

# Pulmonary Infections

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## 1. Introduction

Infections in the respiratory tract are very common but majority involve the upper respiratory system. Pneumonia is usually caused by inhalation of infecting organisms or the same may reach the lung via bloodstream. Pulmonary pathogens can cause tissue damage by a direct invasive cytolytic process or by releasing toxins (endotoxins and/or exotoxins). Acute inflammation may lead to complete resolution, destructive pneumonia with abscess formation, healing by fibrosis or chronic inflammation. Various infective agents causing pneumonia include viruses, bacteria, Mycobacteria, fungi, Chlamydiae, Mycoplasmas or parasites.

The diagnosis of various pulmonary infections is initially based on radiological evaluation depending upon chest X-ray, CT scan or MRI (magnetic resonance imaging). Cytological techniques used for detection of pulmonary infections include sputum examination, bronchial washing & brushing, bronchoalveolar lavage, transbronchial/ transthoracic fine needle aspiration (FNA) and EUS (endoscopic ultrasonography) guided FNA. Transbronchial lung biopsies are performed for histopathological detection of various infections and for histological evidence of invasion. Tissue can be obtained by these techniques for culture or other molecular diagnostic techniques such as polymerase chain reaction (PCR). Special stain most commonly used for bacteria is Gram's stain and for fungi are Gomori's methenamine silver (GMS), Gridley's fungus (GF), and periodic acid-Schiff (PAS) stains.

## 2. Viral infection

Various viruses implicated in viral pneumonia include *influenza*, *parainfluenza*, *adenovirus*, *coxsackie*, *echovirus*, *varicella*, *vaccinia* and *measles*. Most viral pneumonias are mild, but may be more severe or may be complicated by secondary bacterial infection.<sup>1</sup> Microscopically, there may be a diffuse pan-lobular pneumonia characterised by extensive proteinaceous exudative material in alveoli with alveolar wall thickening and infiltration by lymphocytes. Hyaline membranes can be formed lining the alveoli. There may be focal interstitial pneumonia. Cytomegalovirus infection is characterised by cytomegaly with a large eosinophilic intranuclear inclusion surrounded by a pale halo giving an owl's eye appearance.<sup>2</sup> Herpes Simplex Virus (HSV) pneumonia is characterized by intranuclear inclusions with nucleomegaly and basophilic ground-glass alterations in the nucleoplasm.<sup>3</sup>

### 3. Bacterial infection

The bacterial infection in lung usually starts with the introduction of organisms into the airways. The routes by which bacteria can reach air spaces are inhalation of an aerosol, aspiration of respiratory or gastrointestinal secretions, or bacteraemic spread.<sup>4,5</sup> The common bacilli include *Streptococcus pneumoniae*, *Haemophilus influenzae*, anaerobic bacteria, *Staphylococcus aureus*, enteric gram-negative bacilli, *Pseudomonas* spp., *Acinetobacter* spp., *Mycobacterium tuberculosis* and *Legionella* spp.

This usually leads to acute inflammation characterized by sheets of polymorphonuclear neutrophils (figure 1), histiocytes, nuclear debris and necrosis which results in tissue destruction in the form of extensive necrotizing pneumonia with lung abscesses. Long-standing infection can lead to nonspecific chronic inflammation predominated by lymphocytes and histiocytes. Chronic pneumonia is most commonly caused by Mycobacteria and fungi. *Actinomyces* spp., *Nocardia* spp., and *Pseudomonas pseudomallei* can produce such infections. Legionnaire's disease is an acute respiratory infection caused by *Legionella pneumophila*, which stains best in tissue with a silver-based Dieterle stain rather than a Gram stain. Organising pneumonia is characterised by intra-alveolar proliferation of fibroblasts producing nodular structures called Masson bodies.

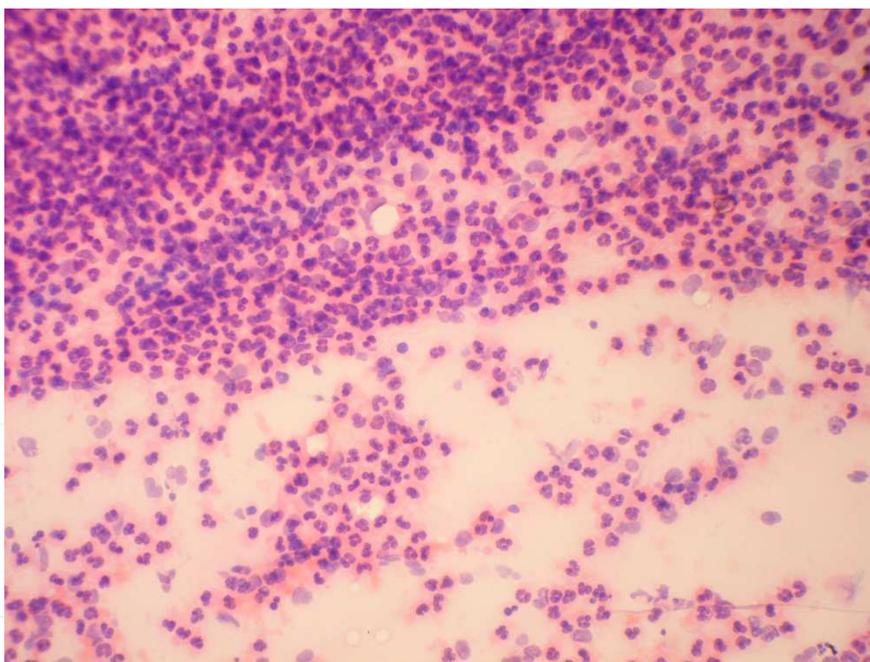


Fig. 1. Sheets of acute inflammatory cells in suppurative inflammation (MGG, 10X)

#### 3.1 Granulomatous inflammation

**Granulomatous Inflammation** is characterized by collection of epithelioid histiocytes and multinucleated giant cells. These epithelioid cells may have an elongated cone like shapes or

may look like tiny carrots in sputum. These need to be differentiated from bronchial epithelial cells as these are elongated columnar cells which can mimic epithelioid cells.<sup>6</sup>

### **Tuberculosis (TB)**

TB can involve various organs but the most common organ involved is lung. TB is more common in the Third World/ developing countries and is much rarer in Western Europe and North America. Primary pulmonary TB usually affects the lower lobes of lung or the anterior segment of an upper lobe, known as the Ghon focus. Microscopically, there are caseating epithelioid granulomas with Langhan's type of multinucleated giant cells and lymphocytes (figure 2 & 3).<sup>7</sup> In tuberculosis, epithelioid histiocytes may be found in about 25% to 50% of sputum specimens.<sup>8</sup> Mycobacteria are identified as elongated beaded acid-fast bacilli (AFB) by Ziehl-Neelsen staining. Auramine-rhodamine stain is another fluorescent dye used to identify these bacilli. Microbiological culture is done using Lowenstein-Jensen medium or Bactec culture. The necrotizing granulomas may be seen in fungal infections or Wegener's granulomatosis. Sarcoidosis is characterised by non-caseating epithelioid granulomas. Secondary pulmonary TB is usually due to re-infection and the lesion is almost always found in the subapical region of an upper lobe. Miliary TB results from seeding of the bacilli via the bloodstream.

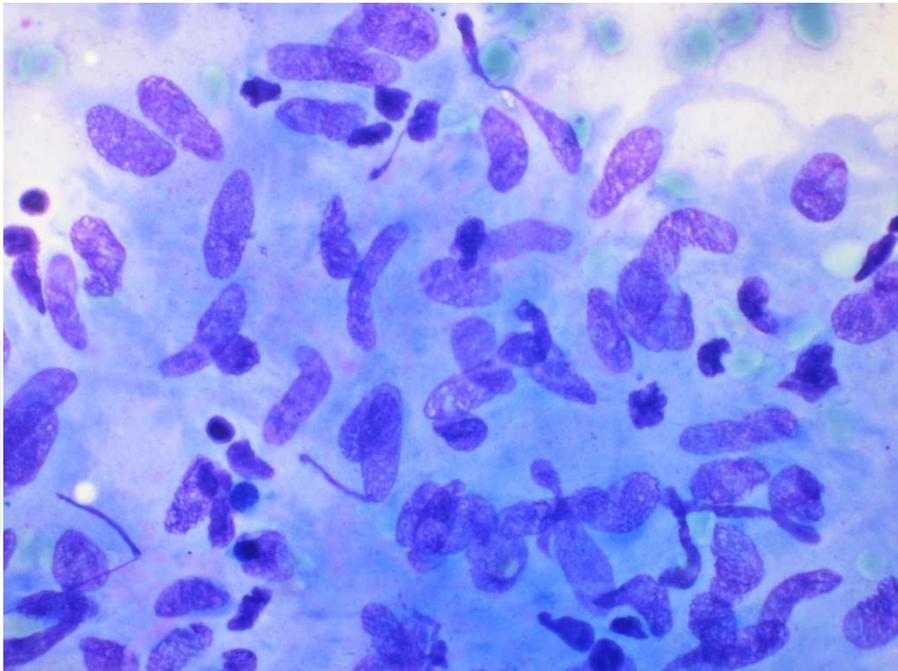


Fig. 2. Epithelioid cell collection and lymphocytes forming a granuloma (MGG, 40X)

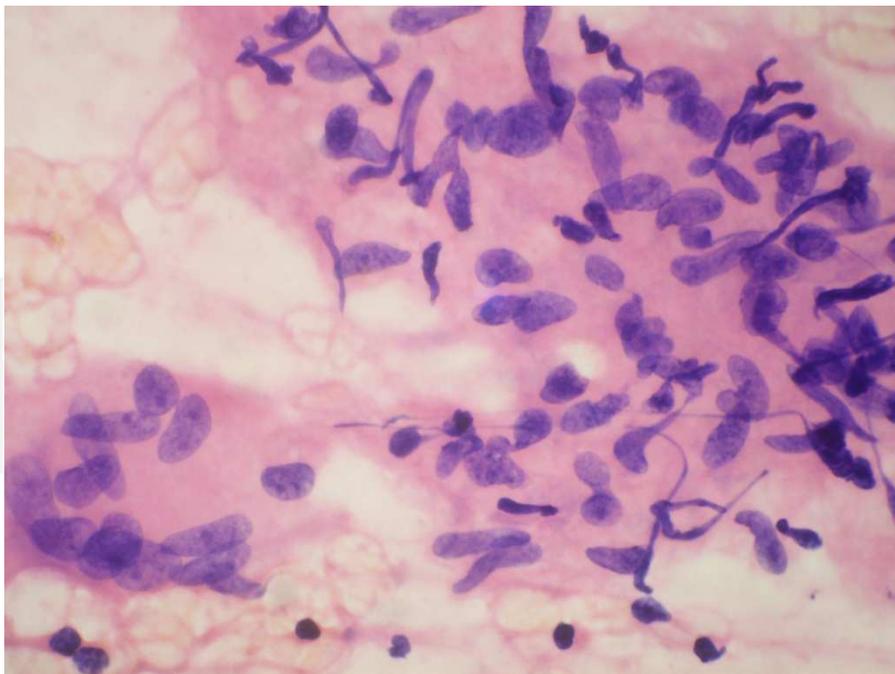


Fig. 3. Epithelioid cell collections in a case of tuberculosis (H&E, 40X)

#### 4. Fungal infections

Fungi are eukaryotic, unicellular to multicellular, or filamentous organisms, that are ubiquitous in nature. The incidence of fungal infections is increased over the last two decades mostly because of increase in immunocompromised patients.<sup>9</sup> The incidence of fungal infections in solid organ transplant recipients is between 5-42% and in bone marrow transplant recipients, the incidence ranges between 15-25% with *Aspergillus*, *Cryptococcus* and *Candida* being the most common fungal infections in these patients.<sup>10,11</sup>

Fungi can elicit various types of tissue reactions such as acute inflammatory, necrosis, granulomatous inflammation. The ability to cause disease depends upon the virulence and the dose of the fungus, the route of infection, immunological status of the host and the organ affected. Lung is one of the most commonly affected organs by opportunistic fungal infections. Majority of the lung infections begin by inhalation of aerosolized fungi from the surrounding environment.<sup>12</sup> The fungi causing invasive pulmonary infection can be primary and opportunistic type of fungi. The primary fungal infection occurs in healthy immunocompetent individuals and the opportunistic fungal infections are common in immunocompromised hosts.

##### 4.1 Aspergillosis

The range of disease caused by fungi of the genus *Aspergillus* include- allergic bronchopulmonary disease, colonization of lung cavities/ intracavitary aspergilloma,

chronic necrotizing bronchial aspergillosis (CNBA), chronic necrotizing pulmonary aspergillosis (CNPA) in mildly immunocompromised individuals and fulminant invasive pulmonary aspergillosis (IPA) with systemic involvement in severely immunocompromised patients.<sup>13,14</sup> *A fumigatus* (most common), *A flavus*, *A niger*, and other *Aspergillus* spp. are the common species causing pulmonary infections.<sup>15</sup>

**Allergic pulmonary reactions** occur due to hypersensitivity to *Aspergillus* antigens especially in patients of bronchial asthma. These include allergic bronchopulmonary aspergillosis, chronic eosinophilic pneumonia, eosinophilic bronchiolitis, mucoid impaction of proximal bronchi or bronchocentric granulomatosis.<sup>16,17</sup> On microscopy, there is an excess of eosinophilic infiltration with Charcot-Leyden crystals, mucus hypersecretion and destructive granulomatous inflammation with degenerated fungal hyphae.<sup>16</sup>

**Pulmonary aspergilloma or fungal/ mycotic ball** is a compact mass of fungal hyphae colonizing pre-existing pulmonary cavity.<sup>14</sup> The cavity may be due to tuberculosis, sarcoidosis, necrotic pulmonary malignancy, bronchiectasis or a bronchial cyst.<sup>18</sup> Majority of the patients develop hemoptysis and the diagnosis is suspected after radiologic detection of thick walled pulmonary cavity with intracavitary mass and a positive serum precipitin reaction to *Aspergillus* antigen.<sup>19</sup>

**Chronic necrotizing bronchial aspergillosis (CNBA)** includes superficial extensive infection of mucosal surface of bronchi resulting in mucosal erosion and ulceration with formation of pseudo-membranes. The patients usually present with wheezing, non-productive cough and dyspnea.

**Chronic necrotizing pulmonary aspergillosis (CNPA)** is a progressive and destructive lesion in mildly immunocompromised individuals with non-cavitary structural lung disease such as sarcoidosis, chronic pulmonary obstructive disease, postradiation fibrosis, diabetes mellitus, tuberculosis, and pneumoconiosis etc. Majority of these patients have history of treatment with low-dose corticosteroids.<sup>20</sup> Treatment includes surgical resection or antifungal therapy with drainage of the pulmonary cavity.

**Invasive pulmonary aspergillosis (IPA)** is a fulminant infection in severely immunocompromised hosts. Vascular invasion is the hallmark of this condition and leads to thrombotic occlusion of arteries and veins. Chest X-ray shows patchy, multifocal or diffuse areas of consolidation, or wedge shaped pleura based infarct like infiltrates or miliary nodules.<sup>21</sup> On microscopy, the nodular infarcts are composed of central ischemic necrosis, surrounded by fibrinous exudates and a peripheral zone of hemorrhage forming a target lesion. Fungal hyphae invade by radial growth and extend from a central occluded vessel. Occlusion of larger vessels lead to formation of wedge shaped pleura-based haemorrhagic infarcts. Disseminated systemic infection occurs in a quarter of patients with IPA involving gastrointestinal tract, central nervous system, kidneys, heart, liver, spleen and thyroid gland.<sup>22</sup>

On microscopic examination, the hyphae of the *Aspergillus* spp. are uniform, narrow (3-6 $\mu$ m in width), septate with regular, progressive and dichotomous branching usually at acute angles (45° angle) from the parent hyphae (figure 4). Conidiophores (fruiting bodies) are seen in lesions exposed to air such as pulmonary/ bronchial lesions. The fungal infection may result in necrotizing or granulomatous inflammation (figure 5) and sometimes is associated with Splendore- Hoeppli phenomenon.

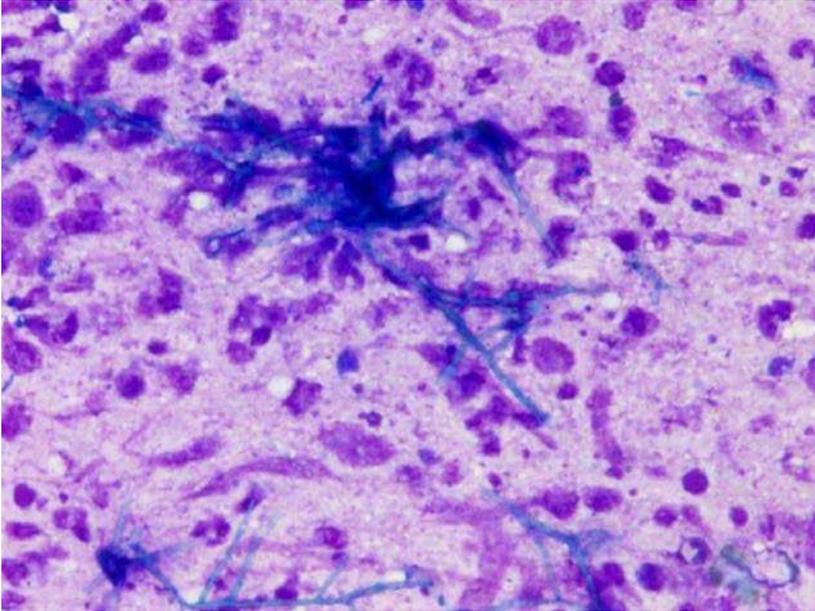


Fig. 4. A long septate hyphae with parallel cell walls of aspergillus in a necrotic background (MGG, 40X)

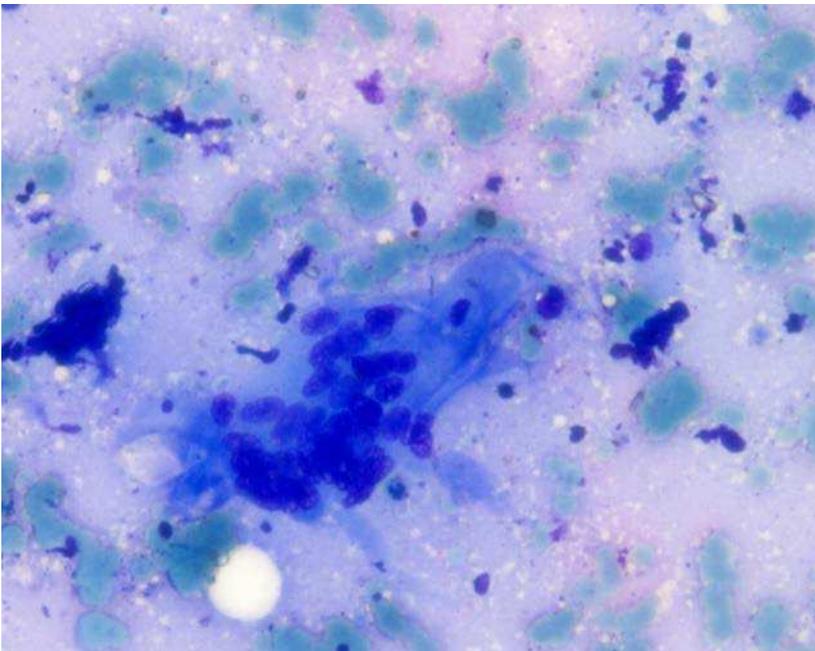


Fig. 5. Occasional hyphae of aspergillus in the multinucleated giant cell (MGG, 40X)

**Differential diagnosis-** The main differential diagnosis of *Aspergillus* includes *zygomycetes*, *Pseudoallescheria boydii*, the *Fusarium* spp. and occasionally *Candida* spp.

**Treatment-** Amphotericin B is the drug of choice followed by Itraconazole or Voriconazole. Localized infections or aspergilloma may be subjected to surgical excision.

#### 4.2 Mucormycosis (Zygomycosis)

Mucormycosis is an opportunistic infection that occurs in immunocompromised hosts especially in patients with acute leukemia or lymphoma, patients treated with corticosteroids, cytotoxic drugs or antibiotic therapy or patients with relapse of an underlying pulmonary disease.<sup>23,24</sup> The agents of mucormycosis include species within the genera *Rhizopus*, *Absidia*, *Mucor*, *Rhizomucor*, *Saksenaea*, *Cunninghamella*, *Mortierella*, *Syncephalastrum*, and *Apophysomyces*. These fungi are widely distributed and the infection is acquired by exposure to their sporangiospores. The patients usually present with fever and progressive pulmonary infiltrates. Chest X-ray usually shows patchy infiltrates, and single or multiple foci of consolidation.<sup>25</sup>

On microscopic examination, the hyphae of mucormycosis are broad (6-25 $\mu$ m or more wide), delicate thin-walled, aseptate, pleomorphic with irregular non-parallel contours. The branching is often irregular arising at right angles to the parent hyphae. The hyphae are often wrinkled and folded upon themselves. The fungal infection is characterized by coagulative necrosis, neutrophilic infiltration and rarely granulomatous reaction. Angioinvasion leads to disseminated infection and ischemic necrotic lesions and infarcts. Amphotericin B is the drug of choice.

#### 4.3 Cryptococcosis

Cryptococcosis starts as lung infection acquired by inhalation of the soil-inhabiting yeast, *Cryptococcus neoformans*.<sup>26,27</sup> The fungus is ubiquitous and is especially abundant in avian, particularly pigeon excreta.<sup>28,29</sup> Although the disease occurs in apparently healthy individuals, it is more often seen as an opportunistic infection especially in patients with haematologic malignancies, AIDS or patients with defective cellular immunity.<sup>30</sup>

The pulmonary lesions include diffuse miliary lesions or patchy consolidation of mucoid nature, which is appreciable in freshly sectioned lungs. On microscopy, cryptococci are of variable size (5-15  $\mu$ m in diameter) present both intra as well as extracellularly. These are ovoid, thin-walled, encapsulated organisms surrounded by a wide, clear capsule and have narrow-based budding (figure 6). This infection may be accompanied by little or no inflammation, a mixed inflammatory response or a granulomatous reaction. The capsule of these organisms is highlighted on PAS-AB (PAS- Alcain blue) or mucicarmine stains.<sup>31</sup> Autofluorescence microscopy in Papanicolaou-stained smears gives auto fluorescence, which helps in rapid diagnosis of cryptococcosis.<sup>32</sup> Cryptococci should be differentiated from Blastomycosis, *Histoplasma capsulatum*, and *Coccidioides immitis*. The combination of amphotericin B and 5-fluorocytosine is used for progressive pulmonary cryptococcosis.

#### 4.4 Histoplasmosis

Histoplasmosis is a pulmonary disease caused by inhalation of airborne infectious conidia of the dimorphic fungus, *Histoplasma capsulatum* var. *capsulatum*.<sup>33</sup> Avian habitat like chicken

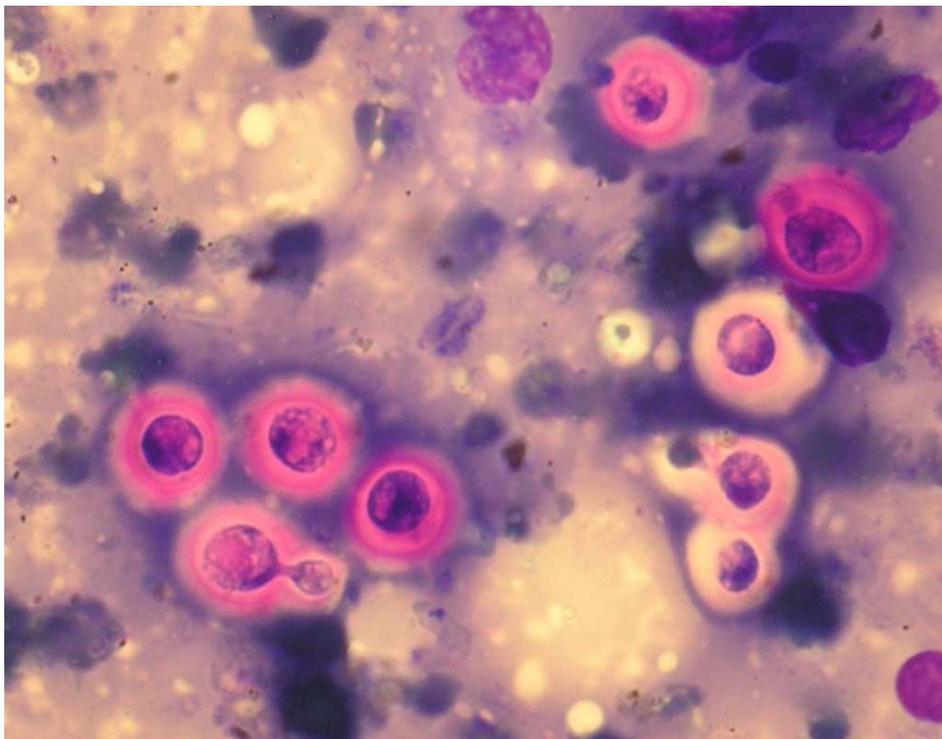


Fig. 6. Extra cellular organisms of *Cryptococcus*; about 5-15  $\mu\text{m}$  in diameter with budding (MGG, 100X)

coops, blackbird roosts, and caves, favor growth and multiplication of the fungus in soil rich in faecal matter. The clinical presentation depends upon the extent of exposure, presence of underlying pulmonary disease and the host immune status. Majority of the infections are asymptomatic. Symptomatic infection occurs in about 10-25% cases and these can be acute pulmonary disease, disseminated disease, chronic pulmonary disease and fibrosing mediastinitis. The confirmation of the recent or past infection is done by a positive reaction to the cutaneous test antigen histoplasmin.

#### **Acute pulmonary disease**

The patients may be asymptomatic or develop influenza-like symptoms after an incubation period of about 15 days. Pathologically, the lesion shows bronchopneumonia with neutrophilic infiltration, along with macrophages, lymphocytes, and plasma cells. Granulomatous reaction with multinucleated giant cells occurs after two weeks followed by caseous necrosis.<sup>34</sup>

#### **Disseminated disease**

Disseminated Histoplasmosis occurs in patients with defective cell mediated immunity and it leads to spread to infection to multiple organs. The patients present with fever with chills, productive cough, hemoptysis, dyspnea, weight loss, headache, drowsiness, diarrhea,

generalized lymphadenopathy, hepatosplenomegaly, purpura, and intestinal ulcerations. Chest X-ray usually reveals diffuse pulmonary interstitial infiltrates.<sup>35</sup> The fungi may be associated with granulomatous reaction and the necrotic lesions may calcify.

### Chronic pulmonary Histoplasmosis

Radiologically, the lesions can be infiltrative, cavitary, fibrosis with emphysema, and the residual solitary nodule or histoplasma (coin lesion).<sup>35</sup> Other findings can be military calcification, pleural thickening, and enlarged hilar nodes.

### Fibrosing mediastinitis

It is a benign condition comprising of fibrosis/ collagenization in mediastinum.<sup>36</sup> The patients present with cough, dyspnea, hemoptysis, and pleurisy. Extensive fibrosis may lead to entrapment of heart or great vessels rarely.

The organisms are yeast like spherical or oval, uniform, 2- 4 $\mu$ m in diameter organisms, which reproduce by single budding (figure 7).<sup>37</sup> The basophilic cytoplasm of the organism is retracted from rigid, thin, poorly stained cell wall, creating a halo/ clear space. The organisms are seen mainly within the macrophages. This may be associated with intense granulomatous reaction with caseation necrosis or calcification, which can mimic tuberculosis. The cell wall intensely stains with special stains especially Gomori methenamine silver stain. Gridley, PAS and Haematoxylin & Eosin stains do not reliably demonstrate these organisms.

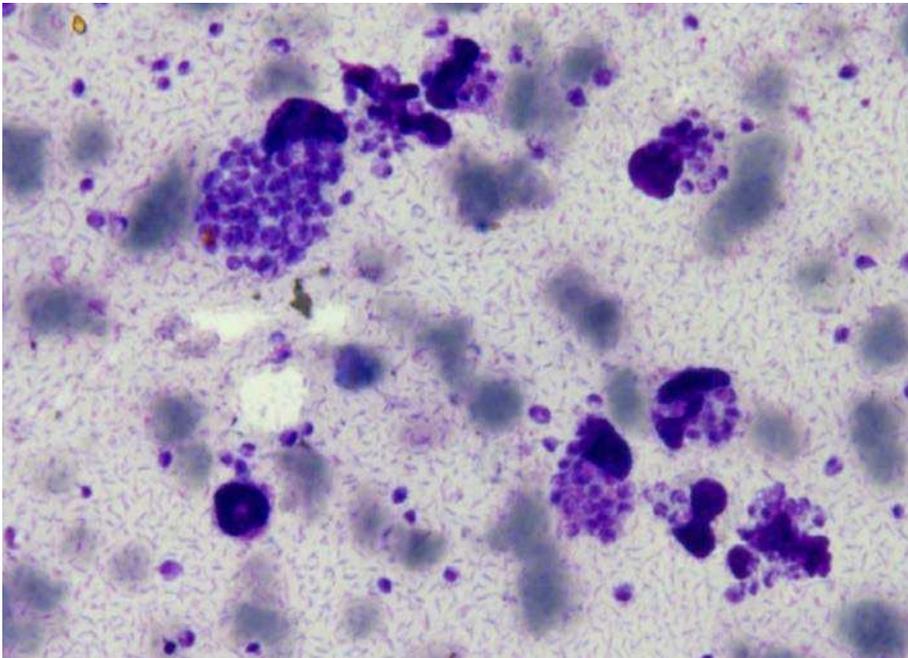


Fig. 7. Extracellular as well as intracellular round to oval, 2-4 $\mu$ m in size, budding yeasts of *Histoplasma* (MGG, 100X)

**Differential diagnosis-** The differential diagnosis of *Histoplasma capsulatum* includes *Cryptococcus neoformans*, *Candida glabrata*, *Coccidioides immitis*, *Blastomycosis dermatitidis* and *Leishmania amastigotes*.<sup>37</sup>

#### 4.5 Blastomycosis

Blastomycosis is a systemic infection caused by the dimorphic fungus, *Blastomyces dermatitidis*. The infection is acquired by inhalation of airborne conidia of the mycelial form forming a pulmonary focus of infection. The pulmonary involvement can be acute or chronic. Acute pulmonary blastomycosis is usually a self-limited illness and the patient may remain asymptomatic or have non-specific symptoms varying from mild influenza-like symptoms to pneumonia. Chest X-ray shows patchy areas of consolidation with involvement of posterior segments of lower lobes of lungs in majority of the cases. The patients with chronic blastomycosis present with chronic respiratory symptoms such as chronic cough and chest pain persisting for weeks or months.<sup>38</sup> Chest X-ray show linear lung infiltrates, mediastinal lymphadenopathy and pulmonary nodules with cavitation mimicking tuberculosis.<sup>39</sup> Multiple organ involvement occurs involving skin, bone and genitourinary tract.

The infection is acquired by inhalation of conidia from woody plant matter. The mold form is transformed into the yeast form in distal airways. In smears or tissue sections, the yeast is seen intra as well as extracellularly in macrophages and polymorphs. The organism may elicit acute abscess like reaction with neutrophilic infiltration to granulomatous reaction with epithelioid granulomas and multinucleated giant cells. The organisms are round to oval, 8-15 $\mu$ m in diameter with thick refractile double contoured walls and single broad based budding. The differential diagnosis includes *H. capsulatum*, *Cryptococcus* and *Coccidioides immitis*.

#### 4.6 Coccidioidomycosis

It is caused by the dimorphic fungus, *Coccidioides immitis*. It is endemic in the southwest United States<sup>40</sup> and north and central Mexico. Pulmonary infection is acquired by inhalation of airborne arthroconidia. The patients may remain asymptomatic or develop influenza-like illness, which is self-limiting. Chronic pneumonia, destructive fibro-cavitary disease or disseminated infection occurs in minority of the patients. Pulmonary lesions can be pneumonic, cavitary, nodulo-caesous and bronchiectatic.<sup>41</sup> Pulmonary lesions are usually associated with acute suppurative or granulomatous inflammation. The organisms are thin-walled, mature spherules, 30-200 $\mu$ m in diameter (figure 8). Rupture of the spherules releases endospores into the surrounding tissue. The differential diagnosis includes sporangia of *Rhinosporidium seeberi*, budding yeast of *Blastomyces dermatitidis* or *Histoplasma capsulatum*.

#### 4.7 Paracoccidioidomycosis (South American blastomycosis)

It is a chronic progressive lung infection caused by *Paracoccidioides brasiliensis* and is endemic in South America. Pulmonary infection may be acute progressive with acute suppurative pneumonia or chronic progressive infection with granulomatous inflammation. The organisms are pleomorphic yeast like, 5-60 $\mu$ m in diameter, reproducing by budding. Yeast cells with fractured walls called mosaic cells are seen in chronic pulmonary lesions. The characteristic multiple budding cells give the appearance of a ship's steering wheel. The

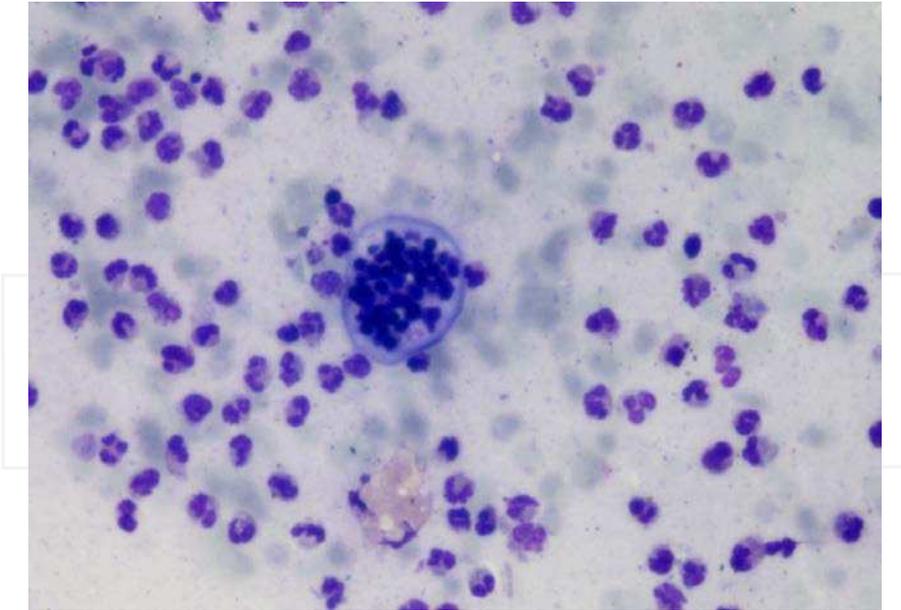


Fig. 8. Thin-walled (30-200 $\mu$ m in diameter) mature spherule of coccidiomycosis (MGG x20X)

blastoconidia produced by these cells can have an oval, tubular appearance or tear-drop blastoconidia attached to the parent cell by narrow necks. This needs to be differentiated from *Histoplasma capsulatum*.

#### 4.8 Candidiasis

Candidiasis comprises of superficial, mucocutaneous, or systemic fungal infection caused by yeast like fungi of the genus *Candida*. *Candida albicans* is the most common type. Pulmonary involvement can be a) endobronchial/ primary pulmonary candidiasis acquired by aspiration of *Candida* spp. from oral cavity or upper respiratory tract, b) hematogenous pulmonary candidiasis and c) embolic pulmonary candidiasis in children with indwelling venous catheters.<sup>42,43</sup> The lesions contain yeast forms and mycelial forms of *Candida*. The yeast-like cells are round to oval, 2-6 $\mu$ m in diameter, and have budding. The mycelia forms have both pseudohyphae and true septate branched hyphae. Pseudohyphae have periodic constrictions at the point where budding yeast cells are joined end to end. The inflammatory response to candida may vary from minimal inflammation to acute suppuration to granulomatous inflammation in chronic infections. The differential diagnosis includes *B. dermatitidis*, *C. neoformans*, *H. capsulatum*, and *S. schenckii*, the tissue forms of these consist of yeast forms.

#### 4.9 *Pneumocystis jirovecii*

This is commonly seen in AIDS patients.<sup>44</sup> Microscopically, the alveoli are usually filled with frothy, eosinophilic, PAS-positive coagulum in which the shadows of the non-staining cysts

are seen. Grocott's Methenamine Silver (GMS) stain is used and the cell wall of the cyst stains black, often with a central dark dot. The cysts are 4 to 6  $\mu\text{m}$  in diameter and spherical or cup/ sickle-shaped. Trophozoites may be up to 8 per cyst, are about 0.5 to 1.0  $\mu\text{m}$  in diameter and stain in Romanowsky (tiny purple dots). The diagnosis may be made on sputum or bronchoalveolar lavage fluid by demonstrating the cysts.

## 5. Bacterial infections that resemble fungal infections

### 5.1 Nocardiosis

Nocardiosis is a localized or disseminated infection caused by aerobic, filamentous, branching gram-positive bacteria.<sup>45</sup> It is an uncommon infection in immunocompetent hosts. Pulmonary lesions may be large cavitating abscesses or diffuse fibrino-suppurative pneumonia. The smears or tissue sections show thin (about 1  $\mu\text{m}$  wide), filamentous, beaded bacilli branching at approximately right angles (figure 9).<sup>46</sup> These are usually obscured by an intense acute necrotizing inflammation as they remain unstained on May-Grünwald Geimsa (MGG) stain, Haematoxylin or Eosin (H&E) or PAS stains. The special stain used for its confirmation is a modified Ziehl- Neelsen stain using a weak decolorizing agent.<sup>47</sup> The main differential diagnosis is *Mycobacterium tuberculosis* and *Actinomyces* (figure 10).

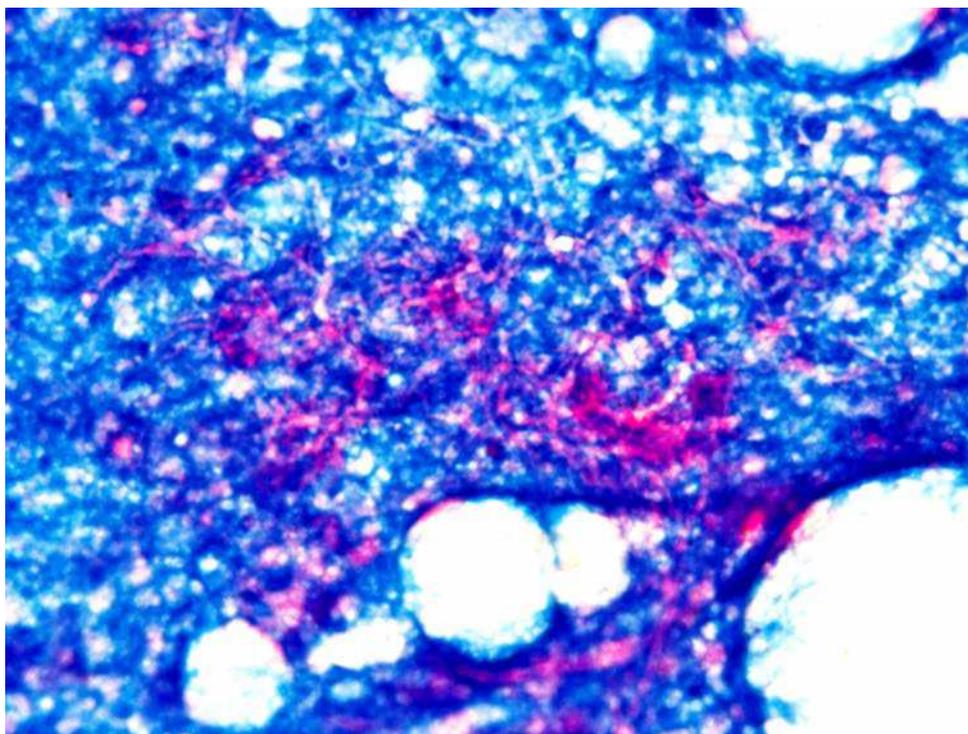


Fig. 9. Multiple long thin filamentous structures (*Nocardia*) in an inflammatory background (Modified Ziehl- Neelsen stain, 100X).

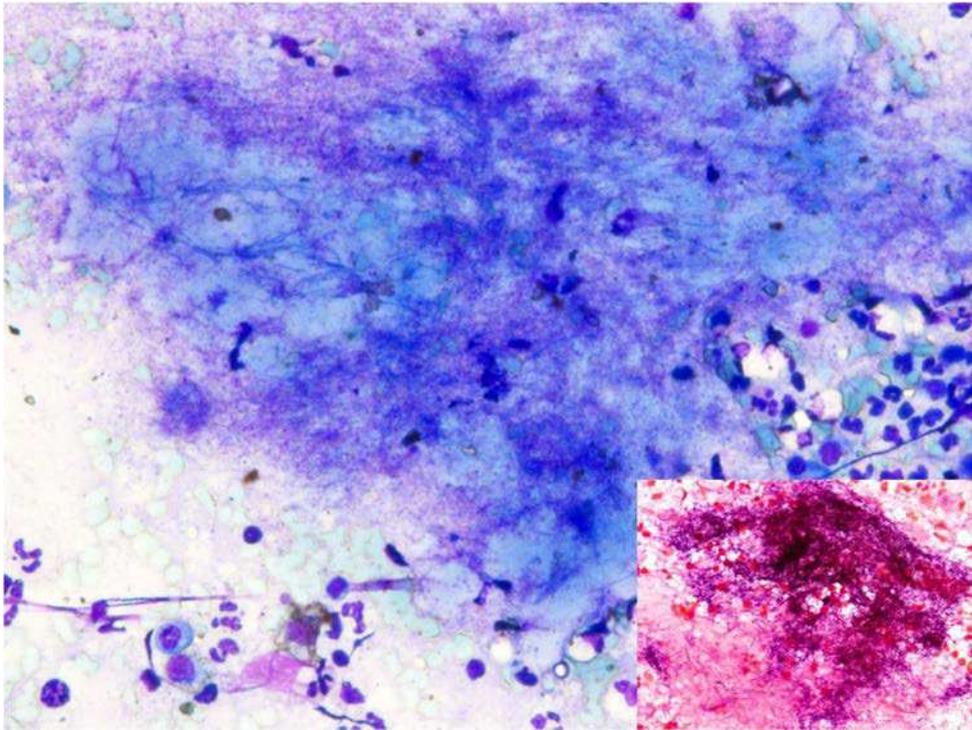


Fig. 10. Filamentous bacilli positive on Gram's stain of Actinomycosis (MGG x40X; Inset-Gram stain- 40X).

### 5.2 Botryomycosis (Bacterial pseudomycosis)

It is a chronic, localized infection of the skin and subcutaneous tissue or various organs including lung and brain.<sup>48</sup> It is caused by non-filamentous bacilli that form granules which include *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Escherichia coli* or *Streptococci*. Pulmonary lesions lead to acute suppurative abscesses with multiple granules which are bordered by eosinophilic, club-like Splendore-Hoeppli material. The differential diagnosis includes nocardiosis and actinomycosis.

### 6. Primary atypical pneumonia

*Mycoplasma pneumoniae* & Chlamydiae are the important causes of primary atypical pneumonia. *Mycoplasma* can be stained by Giemsa but not by Gram's stain and the diagnosis is usually confirmed serologically. Microscopically, a prominent interstitial infiltrate of lymphocytes, histiocytes and plasma cells is seen with interstitial oedema.

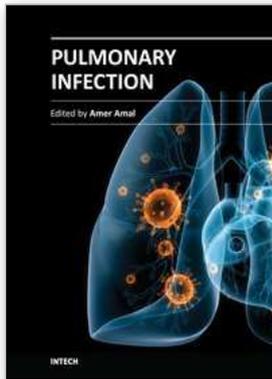
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Pulmonary infections are notorious in causing considerable morbidity and mortality. Caused by bacteria, viruses or fungi, respiratory infections require distinct knowledge of recent advances in pathogenesis. Progress in the understanding of immunopathogenesis of *Acinetobacter baumannii* infection will explain how an atypical organism establishes infection. The chapter regarding pulmonary nontuberculous mycobacterial infections in the State of Para depicts a unique study in an endemic region for tuberculosis in North of Brazil. The diagnosis and treatment of latent tuberculosis is a formidable challenge. Thus, new developments in diagnosis and treatment of latent tuberculosis are included in this book. Challenging in their diagnosis, nontuberculous mycobacterial pulmonary diseases require special education for management. The problems of respiratory infections in the immunocompromised host are increasing in numbers and in resilience to treatment. Therefore, the chapter describing the host immune responses against pulmonary fungal pathogens comes as a necessary section in this book. The insight brought forth from this book can be valuable for both clinicians and scientists.

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