Pulmonary aspergillosis

M.L. Chabi, A. Goracci, N. Roche, A. Paugam, A. Lupo, M.P. Revel

a Service de radiologie polyvalente et oncologique, groupe hospitalier de la Pitié-Salpêtrière – Charles-Fox, AP–HP, 83, boulevard de l’Hôpital, 75651 Paris cedex 13, France
b Département d’imagerie médicale, service de radiologie, IRCCS Istituto Clinico Humanitas, Via Manzoni 56, 20089 Rozzano, Italy
c Service de pneumologie, hôpital d’Instruction des armées du Val-de-Grâce, 74, boulevard de Port-Royal, 75230 Paris cedex 05, France
d Service de parasitologie-mycologie-médecine tropicale, hôpital Cochin, 27, rue du Faubourg-Saint-Jacques, 75679 Paris cedex 14, France
e Service d’anatomie et de cytologie pathologiques, hôpital Cochin, 27, rue du Faubourg-Saint-Jacques, 75679 Paris cedex 14, France
f Service de radiologie A, hôpital Cochin, 27, rue du Faubourg-Saint-Jacques, 75679 Paris cedex 14, France

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Abstract Aspergillosis is a mycotic disease usually caused by Aspergillus fumigatus, a saprophytic and ubiquitous airborne fungus. Aspergillus-related lung diseases are traditionally classified into four different forms, whose occurrence depends on the immunologic status of the host and the existence of an underlying lung disease. Allergic broncho-pulmonary aspergillosis (ABPA) affects patients with asthma or cystic fibrosis. Saprophytic infection (aspergilloma) occurs in patients with abnormal airways (chronic obstructive pulmonary disease, bronchiectasis, cystic fibrosis) or chronic lung cavities. Chronic necrotizing aspergillosis (semi-invasive form) is described in patients with chronic lung pathology or mild immunodeficiency. Invasive aspergillosis (angio-invasive or broncho-invasive forms) occurs in severely immuno-compromised patients. Knowledge of the various radiological patterns for each form, as well as the corresponding associated immune disorders and/or underlying lung diseases, helps early recognition and accurate diagnosis.

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Abbreviations: A. fumigatus, Aspergillus fumigatus; ABPA, allergic broncho-pulmonary aspergillosis; COPD, chronic obstructive pulmonary disease; CF, cystic fibrosis; HRCT, high-resolution computed tomography; CAN, chronic necrotizing aspergillosis; BAL, bronchoalveolar lavage.

* Corresponding author.
E-mail address: marie-laure.chabi@psl.aphp.fr (M.L. Chabi).

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Aspergillosis is a mycotic disease caused by Aspergillus, a filamentous fungus. The most common pathogenic species responsible for pulmonary disease is Aspergillus fumigatus [1].

A. fumigatus is a saprophytic and ubiquitous airborne fungus, whose natural ecological niche is the soil [1]. Heat, moisture and organic matters (carpet, autumn leaves…) promote its development.

Humans constantly inhale numerous conidia (spores) of this fungus, which are normally eliminated by muco-ciliary clearance and innate immune mechanisms in immunocompetent hosts without underlying lung disease [1].

The development of pulmonary aspergillosis requires host’s predisposing factors such as allergic status (asthma), airways diseases (bronchial dilatation, cystic fibrosis), chronic lung cavities (tuberculosis, sarcoidosis…) or immune deficiency.

Allergic reaction to Aspergillus antigens exposes to allergic broncho-pulmonary aspergillosis (ABPA). Alteration of muco-ciliary cells in bronchial dilatation or cystic fibrosis allows colonization of the airways by Aspergillus. The absence of macrophages in tuberculous cavity and other chronic lung cavities promotes the development of a “fungal ball” (aspergilloma). Immunosuppression due to steroids, transplantation, or aplasia may be responsible for chronic necrotizing forms or invasive forms depending on the level of immune deficiency.

Clinical, radiological and histological manifestations of pulmonary aspergillosis depend, besides the number and virulence of the spores, mainly on the immune status of the host and the presence of pre-existing lung disease.

The purpose of this review is to illustrate the radiological appearance of the four categories of Aspergillus-related lung diseases and to point out, for each, the specific immune status of the host.

**Aspergillus fumigatus**

A. fumigatus is a saprophytic and ubiquitous airborne filamentous fungus, whose natural ecological niche is the soil [1]. Its development is favoured by some contexts such as heat, moisture and organic matters (carpet, autumn leaves…).

The conidia released into the atmosphere have a diameter small enough (2 to 3 μm) to reach the lung alveoli [1].

The concentration of spores in the air increases with construction or renovation of buildings (levelling, painting repair…) and must be monitored if it takes place in hospitals. Any increase in the concentration of airborne conidia raises the risk of contracting aspergillosis in susceptible individuals [1]. Mycology laboratories and haematology services are equipped with hoods and laminar flow to avoid aerial contamination.

There are other sources of contamination, less known, such as spices (pepper) [2] and marijuana [3], which contain a lot of fumigatus spores.

**Various presentations of pulmonary aspergillosis**

**Allergic broncho-pulmonary aspergillosis (ABPA)**

ABPA is an immunological pulmonary disorder caused by hypersensitivity to Aspergillus fumigatus [4,5]. It nearly always affects asthmatics (1–2% of asthma patients) or patients with cystic fibrosis (CF; 1–15% of CF patients) [6,7].

The allergic reaction to Aspergillus antigens is responsible for a local inflammatory reaction (with infiltrate of eosinophils, excessive mucus production and bronchial wall damage) and an airways’ filling by mucus plugs, containing Aspergillus and eosinophils. The result is a bronchial dilatation typically involving segmental and subsegmental bronchi [8], with predominance in the upper lung.

Clinical manifestations include poorly controlled asthma, wheezing, haemoptysis and productive cough with expectation of brownish black mucus plugs. However, some patients can remain asymptomatic [4,5].

CT typically demonstrates the presence of central bronchiectasis, usually involving segmental or subsegmental bronchi, with upper lobe predominance. These bronchiectasis are filled by mucoid impactions with an inverted Y or V shape and are also called finger-in-glove opacities [8] (Fig. 1).

High attenuation or calcification of impacted mucus can be seen. High attenuation mucus, characterized by higher density than that of paraspinal muscles, is a pathognomonic finding of ABPA [5]. Hyperattenuating mucus plugging is explained by the presence of calcium salts and even metals (the ions of iron and manganese) or desiccated mucus, such as for Aspergillus sinusitis.

Occasionally, lobar or segmental atelectasis may occur. Rarely, pleural effusion or spontaneous pneumothorax have been described.

If untreated, this disease can evolve to pulmonary fibrosis.

New diagnostic criteria have been recently proposed to improve the accuracy of ABPA diagnosis [5]. These criteria include predisposing conditions (bronchial asthma or cystic fibrosis) associated with both obligatory criteria and at least two out of three other criteria.

Obligatory criteria are type I Aspergillus skin test positivity (immediate cutaneous hypersensitivity to Aspergillus antigen) or elevated levels of specific IgE against Aspergillus fumigatus and elevated total IgE levels (>1000 IU/mL). The other three criteria are presence of precipitating or IgG antibodies against A. fumigatus in serum, radiographic pulmonary opacities consistent with ABPA and total eosinophil count >500 cells/L in steroid naïve patients.

The chest radiographic features consistent with ABPA may be transient (i.e. consolidation, nodules, tram-track opacities, toothpaste/finger-in-glove opacities, fleeting opacities) or permanent (i.e. parallel line and ring shadows, bronchiectasis and pleuropulmonary fibrosis).

High-resolution computed tomography (HRCT) of the chest detects abnormalities not apparent on chest radiograph, and allows better assessment of the pattern and
Pulmonary aspergillosis

Figure 1. A 30-year-old asthmatic man with productive cough and dyspnea. Axial (a) and coronal (b, c) CT images show bilateral subsegmental bronchectasis filled with mucus (arrows). These images are called finger-in-glove opacities and are consistent with ABPA diagnosis. On mediastinal windowing (d), mucus plugs are hyperdense (102 HU); e: coronal CT image after treatment. Mucus plugging has disappeared whereas bronchectasis persist (head arrow).

distribution of bronchectasis, HRCT is therefore the best imaging modality for evaluating patients with suspected ABPA [5].

Saprophytic aspergillosis infection (aspergilloma)

Saprophytic aspergillosis infection is due to Aspergillus colonization of a pre-existing pulmonary cavity or ectatic bronchus. It combines conglomerate of fungal hyphae, inflammatory cells, mucus and cellular debris, without any tissue invasion (Fig. 2).

This infection occurs in patients with abnormal airways (COPD, bronchiectasis, cystic fibrosis) or chronic lung cavities such as tuberculous caverns, sarcoid-related pulmonary cavities, emphysematous bullae, honeycomb cysts...).

Aspergilloma is characterized by the presence of a round or oval mass within a pulmonary cavity, typically surrounded by an airspace, resulting in the “air crescent” sign (Figs. 3 and 4). The “fungus ball” usually moves with changes in position [8,9]. The degree of filling of the lung cavity is variable, responsible for very solid forms (pseudotumoral) and very cavitary forms. The key element is the identification of the “air crescent” sign, for which CT scan is more effective than conventional chest radiography (Figs. 3 and 4).

The lack of “fungus ball” into a cavity does not exclude aspergillosis infection, which can be characterized initially by an isolated wall thickening. All chronic lung cavities can be colonized by Aspergillus and develop aspergilloma (Fig. 5).

Saprophytic aspergillosis may be discovered either incidentally or after an episode of haemoptysis, which is

Figure 2. Aspergilloma. Image of pathologic specimen after lobectomy showing a “fungus ball” within a cavity.
the main complication. Aspergillomas remain stable in the majority of cases, but can also decrease in size or even spontaneously resolve in about 10% of cases. Aspergillomas more rarely show size increase [10].

Other causes of "air crescent" sign include angio-invasive and chronic necrotizing aspergillosis. In these cases, there are no pre-existing cavities; radiological manifestations appear within a few days in the angio-invasive forms and within several weeks or months in the chronic necrotizing forms [11] (Fig. 6).

**Chronic necrotizing aspergillosis (former semi-invasive form)**

Chronic necrotizing aspergillosis (CNA) is a rare and poorly understood form of aspergillosis, which can mimic other chronic pulmonary infections (tuberculosis, histoplasmosis...). Its recognition and diagnosis are often delayed.

CNA is a locally invasive disease that occurs in patients with chronic lung pathology [12] or mild immunodeficiency...
such as long-standing steroid therapy, diabetes, renal failure, COPD...

Radiologically, CNA is characterized by pulmonary consolidations, usually involving the upper lobes, with bronchiectasis. The consolidation progresses with time to cavitation over weeks to months [12,13].

As indicated earlier, a “fungal ball” with “air crescent sign” may develop in CNA as a secondary phenomenon due to the parenchymal destruction by the fungus [11] (Fig. 7).

In 2003, Denning et al. proposed diagnostic criteria for CNA [14] (Boxed text).

**Boxed text: Denning’s criteria [14] for chronic necrotizing aspergillosis.**

- Chronic pulmonary or systemic symptoms (duration 3 months) compatible with CPA, including at least 1 of the following symptoms: weight loss, productive cough, or haemoptysis.
- Cavitary pulmonary lesion with evidence of paracavitary infiltrates, new cavity formation, or expansion of cavity size over time.
- Either positive result of serum *Aspergillus* precipitins test or isolation of *Aspergillus* spp. from pulmonary or pleural cavity.
- Elevated levels of inflammatory markers (C-reactive protein, plasma viscosity, or erythrocyte sedimentation rate).
- Exclusion of other pulmonary pathogens, by results of appropriate cultures and serological tests, that are associated with similar disease presentation, including mycobacteria and endemic fungi (especially *Coccidioides immitis* and *Histoplasma capsulatum*).
- No overt immunocompromising conditions (e.g., HIV infection, leukemia, and chronic granulomatous disease).

**Invasive aspergillosis: angio-invasive and airway-invasive forms**

Invasive pulmonary aspergillosis is an aggressive disease due to the invasion of the bronchial wall and the accompanying arterioles by the hyphae. This form primarily occurs in severely immuno-compromised patients, especially patients with neutropenia due to allogenic bone marrow transplantation or chemotherapy for acute leukemia [15], but also patients who received solid-organ transplantation, especially lung transplantation [16].

The most important risk factor is neutropenia. The risk of invasive aspergillosis is strongly correlated with the duration and degree of neutropenia [11].

Symptoms are non-specific and usually mimic bronchopneumonia, but also include pleuritic chest pain and haemoptysis [11].

Invasive aspergillosis is a diagnostic and therapeutic challenge due to the high morbidity and mortality.

There are two sub-categories of invasive aspergillosis, the airway-invasive form and the angio-invasive form.

The airway-invasive form accounts for 15 to 30% of invasive aspergillosis, and is defined by the presence of *Aspergillus* deep to the basal membrane of the bronchi [17].

Radiologically, it can mimic bronchiolitis with patchy centrilobular nodules with tree-in-bud appearance, similar to those seen in endobronchial spread of tuberculosis. A bronchopneumonia presentation is common, with confluence of peribronchial consolidations, similar to bacterial bronchopneumonia [8,17] (Fig. 8).

In rare cases, the fungal infection is entirely or predominantly confined to the tracheobronchial tree. Acute *Aspergillus* tracheobronchitis usually occurs in lung transplantation recipients [16]. Radiologically, it may appear as tracheal or bronchial irregular wall thickening, with occasionally high attenuation aspect due to ability of *Aspergillus* to fix calcium. Atelectasis or endobronchial masses have even been described. However, most of the time, there are no detectable radiological abnormalities [8,18].

**Figure 6.** “Air crescent” sign. Axial CT images of 3 different patients, showing a lung parenchyma opacity surrounded by an “air crescent” sign. This feature is not specific of saprophytic infection (aspergilloma; a), it can be seen in semi-invasive aspergillosis (chronic necrotizing aspergillosis; b) and in invasive aspergillosis (c). In the latter two cases (b and c), there was not any pre-existing lung cavity; the focal area of necrosis is due to fungal invasion.
Figure 7. Chronic necrotizing aspergillosis; a and b: axial CT images showing a right upper lobe consolidation with bronchectasis; c and d: correspond to CT images of the same patient 5 months (c) and 7 months (d) latter. Progressive cavitation of the initial consolidation is seen; e and f: are chest radiographs corresponding to CT scans images c and d. They show a progressive cavitation of the right upper lobe. Comparison with the first available chest X ray is crucial, to detect the progressive cavitation because changes occur slowly, which is the source of delayed diagnosis.

The angio-invasive form is histologically characterized by the invasion and occlusion of small to medium-size pulmonary arteries by fungal hyphae [8]. Typical CT findings [8,17] consist in larges nodules surrounded by ground glass attenuation, which is called the “halo sign”. Nodules are due to coagulation necrosis, whereas the halo of ground glass is due to surrounding alveolar haemorrhage [19] (Fig. 9). Other findings are pleura-based areas of consolidation, similar to those seen in pulmonary infarcts complicating pulmonary embolism, correspond to haemorrhagic infarcts.

Differential diagnoses of “halo sign” in neutropenic patients include infections due to Candida, Herpes simplex and cytomegalovirus, Wegener granulomatosis, haemorrhagic metastases and Kaposi sarcoma.

Figure 8. Broncho-invasive aspergillosis in a 50-year-old man with allogenic bone marrow transplantation. Axial CT images (a, b) showing bilateral lobular consolidation with centrilobular nodules in the left lower lobe (b). These features are non-specific of fungal infection and could also be due to bacterial bronchopneumonia.
The occurrence of cavitation within a nodule or a consolidation is often concomitant with the resolution of neutropenia. In this late phase, the separation of the necrotic lung fragment from the adjacent lung parenchyma results in an “air crescent” sign similar to that observed in aspergilloma. Unlike saprophytic aspergilliosis infection, the opacity surrounded by a crescent airspace develops in less than 2 weeks and without pre-existing cavity (Fig. 10).

Therefore, it is essential to think in terms of immunological status and fastness of evolution in case of cavitation.

There are increasing numbers of reports documenting invasive aspergillosis in immunocompetent patients with severe COPD, often with prolonged use of corticosteroid therapy [11].

Overlap between these various manifestations

Beyond this segmentation in four forms it should be noted that an overlap between the main categories of *Aspergillus*-related diseases has been reported. Some forms could co-exist, especially allergic broncho-pulmonary aspergillosis and aspergilloma [11,20].

Changes of local or systemic host immunity and of underlying lung pathology can modify aspergillosis pulmonary manifestations with time. For example, an aspergilloma can develop within bronchiectasis in a patient with ABPA. An invasive form can complicate long-standing ABPA in case of systemic immune deficiency, including the use of high-dose of steroids [20].

**Mycological diagnosis: which sample allows diagnosis?**

**Sputum**

Direct examination can be made to identify the presence of filaments.

The significance of isolating *Aspergillus* in sputum samples depends on the immune status of the host. In immunocompetent patients, it represents at least a colonization, while it is highly predictive of invasive disease in immuno-compromised patients [11]. Conversely, negative sputum samples do not rule out aspergillosis, including invasive forms [11]. The results of cultures are often delayed.

**Serum**

Detection of IgG antibodies against *A. fumigatus* in the serum helps the diagnosis of aspergilloma or ABPA, the two forms of aspergillosis observed in immunocompetent individuals [1]. It can be negative in patients on corticosteroid therapy.

In contrast to immunocompetent hosts, growth of *A. fumigatus* in the tissues of an immunosuppressed host is not correlated with an increase in anti-*Aspergillus* antibody titers [1]. Consequently, detection of *Aspergillus* antigens in the serum is more useful for diagnosing invasive aspergillosis in immuno-compromised patients (ELISA, latex agglutination). Galactomannan is the most commonly used antigen, it is a polysaccharide fungal cell wall component released during hyphal growth in tissues. It is reported that serum galactomannan can be detected several days before the presence of clinical symptoms, chest radiographic abnormalities or positive culture [11].

Another possibility is the detection of *A. fumigatus* DNA by PCR.

**Bronchoalveolar lavage (BAL)**

BAL is useful to identify *Aspergillus* by direct examination and culture.
Further, as for serum, *Aspergillus* antigens (galactomannan) and *A. fumigatus* DNA (by PCR) can be detected in BAL.

**Biopsy**

The histopathological examination of lung tissue with positive culture is the gold standard for the diagnosis of invasive aspergillosis [11]. Nevertheless, surgical biopsies are infrequently performed, only for diagnosis purposes in fragile patients.

**Conclusion**

The spectrum of respiratory diseases caused by *Aspergillus* is wide. It includes hypersensitivity in ABPA, saprophytic infection in pre-existing broncho-pulmonary diseases and semi-invasive or invasive forms in immuno-compromised patients.

The correlation between the immunologic status of the host, an essential factor in the occurrence of *Aspergillus*-related lung diseases, and the radiological presentation is of major importance for accurate diagnosis of these diseases.

**Disclosure of interest**

The authors declare that they have no conflicts of interest concerning this article.

**References**


