The spectrum of imaging findings in pulmonary aspergillosis

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Authors: M. Limeme, A. Achour, B. Achour, Y. Ben Youssef, H. Zaghouani Ben Alaya, H. Amara, H. Regaieg, D. Bakir, C. Kraeim; Sousse/TN
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Learning objectives

Aspergillosis is a mycotic disease caused by *Aspergillus* species, usually *A. fumigates* (Fig.1). *Aspergillus* is a genus of ubiquitous soil fungi. The histologic, clinical, and radiologic manifestations of pulmonary aspergillosis are determined by the number and virulence of the organisms and the patient's immune response [1]. The *asergillus fungus* causes a spectrum of pulmonary infections ranging from saprophytic to invasive forms. Pulmonary aspergillosis can be subdivided into five categories: saprophytic aspergillosis (aspergilloma), hypersensitivity reaction (allergic bronchopulmonary aspergillosis), semi-invasive (chronic necrotizing) aspergillosis, airway-invasive aspergillosis (acute tracheobronchitis, bronchiolitis, bronchopneumonia, obstructing bronchopulmonary aspergillosis), and angioinvasive aspergillosis [1].

We propose to attend these objectives:

- Describe and illustrate clinical, histological and imaging findings seen with the spectrum of Aspergillus infection.

- Recognize the high resolution computed tomography (HRCT) findings of both saprophytic and invasive pulmonary aspergillosis.
Background

Aspergillus is an ubiquitous fungus that exists as a saprophyte in nature and when inhaled, is capable of causing considerable pathogenesis within the respiratory tract in humans. Pulmonary aspergillosis represents a common and potentially lethal opportunistic infection. Because of the morbidity and mortality associated with pulmonary Aspergillus infections, early recognition constitutes an important task for all practicing radiologists. Fortunately, each form is associated with specific predisposing host risk factors. In addition, each form possesses characteristic radiologic features, which, when viewed in the appropriate clinical setting, should immediately suggest the diagnosis. Specifically, each manifestation of pulmonary aspergillosis depends primarily on the host's immune response to the organism. A simple classification scheme of pulmonary aspergillosis can therefore be constructed, contingent on the integrity of the host immune system.

1) Invasive aspergillosis

Acute invasive pulmonary aspergillosis (IPA) is the archetypal form of invasive aspergillosis. It is the result of invasion of the lung by Aspergillus spp. mycelia in immunocompromised patients, especially those who are at extraordinary risk of such infection, i.e. those with hematological conditions with or without neutropenia, and bone marrow transplant (85% of all IPA). The small remainder of patients who develop IPA suffer primarily from defects of T-cell mediated immunity, such as AIDS patients with low CD4 counts (B/50 c/mol), solid organ transplant recipients and recipients of high dose corticosteroid therapy in whom it occurs sporadically [2].

1.1 Acute Bronchopneumonia

Chest Radiography

Aspergillus bronchopneumonia typically manifests as patchy air space consolidation sometimes accompanied by small nodules (Fig.2). The differential diagnosis of such a radiographic appearance is extensive, including pyogenic bronchopneumonia, pulmonary hemorrhage, non-cardiogenic pulmonary edema, and other acute lung injury patterns [4].

CT

CT may reveal multifocal areas of air space consolidation (Fig.3) or nodules (Fig.4) that may be peribronchiolar in distribution (Fig.5). Small centrilobular nodules, indicative of bronchiolitis, may also be apparent [4].

1.2 Acute Tracheobronchitis
Chest Radiography

Chest radiographic manifestations in acute tracheobronchitis may be minimal or entirely lacking. Multifocal areas of atelectasis (Fig.6) may be all that is apparent radiographically [4].

CT

CT findings of acute tracheobronchitis due to Aspergillus may be subtle. CT may reveal focal plaques along the tracheal wall, with or without associated minimal thickening of the tracheal mucosa. Such findings may resemble other causes of focal tracheobronchial abnormalities, such as papillomas or adherent mucous [4].

2) Angioinvasive Aspergillosis

Chest Radiography

Shortly after the onset of infection, when the patient's immune system is most profoundly compromised, chest radiography is often nonspecifically abnormal, revealing patchy segmental or lobar consolidations or multiple, vaguely nodular opacities. During this time, Aspergillus hyphae invade the pulmonary vasculature, resulting in thrombosis, pulmonary hemorrhage, and infarction. As the patient's immune system recovers, about 2 weeks after the onset of infection, the chest radiograph may demonstrate the "air crescent" sign. The air crescent sign consists of a nodular opacity that represents retracted and infarcted lung associated with crescentic or circumferential cavitation. Although this finding is not specific for angioinvasive aspergillosis, it is highly characteristic in the proper clinical setting. It may be seen in nearly 50% of patients with invasive aspergillosis, particularly those in whom the initial lesion was consolidation or a mass seen on CT. Once the air crescent sign has developed and antifungal therapy is begun, the cavities frequently become smaller and better defined. They close an average of 2 weeks after onset, resolving to small scars over the ensuing months [4].

CT

Early in the course of infection, while the patient is still profoundly immunocompromised, CT may reveal single or multiple nodules or masses that often have surrounding ground-glass opacity, the so-called "halo" sign (Fig.7). This finding represents pulmonary hemorrhage and coagulative necrosis surrounding central necrotic nodules containing Aspergillus hyphae. These lesions may progress and enlarge, coalescing into confluent consolidations, unless treatment has begun. If antifungal therapy is instituted, lesions may remain stable until the immune system recovers, at which time the air crescent sign may be seen (Fig.8). Angioinvasive Aspergillus infections frequently are associated with extrathoracic spread, and local pulmonary disease may be complicated by extension of infection into the pleural and/or pericardial spaces [4].

3) Semiinvasive Aspergillosis (Chronic Necrotizing Aspergillosis)
Chronic necrotizing aspergillosis (CNA) is an indolent, destructive process of the lung due to invasion by Aspergillus species (usually A fumigatus). Semi-invasive aspergillosis, also known as chronic necrotizing aspergillosis, is characterized at histologic analysis by the presence of tissue necrosis and granulomatous inflammation.

Clinical symptoms are often insidious and include chronic cough, sputum production, fever, and constitutional symptoms [1].

Chest Radiography

Semiinvasive aspergillosis usually presents as upper lobe consolidation and pleural thickening that slowly progresses to cavitation over weeks or months. The cavity may contain an internal opacity, sometimes resembling aspergilloma. The upper lobe disease commonly contacts thickened pleura. The differential diagnosis includes primarily other fungal infections, typical and atypical mycobacterial infections, and neoplasms [4].

CT

CT usually demonstrates irregular upper lobe consolidation that slowly cavitates over time (Fig.9).

The cavity may demonstrate an internal opacity with irregular strands extending from the intracavitary mass to the cavity wall. Occasionally, high attenuation material, presumably calcium, may be evident within the opacity. Other fungal infections may have a similar appearance, although high attenuation material within the intracavitary mass is characteristic of Aspergillus infection [4].

4) Saprophytic aspergillosis (Aspergilloma)

This is the most common and best-recognized form of pulmonary involvement due to Aspergillus. Saprophytic aspergillosis (aspergilloma) is characterized by Aspergillus infection without tissue invasion. The aspergilloma (fungalball) consists of masses of fungal mycelia, inflammatory cells, fibrin, mucus, and tissue debris, usually developing in a preformed lung cavity. Although other fungi may cause the formation of a fungal ball (for example, Zygomycetes and Fusarium), Aspergillus spp (specifically, A fumigatus) are by far the most common etiologic agents [3].

Although patients may remain asymptomatic, the most common clinical manifestation of saprophytic aspergillosis is hemoptysis [1].

Chest Radiography

Aspergilloma usually manifests as a round or oval mass partially filling cavity and creating the characteristic finding of the air crescent sign. If the fungus ball completely fills the pulmonary cavity, the air crescent sign may not be observed. The fungus ball may demonstrate mobility with decubitus imaging. The differential diagnosis of the
appearance of a fungal ball includes a blood clot within a preexisting cavity, necrotic carcinoma, hydatid cyst, and lung abscess with necrosis. Aspergillomas are commonly located in the upper lobes, adjacent to the pleura, and the pleura itself may be thickened. The fungus ball may rarely calcify, and it may diminish or remain unchanged in size over time. An air-fluid level is usually not present. The cavity itself is usually thin walled, although thickening of cavity walls before a discrete internal opacity is evident may herald infection [4].

CT

CT demonstrates to advantage the finding of a mobile intracavitary mass, characteristic of aspergilloma. High resolution CT may also reveal small fungal strands bridging the fungus ball and cavity wall in cases when the air crescent sign was not visible on chest radiographs (Fig.10). CT may also demonstrate foci of increased attenuation within the aspergilloma, presumably reflecting calcium. As with chest radiography, CT may reveal thickening of the wall of a preexisting cavity before the fungus ball is evident [4].

5) Allergic Aspergillosis: Allergic Bronchopulmonary Aspergillosis and Hypersensitivity Pneumonitis

Allergic bronchopulmonary aspergillosis (ABPA) is the archetype of allergic aspergillosis. It is a result of an immune reaction to colonization of Aspergillus fumigatus within the airways of patients who are likely to be atopic and immunocompetent. The syndrome is clinically characterized by chronic asthma, mucus production, elevated Aspergillus-specific and total IgE, and eosinophilia. A small but significant fraction of patients who suffer from chronic asthma have underlying ABPA, including patients with cystic fibrosis [2].

Acute clinical symptoms include recurrent wheezing, malaise with low-grade fever, cough, sputum production, and chest pain. Patients with chronic allergic bronchopulmonary aspergillosis may also have a history of recurrent pneumonia [1].

5.1 Allergic Bronchopulmonary Aspergillosis

Chest Radiography

The characteristic chest radiographic findings of ABPA include central bronchiectasis and mucoid impaction. Mucoid impaction typically appears as branching opacities, usually central and in an upper lobe distribution, often described as a "gloved finger" morphology. The opacities seen on the radiographs of patients with ABPA are commonly transient and recurrent but may occasionally remain unchanged or even grow over time. Rarely, impacted material within an ectatic bronchus may calcify densely enough to be detected by chest radiography [4].
CT demonstrates to advantage the characteristic findings of ABPA: central bronchiectasis and mucoid impaction. Bronchiectasis commonly involves the medial two thirds of the lung, affecting segmental and subsegmental bronchi. While the central distribution of bronchiectasis suggests the diagnosis of ABPA, it is not specific for that diagnosis. The appearance and distribution of bronchiectasis in ABPA do overlap to some degree with other entities such as cystic fibrosis, postinfectious bronchiectasis, and immunodeficiencies. Furthermore, bronchiectasis in ABPA may be widespread, resulting in branching opacities at the lobular level. Occasionally, high attenuation material may be encountered within impacted bronchi, presumably reflecting calcium deposits [4]. Bilateral bronchial and bronchiolar dilatation, large mucoid impactions (mainly in the lower lobes), and diffuse lower lobe consolidation caused by postobstructive atelectasis is an obstructing bronchopulmonary aspergillosis (Fig.11), it is not an invasive aspergillosis disease characterized by the massive intraluminal overgrowth of Aspergillus species, usually *A fumigatus*, in patients with AIDS [1].

5.2 Aspergillus Hypersensitivity Pneumonitis

**Chest Radiography**

Chest radiography in subacute hypersensitivity pneumonitis may reveal ground-glass opacity and/or diffuse small nodules. One may rarely encounter a pattern of recurrent transient opacities superimposed on a fine micronodular pattern that may specifically suggest the diagnosis of hypersensitivity pneumonitis. In most cases, the chest radiograph in hypersensitivity pneumonitis is not specific, and the differential diagnosis includes pneumonia, chronic eosinophilic pneumonia, pulmonary hemorrhage, and interstitial pneumonias such as nonspecific interstitial pneumonitis or smoking-related interstitial lung diseases. Chronic hypersensitivity pneumonitis may show findings of fibrosis such as decreased lung volumes, reticulation, traction bronchiectasis, and honeycombing. The differential diagnosis includes primarily idiopathic pulmonary fibrosis [4].

**CT**

Classic subacute hypersensitivity pneumonitis manifests as diffuse, small centrilobular nodules that are often ground glass in attenuation (Fig.12). Multifocal areas of ground-glass opacity and air trapping are also commonly encountered; occasionally, the latter may be the only finding evident. Although pulmonary hemorrhage, pulmonary venoocclusive disease, and viral infections may also result in centrilobular ground-glass opacities, symmetric, diffuse, centrilobular, ground-glass nodules are characteristic of subacute hypersensitivity pneumonitis. Chronic hypersensitivity pneumonitis typically presents as traction bronchiectasis and interstitial thickening, often associated with areas of ground-glass opacity.
Mosaic perfusion may also be evident (*Fig. 13*). Idiopathic pulmonary fibrosis is the major differential diagnostic consideration [4].
Fig. 1

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Fig. 2: Chest Radiography. Patchy air space consolidation

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Fig. 3: Thin-section CT scan (lung window) shows Patchy air space consolidation

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**Fig. 4:** Thin-section CT scan (lung window) shows multifocal areas of nodules

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Fig. 5: Thin-section CT scan (lung window) shows peripheral branching structures associated with focal areas of consolidation in the right lower lobe.

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**Fig. 6:** Chest radiography. Multifocal areas of atelectasis

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Fig. 7: Angioinvasive aspergillosis in a 40-year-old woman with acute myelogenous leukemia. Thin-section CT scan (lung window) shows multiple cavited nodules and masses with surrounding ground-glass opacity, also-called "halo" sign

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Fig. 8: Angioinvasive aspergillosis in a 54-year-old man. Thin-section CT scan (lung window) shows multiple cavitated nodules with air crescent sign.

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**Fig. 9:** Semi-invasive aspergillosis in a 68-year-old man with chronic bronchitis and recurrent episodes of mild hemoptysis. Thin-section CT scan (lung window) shows right rounded mass of consolidation with associated cavitation in the upper right lobe.

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**Fig. 10:** Aspergillomas in a 55-year-old man with residual tuberculosis. Chest computed tomographic (CT) scan (lung window) shows a large cavity in the upper lobe containing fungus balls.

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**Fig. 11:** Obstructing bronchopulmonary aspergillosis in a 30-year old woman with AIDS. CT scan shows multiple rounded and tubular areas of increased, findings that are consistent with mucus-filled airways. Bronchoscopy revealed that the lumen was packed with inflammatory material.

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Fig. 12: 12. Chest computed tomographic (CT) scan (lung window) shows small centrilobular nodules that are often ground glass in attenuation.

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Fig. 13: Chest computed tomographic (CT) scan (lung window) shows mosaic perfusion.

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Imaging findings OR Procedure details

Chest radiography and high resolution computed tomography (HRCT) with multiplanar reconstructions are used to perform exams.
Conclusion

Aspergillosis is a serious complication that is frequently seen in immunocompromised patients. The radiologist plays a major role in the diagnosis of pulmonary *Aspergillus* infection. When radiographic findings are subtle or equivocal, CT frequently allows identification of the disease process. Although imaging findings in various types of pulmonary aspergillosis may be nonspecific, in the appropriate clinical setting, familiarity with the thin-section CT findings may suggest and even help establish the specific diagnosis.
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