The radiological spectrum of pulmonary aspergillosis

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Imaging findings in the pulmonary aspergilloses can answer important clinical questions. Steroid-responsive chronic asthma due to allergic bronchopulmonary aspergillosis can be differentiated from simple asthma by computed tomography (CT) evidence of extensive and severe central bronchiectasis, mucoid impaction, or small airways lesions. The simple aspergilloma can be differentiated from the complex aspergilloma by the absence of: constitutional symptoms, para-cystic lung opacities, cyst expansion, or progressive pleural thickening. The CT halo sign is a transient finding that can provide a probable diagnosis of early invasive pulmonary aspergillosis in patients who are at extraordinarily high risk of the infection. Patients with a halo sign at baseline are more likely to have a satisfactory treatment response than those without this indicator.

Keywords aspergillosis, computed tomography, halo sign

Introduction

The three main categories of pulmonary aspergillosis, i.e., allergic, saprophytic, and acute invasive aspergillosis, have varied but also distinctive imaging patterns that are important to recognize. They may simulate other serious conditions, and even be confused with other categories of aspergillosis. The characteristics of an uncommon but important form of aspergillosis, i.e., chronic pulmonary aspergillosis, may overlap one or more of the three main categories from which it should be distinguished [1,2]. The risk of developing a particular pulmonary aspergillosis is strongly influenced by the patient’s immune status and the presence of underlying lung disease. This paper will discuss the diagnostic imaging challenges posed by these conditions.

Radiological imaging is an essential tool in the management of patients with pulmonary aspergillosis because the main portal of entry of Aspergillus spores is the lung, by way of respiration. Computed tomography (CT) of the chest and the plain chest X-ray (CXR) are used to screen patients at high risk for aspergillosis, detect aspergillosis in patients with compatible illnesses, differentiate aspergillosis from other diseases, guide interventional procedures aimed at establishing a specific diagnosis, and assess treatment response. CT is much more sensitive and specific than the CXR in the evaluation of chest lesions. Widely accepted as the gold standard for chest imaging, CT must be relied upon over the CXR at critical decision-making junctures. The CXR, however, because of its lower complexity, cost and radiation exposure to the patient, is particularly needed when high frequency repetitive, or bedside imaging of critically ill patients is required.

Allergic bronchopulmonary aspergillosis

Clinical background

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. The main clinical-imaging challenge posed by ABPA is to differentiate between patients with simple chronic asthma and those who might have steroid-responsive asthma due to ABPA.

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**Imaging features**

The allergic reaction to *A. fumigatus* results in local hypersensitivity damage to the large and small airways where the reaction occurs, and also in the adjacent lung. The damage in the large central airways, i.e. the segmental and sub-segmental bronchi, is expressed on CT as dilatation and mucoid impaction. The dilatation of central airways is usually in the upper lobes, and extensive and severe in the form of varicose or cystic bronchiectasis. Branching, “finger-in-glove” opacification of the dilated bronchi due to mucoid impaction is identified in many cases (Fig. 1). On CT, attenuation of mucoid impaction is generally low relative to soft tissues, but occasionally is increased, possibly due to dystrophic calcification which may be identified. The damage to the small airways is expressed on CT as bronchiolar dilatation and impaction resulting in centrilobular nodules and branching tree-in-bud opacities. Damage to the peripheral lung is expressed as transient, migratory patches of consolidation and/or ground-glass opacities that may regress spontaneously or on corticosteroid therapy. The above imaging findings occur preferentially in the upper lobes. Other imaging findings may include regional and overall lung hyperinflation, and atelectasis distal to airway obstruction.

**Clinical-imaging challenge**

The challenge posed by ABPA is to differentiate patients with simple chronic asthma from those with chronic asthma due to ABPA. The differentiation is important because the airway damage caused by ABPA is corticosteroid-responsive. Ward et al. [3] have identified three main imaging features, each of which can help to distinguish between groups of patients with simple chronic asthma and those with asthma associated with ABPA, especially when the findings typical of ABPA are extensive and severe. These findings include varicose or cystic bronchiectasis of segmental and sub-segmental bronchi (>90% of patients with ABPA but <30% of patients with simple asthma), mucoid impaction of segmental and sub-segmental airways (67% of patients with ABPA but only 4% of those with simple asthma), and small airways abnormalities in the form of centrilobular nodules (93% of patients with ABPA, but only 28% of patients with simple asthma) [3]. In patients with simple chronic asthma, bronchiectasis, when it is present, is usually mild and limited to the cylindrical variety, i.e. with parallel dilated walls but without varicosities or cysts. Although these imaging features of ABPA are highly discriminatory, they suggest that significant hypersensitivity lung damage has already occurred. Corticosteroid therapy, however, may help prevent further airway damage. Screening CT has been advocated for asthmatics who have skin-prick hypersensitivity to *A. fumigatus* to help identify ABPA at an early stage of disease [4].

Bronchocentric granulomatosis, when it is severe, is a condition sometimes associated with ABPA. It is characterized by necrotizing lung granulomas that obstruct and destroy small airways that sometimes harbor *A. fumigatus* mycelia [5]. In the lung parenchyma, there is eosinophilic inflammatory reaction and fibrosis, but no evidence of *Aspergillus* invasion. Patients with severe bronchocentric granulomatosis share clinical and imaging features of ABPA, such as steroid-responsiveness of the chronic asthma, fever, cough, peripheral eosinophilia and increased serum IgE [2,6,7]. More than half of patients with bronchocentric granulomatosis have one or more masses of necrosis associated with bronchiectasis, lung fibrosis, and/or lung cysts, especially in the upper lobes where mucoid impactions may also be identified. Image findings of multiple nodular masses simulate metastatic carcinoma [8].

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Fig. 1 ABPA. Varicose bronchiectasis (arrow heads) and mucoid impaction (arrows) in a segmental bronchus (arrows). Note the “finger-in-glove” appearance of the opaque mucoid impaction.
Aspergilloma

Clinical background

The simple aspergilloma, or fungus ball, is the archetype of saprophytic (non-invasive) aspergillosis, and the most common aspergillosis detected in imaging studies. It is the result of saprophytic proliferation of Aspergillus mycelia within a pre-formed cavity in the lungs of patients who are generally immunocompetent and asymptomatic [2,9]. Mycelial invasion of lung or vasculature is not a feature of aspergilloma [10,11]. The prevalence of aspergillomas in post-tuberculous cavities in the UK may be as high as 10% [12]. Other common causes of the pre-formed cystic host cavity of the aspergilloma include end-stage sarcoidosis [13] or other interstitial lung disease such as pneumoconiosis, bronchiectasis [14] as in cystic fibrosis [15] and/or ABPA, lung abscess, cavitating lung neoplasm [16], pulmonary infarct [17], atypical mycobacterial infection [18], bullous emphysema, hematoma, Pneumocystis jirovecii (formerly P carinii) pneumonia (PCP) [19,20], lung surgery [21–23] ankylosing spondylitis, and the cavitary residue of invasive fungal infection [24,25]. Unusually, aspergillomas have been described in immunocompetent patients who do not appear to have had a pre-existing dilated lung space [26,27]. The presumptive diagnosis of aspergilloma is made by imaging, but the definite diagnosis relies on other clinical data. Positive serology precipitins to A. fumigatus are diagnostic, but the test will be negative if some species other than A. fumigatus, or another fungus, such as Zygomycetes or Fusarium spp. is causative [11]. Recovery of A. fumigatus from respiratory secretions can be documented in only about half of patients [28]. The main clinical-imaging challenge posed by aspergillomas is to differentiate them from other lung conditions that require specific treatment.

Imaging features

Initial radiological detection is usually the incidental result of CXR evaluation of the underlying lung condition that is responsible for the cystic host cavity [9]. The diagnosis is based on identification of a usually well-defined mycelial mass occupying a pre-formed cyst cavity, usually solitary and in an upper lobe [2,9] (Fig. 2). On CT, globules of gas are often visible within the interstices of the hyphal mass. A crescentic cap of air can usually be identified separating the aspergilloma from the cyst wall [29]. With effort, the fungus ball can often be shown to be mobile within the cavity when the ball does not fill the entire cavity [2,30,31]. Spontaneous shrinkage or disappearance of the aspergilloma can be documented in about 10% of patients [32]. The aspergilloma only rarely increases in size [33]. The cyst wall is generally smooth and thin, but may be irregular and thick. The pleural surface overlying the host cavity may be thin or thick. Dystrophic, cage-like calcification may occasionally be detected over the surface of the aspergilloma. In a minority of patients, such as those with end-stage sarcoidosis, the aspergilloma may be discovered for symptoms referable to it, most often hemoptysis that may be life-threatening [9,17,34]. In these patients CT angiography may identify hypertrophic bronchial arteries supplying the cyst wall. Blood may cause CT hyper-dense fluid within the cyst, and aspirated blood may cause ground-glass or consolidative opacities with air bronchograms in the para-cystic lung and elsewhere.

Clinical-imaging challenge

The challenge posed by aspergillomas which usually do not require treatment is to differentiate them from serious lung conditions that do require specific therapy. Cavitary lung cancer and cavitating Wegener’s granulomatosis may simulate an aspergilloma. The air-filled mycelial meshwork typical of the aspergilloma is a helpful diagnostic finding, but lung biopsy and other clinical information may be needed for a definite diagnosis. In lung cancer, the cavity is usually but not always thick-walled, the mass is usually immobile, the
cavity is not usually known to be pre-existing, gas is not often demonstrable in its interstices, and para-cystic lung opacities are common. In bacterial lung abscess, the patient is often symptomatic, the course is acute, and constitutional symptoms are usually present. Air-fluid levels are common in bacterial abscesses, and less so in aspergillomas. Images of the air gap between the aspergilloma and the host cyst wall of the simple saprophytic aspergilloma are easily confused with findings in two other forms of aspergillosis, the air crescent sign of late invasive pulmonary aspergillosis (IPA) and the complex aspergillomas of chronic pulmonary aspergillosis (CPA). The clinical circumstances surrounding the simulators make the differentiation possible. Patients with IPA or the complex aspergillomas of CPA are usually constitutionally ill. Furthermore, the cavity of the air crescent sign in acute IPA is not pre-formed, the size of the intracavitary mass can be seen to evolve in a matter of days, and the intracavitary mass is not usually mobile. The immunocompetent status of the patient with simple aspergilloma is very different from the typical hematologic immunosuppression of the patient with IPA. The simple aspergilloma is differentiated from the complex aspergilloma in CPA by the absence of constitutional symptoms, para-cystic lung opacities, new or progressive cavity enlargement, new or progressive irregularity and thickening of the cyst wall, new or progressive thickening of the pleura, and extension of inflammatory change into the chest wall or ribcage. Predictors of poor prognosis for the saprophytic aspergillomas include an increase in the size or number of cysts (a finding not compatible with the diagnosis of simple aspergilloma), severe underlying lung disease, immunosuppressive therapy, AIDS, sarcoidosis, rising *Aspergillus*-specific IgG titer, and repetitive severe hemoptysis [35].

AIDS patients are at particularly high risk of having abnormally dilated host cysts for aspergillomas, due to the high frequency of infections from *P. jirovecii*, *Mycobacterium tuberculosis*, *M. avium* intracellulare, other bacteria and fungi [5]. Aspergillomas behave much differently in the patient with AIDS than in the immunocompetent patient. They behave more like complex aspergillomas than simple aspergillomas. In the AIDS patient, especially one with markedly decreased CD4 counts (<100 cells/L), the aspergilloma is usually discovered because of symptoms related to the aspergilloma, such as hemoptysis [36], cough or fever. The aspergilloma is often associated with para-cystic lung opacities, and may progress to mycelial lung invasion. Obstructing bronchopulmonary aspergillosis, a unique non-invasive, saprophytic variety of aspergillosis characteristic of AIDS is diagnosed by massive central bronchial dilatation, and mucoid impaction due to non-invasive endobronchial fungal overgrowth [37].

**Acute invasive pulmonary aspergillosis**

**Clinical background**

Acute invasive pulmonary aspergillosis (IPA) is the archetype 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) [38]. 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 (<50 c/mol), solid organ transplant recipients and recipients of high dose corticosteroid therapy in whom it occurs sporadically [39]. A definite diagnosis of IPA is notoriously difficult to establish, and late-treatment is associated with a dismal outcome. Because of significant impediments to the early clinical, mycological, interventional, and serological diagnosis, imaging has come to the fore in efforts to identify early IPA.

**Imaging features**

The main pathology of early IPA corresponds to one or more ‘target lesions’, each consisting of a central nidus of mycelial infection in a peripheral airspace surrounded by a zone of vascular thrombosis and hemorrhage due to angio-invasion [40]. The CT halo sign consists of an opaque nodule (usually a macronodule >1 cm in diameter) [41] that is the equivalent of the central infective nidus, and a perimeter of ground-glass opacification, i.e. slightly increased lung density through which lung vasculature is still visible that is equivalent to the rim of surrounding thrombosis and hemorrhage [42] (Fig. 3). As the CT equivalent of the ‘target lesion’, the halo sign has become widely adopted as a specific indicator of early of probable IPA in patient groups who are at extraordinarily high risk of such infection [38,43–45].

At baseline, the macronodule is by far the most common CT finding; one or more are present in >90% of patients [41]. Macronodules exhibiting halo signs are identified in almost two-thirds of patients with confirmed diagnoses of IPA [41]. At baseline, all other categories of CT findings occur in no more than one quarter of patients with confirmed IPA. For instance, consolidations occur in about one quarter, and air crescent signs occur in one tenth [41]. The above
prevalence of findings reflects the dominance of angio-invasion as the pathogenesis of IPA. In a very small minority of patients (<10%), CT findings are due to airway-invasive pathogenesis, and include peri-bronchiolar consolidation, small centrilobular nodules (<1 cm), ground-glass opacities and lobar consolidation [46].

**Clinical-imaging challenge**

The main challenge posed by IPA is to improve outcome by promptly identifying the CT halo sign as a probable indicator of early infection. In individuals, small series of patients at extraordinarily high risk of the infection, systematic search for the halo sign, and initiation of anti-*Aspergillus* therapy based on identification of the sign found improved outcome compared to a historical standard [47]. More recently, a similar group of patients who presented with a CT halo sign in a large multi-center treatment trial, had a higher rate of satisfactory treatment response than those presenting without a halo sign [41].

Although angio-invasive fungal infections, such as those caused by Mucorales, can cause identical imaging findings to IPA, and require quite different specific therapy, *Aspergillus* is by far the most common cause of angio-invasive fungal infection in this group of patients with a compatible illness. Angio-invasive infection caused by *Pseudomonas aeruginosa* could produce similar findings but would be expected to respond to pre-emptive broad spectrum antibiotic therapy for fever.

The halo sign must be searched for at an early stage of the infection because its prevalence decreases four-to-five fold over the first week to ten days following its initial identification [44]. The air crescent sign, which consists of a macronodule that contains a crescent-shaped rim of air along the inner margin of the nodule, represents a non-viable sequestrum that is in the process of separating itself from surrounding viable lung [48,49]. In contradistinction to the halo sign, the frequency of the air crescent sign increases from near zero at initial identification of a halo sign to about 28% during the following week to ten days [44] (Fig. 4). The air crescent sign occurs with too low frequency at baseline to be value in the early identification of IPA. The sign is usually detected after partial recovery of neutrophil function that facilitates the formation of necrosis. The crescentic cap of air of the air crescent sign differentiates it from the non-specific cavity in which it is absent.

The CT assessment of treatment response is confounded by a substantial increase in the volume of CT opacities attributable to IPA that have been reported (three- to four-fold increase over the first 7–14 days of treatment). The increase in lesion volume does not appear to indicate a pejorative short term outcome [44].

**Chronic pulmonary aspergillosis**

**Clinical background**

CPA is an uncommon form of aspergillosis that overlaps with the three other categories. It is characterized

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by indolent progression over months or years, underlying chronic cavitary lung disease, constitutional symptoms, serum precipitans to *A. fumigatus*, elevated acute phase markers of inflammation, and an immune status that ranges from normal to mild immunosuppression. Patients with CPA share with those with IPA the development of constitutional symptoms, but in CPA the disease progresses lethargically rather than acutely. Locally invasive disease occurs, but both angio-invasion and dissemination are absent. The underlying chronic cavitary lung disease may be due to prior tuberculosis, chronic obstructive lung disease, chronic interstitial lung disease, lung irradiation, surgical lung resection, lung infarction and cystic fibrosis [50].

Chronic necrotizing pulmonary aspergillosis (CNPA) is a form of CPA that has sometimes been referred to as semi-invasive or subacute pulmonary aspergillosis [2,51–53]. CNPA is a regionally destructive lung process due to locally invasive aspergillosis, and may run a more subacute than chronic course. A progressive consolidative lung opacity may undergo cavitation, and become the host site for an aspergilloma, or have thin walls and rapidly expand [52]. CNPA differs from the simple aspergilloma in having associated locally invasive disease, constitutional symptoms, and the possibility of producing *de novo* cavitary lung disease due to locally invasive aspergillosis. Mycelia may invade the pleural space. The development of pleural thickening adjacent to lung cavities and/or para-cavitary lung opacities are signals of active disease. *A. fumigatus* may be recovered from the pleural space in the case of bronchopleural fistula and empyema [52]. Patients with CNPA may have mild immune dysfunction caused by diabetes or corticosteroid use. A definite diagnosis requires exclusion of other pulmonary infection and biopsy proof of local invasion. Denning [52] has identified a sub-group of patients with CPA called chronic cavitory pulmonary aspergillosis (CCPA) that is characterized by the development of multiple expanding cavities that may contain aspergillomas. Para-cavitary lung opacities are characteristic. The course of CCPA is relatively slower than that of CNPA, and may end with extensive inactive lung fibrosis [52].

The main challenge is to differentiate CPA from other serious conditions that require specific therapy. The most difficult challenge is differentiate CPA from other chronic lung conditions, such as, upper lobe lung cancers, and chronic cavitory lung infections due to *M. tuberculosis*, atypical mycobacterial infection, and endemic fungal infection, such as *Coccidioides immitis* and *Histoplasma capsulatum* [52]. In these cases, imaging is not distinguishing, so biopsy and/or mycological studies must to be used to exclude other disease. CPA differs from the simple aspergilloma, not only by the presence constitutional symptoms but also by the development of persistent para-cystic lung nodules, consolidations or ground-glass opacities and by the development and/or progression of cavitory disease, or para-cystic pleural thickening (Fig. 5). In simple aspergilloma, thickening of the cyst wall and/or para-cystic pleural thickening may be present, but evidence of progression is suggestive of CPA. Cavity wall thickness alone does not to correlate with disease activity [52].

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