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Educational Case: Chronic Pulmonary Aspergillosis

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The following fictional case is intended as a learning tool within the Pathology Competencies for Medical Education (PCME), a set of national standards for teaching pathology. These are divided into three basic competencies: Disease Mechanisms and Processes, Organ System Pathology, and Diagnostic Medicine and Therapeutic Pathology. For additional information, and a full list of learning objectives for all three competencies, see http://journals.sagepub.com/doi/10.1177/2374289517715040.[1]

Keywords
pathology competencies, organ system pathology, respiratory system, pulmonary infection, immunocompromised, pneumonia, fungi, *Aspergillus* spp

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Primary Objective

Objective RS2.11: Features of Pulmonary Infections in the Immunocompromised and Immunocompetent. Discuss the differences in clinical presentation and etiologic agents of pneumonia in immunocompetent versus immunocompromised hosts.

Competency 2: Organ System Pathology; Topic RS: Respiratory System; Learning Goal 2: Pulmonary Infection

Secondary Objective

Objective M5.1: Types of Fungi and Yeast. Differentiate among filamentous fungi, dimorphic fungi, and yeast and describe the diagnostic approaches for each type.

Competency 3: Diagnostic medicine and Therapeutic Pathology; Topic M: Microbiology; Learning Goal 5: Mycology

Patient Presentation

A 45-year-old female smoker with a past medical history significant for pulmonary bronchiectasis and systemic lupus erythematosus treated with hydroxychloroquine presented with progressive shortness of breath, cough, and pleuritic chest pain. Physical examination was notable for decreased breath sounds over the left posterior lobe of the lung, and rhonchi and crackles bilaterally. Extremities showed no signs of cyanosis, clubbing, or edema.

Diagnostic Findings, Part 1

Computed tomography of the chest showed a 4.4 × 2.6 cm cavitary lesion in the left lower lobe of the lung.

Questions/Discussion Points, Part 1

What Is the Clinical Differential Diagnosis Based on the Imaging Findings?

A cavity is defined as "a gas-filled space, seen as a lucency or low attenuation area, within pulmonary consolidation, a mass,

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or a nodule."[2,3] The differential diagnosis for cavitary lung lesions includes infection, systemic disease, and malignancy. The infectious etiologies to consider include bacteria *Mycobacterium tuberculosis*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, lung abscess due to mixed anaerobes, and fungi (most commonly *Aspergillus*), while less likely, dimorphic fungi *Histoplasma capsulatum and Blastomyces dermatitidis* may present as cavity lesions. Additionally, systemic diseases such as granulomatosis with polyangiitis, rheumatoid arthritis, and sarcoidosis can lead to cavitary lung disease. Uncommonly, pulmonary embolism can also cause cavity formation. It is also extremely important to consider malignancies in the differential diagnosis. Primary lung cancer as well as metastatic cancers can present as cavitary lesion in the lung.[4,5] In order to elucidate the possible cause of lung lesion, patient underwent pulmonary endoscopy to obtain bronchial alveolar lavage (BAL).

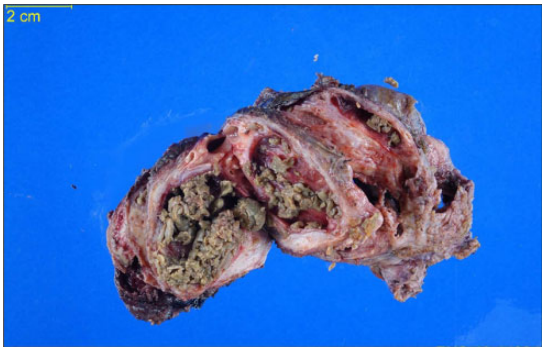

Figure 1. Gross image of the lobectomy specimen. There is ink on the external surface (pleural surface) of the specimen. There is no normal spongy lung tissue to be seen; however, there are multiple cystic spaces lined by thickened fibrotic tissue, ranging in size, containing yellow to green friable necrotic tissue.

Diagnostic Finings, Part 2

The culture of the BAL specimen was positive for *Aspergillus fumigatus* complex.

Question/Discussion Points, Part 2

What Additional Investigations Can Be Performed if Suspecting Fungal Infection?

While a positive fungal culture plays an important role in definitive diagnosis of invasive fungal infections, the sensitivity of culture is low.[5] Additionally, the isolation of fungi from nonsterile site such as sputum or BAL should be interpreted with caution as they can represent colonization rather than infection. In addition, identification of species (which is often based on macroscopic and microscopic morphology of growth in culture) can require days to weeks. Therefore, histopathology often provides a rapid, presumptive diagnosis of invasive fungal infections. Although fungal culture has low sensitivity,[6] when positive, fungal culture plays an important and complementary role in the definitive diagnosis of invasive disease.

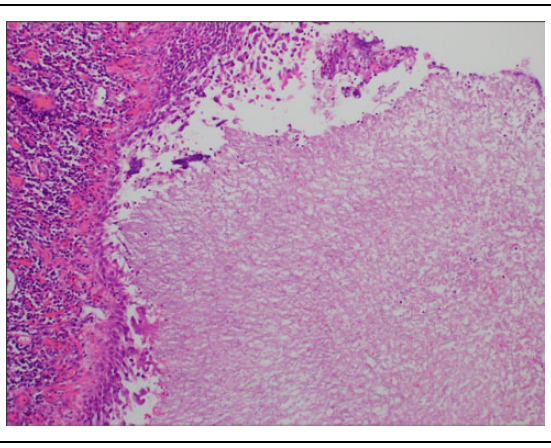

Figure 2. H&E stain of lung airspace, ×20. The fungal organisms are on the right side and the cystic wall with inflammatory cells is on the left. There is extensive necrosis and cavitation of the lung, with aggregates of septate fungal hyphae present within the cavitated space as well as within the larger airways. No angioinvasion is identified.

Diagnostic Findings, Part 3

Her condition remained refractory to antifungal treatment and she underwent a robotic-assisted left lower lobectomy. The lobectomy specimen is shown in Figure 1, and the histology is shown in Figures 2, 3, and 4.

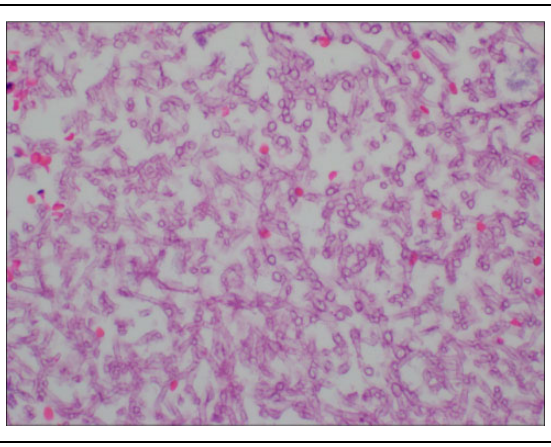

Figure 3. H&E stain, ×100. Higher magnification from the necrotic center of the fungus ball (aspergilloma) showing numerous slender and septate hyphae that branch at acute angles.

Questions/Discussion Points, Part 3

Describe the Gross Findings Seen in Figure 1

Figure 1 shows the lobectomy specimen. There is ink on the external surface (pleural surface) of the specimen. There is no normal spongy lung tissue to be seen; however, there are multiple cystic spaces lined by thickened fibrotic tissue, ranging in

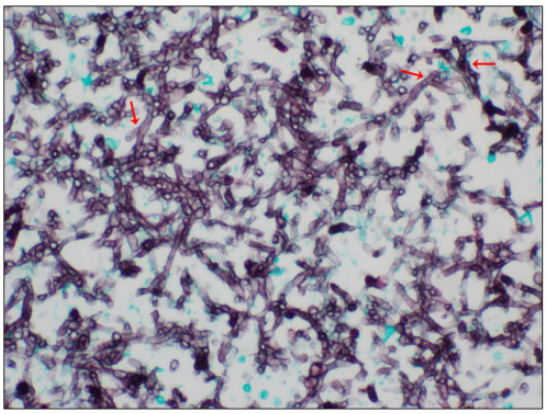

Figure 4. Grocott-Gomori Methenamine Silver (GMS) stain, ×100. The mass of hyphal structures in the center of an aspergilloma, GMS stain highlights nonpigmented (hyaline) septated narrow hyphae with acute angle branching (red arrow).

size from 3.5 to 1.2 cm in greatest dimension, containing yellow to green friable necrotic tissue.

Describe the Histologic Features Seen in Figures 2 and 3

Figure 2 shows extensive necrosis and cavitation of the lung with aggregates of septate fungal hyphae present within the cavitated space as well as within the larger airways. The fungal organisms are on the right side and the cystic wall with inflammatory cells is on the left. No angioinvasion is identified. Figure 3 shows higher magnification from the necrotic center of the fungus ball (aspergilloma) showing numerous slender and septate hyphae that branch at acute angles.

Grocott-Gomori Methenamine Silver Stain Is Performed. How Do You Interpret the Findings (Figure 4)?

The Grocott-Gomori Methenamine Silver (GMS) stain is useful for demonstrating fungal organisms in formalin-fixed tissue. In the appropriate clinical and pathologic context, the morphologic features seen in the GMS stain and in conventional light microscopy can strongly suggest the causative organism. In this image, we see nonpigmented (hyaline) septated hyphae with acute angle branching. While this morphology is highly suggestive of *Aspergillus* spp, there are other fungal pathogens that can demonstrate similar morphology on histopathology. These include *Fusarium* spp, *Scedosporium* spp, *Penicillium* spp, *Paecilomyces variotii, Purpureocillium lilacinum, Acremonium* spp, and other hyaline molds. Pigmented (dematiaceous) fungi can occasionally mimic the morphology of hyaline molds in tissue. *Bipolaris* and *Curvularia* spp are the most common of the pigmented molds that can cause allergic lung disease. While hyphae of dematiaceous fungi are often pigmented and are irregularly swollen forming yeast-like structures, variations in morphology that are observed should be included in a broad differential diagnosis. It is important to note that in most cases histopathology alone cannot be relied upon for definitive fungal species identification.[7,8] Therefore, fungal culture plays an important and complementary role in diagnosis and management of invasive disease. In this case, a fungal culture of the BAL specimen was positive for *A fumigatus* complex.

What Is the Clinical Spectrum of Aspergillus *Lung Disease?*

Members of the *Aspergillus* spp cause a variety of lung diseases depending on the immune status of the patient (Figure 5). Allergic bronchopulmonary aspergillosis (ABPA) is an allergic response to the inhaled conidia of *Aspergillus* spp, which can exacerbate asthma and cystic fibrosis. The diagnosis of ABPA is usually made clinically. However, microscopically, mucoid plugs with degenerating eosinophils and eosinophilic pneumonia will be seen within the airways.

Chronic pulmonary aspergillosis is a long-term infection that usually affects immunocompetent individuals. It is noninvasive colonization of preexisting lung cavities by *Aspergillus* spp. In lung, cavities caused by tuberculosis are the most frequently described predisposing condition; however, emphysema, sarcoidosis, bronchiectasis, ankylosing spondylitis, and other infections have also been described. Colonization leads to formation of a fungus ball (aspergilloma).[7,9] Patients with aspergilloma can remain asymptomatic or present with a massive hemoptysis. It is also important to consider another related entity of chronic cavity/necrotizing pulmonary aspergillosis which can also clinically present as slowly evolving lesion over several months to years. Microscopically, aspergilloma shows layers of fungal hyphae with a surrounding fibrotic reaction.[7-9] In contrast, chronic cavitary/necrotizing pulmonary aspergillosis has a necrotic tissue layer with abundant hyphae surrounded by granulation tissue and an outer layer of fibrosis. It is crucial to examine the entire wall to look for areas of necrosis and exclude fungal invasion of lung parenchyma and vasculature.[7]

Acute invasive aspergillosis may be seen in the setting of modest immunosuppression accompanying disorders such as diabetes mellitus or aerosolized steroid use in asthmatic patients. Fungal hyphae may be seen filling the lumens of airways without evidence of chronic commensal growth (microorganisms that are present on body surfaces covered by epithelial cells and are exposed to the external environment). Microscopically, foci of necrosis and hemorrhage associated with the invasion of vascular lumina by hyphae are seen. Wedge-shaped infarcts can also occur when large arteries are involved. In some cases, these infarcts may lead to progressive cavitation in which future fungus balls may develop.[9] There is high morbidity and mortality associated with invasive aspergillosis, and timely initiation of treatment is imperative. The treatment options include single-agent or combination antifungal therapy, immunotherapy, and surgery for refractory disease. It is to be noted that globally resistance to azole antifungals has been reported in *A fumigatus*, which is the most frequent cause of invasive aspergillosis worldwide.[10]

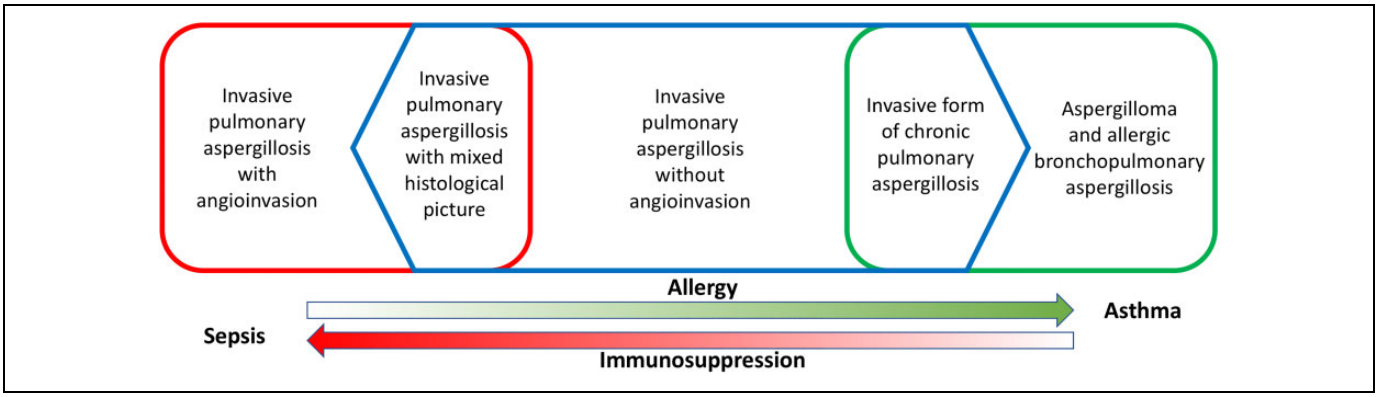

Figure 5. Diagram of a spectrum of pulmonary disorders caused by *Aspergillus* spp.

Patients who have been chronically immunosuppressed and/or are neutropenic (ie, bone marrow or solid organ transplant recipients) are at an increased risk of angioinvasive aspergillosis, a serious and potentially life-threatening manifestation of this disease spectrum. Remarkably, angioinvasive aspergillosis is rather uncommon in patients with HIV.[7] In this condition, fungal hyphae invade blood vessels and disseminate to other organs. The presence of sunburst vasculocentric hyphal growth is diagnostic of disseminated foci of infection. Identification of angioinvasion is augmented with utilizing silver and elastic stains. Microscopically, it appears as dilated spaces filled with necrotic debris and fibrin filled with organisms. Furthermore, destruction of vessel walls by a necrotizing process with central areas of necrosis admixed with abundant polymorphonuclear leukocytic infiltrates is seen.[9,11]

Teaching Points

- When diagnosing *Aspergillus*-related disease, it is important to have a complete clinical picture, including the immune status of the patient.
- Correlating H&E, GMS, and culture is important in developing an accurate diagnosis.
- It is imperative to keep in mind potential morphological mimickers of *Aspergillus* spp.
- Allergic bronchopulmonary aspergillosis is an allergic response and is seen in patients with asthma and cystic fibrosis.
- Chronic pulmonary aspergillosis is a chronic colonization of preexisting cavities by *Aspergillus* spp.
- It is important to identify areas of invasive growth in chronic pulmonary aspergillosis.
- Allergic bronchopulmonary aspergillosis, chronic pulmonary aspergillosis, and necrotizing pulmonary aspergillosis are commonly found in immunocompetent individuals. Conversely, acute invasive aspergillosis is seen in modestly immunosuppressed patients and angioinvasive aspergillosis is often diagnosed in chronically immunocompromised individuals.

Declaration of Conflicting Interests

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