground-glass attenuation (“halo sign”) corresponding to hemorrhagic infarcts are the typical radiological findings in angioinvasive aspergillosis [188, 191]. According to the current international guidelines, voriconazole is the antifungal drug of choice in the invasive types of aspergillosis, and itraconazole is the mainstay of therapy for the chronic and allergic disease forms [91, 192]. The optimal treatment strategy for aspergillosis is yet to be determined but primarily consists of surgical removal as the definitive treatment in cases with life-threatening hemoptysis, while endobronchial and intracavitary instillation of antifungals or oral itraconazole may be useful for patients without hemoptysis.

1.3.8.2 Pathological Features

Pathological examination of aspergilloma shows a well-circumscribed pale tan oval mass with serpiginous laminations. The mass is usually solid but may contain more friable areas. Microscopically, the lesion is composed of numerous intertwined fungal hyphae mixed with inflammatory cells, mucus, and cellular debris. The mass is surrounded by a fibrous cavity wall which may contain a chronic inflammatory cell infiltrate. A granulomatous reaction is rare and fungal invasion into the surrounding wall absent [189]. The diagnosis of ABPA often remains a clinical one and very rarely histologic material needs to be reviewed. In cases with atypical clinical presentation, pathological examination may become necessary and will reveal the presence of mucus plugs containing numerous eosinophils in a laminated distribution. Fungal hyphae may or may not be apparent on H&E stain alone and may become more apparent with the use of silver stains. The most characteristic finding in lung biopsies is the presence of bronchocentric granulomatosis, a necrotizing granulomatous process centered around bronchi and bronchioles (Fig. 1.43a, b). A palisade of epithelioid histiocytes typically replaces the airway epithelium and surrounds intraluminal necrotic debris (Fig. 1.43c); fungal hyphae are often seen admixed within this necrotic material (Fig. 1.43d). The adjacent lung parenchyma can be variably affected and most often shows a degree of obstructive pneumonitis or eosinophilic pneumonia [189]. The histologic spectrum of CNPA varies and can include necrotizing granulomatous pneumonia, granulomatous bronchiectatic cavities, or a bronchocentric granulomatosis-like process. Necrotizing granulomatous pneumonia shows parenchymal consolidation by necrotizing granulomatous inflammation surrounding central areas of infarct-like necrosis containing masses of fungal hyphae. The fungal organisms can be found in small vessels leading to coagulative parenchymal necrosis. Bands of dense fibrous tissue infiltrated by mixed inflammatory cells or lymphoid follicles often surround the necrotizing granulomas (Fig. 1.44). Another pattern of CNPA is a cavity centered on an airway which is partly lined by respiratory or metaplastic squamous epithelium (so-called granulomatous bronchiectatic cavity). Fibrinopurulent

Fig. 1.42 Air crescent sign on computed tomography scan in a patient with pulmonary aspergilloma
inflammation or a granulomatous reaction often extends into a thick fibrous capsule and into the adjacent lung parenchyma. A rarer form of CNPA resembles a bronchocentric granulomatosis-like reaction in which the airways are replaced by a granulomatous reaction and the lumina filled with mucus, necrotic debris, inflammatory cells, and fungal elements. In addition, lymphoid aggregates and well-formed granulomas in a lymphangitic distribution distant to the inflammatory foci can be seen in this form of CNPA [190].

Airway-invasive aspergillosis can present as acute tracheobronchitis, bronchiolitis, bronchopneumonia, or obstructing bronchopulmonary aspergillosis. In acute tracheobronchitis, the disease is predominantly limited to the tracheobronchial tree. In these cases, the airway lumen is occluded by mucus or fungus plugs, and the airway wall is acutely inflamed or necrotic. Importantly, the disease is limited to the mucosa and extension of fungal hyphae beyond the bronchial wall is unusual. Smaller bronchi and bronchioles may be affected...
by a bronchocentric granulomatosis-like reaction similar to the one seen in ABPA but with an absence of eosinophils and more dense fungal colonies. *Aspergillus* bronchopneumonia primarily involves small membranous and proximal respiratory bronchioles and mirrors bacterial pneumonias. Grossly, early stages of the disease can show a finely nodular appearance that extends to form larger areas of consolidation as the disease progresses. Microscopically, an intense neutrophilic reaction is associated with necrosis of airways and adjacent lung parenchyma. The fungal elements are often confined to the necrotic areas but may drain via involved airways resulting in cavitary disease. *Angioinvasive aspergillosis* may present as two distinct pathologic variants. In the first, the lung contains well-circumscribed spherical nodules, no more than 3 cm in diameter (Fig. 1.45). These nodules have a pale center and hemorrhagic outer rim (“target lesion”). Histologically, the pale areas consist of coagulative necrosis with extensive permeation by fungal hyphae. Vascular infiltration is prominent and affects large vessels in the center of the lesions (Fig. 1.46). The peripheral rim consists of zones of congested and hemorrhagic lung parenchyma with no or minimal inflammatory reaction. The second variant is characterized by areas of parenchymal hemorrhage or infarction. While hemorrhage alone can occur anywhere, the infarcted areas are usually restricted to a subpleural location. Histological examination of affected vessels reveals disruption of the vessel wall due to either secreted fungal toxins or ensuing inflammatory reaction [89, 188–190].

1.3.8.3 Laboratory Diagnosis and Histochemical Stains

Histopathological examination remains the gold standard in the diagnosis of aspergillosis. *Aspergillus* is a dimorphic
fungus that typically grows in regular septate hyphae that measure 2–5 μm in diameter. These hyphae often have a fan-like appearance and branch dichotomously at an angle of 45°. Although the hyphae are usually identifiable in tissue sections with an H&E stain, PAS or GMS stains facilitate their recognition (Fig. 1.47). Two specific histological findings that are good evidence for an infection caused by Aspergillus species are the deposition of calcium oxalate crystals produced by certain Aspergillus species, especially A. niger and the presence of conidiophores. Calcium oxalate forms when oxalic acid produced by the organism combines with host derived calcium to form irregularly shaped, angulated, strongly refractile crystals that may be visible in body fluids or tissue sections. Conidiophores are the asexual reproductive organs of the fungus consisting of elongated hyphae that terminate in a swollen vesicle from which numerous spore-producing tubes arise. These spores or conidia are 1–3 μm in diameter and located adjacent to the tubes. The presence of conidiophores is rare and usually only observed when the site of infection is exposed to air. Hence, they are most often seen in aspergillomas or airway-invasive aspergillosis [189]. In addition to histological examination, various other diagnostic methods can be utilized. These primarily include cultures of sputum, bronchoalveolar lavage, or tissue samples. More recent advances in the diagnosis of aspergillosis are related to the detection of aspergillus antigens in body fluids. Galactomannan is a polysaccharide cell wall component of the fungus, and an assay for the detection of galactomannan in serum can be used for early confirmation of the diagnosis [193]. Other ways to diagnose Aspergillus infection include specific antibody assays and PCR-based techniques [193, 194].

1.3.8.4 Differential Diagnosis
On histopathological examination aspergillus hyphae may be confused with Zygomycetes hyphae. As opposed to Zygomycetes hyphae, those of Aspergillus are thinner and regular and show more acute-angled branching.

1.3.9 Pulmonary Mucormycosis
Mucormycosis is an invasive often lethal opportunistic fungal infection caused by fungi in the order Mucorales [195]. Mucorales are ubiquitous, saprophytic, and not fastidious fungi located in soil or decaying organic matter, with three genera that are known to be human pathogens, namely, Rhizopus, Absidia, and Mucor. Humans acquire the disease by inhalation of the spores or direct inoculation into abraded skin [196]. Numerous predisposing risk factors have been described including hematologic malignancies, diabetes mellitus, organ transplantation, immunosuppression, thermal burns, and surgery [197]. The infection can present as six distinct clinical syndromes that encompass rhinocerebral, pulmonary, abdominopelvic, cutaneous, widely disseminated, and miscellaneous forms [89]. Pulmonary mucormycosis was described in 1876 by Fürbringer [198] and in modern time accounts for approximately 30% of all human mucormycosis infections [199]. Mucorales are known to be angiotropic organisms, and a hallmark of the infection is vascular invasion with associated tissue infarction. In pulmonary mucormycosis, this leads to clinical presentation as a rapidly progressive pneumonia with angioinvasion and tissue necrosis. The mortality rate of pulmonary mucormycosis is high due to frequent complications such as massive hemoptysis, secondary bacterial infection, and acute respiratory failure. Successful treatment of pulmonary mucormycosis therefore relies on a timely diagnosis. Amphotericin B, along with surgical resection of the involved areas of the lung and treatment of the underlying disease, is the mainstay of treatment [91], yet the outcome is typically fatal when pulmonary mucormycosis develops in a patient with hematological disease [200].

1.3.9.1 Clinical Features
Mucormycosis is an opportunistic infection that preferentially affects patients with altered immune status, especially patients with hematologic malignancies, and rarely affects healthy individuals [89, 197, 201]. The symptoms of pulmonary mucormycosis are typically non-specific, even at late...
stages of infection, and may include fever, dyspnea, cough, and chest pain. Hemoptysis commonly occurs with vascular invasion, which can occasionally be fatal [202]. The radiological features of pulmonary mucormycosis include progressive lobar or multilobar consolidation, pulmonary masses and nodules, and the reversed halo sign (central ground-glass opacity surrounded by denser consolidation of crescentic or ring-forming shape) [185, 199, 203]. Cavitation is seen in up to 40% of cases, and the upper lobes are more commonly affected. Mediastinal lymphadenopathy, vascular invasion, and extrapulmonary involvement may be accompanying features [199].

1.3.9.2 Pathological Features
The most common histological feature in pulmonary mucormycosis is extensive angioinvasion often involving more than 50% of the vessels (Fig. 1.48). In the vast majority of cases, angioinvasion is accompanied by hemorrhagic infarction and intravascular thrombosis. Intraalveolar hemorrhage and coagulative tissue necrosis are other common findings (Fig. 1.49). Inflammatory infiltrates consisting of neutrophils and/or lymphocytes only seen in 30% of patients and granuloma formation or perineural invasion by fungal hyphae are other less frequent findings [204, 205] (Fig. 1.50).

1.3.9.3 Laboratory Diagnosis and Histochemical Stains
The diagnosis of pulmonary mucormycosis is achieved by demonstrating broad (10–25 μm in diameter), non-septate ribbonlike hyphae, with right-angled branching in a tissue specimens stained with routine hematoxylin and eosin. Although special fungal stains are usually not necessary for diagnosis, PAS or silver (GMS) stains may serve to highlight the fungi. Contrary to *Aspergillus* species, branching is usually right angled, septations are rare (pauci-septate), and hyphal elements often appear distorted or twisted
Diagnostic techniques used to achieve identification include percutaneous needle biopsy, open lung biopsy, and pleural fluid culture. Fiberoptic bronchoscopy is another useful diagnostic method, and an adequate bronchoalveolar lavage specimen usually provides enough diagnostic material for cytological diagnosis [206]. Despite this, morphological examination alone may lead to misclassification, and tissue culture is usually performed for speciation [204, 205]. Additional techniques used for confirmation of the diagnosis include in situ hybridization or PCR analysis [207].

1.3.9.4 Differential Diagnosis
Once the inflammatory nature of the lesion is established and fungal hyphae are identified, the most important differential diagnosis is with aspergillosis. As mentioned above, the hyphae in mucormycosis are broad and irregular and show right-angled branching as opposed to *Aspergillus* hyphae that are slender and show acute-angled branching in comparison. If in any doubt, ancillary techniques as described above should be applied for definitive diagnosis [204, 205].

1.3.10 Pulmonary Sporotrichosis
Sporotrichosis is a chronic infection caused by *Sporothrix schenckii*, a saprophytic biphasic organism which is found in soil, plants, and timber [208]. Implantation of the spores into the skin can produce a skin infection that is characterized by a chancre or rodent-like ulcer and frequent lymphangitic spread. Excutaneous infections are rare but may occur secondary to disseminated skin infection. When spores are inhaled or aspirated along with gastric contents, the lungs may be the primary site of infection. Primary pulmonary sporotrichosis occurs infrequently with less than 100 reported cases in the medical literature [209].

1.3.10.1 Clinical Features
Primary pulmonary sporotrichosis appears to affect predominantly middle-aged alcoholic males with or without pre-existing lung disease. The common correlation with occupation or hobby related to gardening that is typical for cutaneous sporotrichosis is not a prominent feature in primary pulmonary disease. Presenting symptoms are non-specific and include fever, chills, cough, hemoptysis, dyspnea, chest pain, and weight loss [208]. Chronic cavitary disease is the main radiological manifestation of primary pulmonary sporotrichosis. The bilateral and often apical location of the cavities makes sporotrichosis undistinguishable from other granulomatous diseases. Sporotrichosis may also present as solitary lung nodules. Underlying chronic lung disease in the form of emphysema or bronchiectasis is another common finding [208]. Treatment options for pulmonary sporotrichosis are medical treatment alone for patients with non-cavitary disease and surgical intervention for those with cavitation or after failed medical treatment. The mainstay of medical treatment has shifted toward azole-based regimens with itraconazole as the first-line agent and amphotericin B in life-threatening situations. Early surgery should be considered once cavitations develop as late surgery results in poorer outcomes and complications [209].

1.3.10.2 Pathological Features
The cavitary lesions in the lung are often cystic and range in size from 0.5 to 6 cm. The cysts are thin-walled and filled with hemorrhagic debris. Solitary lung nodules are yellow to tan in color and of soft consistency and can reach a size up to 1.7 cm in diameter. Microscopically, pulmonary sporotrichosis is characterized by numerous often confluent granulomas with central, sometimes cavitating necrosis. In the periphery, these granulomas are separated from the surrounding lung parenchyma by a rim of palisading epithelioid histiocytes that can contain scattered multinucleate giant cells. Chronic inflammatory cells, hemosiderin deposition, and fibrotic areas are commonly observed. Primary vasculitis is not a feature of pulmonary sporotrichosis. Further changes in the histopathological spectrum of the disease include organizing pneumonia, bronchiolitis obliterans, accumulation of intraalveolar pigmented macrophages, and obstructive pneumonia (Fig. 1.52). Solitary lung nodules consist of isolated granulomas with a similar appearance as those in the more confluent form. Yeast elements can be identified in the necrotic centers of the granulomas and can vary in number between cases or even from section to section. An uncommon finding in
pulmonary sporotrichosis compared to the cutaneous form is the presence of radiating star-like elongations of richly eosinophilic material around the organism, the so-called asteroid body [208, 210].

### 1.3.10.3 Laboratory Diagnosis and Histochemical Stains

*S. schenckii* in tissue appears as round, oval, or cigar-shaped yeasts of 2–6 μm or larger in diameter that may show narrow-based or tube-like budding. Hyphal elements containing sessile cigar-shaped budding yeasts are a more infrequent finding. *S. schenckii* yeasts are not easy to identify with H&E stains, and thus GMS and PAS stains should be used to highlight their contour (Fig. 1.53). In cases of sporotrichosis, star-like, eosinophilic material (Splendore-Hoeppli phenomenon) surrounding yeasts can be observed in 40 to 92% of cases. These structures have been called asteroid bodies, and *Sporothrix* has been demonstrated in the centers of these structures using immunohistochemistry. The diagnosis can further be confirmed by culturing cytological preparations or lung tissue [208–210].

### 1.3.10.4 Differential Diagnosis

The dichotomy of *Sporothrix* in tissue sections may resemble that of other yeast-like organisms such as *Histoplasma* or *Candida*. A delicate “capsule” or “coat” in sporotrichosis highlighted by PAS staining may be used to distinguish *Sporothrix* from the other organisms [210].

### 1.4 Parasitic Infections

Parasitic disease remains a major cause of morbidity and mortality worldwide. Although most parasitic infections are endemic to tropical and subtropical regions of the world [211], in the last few decades, several factors have led to an increased recognition of parasitic lung infections also in other parts of the world. Global climate change and an increase in the world population have led to changes in the natural ecosystem, and immigration and travel practices have resulted in a higher transmission of parasites to humans. In addition, the emergence of HIV/AIDS, the increase use of immunosuppressive drugs, and rising number of organ transplantations are also the reason why parasitic lung infections are on the rise again [211]. The pulmonary system can be affected by a variety of parasitic organisms. These can involve the lungs during the migration phase of their life cycle before they reach their target destination or they can be deposited in the lungs as a result of embolic spread or via direct invasion during generalized disease [212]. In this chapter, particular emphasis is paid to those parasitic infections that can clinically or radiologically mimic lung cancer and often require tissue diagnosis. These include *pulmonary schistosomiasis, dirofilariasis, paragonimiasis, strongyloidiasis*, and *echinococcosis*. Furthermore, in cases that usually cause generalized disease, only the pulmonary manifestations will be described. The most important characteristics of pulmonary parasitic infections are summarized in Table 1.5.
Table 1.5: Pertinent characteristics of pulmonary parasitic infections

| Infectious agent | Schistosoma mansoni, haematobium, japonicum | Dirofilaria immitis | Paragonimus westermani | Strongyloides stercoralis | Echinococcus granulosus |
|------------------|---------------------------------------------|--------------------|------------------------|--------------------------|-------------------------|
| Distribution     | Africa, Arabia, South America, China, Japan | Southeastern US, Brazil | Southeast Asia, China | Tropics, subtropics | Mediterranean, Middle East, Africa, South America, Australia, New Zealand |
| Predisposing condition | Contact with contaminated water | Exposure to infected dogs | Ingestion of undercooked seafood | Disseminated disease in immunosuppression | Exposure to sheep or cattle |
| Histological pattern | Ill-defined granulomatous reaction with central suppuration | Well-demarcated necrotic nodule with palisading epithelioid histiocytes | Chronic eosinophilic pneumonia with granulomatous inflammation | Inflammatory reaction around larval forms, granulomatous reaction | Cystic structure with laminated hyaline wall surrounded by fibrous layer |
| Special stains | Acid-fast stains may highlight shells and spines | PAS +, Movat + | None | None | GMS+, PAS + |
| Morphology of etiologic agent | Ova with terminal (S. haematobium), large lateral (S. mansoni), or vestigial lateral (S. japonicum) spine, 100–150 μm | Parasite with eosinophilic cuticle, diametrical internal thickenings, somatic muscle and thinned walled tubules, 125–250 μm | Ova with flat-shouldered operculum and thickened aboperculated end, 80 μm | Larvae with eosinophilic cuticle, cylindrical esophagus, and notched tail, 600 μm | Spheroid vesicle with layered wall and liquid contents containing “hydatid sand,” 35 μm |
| Ancillary testing | Urine or stool examination for ova | Serologic antigen tests | Antibody assays | Serologic antigen tests | |
| Treatment | Antihelminthic | None required | Antihelminthic | Antihelminthic | Antihelminthic |

GMS Grocott methenamine silver stain, PAS periodic acid-Schiff, US United States

1.4.1 Pulmonary Schistosomiasis

Schistosomiasis is a parasitic illness caused by blood flukes of the genus Schistosoma and represents one of the most common helminth infections in man. Of the seven species known to infect humans, three species are responsible for the greatest burden of disease: Schistosoma mansoni in Africa, Arabia, and South America, Schistosoma haematobium in Africa and Arabia, and Schistosoma japonicum in Japan and China [213]. Schistosomiasis is one of the ten leading causes of morbidity among returning travelers, accounting for 2% of illness in travelers returning from sub-Saharan Africa [214]. Schistosomiasis is developed after contact with natural water containing cercariae, the infective form of the parasite [215] (Fig. 1.54). Cercariae are released into water from species-specific intermediate snail hosts [213] and can then penetrate the skin of humans, transform into schistosomules, and migrate via the hemolymphatic system, through the lungs, to the portal circulation of the liver, where they mature into sexually distinct adults. From there they then migrate either to the mesenteric venules of the intestinal tract (S. mansoni and S. japonicum) or to the venous vasculature of the bladder (S. haematobium). Here, the females begin shedding their eggs which can then penetrate through the soft tissues to enter the lumen of the gut or bladder from where they are released back into environment or are retained in the host tissues where they can elicit a granulomatous response [213, 216–219]. Based on the migration of the helminth, the infection can be divided into three phases: an allergic (cercarial) dermatitis, which is the result of the penetration of cercariae into the skin; acute schistosomiasis which is due to the migration of eggs and schistosomula in the blood and which occurs in patients not previously exposed to the parasite [215, 220, 221]; and chronic schistosomiasis, which is caused by the formation of granulomas and fibrosis around the helminth eggs retained in the host tissues and which occurs in individuals living in endemic areas, although acute reinfection can also occur in individuals with the chronic form [215, 221, 222]. Pulmonary involvement occurs in approximately 1/3 of cases of clinically established cases of schistosomiasis [223]. The pathological changes seen in the lungs are primarily the result of granuloma formation around schistosomes or schistosomal ova most often represented by multiple pulmonary nodules on chest imaging. In the chronic phase, fibrosis can ensue and can lead to pulmonary hypertension and cor pulmonale. An atypical presentation of pulmonary schistosomiasis can occur
in the form of a solitary granulomatous lesion (pulmonary bilharzioma), clinically and radiologically closely mimicking lung cancer or tuberculosis [217–219, 224, 225]. Heavy localization of embolic ova at sites of previous disease in combination with a local hypersensitivity reaction caused by antibilharzial treatment has been proposed as the underlying etiology [217, 219].

1.4.1.1 Clinical Features
Acute pulmonary schistosomiasis may develop in infected individuals from non-endemic areas after their first exposure and is thought to be related to an allergic immune response to the various developmental stages of the parasite, its eggs, or both, likely related to the release of inflammatory cytokines [216, 226–229]. Pulmonary symptoms are rather nonspecific and include cough, pyrexia, night sweats, cough, chest pain, and weight loss [217–219]. Imaging tests in the acute phase will typically demonstrate bilateral small nodular infiltrates or areas of ground glass attenuation that are transitory and spread throughout both lungs. Multiple larger nodular lesions that are thought to reflect granuloma formation may also be seen. This may or may not be associated with hilar adenopathy [215]. Pulmonary bilharzioma often presents as a solitary irregular mass-like lesion in the lung that can show signs of cavitation. Such radiological features are often highly suspicious for tuberculosis or a primary lung tumor, the latter especially in patients with underlying smoking history [217–219]. It is imperative that the disease
is treated and diagnosed early in order to prevent late complications, such as pulmonary hypertension, cor pulmonale, and pulmonary arteriovenous fistulas [215, 230]. In the acute phase, treatment is primarily aimed at preventing immunologic complications and consists of steroids or non-steroidal agents; in later stages of the disease, antihelminthic therapy with praziquantel as the most widely recommended agent is also indicated [211, 212, 231].

1.4.1.2 Pathological Features
The lesions in pulmonary schistosomiasis are typically granulomatous and are usually distributed along the alveolar septa, within bronchioles and arterioles (Fig. 1.55a). Schistosomes or schistosomal ova, with or without calcification, are surrounded by a foreign body-type reaction along with a mixed inflammatory cells composed of eosinophils, lymphocytes, and plasma cells. Central suppuration and multinucleated giant cells may also be observed. The ova may later be replaced by a fibroblastic proliferation, obliterating the eliciting agent. Eosinophilic pneumonia has also been observed in some cases [223]. The deposition of the lesions in the pulmonary vasculature is the cause of late complications of the disease including arteriolitis obliterans, pulmonary hypertension, and cor pulmonale [221, 222] (Fig. 1.55b).

1.4.1.3 Laboratory Diagnosis and Histochemical Stains
One of the most critical steps in the diagnosis of schistosomiasis is a detailed travel history or history of exposure along with blood eosinophilia. Stool and urine samples should be examined for the presence of ova. Serologic tests may be of utility in patients with first time exposure to the parasite, but they cannot distinguish between prior and current infection. In times where molecular diagnostic methods are still being explored, detection of the ova in clinical specimens or tissues remains the gold standard in the diagnosis of schistosomiasis. The ova are 100–150 μm in size and possess a terminal (S. haematobium), large lateral (S. mansoni), or vestigial lateral (S. japonicum) spine [218, 231].

1.4.1.4 Differential Diagnosis
Ultimately, the diagnosis of pulmonary schistosomiasis rests on an appropriate travel history, typical transient micronodular infiltrates on chest imaging, and strong clinical suspicion for the disease. From a pathological standpoint, a granulomatous tissue response can be seen in a wide range of other infectious and non-infectious diseases that can enter the differential diagnosis. In this context, diligent search for the typical schistosomal ova will typically lead to the correct diagnosis.

1.4.2 Pulmonary Dirofilariasis
*Dirofilaria immitis*, the dog heartworm, is a parasitic roundworm that is transmitted from host to host via mosquito vectors. The definitive host is the dog in which the worm can cause congestive heart failure by lodging in the heart and...
the pulmonary arterial system. Aberrant human infection can occur when infective larvae of the parasite are accidentally transmitted from dogs to humans through mosquito bites. Thus, the geographic distribution and prevalence of the disease closely parallels the disease in the canine population. The disease can be found worldwide; however, most of the cases have been reported in the Southeast United States and Brazil [232–234]. After inoculation into the skin by infected mosquitoes, the filarial larvae migrate to the right ventricle where they lodge and mature into nematodes with a multilayered cuticle, two internal longitudinal ridges, thick muscle bands, an intestinal tract, and reproductive tracts – two in the female and one in the male [235, 236] (Fig. 1.56). While in the dog, the mature worm produces more microfilariae, whereas humans are a dead-end host and larvae are prevented from reaching maturity. Instead, the larval forms die and embolize to the lung where they get lodged in the pulmonary vasculature. The resulting endarteritis will lead to pulmonary infarction that clinically presents as a solitary pulmonary nodule. Since affected patients are often in the sixth to seventh decade of life, the lesions are almost invariably interpreted radiologically to represent lung neoplasia, and the diagnosis is almost always delayed until after surgical resection [232–234].

**Fig. 1.56** Life cycle of *Dirofilaria immitis*. During a blood meal, an infected mosquito introduces filarial larvae of *D. immitis* into the skin of the definitive host, which is usually a domestic dog (1). In the definitive host, the larvae mature into adults (2) which reside in the pulmonary arteries and the right ventricle of the heart (2). In the heart of the dog, the female worms produce microfilariae which are subsequently found in the peripheral blood (3). A mosquito ingests the microfilariae during a blood meal, and after ingestion, microfilariae develop into larval forms (4). The infective larvae can then infect another definitive host when it takes a blood meal (5). Aberrant human infection can occur when infective larvae of the parasite are accidentally transmitted from dogs to humans through mosquito bites (6). In humans, *D. immitis* larvae tend to follow a similar course as in the canine host, ending up in the lungs, where they often lodge in small-caliber vessels, causing infarcts and characteristic ‘coin lesions’ visible on radiologic imaging.
1.4.2.1 Clinical Features

Human pulmonary dirofilariasis is a disease that predominantly affects older men, usually in the 6th decade of life [233]. In humans, the disease is generally a self-limited process, and more than half of the patients remain asymptomatic. Upper respiratory symptoms including cough, shortness of breath, chest pain, dyspnea, and hemoptysis are the major presenting symptoms in the remaining patients [232–234, 237]. Systemic eosinophilia may be an accompanying phenomenon, but contrary to other parasitic diseases, less than 10% of patients with human pulmonary dirofilariasis present with elevated peripheral eosinophil counts [238]. The radiological findings consist of the presence of a single, peripherally located well-circumscribed and non-calcified nodule ranging in size from 0.5 to 4.0 cm. PET-CT scan may show increased 18-FDG uptake further raising the suspicion of a neoplastic process [239]. Although the vast majority are solitary lesions, in 10% of cases, multiple nodules may be discovered [237]. The right lung is more commonly affected than the left, with the highest incidence in the right lower lobe [233, 234]. Pulmonary dirofilariasis does not require any specific treatment as humans are dead-end hosts interrupting the parasite’s life cycle. Care should be taken to keep dirofilariasis in the differential diagnosis in endemic areas in order to avoid overly aggressive surgery [211, 212]. Avoidance of mosquito bites during peak biting times in areas known to be endemic for the parasite is the best method of preventing dirofilariasis.

1.4.2.2 Pathological Features

On gross examination, the lesions are round, well-circumscribed, spherical nodules usually located near the pleural surfaces. The cut surface is soft and granular, necrotic, and focally hemorrhagic. The helminths are not usually visible at the time of dissection. Microscopic examination reveals the presence of necrotic lung parenchyma surrounded by a peripheral zone of palisading epithelioid histiocytes, occasional Langerhans giant cells, and lymphocytes (Figs. 1.57 and 1.58). The necrotic areas may show preserved alveolar outlines and contain a central thrombosed pulmonary artery that contains fragments of the non-viable roundworm. The degenerate parasite may on occasion also be identified in the adjacent necrotic parenchyma (Fig. 1.59a, b). The cross-sectional diameter of the worm ranges from 125 to 250 μm. It possesses a multilayered faintly eosinophilic cuticle with prominent diametrically opposed internal thickenings, abundant somatic muscle, and thin-walled tubules representing the digestive and genital tracts. The surrounding lung parenchyma can show non-specific chronic inflammatory changes, a desquamative interstitial pneumonia-like reaction, follicular bronchiolitis, or organizing pneumonia. Scattered eosinophils, Charcot-Leyden crystals, and discrete necrotizing and non-necrotizing granulomas can also be noted [233, 234].
1.4.2.3 Laboratory Diagnosis and Histochemical Stains

Although serologic tests such as complement fixation tests, indirect hemagglutination, and enzyme-linked immunosorbent assay are available for the detection of dirofilariasis, these have low sensitivity probably because the antigenic stimulus of a single worm is too limited to produce a systemic response in humans, and the final diagnosis is almost always made on biopsy and histologic tissue examination [232]. Although the worms can be identified in tissue on H&E section, the anatomic features are better appreciated on PAS or Movat special stains [233, 234] and will show a cross-sectional diameter of 125–250 μm and a thick multilayered cuticle (5–25 μm), diametrically opposed lateral ridges, and abundant somatic muscle [233, 234].

1.4.2.4 Differential Diagnosis

From a pathological perspective, the differential diagnosis for human pulmonary dirofilariasis includes non-infectious pulmonary infarction and necrotizing granulomatous inflammation of other etiology. Pulmonary infarcts are classically wedge-shaped and devoid of any distinct palisade of epithelioid histiocytes. Necrotizing granulomas usually show complete liquefactive infarction with loss of the underlying tissue architecture and an absence of an eosinophilic infiltrate. Another parasite capable of causing pulmonary infarction is Brugia malayi. However, B. malayi is very common throughout southeast Asia but not the Western Hemisphere and contrary to D. immitis has a very slender shape with a thinner cuticle, inconspicuous lateral ridges, and sparse musculature [234].

1.4.3 Pulmonary Paragonimiasis

Human paragonimiasis is a food-borne infection caused by a parasitic lung fluke of the member of the genus Paragonimus. Kerbert in 1878 provided the first morphologic description of the adult worm in an autopsy of a Bengal tiger in an Amsterdam zoo [240]. The vast majority of infections with Paragonimus species occur in Southeast Asia and China where the disease is endemic [241]. In the United States, the infection is mainly found among immigrants or travelers who acquired the disease abroad. The main species to cause human pleuropulmonary paragonimiasis is Paragonimus westermani, a lung fluke with a complex life cycle (Fig. 1.60). Humans acquire the infection after ingestion of raw or undercooked crabs, crayfish, or wild boar meat harboring infective metacercariae [242, 243]. After the organisms are ingested, they penetrate the wall of the intestine and enter the peritoneal cavity. From here they progress through the diaphragm into the pleural space and the lungs where they reside and develop into adult parasites. From here, the parasite may also travel to the central nervous system, soft tissues, or skin although this ends their life cycle as eggs excreted in these sites will not be able to exit the host.
In contrast, eggs produced in the lungs can be excreted in the sputum or swallowed and passed in the stool. Once in the environment, the eggs become embryonated, miracidia hatch and develop through various stages in the first intermediate host, a snail to become cercariae. Cercariae then emerge from the snail and enter the second intermediate host such as crustaceans or wild boars where they progress to metacercariae completing the cycle [234, 242].

1.4.3.1 Clinical Features
Pulmonary paragonimiasis typically presents with non-specific symptoms including fever, chest pain, cough, hemoptysis, and dyspnea [242, 243, 245, 246]. Almost all patients report a history of eating or handling live, raw, or undercooked foods such as crabs, crayfish, or wild boar meat [242, 243]. The incubation period is highly variable and can range from a few days to as long as several months [247]. Peripheral blood eosinophilia and elevated serum IgE levels are seen in the vast majority of patients with paragonimus infection [245]. Imaging studies will show pleural effusions, pleural thickening, or pneumothoraces and parenchymal changes such as consolidation or ground glass opacities. In particular, pulmonary paragonimus will show a high frequency of solitary nodular lesions with or without cavitation closely simulating neoplastic, fungal, or mycobacterial disease [248, 249]. Of note, these lung lesions may show increased uptake values on PET-CT scans further complicating the distinction from primary lung malignancy [250]. Praziquantel is the drug of choice to treat pulmonary paragonimiasis with a treatment course of 2 days. Bithionol, niclofolan, and triclabendazole are alternative choices [211, 212]. Thoroughly cooking seafood and meat is the best way to prevent the infection.

1.4.3.2 Pathological Features
Chronic eosinophilic pneumonia is the most consistent finding in lung biopsies from patients with pulmonary paragonimiasis infection [244]. This manifests as inflammation of the
airspaces and interstitial spaces with an inflammatory cell infiltrate consisting of lymphocytes, plasma cells, histiocytes, and large numbers of eosinophils and areas of eosinophil abscesses. Cavitary geographic necrosis with granulomatous features and a rim of giant cells are another typical finding. Granulomatous vasculitis and acute and chronic bronchiolitis may also be seen. In addition, the pleura may show acute or chronic fibrinous or eosinophilic pleuritis. The parasite and/or its eggs are not always identified in tissue samples but when present secure the diagnosis (Fig. 1.61). *Paragonimus* eggs are characteristically golden yellow, oval, and widest in the center (Fig. 1.62). The ova are 80 μm in length and 40–50 μm in width and have a characteristic flat-shouldered operculum and thickening of the aboperculated end [251]. Birefringence is present on polarization [252]. The adult fluke is red-brown and ovoid, with a length of 7–16 mm and diameter of 4–8 mm. It possesses oral and ventral suckers and has a lobed ovary which is located anterior to two branching testes.

1.4.3.3 Laboratory Diagnosis and Histochemical Stains

The diagnosis of pulmonary paragonimiasis requires a high index of suspicion, although the rarity of the disease in non-endemic areas and non-specific clinical presentation often delay the diagnosis. Identification of typical patient risk factors and travel history may aid in the correct diagnosis. However, frequently, the disease is only diagnosed after histological examination and identification of the eggs in involved tissue, pleural fluid, or sputum cytology. In addition, serologic testing such as immunoblot, complement fixation, or enzyme immunoassay tests are available and extremely useful in the appropriate clinical setting as they may obviate the need for tissue biopsy [243, 253].

1.4.3.4 Differential Diagnosis

Clinically and radiologically, paragonimiasis can be easily confused with pulmonary tuberculosis, fungal infections, nocardiosis, or primary lung cancer [250, 251]. The pathologic differential diagnosis is more limited and restricted to diseases that are characterized by an eosinophilic pneumonia. Attention should be paid to the more unusual features associated with pulmonary paragonimiasis such as marked pleuritis, geographic necrosis, and granulomatous vasculitis [244]. A high index of suspicion, serological testing, and identification of the organism in tissue or fluids will provide the key to the diagnosis.

1.4.4 Pulmonary Strongyloidiasis

*Strongyloides stercoralis* is an endemic intestinal parasite that is usually the cause of a subclinical infection of residents in tropical or subtropical regions [254, 255]. Sporadic cases in cooler climates can occur in patients who have travelled to endemic areas. Unlike other nematodes, the parasite may persist in the host for many years and cause autoinfection many years after first exposure to the organism. In immunocompromised hosts, such as those with hematologic or solid malignancies or patients receiving systemic corticosteroids *S. stercoralis* can cause severe life-threatening disease through
hyperinfection or disseminated infection. Hyperinfection syndrome represents an accelerated form of the normal life cycle of the parasite resulting in excessive worm burden within the traditional reproductive route (skin, gastrointestinal tract, and lungs), while disseminated strongyloidiasis involves widespread dissemination of larvae outside of the gastrointestinal tract and lungs, often involving the liver, brain, heart, and urinary tract [256–262]. Human infection begins when the filariform larvae penetrate the skin, migrate hematogenously to the lungs, ascend the airways, get swallowed, and finally mature in the intestine [263, 264] (Fig. 1.63). Changes in the larval phase can lead to dissemination which primarily affects the lungs. Although the changes in the lungs are usually characterized by diffuse or patchy bronchopneumonia and pulmonary abscesses, occasionally, chest imaging may reveal a mass-like lesion that can be mistaken for a neoplastic process [265, 266].

### 1.4.4.1 Clinical Features

Although it is not necessary for patients to be immunocompromised, such individuals are more prone to systemic infection which can be more severe and even fatal [267]. Signs and symptoms of pulmonary involvement include shortness of breath, cough, wheezing, hemoptysis, and asthma [245]. In fact, if new-onset asthma is noted in immunosuppressed patients, *S. stercoralis* should be suspected [230]. Peripheral blood eosinophilia is usually present but may be absent in cases of disseminated disease or in the context of immunosuppression [268]. The most common findings on chest radiograph are pulmonary infiltrates or airspace opacities due to hemorrhage, pneumonitis, or abscess formation [230]. Rare manifestations include the presence of solitary ill-defined pulmonary masses that can closely mimic primary lung tumors [265, 266]. The first-line therapy for strongyloidiasis is ivermectin which can achieve eradication rates of approximately 80% [257, 269–271]. Other effective agents include thiabendazole and albendazole. High-dosage thiabendazole is the first-line agent in immunocompromised individuals. Of note, corticosteroids should be avoided in *Strongyloides* infection to prevent life-threatening hyperinfection syndrome [211, 212, 272].

**Fig. 1.63** Life cycle of *Strongyloides stercoralis*. Filariform larvae of the organism in contaminated soil penetrate the human host skin to initiate the parasitic cycle (1). From here the larvae migrate hematogenously to the lungs (2), ascend the airways, get swallowed, and finally mature in the intestine (3). In the small intestine, the larvae develop into adult female worms which produce eggs and eventually yield rhabditiform larvae (4). The rhabditiform larvae may then proceed to become infective filariform larvae that can either result in autoinfection (or hyperinfection in immunocompromised patients) (5a) or direct reinfection of another host (5b). Rhabditiform larvae passed in the stool can also develop into free-living adults (6). This free-living cycle is characterized by mating of male and female adult worms with production of eggs from which rhabditiform larvae hatch (7) and eventually become infective filariform larvae.
1.4.4.2 Pathological Features
Larvae of *S. stercoralis* can be identified in histological sections within the bronchi, bronchial mucosa, bronchial mucous glands, lymphatic spaces, or free within the air spaces [264]. These elicit an inflammatory response and cause deposition of mucin and inflammatory cells, mostly lymphocytes, neutrophils, and eosinophils, in the lumina of the airways or within the bronchial mucosa [264]. Massive pulmonary hemorrhage or a granulomatous reaction to the parasite are other common pathological findings [230, 273].

1.4.4.3 Laboratory Diagnosis and Histochemical Stains
A definitive diagnosis of strongyloidiasis can be made by the identification of larvae or adult parasites in sputum, bronchoalveolar lavage, stool specimens, or histological sections. Larvae typically measure 200–600 μm in length and 10–15 μm in width, while adult female measure 220–250 mm [264, 265]. They possess an eosinophilic cuticle, long, slim, cylindrical esophagus, and notched tail [265]. Antibody assays exist and have sensitivities of approximately 90%; however, cross reactions occur with other helminth infections and antibody levels may be low in immunocompromised patients [230].

1.4.4.4 Differential Diagnosis
Identification of the parasite in body fluids or histological sections usually confirms the diagnosis of pulmonary strongyloidiasis. However, based on morphology, the most important differential diagnosis is that of hookworm infection (*Ancylostoma duodenale* and *Necator americanus*) [245]. On detailed review, these can be distinguished from *S. stercoralis* based on their longer buccal cavity and smaller genital primordia [274].

1.4.5 Pulmonary Echinococcosis (Hydatid Cyst)
Echinococcosis (hydatid disease) is one of the most widespread zoonoses in the world. It is caused by the larvae of dog or fox tapeworms of the genus *Echinococcus* [275–277]. The two major species of medical importance globally are *Echinococcus granulosus* as the cause of cystic unilocular echinococcosis (hydatid cyst) and *Echinococcus multilocularis* which causes the alveolar multicystic form of echinococcosis [278]. Both types can produce serious chronic disease associated with poor prognosis and high mortality if inadequately treated [275–277]. *E. granulosus* is endemic in sheep raising areas such as the Mediterranean area, Eastern Europe, the Middle East, Africa, South America, Australia, and New Zealand [279] and accounts for more than 90% of human hydatid cysts, mostly in the liver and lungs. *E. multilocularis*, on the other hand, is restricted to the northern hemisphere and causes hepatic disease; extrahepatic primary disease is very uncommon (<1% of cases) but metastasis can in some cases lead to lung involvement. The adult form of *Echinococcus* lives in the intestine of dogs (*E. granulosus*) or foxes (*E. multilocularis*) and sheds eggs that are eventually ingested by intermediate hosts (sheep in *E. granulosus*; rodents in *E. multilocularis*) (Fig. 1.64). Humans are infected accidentally and are usually dead-end hosts for the parasite. Once within the intermediate host, oncospheres are released from eggs in the gastrointestinal tract and penetrate the intestine to enter the bloodstream. In the capillary bed of the target organ (mainly liver and lung), the oncospheres develop into a larval stage called metacestode that slowly grows to form a tumor-like parasitic tissue mass in *E. multilocularis* infection or a cyst like structure in *E. granulosus* infection. The metacestode consists of a germinal layer surrounded by a laminated layer. In natural intermediate hosts, protoscoleces with characteristic birefringent hooklets under polarization microscopy arise within brood capsules which bud from the germinal layer [280]. In humans who are accidental hosts, the pathogenicity of *Echinococcus* is determined by the growth capacity of metacestodes; particularly in *E. multilocularis* infection this is coupled with potential metastatic dissemination. Lung involvement in *E. granulosus* infection may occur through hematogenous or lymphatic dissemination and is detected in 20–35% of cases [281–283], while larvae of *E. multilocularis* in the liver remain indefinitely in the proliferative stage, resulting primarily in local invasion of the surrounding tissues [275]. Contrary to those of *E. granulosus*, the cysts of *E. multilocularis* are tumor-like, infiltrating structures consisting of many small vesicles embedded in the stroma of connective tissues. The metacestode mass usually contains a semisolid matrix rather than fluid. Since most hydatid cysts are solitary and unilateral, primary lung tumors are often suspected based on the clinical and radiological impression [284].

1.4.5.1 Clinical Features
The incubation time for *E. granulosus* ranges from many months to years and is even longer in *E. multilocularis* [275]. The cysts will only become symptomatic once they rupture or cause mass effect. Cysts in the lung may thus cause non-specific symptoms such as chest pain, cough, fever, and dyspnea. Rupture of the cysts into a bronchus can lead to hemoptysis or expectoration of cystic fluid. Remnants of the parasitic membrane in the cyst fluid can cause anaphylactic shock, respiratory distress, asthma-like symptoms, pneumonia, or sepsis [212, 285]. Perforation into the pleural space can result in pneumothorax, pleural effusion, empyema, and allergic or anaphylactic reaction [286, 287]. Because of the latter, diagnosis by radiologic or immunologic means is preferable to biopsy techniques in order to avoid allergic com-
plications or spread of the disease [288]. Patients as young as 1 year and older than 75 years have been reported in *E. granulosus* infection, while the peak age in *E. multilocularis* infection ranges from 50 to 70 years [275]. Not surprisingly, certain occupations such as farm laborers and animal herders are associated with an increased risk of the disease. The diagnosis of pulmonary echinococcosis relies to a large degree on radiologic imaging. Chest radiographs show solitary lesions in up to 60% of cases; multiple lesions either unilateral or bilateral can be identified in the remaining cases [289]. The cysts are round or oval homogenous lesions with well-defined borders that can easily mimic primary lung tumors [211]. These lesions are surrounded by normal lung parenchyma if unruptured. If the cyst has ruptured, a parenchymal reaction in the form of consolidation is often apparent. If the cyst ruptures into the tracheobronchial system, air between the pericyst and laminated membrane can cause an air-fluid level (“Cumbo sign”). On CT scans, several characteristic signs have been described including the water lily, crescent, serpent, spin, and mass-within-cavity signs, among others [278, 289, 290]. Pulmonary echinococcosis is primarily treated surgically, but pharmacotherapy with albendazole or mebendazole has been found useful in cases of recurrent or multifocal disease. The efficacy of pharmacotherapy can be improved by combining albendazole with praziquantel. Inoperable cases may require long-term medical therapy [211, 212].

1.4.5.2 Pathological Features

Grossly, the cysts of *E. granulosus* and *E. multilocularis* can be discriminated by the different growth patterns of the metacestode. *E. multilocularis* is characterized by a multilocular cystic structure with root-like formations of vesicles extending to the surrounding host tissue [280]. In contrast, the macroscopic lesion of *E. granulosus* infection is less complex and consists of a unilocular cyst, that may contain small daughter cysts of various millimeters filled with clear fluid. Although hydatid cysts can develop anywhere in the lung, there is a predilection for the right side and lower lobes of the lung. Single cysts predominate over multiple

**Fig. 1.64** Life cycle of *Echinococcus granulosus* and *Echinococcus multilocularis*. Adult parasites reside in the intestine of definitive hosts, usually dogs (*E. granulosus*) or foxes (*E. multilocularis*) (1). Eggs released in the animal feces are ingested by intermediate hosts (sheep in *E. granulosus*; rodents in *E. multilocularis*) (2). Humans may become infected accidentally and are typically dead-end hosts. Once in the intermediate host, oncospheres are released from eggs in the intestine to penetrate the gut wall and enter the blood system to various internal organs (3). In the target organs, mainly liver and lung, the oncospheres develop into cyst-like structures (hydatid cysts) in *E. granulosus* infection or tumor-like parasitic masses in *E. multilocularis* infection (4). The definitive host in turn becomes infected by ingesting the cyst-containing organs of the infected intermediate host. After ingestion, the protoscolices mature into scolices (5), attach to the intestinal mucosa, and develop into adult stages (6) completing the cycle.
ones which can be unilateral or bilateral. At a microscopic level, the parasitic element consists of a spheroid vesicle with a two-layered wall and liquid contents [291] (Fig. 1.65). Multiple layers of concentric hyaline sheets constitute the outer layer, while the inner layer (germinal layer) is transparent, granular, and of poor consistency (Fig. 1.66). The content of the cyst consists of a clear, colorless liquid that also contains some solid elements, the so-called hydatid sand, that constitute remnants of hooklets and scolices (Figs. 1.67 and 1.68). This liquid contains the antigenic elements that are responsible for anaphylactic phenomena should the cyst rupture [291]. The lung parenchyma is separated from the hydatic cyst by the pericyst, which consists of three layers with a fibrous consistency. The adjacent lung parenchyma may simply be compressed and atelectatic or can show non-specific inflammatory changes. Rupture into the bronchial tree or pleural cavity can lead to bronchial fistulization and pleural effusion, respectively [291].

1.4.5.3 Laboratory Diagnosis and Histochemical Stains

The definitive diagnosis for most cases of echinococcosis in humans is by physical imaging methods, such as radiology, ultrasonography, CT scanning, and magnetic resonance imaging [290]. Laboratory findings are often non-specific. Serologic tests can be used to confirm the diagnosis but are only positive in approximately 50% of cases of pulmonary echinococcosis [278]. Combination of qualitative (immunoelectrophoresis) and quantitative (ELISA or hemagglutinin) tests may increase the diagnostic yield. More recently, a specific immunoglobulin (IgG) ELISA test has been proven to be sensitive tool in the diagnosis of pulmonary echinococcosis [292]. The development of highly sensitive PCR-based methods in recent years has allowed molecular character-
Differential Diagnosis

The differential diagnosis is predominantly radiologic. The nodular lesions of hydatic cysts can be mistaken for a primary lung tumor; in case of a multiple cysts, they may be confused with pulmonary metastasis. Since surgical treatment is the mainstay of therapy in pulmonary echinococcosis, pathological examination will usually reveal the true nature of the lesion [291].

Viral Pneumonias

Viruses cause more infections than all other microorganisms and commonly involve the respiratory tract. Over the past decade, the incidence of viral pneumonia has increased primarily because of improved diagnostic techniques such as the introduction of highly sensitive nucleic acid amplification tests and a growing population of immunocompromised patients [294]. Clinically, viral pneumonia in adults can be divided into two groups: so-called atypical pneumonia in otherwise normal hosts and viral pneumonia in immunocompromised hosts. Influenza virus types A and B account for the majority of viral pneumonias in immunocompetent adults, while immunocompromised hosts are susceptible to pneumonias caused by cytomegalovirus and herpesviruses, as well as measles virus and adenovirus [295]. The latter patients generally experience longer infections with a higher mortality rate than their immunocompetent counterparts, and lung infection remains the most common form of tissue-invasive infection in these patients [296]. Viral infections are generally mild and self-limited in otherwise healthy individuals, but can cause life-threatening infections especially in immunocompromised patients and infants [297]. Polymicrobial infections involving bacterial and viral pathogens or several viruses are common in adults and can enhance the severity of viral pneumonia [298]. Tissue injury in viral pneumonias can show various reaction patterns and include bronchitis, bronchiolitis, interstitial pneumonia, diffuse alveolar damage, giant cell reaction, or minimal pathological changes [297, 299]. Characteristic virus-associated nuclear and cytoplasmic alterations named “cytopathic effect” (CPE) may provide useful clues in the search for the causative etiologic agent in cytological preparations or H&E-stained tissue sections [297]. In addition, four less invasive methods for the detection of respiratory viruses are currently available and include viral culture, rapid antigen detection, serology, and nucleic acid amplification methods [298]. Viral culture has traditionally been the gold standard but has considerable limitations and lower sensitivity in relation to other detection methods such as serology or RT-PCR [298, 300, 301]. Viral antigens can also be detected in respiratory secretions by immunofluorescence or enzyme immunoassay, but generally have lower sensitivity in detecting dual infections compared with nucleic acid amplification methods [298, 302]. Nucleic acid amplification tests, particularly PCR, combine improved sensitivity and specificity with very rapid results compared with conventional methods and are often the preferred means of diagnosis [298]. While most of the viral pneumonias associated with disease in immunocompetent patients often show non-specific histological changes and will likely be diagnosed based on clinical, radiological, and laboratory findings alone, more invasive techniques are more often applied in the diagnostic workup of viral pneumonias in immunocompromised individuals. This is likely due to the fact that these patients often present with unusual or atypical symptomatology and high frequency of characteristic CPE, the histologic identification of which is still considered the gold standard in the diagnosis for certain entities. For these reasons, the following discussion includes primarily the latter entities. The most important characteristics of viral pneumonias are summarized in Table 1.6.

1.5.1 Adenovirus Pneumonia

Adenoviruses are ubiquitous double-stranded DNA viruses [303]. They are the cause of a range of upper and lower
respiratory tract diseases that are usually indolent and self-limited and induce type-specific immunity [304]. Adenovirus infections are endemic worldwide, but epidemics can occur in areas of close living conditions such as among military recruits or in day care facilities for children. Adenovirus infection can present in several different forms. In children, pharyngoconjunctival fever is commonly seen, while gastroenteritis with watery diarrhea is another common presentation. More than 50 serotypes of the virus are currently recognized in humans; the most common serotypes isolated from adults with respiratory disease are 4 and 7, while in children, serotypes 1, 2, 3, 5, 6, and 7 prevail [305]. In the respiratory tract, acute pharyngitis, tracheitis, and pneumonia are the most common manifestations. Serious adenovirus pneumonia with a potential for systemic dissemination can occur in immunocompromised patients, neonates, patients with HIV or malignancy, and organ transplant recipients [306]. The spread of infection is usually fecal-oral among children, though other modes of transmission include aerosol droplet inhalation or direct inoculation [307]. Once pneumonia develops, the infection can spread to other organs, more frequently in children than in adults. Disseminated adenovirus infection is associated with mortality rates as high as 50–80% [308, 309].

1.5.1 Clinical Features

The clinical signs and symptoms of adenovirus pneumonia are non-specific and include cough, dyspnea, purulent sputum, fever, lethargy, sore throat, and myalgia [310]. In this setting, a history of immunosuppression, organ transplantation, military service, or young ages should raise a clinical suspicion of adenovirus pneumonia, especially if patients fail to respond to antibiotic therapy. The most common radiographic findings in adenovirus pneumonia are unilateral or bilateral parenchymal opacities in a patchy distribution. On CT, adenovirus pneumonia usually manifests as diffuse bilateral ground glass opacities with or without consolidation [311]. Cidofovir is the drug of choice for severe adenovirus infections, although not all patients require treatment. Live oral vaccines are

| Table 1.6 Characteristics of pulmonary viral infections |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Virus type      | Adenovirus      | Measles virus   | Cytomegalovirus  | Herpes simplex virus type I | Varicella zoster virus |
| Distribution    | Worldwide       | Worldwide       | Worldwide       | Worldwide       | Worldwide       |
| Predisposing condition | Epidemics in close living conditions; immunosuppression; neonates | Immunosuppression, neonates, malnourished children, older patients | Immunosuppression (especially cell-mediated immunodeficiency) | Immunosuppression, neonates, alcoholics | Smoking, pregnancy, chronic lung disease, immunosuppression |
| Histological pattern | Necrotizing hemorrhagic pneumonia; DAD | Giant cell pneumonia; necrotizing bronchiolitis; squamous metaplasia | Diffuse interstitial pneumonia; miliary pneumonia; minimal change pneumonia; DAD | Necrotizing tracheobronchitis; necrotizing hemorrhagic pneumonia; diffuse interstitial pneumonia | DAD; miliary nodules and calcifications |
| Cytopathic effect | Cowdry A and smudgy intranuclear inclusions | Eosinophilic intranuclear and intracytoplasmic inclusions | Cowdry A (owl’s eye) intranuclear inclusions; basophilic intracytoplasmic inclusions | Cowdry A and B intranuclear inclusions | Cowdry A and B intranuclear inclusions |
| Ancillary testing | Immunohistochemistry; viral culture, PCR | Serology; immunohistochemistry; viral culture, PCR | Serology; histochemistry; immunohistochemistry; viral culture, PCR | Immunohistochemistry; viral culture, PCR | Serology; immunohistochemistry; viral culture, PCR |
| Treatment | Cidofovir | Supportive care, vitamin A, ribavirin | Ganciclovir, foscarnet | Acyclovir | Acyclovir, corticosteroids, mechanical ventilation |
| Vaccine | Live oral vaccine for military personnel, none for civilians | Attenuated live vaccine (MMR) | Currently none | Currently none | Attenuated live vaccine |

DNA deoxyribonucleic acid, RNA ribonucleic acid, DAD diffuse alveolar damage, PCR polymerase chain reaction, MMR measles-mumps-rubella
highly effective in reducing the risk of respiratory adenovirus infection and are in routine use in the military in the United States, but are not currently available to civilians [312].

1.5.1.2 Pathological Features
The lungs of patients with adenovirus pneumonia are typically voluminous and overexpanded and contain multiple small purple red areas of consolidation [313]. Multifocal hemorrhage, emphysematous changes, edema, and atelectasis are other frequent gross findings [313, 314]. Microscopically, pulmonary adenovirus infection is characterized by a necrotizing and hemorrhagic pneumonia which is the result of a necrotizing process affecting the bronchi, bronchioli, and alveolar spaces (Fig. 1.69a). In the interstitium, a prominent mononuclear cell and neutrophilic infiltrate can be found, and hemorrhage, necrotic, and karyorrhectic debris is seen filling the alveolar spaces. Diffuse alveolar damage typically develops with hyaline membranes, type II pneumocyte hyperplasia, and interstitial edema. Cells infected by adenovirus including pneumocytes, bronchial epithelial cells and macrophages can demonstrate two types of intranuclear inclusions: (a) Cowdry type A eosinophilic intranuclear inclusions separated from the nuclear membrane by a halo and (b) dark basophilic or amphophilic nuclear inclusions that completely fill the nucleus and obliterate the nuclear membrane and that display a prominent “smudge” appearance [313–315] (Fig. 1.69b).

1.5.1.3 Laboratory Diagnosis and Immunohistochemical Stains
The diagnosis of adenovirus infections is primarily performed using direct methods including virus isolation in cell culture, antigen detection, and genome detection, with or without amplification. Cell culture from respiratory specimens such as nasopharyngeal aspirates, sputum, cytology preparations, or unfixed tissue specimens remains the gold standard, but can be insensitive and slow. In fixed tissue, techniques such as in situ hybridization, immunohistochemistry, or PCR can further identify the virus [316]. As mentioned above, characteristic viral Cowdry A or “smudgy” inclusions can usually be identified on conventional H&E stains in respiratory epithelium and macrophages.

1.5.1.4 Differential Diagnosis
Adenovirus pneumonia shares features of other viral infections showing interstitial infiltrates, diffuse alveolar damage, and necrotizing bronchitis and bronchiolitis. In addition, other viral agents may induce intranuclear inclusions in the respiratory tract but are usually distinct enough to be separated from adenovirus infection. Herpes pneumonia may on occasion present with necrotizing tracheobronchitis and bronchopneumonia and can produce similar intranuclear inclusions. However, the inclusions of herpes virus show a typical ground glass appearance which can usually be distinguished from the smudge-like inclusions of adenovirus. A severe necrotizing pneumonitis with intranuclear viral inclusions may also be seen in cytomegalovirus infection.

Fig. 1.69 (a) Necrotizing pneumonitis in a case of pulmonary adenovirus infection; (b) higher magnification shows numerous intranuclear inclusions consistent with the characteristic smudge cells of adenovirus. (Courtesy of Dr. C Moran, Houston, USA)
The inclusions in cytomegalovirus infection are large and deeply eosinophilic and have a characteristic halo imparting an “owl’s eye” appearance. Although the typical appearance of the inclusions in different viral diseases should be easily distinguishable, some cases may show non-diagnostic features only. In such cases, immunohistochemical, in situ hybridization, or PCR techniques may be employed to confirm the diagnosis.

### 1.5.2 Measles Virus Pneumonia

Measles (rubeola) is a highly communicable viral infection caused by single-stranded RNA virus of the family Paramyxoviridae of the genus Morbillivirus. The virus can be found worldwide but has particular prevalence in underdeveloped countries. Low vaccination uptake has seen a recent reemergence of measles infection also in areas where the infection was previously considered eliminated [317]. Viral spread occurs from person to person through respiratory droplets caused by coughing or sneezing or through direct contact. Clinically, patients present with fever, generalized maculopapular rash, cough, coryza, or conjunctivitis. Koplik spots (small white spots on the buccal mucosa) are pathognomonic, but are not always present [317, 318]. These symptoms usually resolve spontaneously with complete resolution, and successful clearance of the infection (or vaccination) imparts lifelong immunity. Measles pneumonia is a rare but potentially devastating complication of measles infection and the leading cause of measles-associated death [318, 319]. Measles pneumonia classically occurs in very young, malnourished, or immunocompromised children and young adults [320] with mortality rates among this group as high as 40–70% [321]. The type of pneumonia in measles infection can take two forms: primary measles virus pneumonia often with secondary bacterial superinfection and atypical measles virus pneumonia in children previously immunized with inactivated vaccines and reexposed to the virus [322, 323]. Other rare but serious complications of measles involve the central nervous system and include encephalomyelitis, inclusion body encephalitis, and subacute sclerosing panencephalitis. These rare but serious complications have reinforced the importance of measles control and eventual eradication through active immunization [324].

#### 1.5.2.1 Clinical Features

The prevalence of measles pneumonia is higher in immunocompromised patients, those on immunosuppressive therapy, those who have acquired immunodeficiency syndrome, very young or very old patients, and pregnant women [325–327]. In addition to the classic clinical findings of measles infection (fever, skin rash, cough, coryza, or conjunctivitis and Koplik spots) in these patients, measles pneumonia generally presents with progressive respiratory distress and bilateral air space consolidation on chest radiographs. CT findings include ground glass attenuation, air space consolidation, and small centrilobular nodules [322, 328]. Atypical measles pneumonia shows spherical or segmental consolidation which clears rapidly. Enlargement of hilar lymph nodes and pleural effusions may be associated findings [323]. Supportive care, identification and treatment of complications, and prevention of viral spread are the most important factors in management of measles infection. Vitamin A has been shown to be another effective agent in the treatment of measles with resulting reduction in morbidity and mortality [329]. Ribavirin, interferon α, and other antiviral drugs have been used to treat severe measles infection and its complications [318], and prompt antibiotic treatment is the mainstay of therapy in secondary bacterial infection [330].

#### 1.5.2.2 Pathological Features

The classic pathological finding in measles pneumonia is an interstitial pneumonia characterized by a mononuclear inflammatory infiltrate in the interstitial spaces and prominent giant cells lining the alveolar spaces (“giant cell pneumonia” or “Hecht’s pneumonia”) (Fig. 1.70). The giant cells are epithelial in nature and typically contain multiple distinctive eosinophilic intranuclear and intracytoplasmic viral inclusions [320] which can also be observed in endothelial cells and macrophages [331] (Fig. 1.71). These changes are frequently associated with diffuse alveolar damage with hyaline membranes, reactive type II pneumocyte hyperplasia,

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Fig. 1.70 Florid interstitial giant cell pneumonia due to measles infection. (Courtesy of Dr. C Moran, Houston, USA)
and proliferation of bronchiolar epithelium with extensive squamous metaplasia. A further common finding is the presence of a necrotizing bronchiolitis with extensive destruction of the epithelial surface lining. Of note, the typical giant cells may not always be identified, and bacterial superinfection may obscure the viral etiology in some cases [320].

1.5.2.3 Laboratory Diagnosis and Immunohistochemical Stains

The diagnosis of measles pneumonia is based on the clinical picture and can be confirmed with results of laboratory testing including serologic tests, culture, and polymerase chain reaction. Among these, serological detection of virus-specific IgM in serum or oral fluid is the most common method of laboratory confirmation [332]. In tissue sections, presence of the virus can be confirmed by immunohistochemistry using measles-specific antibodies.

1.5.2.4 Differential Diagnosis

Although the typical inclusion-bearing giant cells in the setting of an interstitial pneumonia are highly suggestive of measles pneumonia, giant cell pneumonia has also been reported in other viral infections [320]. Parainfluenza and respiratory syncytial virus (RSV) infection can produce histological findings in the lung of similar appearance. In these cases, viral inclusions are usually absent or confined to the cytoplasm; however, definitive diagnosis often requires adjunct techniques, such as serologic testing [320]. Another viral infection characterized by giant cell pneumonia is varicella zoster virus infection. Varicella zoster virus can produce prominent intranuclear inclusions similar to measles virus; intracytoplasmic inclusions on the other hand are absent, and the inflammatory process is typically more acute and necrotizing and restricted to the air spaces rather than the interstitial lymphocytic infiltrate seen in measles pneumonia. Further inclusion-bearing viral pneumonias can be caused by adenovirus or cytomegalovirus. The inclusions formed by those infections however are fairly characteristic and easily distinguishable from the multinucleated cells of measles pneumonia [320].

1.5.3 Cytomegalovirus Pneumonia

Cytomegalovirus (CMV) is a double-stranded DNA virus that belongs to the human herpesvirus family. It is a ubiquitous pathogen that infects the majority of humans, with seropositivity ranging from 60 to 70% in the United States to over 90% in developing countries [333–335]. Following primary infection, CMV is maintained in a latent state by persistent low-level viral replication that is adequately controlled in immunocompetent hosts with intact cell-mediated immunity. Most primary infections manifest as asymptomatic or self-limited illness. CMV then establishes lifelong latency in infected cells, primarily lymphoid organs and myeloid cells, which serve as reservoirs for reactivation and as carriers of infection to susceptible individuals [336, 337]. On the other hand, CMV is an important cause of morbidity and mortality among immunocompromised patients especially those with cell-mediated immunodeficiencies, such as bone marrow and solid organ transplant recipients and patients with AIDS. In this patient population, CMV infection can cause a wide variety of disease manifestations, including fever, cytopenia, esophagitis, enterocolitis, hepatitis, adrenalitis, retinitis, encephalitis, and disseminated disease. Pneumonia is among the most serious complications of CMV infection which can result in acute and life-threatening pulmonary disease requiring early diagnosis and intervention to prevent mortality. In some autopsy series focusing on patients with AIDS, CMV was identified as the most common AIDS-defining infection and the most frequent opportunistic infection in the lungs [338].

1.5.3.1 Clinical Features

Patients are considered to have a clinical syndrome compatible with CMV pneumonia based on the following criteria: predisposing host condition, signs, and symptoms of respiratory disease and pertinent radiographic findings. As mentioned above, predisposing conditions primarily include patients with bone marrow transplant, solid organ transplant, leukemia or lymphoma, exposure to chemotherapy, or HIV/AIDS. Signs and symptoms indicative of CMV pneumonia in this context are fever, cough, dyspnea, or tachypnea and new
or increasing oxygen requirement [339]. The radiographic changes associated with CMV pneumonia are defined as the presence of reticulonodular or interstitial infiltrates on chest X-ray, while common findings on CT scan include ground glass opacities, areas of consolidation, small centrilobular nodules, bronchial dilatation, and thickened interlobular septa [339, 340] (Fig. 1.72). First-line antiviral agents used for the treatment of acute CMV disease are intravenous ganciclovir and foscarnet [341, 342] although major treatment strategies, especially in transplant patients, focus on prevention of CMV infection. In this patient group, antiviral prophylaxis and preemptive therapy with the goal to initiate early antiviral treatment to prevent progression from asymptomatic infection to clinical disease are recommended [342].

1.5.3.2 Pathological Features

By light microscopic examination of lung tissue in CMV infection, three different patterns can be observed. The first is a diffuse interstitial pneumonia with inclusion bearing cells lining the alveolar walls or lying detached within alveolar spaces. The interstitial infiltrate is composed mainly of lymphocytes and can result in alveolar wall or interlobar septal thickening. Diffuse alveolar damage with hyaline membrane formation, type II pneumocyte hyperplasia, and intraalveolar exudate may accompany the interstitial process [340, 343, 344] (Figs. 1.73 and 1.74). The second pattern is the miliary pattern characterized by multiple distinct spherical lesions in the lung parenchyma consisting of acute inflammatory and necrotizing nodules with extensive inclusion bearing cells. In the center of the nodules, there is usually total obliteration of the alveolar septa caused by hemorrhage, fibrin deposition, and an acute inflammatory cell infiltrate (Fig. 1.75). These nodules appear to be sharply demarcated from the surrounding lung parenchyma which shows minimal histologic changes [340, 343, 344]. Finally, a “minimal change” pattern may
be seen which contains only scattered inclusion bearing cells with a minimal pathological reaction [344]. As the name implies, CMV causes cytomegaly and is associated with basophilic to amphophilic intranuclear (Cowdry A) inclusions surrounded by a clear halo (“owl’s eye”) as well as intracytoplasmic inclusions with a basophilic granular quality [344] (Fig. 1.76a-c).

1.5.3.3 Laboratory Diagnosis, Histochemical and Immunohistochemical Stains

The gold standard in the diagnosis of CMV pneumonia is the detection of characteristic intranuclear inclusions or positive immunohistochemical staining with monoclonal antibodies directed against CMV in biopsied lung tissue [345]. Additional histochemical stains may be used to confirm the diagnosis and will result in positive staining of the intranuclear inclusions with a Feulgen stain and the cytoplasmic inclusions with PAS or GMS stains. In patients with risk factors precluding biopsy, less invasive diagnostic procedures may be required. Several other methods can detect CMV infection include blood antigen tests, viral culture, or PCR-based testing of bronchoalveolar lavage (BAL) fluid or nasopharyngeal swabs [339, 341].

1.5.3.4 Differential Diagnosis

The clinical context and the characteristic inclusions are normally distinct enough to separate CMV pneumonia from other viral infections with cytopathic inclusions. In this context, the closest mimic is herpes simplex virus (HSV) pneumonia. As opposed to other organ sites, HSV typically does not produce multinucleated giant cells if affecting the lung and the histological features may closely resemble those of CMV pneumonia. Contrary to the inclusions seen in CMV,

![Fig. 1.75](image)

**Fig. 1.75** Cytomegalovirus pneumonia with necrotizing hemorrhagic parenchymal nodule

![Fig. 1.76](image)

**Fig. 1.76** (a) Several inclusion bodies are identified in this case of cytomegalovirus pneumonia; (b) characteristic “owl’s eye” inclusion caused by cytomegalovirus infection of the lung. (Courtesy of Dr. C Moran, Houston, USA); (c) in addition to the nuclear inclusions, multiple basophilic cytoplasmic inclusions may be seen in pulmonary cytomegalovirus infection
HSV does not produce cytomegaly and often demonstrates inclusions with characteristic “ground glass” appearance that fill the entire nucleus [344]. If morphologic examination fails to distinguish these etiologic agents, immunohistochemistry and/or further ancillary techniques as outlined above may be required for definitive diagnosis.

1.5.4 Herpes Simplex Virus Pneumonia

Herpes simplex virus (HSV) pneumonia is caused by double-stranded DNA herpes simplex virus type I, a common pathogen with worldwide distribution [346]. HSV is frequently isolated from the upper respiratory tract of healthy individuals, and it is estimated that 85% of the world population have serologic evidence of exposure [346, 347]. Infection in the immunocompetent host usually remains localized and self-limited often in the form of gingivostomatitis and pharyngitis [348]. Patients at risk for lower respiratory tract infection and disseminated disease include immunocompromised patients, individuals with HIV/AIDS, transplant recipients, alcoholics, patients who have undergone chemotherapy, and neonates [349–352]. As HSV has a predisposition to infect squamous epithelium, another group of patients prone to develop HSV pneumonia includes those that have developed areas of squamous metaplasia in the lower respiratory tract such as smokers, burn victims, or individuals who have undergone intubation [353, 354]. HSV can involve the lower respiratory tract by two different mechanisms: aspiration or extension of oropharyngeal infection into the lower respiratory system and hematogenous spread in patients with viremia [355]. Based on the route of infection, HSV infection may cause tracheobronchitis with mucosal ulcerations or pulmonary involvement with either focal infiltrates or diffuse interstitial disease. HSV pneumonia may also present as a complication of adult respiratory distress syndrome (ARDS) or in the setting of polymicrobial pneumonia [356]. Since the mortality rate of patients with HSV pneumonia is high, especially in immunocompromised individuals, rapid diagnosis and antiviral treatment can have significant impact on survival [357].

1.5.4.1 Clinical Features

The clinical symptoms of HSV pneumonia are non-specific and often mimic bacterial pneumonia with fever, cough, respiratory distress, and purulent pulmonary secretions. However, because HSV orolabial lesions are frequently concurrent, the appearance of such lesions in patients with respiratory symptoms should alert clinicians to suspect HSV pneumonia [358, 359]. Radiologic abnormalities of HSV pneumonia include segmental or subsegmental consolidation and ground glass opacities [340, 356, 358]. CT scans demonstrate multifocal segmental and subsegmental areas of ground-glass attenuation and focal areas of consolidation. Pleural effusions are another common finding [340, 360]. The treatment of confirmed HSV pneumonia consists of antiviral therapy with acyclovir or other antiviral agents such as fosfamet, cidofovir, or ganciclovir [361]; acyclovir is also widely used in the prophylactic treatment for HSV infection in immunocompromised patients [351].

1.5.4.2 Pathological Features

Depending on the mechanism of infection, HSV infection of the lung can present in different patterns. A multifocal necrotizing and hemorrhagic type of pneumonia is the result of direct spread of the virus from the upper to the lower respiratory tract and is usually preceded or accompanied by oral HSV infection and necrotizing tracheobronchitis characterized by necrotic mucosal ulcerations [355]. In the lung, this disease pattern is primarily centered on the bronchi and bronchioles and will show multiple well-defined areas of hemorrhage and necrosis with destruction of the underlying lung parenchyma, loss of the normal lung architecture, karyorrhectic debris, and neutrophilic inflammatory cell response (Fig. 1.76). Infected cells with characteristic intranuclear inclusions are typically found in the periphery of the necrotic nodules. Diffuse interstitial pneumonia appears to be the manifestation of hematogenous dissemination of the virus. In this pattern, the lung architecture is largely preserved with thickening of the alveolar septa by a chronic inflammatory cell infiltrate. In some cases, this pattern can closely resemble diffuse alveolar damage and demonstrate hyaline membrane formation,
alveolar necrosis, and proteinaceous exudate with neutrophilic inflammation [355]. The intranuclear inclusions of HSV infection can show two forms: eosinophilic intranuclear inclusions separated from the nuclear membrane by a halo (Cowdry A) or homogenous amphophilic and glassy appearing inclusions (Cowdry B) (Fig. 1.78).

1.5.4.3 Laboratory Diagnosis and Immunohistochemical Stains

There are currently no standardized diagnostic criteria for HSV pneumonia, and definitive diagnosis usually depends on detection of the virus in lung tissue in the clinical setting of severe respiratory symptoms. This is due to the unknown clinical relevance of detection of the virus from the lower respiratory tract by viral culture from respiratory secretions or bronchoalveolar lavage (BAL) fluid which cannot distinguish between active disease, oropharyngeal contamination, or asymptomatic shedding of the virus [362]. On the other hand, lung biopsy is rarely performed in patients who are acutely ill due to great risk of complications, and isolation of the virus from BAL by means of viral culture or PCR testing in such patients is usually considered sufficient to start antiviral therapy [363]. If tissue specimens are available, careful search for cells infected with HSV demonstrating characteristic Cowdry A or B inclusions becomes mandatory and search for the virus can be assisted by use of monoclonal antibodies to HSV by means of immunohistochemistry.

1.5.4.4 Differential Diagnosis

The presence of Cowdry A inclusions is also a feature of other viral pneumonias such as adenovirus pneumonia, measles pneumonia, or varicella zoster pneumonia. In adenovirus pneumonia, Cowdry A inclusions are similar to those seen in HSV pneumonia, but they are usually also accompanied by “smudge cells.” In measles pneumonia, the inclusions are typically intranuclear and intracytoplasmic, while HSV produces inclusions that are exclusively located in the nucleus of infected cells. Varicella zoster virus, another member of the herpes family, is characterized by inclusions that are identical to those of HSV pneumonia, and definitive diagnosis may require the use of immunohistochemical or molecular techniques.

1.5.5 Varicella Zoster Virus Pneumonia

Varicella infection (chickenpox) is a common, highly contagious infection caused by another member of the herpes virus family, varicella zoster virus (VZV). The disease primarily affects children and young adults and results in a characteristic skin rash which may be accompanied by fever, tiredness, and headache and a generally benign clinical course. Contrary to that, VZV infection can cause severe disease in adults with pneumonia being the most serious and frequent complication in healthy adult individuals [364, 365]. In fact, healthy adults are more than 25-fold more susceptible to develop VZV pneumonia than children with an overall mortality rate between 10% and 30% [366, 367]. Risk factors linked to the development of VZV pneumonia are smoking, pregnancy, underlying chronic lung disease, and immuno-
suppression [368–371] with associated more aggressive clinical course and higher mortality rates. The incidence of varicella pneumonia has been difficult to establish but is estimated to be between 0.32 and 1.36 cases per 100,000 person-years [372, 373]. Overall, the introduction of a universal vaccination in many countries worldwide has led to a dramatic reduction in the incidence of varicella infection, its associated complications, and fatality rates [374, 375].

1.5.5.1 Clinical Features
Varicella pneumonia typically develops 1–6 days after the onset of the characteristic skin rash with symptoms including cough, dyspnea, tachypnea, fever, chest pain, or less commonly hemoptysis; occasionally, respiratory symptoms may precede the skin rash [368, 376, 377]. Chest radiographs will typically reveal diffuse nodular opacities which may progress to air space consolidation and coalesce in the hilar regions and lung bases [378]. Calcific densities may remain as the opacities resolve [379]. High-resolution CT identifies the nodules as ill-defined lesions 5–10 mm in diameter with surrounding ground glass attenuation and focal coalescence [380]. Acyclovir has become the standard of therapy in patients with or at risk of developing VZV pneumonia and should be initiated early along with supportive therapy [381]. More recently, acyclovir in combination with corticosteroids have had a positive influence on recovery rate and outcome [382]. Mechanical ventilation is indicated in cases of fulminant respiratory failure which may otherwise become refractory to treatment [365].

1.5.5.2 Pathological Features
The histological features of VZV pneumonia are those of an interstitial mononuclear inflammatory infiltrate associated with intraalveolar proteinaceous exudate, hyaline membrane formation, and type II pneumocyte hyperplasia (diffuse alveolar damage) (Fig. 1.79). With recovery from the acute phase, spherical nodules develop that are scattered randomly throughout the lung parenchyma. Histologically, the nodules are composed of an outer, often lamellated fibrous capsule frequently enclosing areas of hyalinized collagen or necrotic tissue. Miliary calcifications of varying intensity are another common finding in VZV pneumonia [383]. The cytopathic effect of VZV will be identical to the inclusions seen in HSV pneumonia requiring adjunct techniques such as immunohistochemistry or PCR methodologies to confirm the diagnosis (Fig. 1.80).

1.5.5.3 Laboratory Diagnosis and Immunohistochemical Stains
The diagnosis of VZV pneumonia is primarily based on the typical signs and symptoms of the disease, especially the characteristic skin rash, history of exposure, and nodular opacities on radiologic imaging. Search for specific antibodies by serologic testing, virus isolation in tissue cultures, or PCR testing from BAL or nasopharyngeal secretions may become necessary if the status of exposure is unclear.
or patients present with atypical symptomatology [384]. In lung tissue sections, Cowdry A inclusions may be identified which require immunohistochemistry or molecular methods for separation from HSV-induced inclusions.

1.5.5.4 Differential Diagnosis
Since the pathological findings in VZV pneumonia are often non-specific showing features of acute alveolar damage, careful attention should be paid to the clinical context which will often give clues as to the etiologic agent. To confirm the diagnosis, careful search of lung tissue sections for the presence of any inclusion-bearing cells should be performed. In VZV-infected cells, the inclusions are virtually identical morphologically to those produced by HSV requiring additional workup by immunohistochemical or PCR techniques to confidently identify the causative agent. Separation from other viral pneumonias that can produce a pattern of acute alveolar damage such as adenovirus or CMV pneumonia is accomplished by the different quality of viral inclusions as well as careful attention to the clinical circumstances.

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