Spectrum of Pulmonary Aspergillosis: Histologic, Clinical, and Radiologic Findings

Tomás Franquet, MD • Nestor L. Müller, MD, PhD • Ana Giménez, MD
Pedro Guembe, MD • Jesús de la Torre, MD • S. Bagué, MD

Aspergillosis is a serious pathologic condition caused by Aspergillus organisms and is frequently seen in immunocompromised patients. At computed tomography (CT), saprophytic aspergillosis (aspergilloma) is characterized by a mass with soft-tissue attenuation within a lung cavity. The mass is typically separated from the cavity wall by an airspace (“air crescent” sign) and is often associated with thickening of the wall and adjacent pleura. CT findings in allergic bronchopulmonary aspergillosis consist primarily of mucoid impaction and bronchiectasis involving predominantly the segmental and subsegmental bronchi of the upper lobes. Aspergillus necrotizing bronchitis may manifest as an endobronchial mass, obstructive pneumonitis or collapse, or a hilar mass. Bronchiolitis is characterized by centrilobular nodules and branching linear or nodular areas of increased attenuation (“tree-in-bud” pattern). Obstructing bronchopulmonary aspergillosis mimics allergic bronchopulmonary aspergillosis at CT and manifests as bilateral bronchial and bronchiolar dilatation, large mucoid impactions, and diffuse lower lobe consolidation caused by postobstructive atelectasis. Characteristic CT findings in angioinvasive aspergillosis consist of nodules surrounded by a halo of ground-glass attenuation (“halo sign”) or pleura-based, wedge-shaped areas of consolidation. Although imaging findings in pulmonary aspergillosis may be nonspecific, in the appropriate clinical setting, familiarity with the CT findings may suggest or even help establish the diagnosis.

Abbreviation: AIDS = acquired immunodeficiency syndrome

Index terms: Aspergillosis, 60.2056, 60.254, 60.634 • Lung, cavitation, 60.2812 • Lung, consolidation • Lung, CT, 60.1211, 60.12118 • Lung, infection, 60.2056, 60.254, 60.634 • Lung, necrosis • Lung, nodule, 60.2812


1From the Departments of Radiology (T.F., A.G.) and Pathology (S.B.), Hospital de Sant Pau, Universidad Autónoma de Barcelona, Avda San Antonio María Claret 168, Barcelona 08025, Spain; the Department of Radiology, Vancouver General Hospital, University of British Columbia, Vancouver, British Columbia, Canada (N.L.M.); and the Department of Radiology, Hospital Universitario Gregorio Marañón, Madrid, Spain (P.G., J.d.l.T.). Presented as a scientific exhibit at the 1999 RSNA scientific assembly. Received September 1, 2000; revision requested October 10 and received November 22; accepted December 20. Address correspondence to T.F. (e-mail: 19429tfc@comb.es).

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Introduction

Aspergillosis is a mycotic disease caused by *Aspergillus* species, usually *A. fumigatus* (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 (1–3).

Pulmonary aspergillosis can be subdivided into five categories: (a) saprophytic aspergillosis (aspergilloma), (b) hypersensitivity reaction (allergic bronchopulmonary aspergillosis), (c) semi-invasive (chronic necrotizing) aspergillosis, (d) airway-invasive aspergillosis (acute tracheobronchitis, bronchiolitis, bronchopneumonia, obstructing bronchopulmonary aspergillosis), and (e) angioinvasive aspergillosis.

In this article, we correlate the radiologic manifestations of each of the five types of pulmonary aspergillosis with the relevant clinical and histologic findings.

**Saprophytic Aspergillosis (Aspergilloma)**

Saprophytic aspergillosis (aspergilloma) is characterized by *Aspergillus* infection without tissue invasion. It typically leads to conglomeration of intertwined fungal hyphae admixed with mucus and cellular debris within a preexistent pulmonary cavity or ectatic bronchus (Fig 2) (3,4).

The most common underlying causes are tuberculosis and sarcoidosis. Other conditions that occasionally may be associated with aspergilloma include bronchogenic cyst, pulmonary sequestration, and pneumatoceles secondary to *Pneumocystis carinii* pneumonia in patients with acquired immunodeficiency syndrome (AIDS) (3–5). Although aspergillomas are usually single, they may also be present bilaterally (Fig 3).

Although patients may remain asymptomatic, the most common clinical manifestation of saprophytic aspergillosis is hemoptysis. Surgical resection is indicated for patients with severe life-threatening hemoptysis (6), and selective bronchial artery embolization can be performed in those with poor lung function.
At radiography, mycetomas are characterized by the presence of a solid, round or oval mass with soft-tissue opacity within a lung cavity (3). Typically, the mass is separated from the wall of the cavity by an airspace of variable size and shape, resulting in the “air crescent” sign (Fig 4) (4,5). The aspergilloma usually moves when the patient changes position (Fig 5). Other causes of the air crescent sign include angioinvasive aspergillosis, echinococcal cyst, and, rarely, tuberculosis, Rasmussen aneurysm in a tuberculous cavity, lung abscess, bronchogenic carcinoma, hematoma, and *P carinii* pneumonia (1–3).
Figure 5. Mobile aspergilloma within a pulmonary cystic cavity in a 43-year-old man. Chest CT scans obtained with the patient supine (a) and prone (b) show a change in the position of the aspergilloma. *A. fumigatus* was discovered at bronchoscopy. (Courtesy of Josep M. Mata, MD, Unidad Diagnóstica de Alta Tecnología, Sabadell, Spain.)

Figure 6. (a) Posteroanterior chest radiograph obtained in a 56-year-old man in October 1994 demonstrates large cystic spaces that are bilaterally margined by lateral and apical pleural thickening and by a poorly defined infiltrate in the right upper lung. A mass is also visible in the inferior aspect of the left lung cavity (arrowheads). (b) CT scan (mediastinal window) shows bilateral pulmonary cavities in the upper lungs surrounded by circumferential pleural thickening and containing aspergillomas. (c) On a posteroanterior chest radiograph obtained 4 years later in August 1998, the intracavitary aspergilloma in the right upper lobe is no longer seen, and the right-sided pleural thickening has spontaneously regressed toward a normal size. The left intracavitary aspergilloma has increased in size without noticeable pleural changes. (d) CT scan (mediastinal window) shows normal pleural thickness in the right upper lobe cavity as well as a left intracavitary aspergilloma with associated pleural thickening.
Aspergillomas are often associated with thickening of the cavity wall and adjacent pleura (7,8). In such cases, pleural thickening may be the earliest radiographic sign before any visible changes are seen within the cavity. Approximately 10% of mycetomas resolve spontaneously. Reversibility of the pleural thickening corresponding to the resolution of intracavitary fungal material has been demonstrated at follow-up radiography (Fig 6). This reversibility suggests that the thickening of the cavity wall and pleura is due to a hypersensitivity reaction (7).

**Hypersensitivity Reaction (Allergic Bronchopulmonary Aspergillosis)**

Allergic bronchopulmonary aspergillosis is seen most commonly in patients with long-standing bronchial asthma (9). At pathologic analysis, this form of aspergillosis is characterized by the presence of plugs of inspissated mucus containing *Aspergillus* organisms and eosinophils. This results in bronchial dilatation typically involving the segmental and subsegmental bronchi.

Allergic bronchopulmonary aspergillosis is caused by a complex hypersensitivity reaction to *Aspergillus* organisms. The fungi proliferate in the airway lumen, resulting in the production of a constant supply of antigen. A type I hypersensitivity reaction with immunoglobulin E and immunoglobulin G release occurs. Immune complexes and inflammatory cells are then deposited in the bronchial mucosa, producing necrosis and eosinophilic infiltrates (type III reaction) with bronchial wall damage and bronchiectasis (9). Excessive mucus production and abnormal ciliary function lead to mucoid impaction. Many patients cough up thick mucous plugs in which hyphal fragments can be demonstrated at culture or histologic analysis.

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.

Radiologic manifestations include homogeneous, tubular, finger-in-glove areas of increased opacity in a bronchial distribution, usually predominantly or exclusively involving the upper lobes (Fig 7) (6,10,11). These shadows are related to plugging of airways by hyphal masses with distal mucoid impaction and can migrate from one region to another. Occasionally, isolated lobar or segmental atelectasis may occur. CT findings in allergic bronchopulmonary aspergillosis consist primarily of mucoid impaction and bronchiectasis involving predominantly the segmental and subsegmental bronchi of the upper lobes (Fig 8). In approximately 30% of patients, the impacted mucus has high attenuation or demonstrates frank calcification at CT.

Differential diagnosis includes other causes of mucoid impaction such as endobronchial lesions, bronchial atresia, and bronchiectasis.
Semi-invasive (Chronic Necrotizing) Aspergillosis

Semi-invasive aspergillosis, also known as chronic necrotizing aspergillosis, is characterized at histologic analysis by the presence of tissue necrosis and granulomatous inflammation similar to that seen in reactivation tuberculosis. Factors associated with the development of this form of aspergillosis include chronic debilitating illness, diabetes mellitus, malnutrition, alcoholism, advanced age, prolonged corticosteroid therapy, and chronic obstructive pulmonary disease (11,12).

Clinical symptoms are often insidious and include chronic cough, sputum production, fever, and constitutional symptoms. In patients with chronic obstructive pulmonary disease, semi-invasive aspergillosis may manifest with a variety of nonspecific clinical symptoms such as cough, sputum production, and fever lasting more than 6 months. Hemothysis has been reported in 15% of affected patients (12,13).

Radiologic manifestations of semi-invasive aspergillosis include unilateral or bilateral segmental areas of consolidation with or without cavitation or adjacent pleural thickening, and multiple nodular areas of increased opacity (12,13). The findings progress slowly over months or years (Figs 9, 10).
Figure 9. Semi-invasive aspergillosis in a 68-year-old man with chronic bronchitis and recurrent episodes of mild hemoptysis. (a) Thin-section CT scan (lung window) shows bilateral rounded areas of consolidation with associated cavitation in both upper lobes. (b) Photograph of an autopsy specimen from the left upper lobe shows an irregular cavitary lesion with regular margins and a dark brown appearance caused by necrotic material and *Aspergillus* infection.

Figure 10. Semi-invasive aspergilloma in a 54-year-old alcoholic man with chronic bronchitis and recurrent episodes of hemoptysis. (a) Linear tomogram (magnified view) shows a large cavity containing multiple fungus balls in the left upper lobe with associated adjacent pleural thickening. (b) Photograph of an autopsy specimen from the left upper lobe shows an irregular cavitary lesion with regular margins and a dark brown appearance caused by necrotic material and superimposed *Aspergillus* infection. (c) High-power photomicrograph shows massive *A. niger* with its characteristic black appearance.
Aspergillus necrotizing bronchitis may be seen at CT as an endobronchial mass, obstructive pneumonitis or collapse, or a hilar mass. Only a few reports have described CT findings in Aspergillus necrotizing bronchitis involving the central airways; reported abnormalities include circumferential bronchial wall thickening and bronchial obstruction. In clinical practice, the diagnosis of Aspergillus necrotizing bronchitis is usually based on the presence of abnormal findings at chest radiography and bronchoscopic biopsy, which are consistent with tissue invasion (Fig 11) (13,14).

The differential diagnosis in a patient with thickening and narrowing of a central bronchus at CT should also include mucormycosis, tuberculosis, amyloidosis, and sarcoidosis.

Airway-invasive Aspergillosis
Airway-invasive aspergillosis is characterized at histologic analysis by the presence of Aspergillus organisms deep to the airway basement membrane (15). It occurs most commonly in immunocompromised neutropenic patients and in patients with AIDS (16,17). Clinical manifestations include acute tracheobronchitis, bronchiolitis, and bronchopneumonia. Patients with acute tracheobronchitis usually have normal radiologic findings. Occasionally, tracheal or bronchial wall thickening may be seen. Bronchiolitis is characterized at high-resolution CT by the presence of
centrilobular nodules and branching linear or nodular areas of increased attenuation having a “tree-in-bud” appearance (Fig 12). The centrilobular nodules have a patchy distribution in the lung. Aspergillus bronchopneumonia results in predominately peribronchial areas of consolidation (15). Rarely, the consolidation may have a lobar distribution.

Centrilobular nodular areas of increased opacity similar to those seen in Aspergillus bronchiolitis have been described in a number of conditions, including endobronchial spread of pulmonary tuberculosis, Mycobacterium avium-intracellulare, and viral and mycoplasma pneumonia (10,17). The radiologic manifestations of Aspergillus bronchopneumonia are indistinguishable from those of bronchopneumonias caused by other microorganisms (Fig 13).

**Figure 12.** Invasive bronchiolar aspergillosis in a patient who had undergone bone marrow transplantation. **(a)** Thin-section CT scan (lung window) shows peripheral branching structures associated with focal areas of consolidation in the right lower lobe. **(b)** Photograph of the corresponding autopsy specimen shows multiple yellowish acinar nodules. **(c)** High-power photomicrograph of a lung biopsy specimen demonstrates complete destruction of the bronchiolar wall by Aspergillus infection.
Obstructing bronchopulmonary aspergillosis is a noninvasive form of aspergillosis characterized by the massive intraluminal overgrowth of *Aspergillus* species, usually *A. fumigatus*, in patients with AIDS (18). Affected patients exhibit cough, fever, and new onset of asthma. Patients may cough up fungal casts of the bronchi and present with severe hypoxemia. The characteristic CT findings in obstructing bronchopulmonary aspergillosis mimic those in allergic bronchopulmonary aspergillosis and consist of bilateral bronchial and bronchiolar dilatation (Fig 14), large mucoid impactions (mainly in the lower lobes), and diffuse lower lobe consolidation caused by postobstructive atelectasis (18).
Angioinvasive Aspergillosis

Angioinvasive aspergillosis occurs almost exclusively in immunocompromised patients with severe neutropenia (19). For many reasons, however, there has been a substantial increase in the number of patients at risk for developing invasive aspergillosis. These reasons include the development of new intensive chemotherapy regimens for solid tumors, difficult-to-treat lymphoma, myeloma, and resistant leukemia as well as an increase in the number of solid organ transplantations and increased use of immunosuppressive regimens for other autoimmune diseases. Despite having a normal neutrophil count, affected patients have functional neutropenia because the function of the neutrophils is inhibited by the use of high-dose steroids. Angioinvasive aspergillosis is characterized at histologic analysis by the invasion and occlusion of small to medium-sized pulmonary arteries by fungal hyphae (19). This leads to the formation of necrotic hemorrhagic nodules or pleura-based, wedge-shaped hemorrhagic infarcts. The clinical diagnosis is difficult, and the mortality rate is high (20,21).

Characteristic CT findings consist of nodules surrounded by a halo of ground-glass attenuation (“halo sign”) or pleura-based, wedge-shaped areas of consolidation (Fig 15) (22). These findings correspond to hemorrhagic infarcts. In severely neutropenic patients, the halo sign is highly suggestive of angioinvasive aspergillosis. However, a similar appearance has been described in a number of other conditions, including infection by Mucorales and Candida, herpes simplex and cytomegalovirus, Wegener granulomatosis, Kaposi

Figure 15. Angioinvasive aspergillosis in a 42-year-old man with acute myelogenous leukemia. (a) Chest CT scan (lung window) reveals a 2-cm nodular lesion with a wide halo of ground-glass attenuation representing adjacent hemorrhage. (b) Photograph of a cut section of the lung demonstrates a rounded tan nodule, a finding that is consistent with pulmonary infarction. (c) Low-power photomicrograph (original magnification, ×40; hematoxylin-eosin stain) shows vascular invasion by Aspergillus species (arrows).
sarcoma (Fig 16) (23), and hemorrhagic metastases (Fig 17). Separation of fragments of necrotic lung (pulmonary sequestra) from adjacent parenchyma results in air crescents similar to those seen in mycetomas (Fig 18). The air crescent sign in angioinvasive aspergillosis is usually seen during convalescence (ie, 2–3 weeks after initiation of treatment and concomitant with resolution of the neutropenia) (Fig 19) (21,22).

**Figures 16, 17.** (16) Cutaneous Kaposi sarcoma in a 34-year-old homosexual man with AIDS. Thin-section CT scan shows multiple hemorrhagic pulmonary nodules with an associated halo sign. (17) Hemorrhagic metastases in a 62-year-old man. High-resolution CT scan demonstrates multiple lung nodules, some of them with surrounding halos of ground-glass attenuation representing hemorrhage.

Figure 18. Angioinvasive aspergillosis in a 54-year-old man. (a) Thin-section CT scan (lung window) shows a cavitated nodule with air crescent formation. (b) Photograph of the pathologic specimen shows a thick-walled cavity with corresponding air crescent formation.

Conclusions
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.
Figure 19. Angioinvasive aspergillosis in a 43-year-old woman who had undergone bone marrow transplantation. (a) CT scan shows a peripheral Aspergillus nodule in the right upper lobe. (b) CT scan obtained 4 weeks later shows cavitation of the nodule with the air crescent sign.

References

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