Eur Radiol (2003) 13:1786–1800
DOI 10.1007/s00330-002-1813-4

Susan J. Buckingham
David M. Hansell

Aspergillus in the lung: diverse and coincident forms

Received: 15 July 2002
Revised: 29 November 2002
Accepted: 16 December 2002
Published online: 29 May 2003

S. J. Buckingham · D. M. Hansell (✉)
Department of Radiology,
Royal Brompton Hospital,
Sydney Street, London SW3 6NP, UK
e-mail: d.hansell@rbh.nthames.nhs.uk
Tel.: +44-20-73528034
Fax: +44-20-73518098

Abstract Pulmonary disease caused by the fungus *Aspergillus* has traditionally been regarded as belonging to one of the following, apparently distinct, entities: saprophytic aspergilloma; allergic bronchopulmonary aspergillosis (ABPA); and invasive aspergillosis (IPA); which may be further categorised as angioinvasive, acute or chronic airway invasive) [1]. It is not always obvious that there is overlap between these entities, and that in any given patient more than one *Aspergillus*-related pathological process can co-exist [2]. The aim of this article is to review the clinical and imaging features of the main categories of *Aspergillus*-related pulmonary disease and, in particular, to highlight the overlap between them.

Keywords Computed tomography · Mycetoma · Immunocompromise · Allergic bronchopulmonary aspergillosis · Aspergillosis

Introduction

The recognition of the diversity of diseases caused by *Aspergillus* in the lung has increased over recent years. Broadly there are three main categories: saprophytic aspergilloma; allergic bronchopulmonary aspergillosis; and invasive aspergillosis [3]. Invasive aspergillosis has been further subdivided in recent years to angioinvasive and airway invasive aspergillosis [4, 5]. The form that *Aspergillus* lung disease takes is heavily dependent on the immune response of the patient [6]. Indolent forms of locally invasive aspergillosis in the form of chronic necrotising or semi-invasive aspergillosis in apparently immune competent individuals are now recognised [7]. There is considerable, and sometimes surprising, overlap between the main categories of *Aspergillus*-related disease, and often more than one form can co-exist (e.g. aspergilloma in allergic bronchopulmonary aspergillosis).

In this review we discuss the issues of classification, the main categories of *Aspergillus* disease and, more particularly, the potential for overlap between these entities.

Historical background

The *Aspergillus* genus of moulds was probably first described by Micheli in 1729 [8]. The name probably comes from the similarity between fruiting heads of this particular fungus, and the brush, or aspergillum, used for the sprinkling of holy water.

The spores of the *Aspergillus* fungus are ubiquitous and are found in the soil, in decaying organic matter, and even in the sand of the Sahara Desert. By far the most common pathogenic species is *Aspergillus* fumigatus (also a common avian pathogen). There are at least 17 other *Aspergillus* species known to cause respiratory disease in humans [8, 9].

Reports of human cases of *Aspergillus* infection date back to the mid-nineteenth century when a post-mortem study described the fungus in the lungs of a patient who died of an undiagnosed pulmonary disease. *Aspergillus* growing as a fungus ball in tuberculous cavities was first reported in pathological specimens in 1856 by Freidreich. The first English report was by Wheaton in 1890, who described disseminated *Aspergillus* in the lungs and nodes of a 2-year-old child who died from "pneumonia" [10].

Table 1 Original classification and current classification/terminology. *ABPA* allergic bronchopulmonary aspergillosis

Early literature (pre-1950)	Hinson et al. [8]	Finegold et al. [13]	Gefter [6]	Potential classification
Aspergillosis	Allergic bronchopulmonary aspergillosis	Primary	Spectrum from:	Aspergilloma
	Mycetoma	Localised	Hypersensitivity	Allergic bronchopulmonary aspergillosis
	Invasive aspergillosis	Invasive	Bronchocentric granulomatosis	Invasive
		Disseminated	ABPA	Angioinvasive
		Secondary	Non-invasive (mycetoma)	Airway invasive
		Localised	Semi-invasive	Acute
		Invasive	Invasive	Chronic (also known as semi-invasive and chronic necrotising aspergillosis)
		Disseminated	Immunosuppression	

At around this time the term "aspergillosis" referred to any infection of the lung caused by *Aspergillus*. In 1928 it was suggested that the diagnosis of aspergillosis could be made in symptomatic individuals by the culture of *Aspergillus* from their sputum [8].

Hemphill in 1936 described the radiological appearance of a "loose body within a cavity which shifted with change of position" in a patient with previous tuberculous disease. The "loose body" was shown at resection to be composed of mycotic material [11]. Twinning and Kerley later illustrated this in their radiological text, and coined the term "mycetoma" [12]. Hinson et al. in 1952 described three patients with wheezy bronchitis, fever, consolidation, peripheral eosinophilia and bronchi plugged by viscid secretions containing scanty *Aspergillus* fumigatus hyphae. They termed this allergic bronchopulmonary aspergillosis [8]. In their report they segregated *Aspergillus* pulmonary disease into three groups, and it is this basic clinical classification that is still used presently: (a) saprophytic growth in cavities (mycetoma); (b) allergic bronchopulmonary aspergillosis (ABPA); and (c) invasive aspergillosis [8]. Finegold et al. subsequently modified this classification subdividing the aspergilloses into primary (absence of underlying disease or other predisposing factors), and secondary (associated with a pre-existing lung disease or host immune deficiency; see Table 1) [13]. This classification was confusing, and with the discovery of a more indolent invasive form of *Aspergillus* (semi-invasive/chronic necrotising aspergillosis) a modified version of the classification of Hinson et al. [8] was proposed by Gefter [6]. More recent literature, in particular CT studies, have further subdivided invasive aspergillosis into angioinvasive and airway invasive (Table 1). It has become increasingly evident over the past decade that *Aspergillus* colonisation or infection, and its consequences, may be highly variable and complex, and depend to a large extent on local and systemic host immunity [6, 14].

Immune considerations

Local response to inhaled *Aspergillus* spores in the normal host involves alveolar macrophage phagocytosis which kills the spores before they convert to potentially invasive hyphal forms. Germinating spores and hyphal forms which are too large in size to be phagocytosed by macrophages are inactivated by neutrophils [15].

Aspergillus colonises cavities in the lung where conditions are favourable for growth, and where local host defences are impaired (particularly in large avascular cavities and bronchiectactic airways).

Qualitative and quantitative deficiencies in neutrophil function can allow hyphal growth and invasion, initially through the bronchiole walls, with subsequent invasion of blood vessels and systemic dissemination.

Immunocompromised patients, particularly with neutropaenia, are susceptible to acute airway invasive and angioinvasive aspergillosis in the absence of pre-existing lung pathology. Patients with modest immunodeficiency (e.g. an elderly patient with a connective tissue disorder), with or without pre-existing local lung pathology, are susceptible to localised chronic airway invasive *Aspergillus* infection [1, 7].

Patients may also exhibit a hyperimmune response to *Aspergillus*. Allergic bronchopulmonary aspergillosis is usually encountered in asthmatics, and is characterised by both type-I and type-III immune reactions to *Aspergillus*. Type-I reaction results in elevated serum IgE, eosinophilia in the blood, sputum, and lung tissue, and immediate skin test reactivity to *Aspergillus* antigens. Confusingly, approximately 25% of patients with chronic asthma show an immediate cutaneous reactivity to *Aspergillus* species, whether or not they have other features of ABPA; however, patients with ABPA have consistently far greater levels of isotypic antibodies to *Aspergillus* fumigatus (IgE-a-Af, IgG-a-Af, and IgA-a-Af) than patients with allergic asthma or non-atopic controls [16].

The immune complex driven type-III reactions accounts for a positive late (Arthrus) skin reaction. The combination of these two immune responses leads to a marked inflammatory reaction with consequent bronchospasm, bronchial oedema, bronchial plugging, bronchial wall damage, and bronchiectasis [6]. Hyphae grow in the thickened bronchial secretions perpetuating reaction and damage. *Aspergillus* fumigatus, the usual culprit in ABPA, produces a chymotrypsin-like proteinase which causes bronchial epithelial damage [17]. There are also some features of a type-IV (cell-mediated) reaction producing a granulomatous reaction. In advanced cases severe granulomatous fibrosis supervenes. Up to one-third of cases of bronchocentric granulomatosis are associated with ABPA. It is thought to represent a response to endobronchial aspergillosis [18]. This is reflected by the abundance of eosinophils at the site of inflammation in pathological specimens [19].

Immediate hypersensitivity may also be seen as a reaction to *Aspergillus*, where *Aspergillus* acts as an inhaled antigen similar to other organic dusts producing an allergic alveolitis (hypersensitivity pneumonitis). This reaction is mediated by type I (IgE) with contributions from cell-mediated (type IV) and immune complex (type III), and can be seen in some asthmatic patients inhaling a heavy spore load [20, 21].

Although it is clear that immune defects play a central role in the evolution of invasive aspergillosis, a few cases of invasive aspergillosis in apparently healthy individuals are described in the literature [22, 23, 24, 25]. It seems likely that such patients have an occult immune deficiency, but this is a matter of speculation.

The predominant pathology caused by *Aspergillus* is largely dependent on systemic and local host immunity, the presence or absence of pre-existing parenchymal lung damage, and the load of spores inhaled [2, 3, 6].

Aspergilloma

The term mycetoma is used to describe a mobile fungus ball within a pre-existing, usually fibrotic, lung cavity. Mycetomas are usually caused by *Aspergillus* (aspergilloma), but other fungi may occasionally be responsible including *Candida*, streptomycetes, coccidioides and phycomycetes [6]. Pathologically, aspergillomas consist of a tangled growth of *Aspergillus* hyphae admixed with mucous and cellular debris in a cavity. The cavity wall is often thick and consists of a zone of fibrotic tissue, with necrosis of the inner layer [4, 11]. The cavity wall has a rich blood supply from the bronchial and other branches of the systemic circulation, and thus has a propensity to bleed [26].

Aspergillomas have been most frequently documented as occurring in residual tuberculous cavities. A survey in Britain in 1970 showed that 11–20% of patients with residual tuberculous cavities of 2.5 cm diameter or greater had radiographic evidence of aspergilloma [27]. Aspergillomas are also a common accompaniment to advanced fibrotic disease in sarcoidosis, with up to 53% of such patients having radiographic evidence of aspergillomas [28]. Indeed, any cavity within the lung is a potential focus for the development of aspergilloma, and predisposing conditions include bulla in emphysematous lung [29], cystic spaces from end-stage fibrosis [29], pneumatocoeles caused by *Pneumocystis carinii* [30], miscellaneous cavitatory infections (e.g. histoplasmosis) [26, 31], bronchogenic/congenital lung cysts [31], Wegener's granulomatosis [32], cavitary pulmonary infarction [29] and lung fibrosis from radiotherapy [26]. The most common location, whatever the predisposing cause, is the upper lobes.

Bronchiectatic airways may also harbour aspergillomas, and the location of the aspergillomas in these cases is more variable. Jewkes et al. found that of 85 patients with symptomatic aspergillomas, 16 patients were within bronchiectatic airways (10 with allergic bronchopulmonary aspergillosis, and 6 with other causes of bronchiectasis) [29].

The typical radiographic appearances are of a rounded mass sitting inside a cavity (usually thick walled), with air around the mass (crescent sign; Fig. 1). The mass is seen to gravitate freely on images of the patient in different positions [11]. The air-crescent sign is often considered to be characteristic of mycetomas but has also been described in bronchogenic carcinoma [33], retained foreign body following thoracotomy [34], haemorrhage into a cavity [35], Wegener's granulomatosis, sclerosing haemangioma [36], echinococcal cyst [37], tuberculosis, and Rasmussen aneurysm in a tuberculous cavity [38]. Confusingly, the air-crescent sign may also be seen in

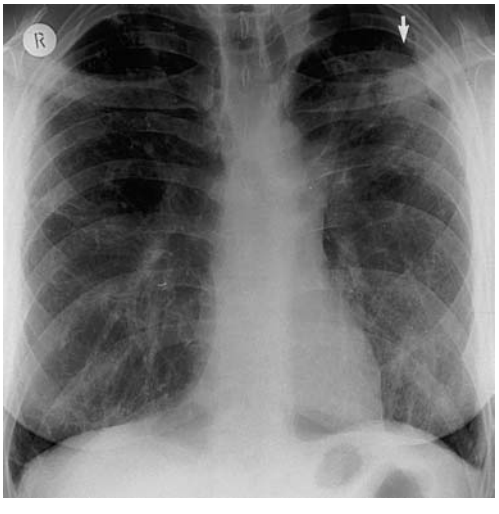


Fig. 1 The classical mycetoma. Large rounded mass at the left apex with an air-crescent sign (*arrow*), and associated lateral pleural thickening

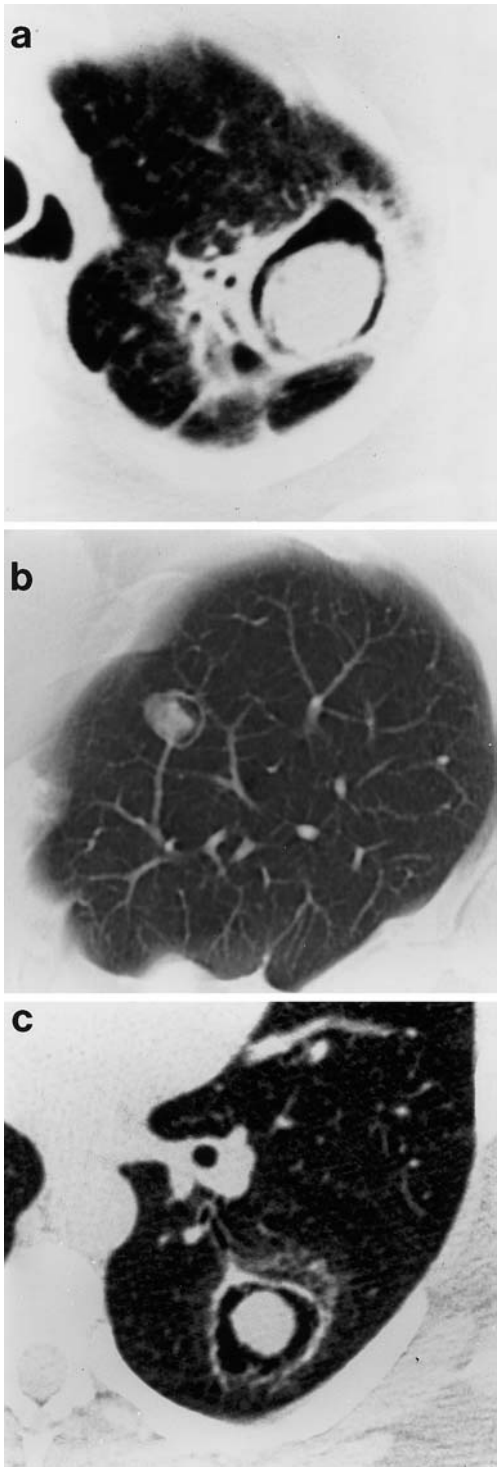


Fig. 2a–c Imaging similarities between mycetoma and invasive *Aspergillus*. Both can present with an air-crescent sign. **a** Mycetoma, with a large fungus ball and small rim of air in a pre-existing cavity, with associated pleural thickening. **b** Invasive aspergillosis with an air-crescent sign in which the infarcted lung retracts and air-crescent sign results (note no pleural thickening evident). **c** A case of sclerosing haemangioma which also shows the air-crescent sign (emphasising that this sign is not specific to *Aspergillus* infection)

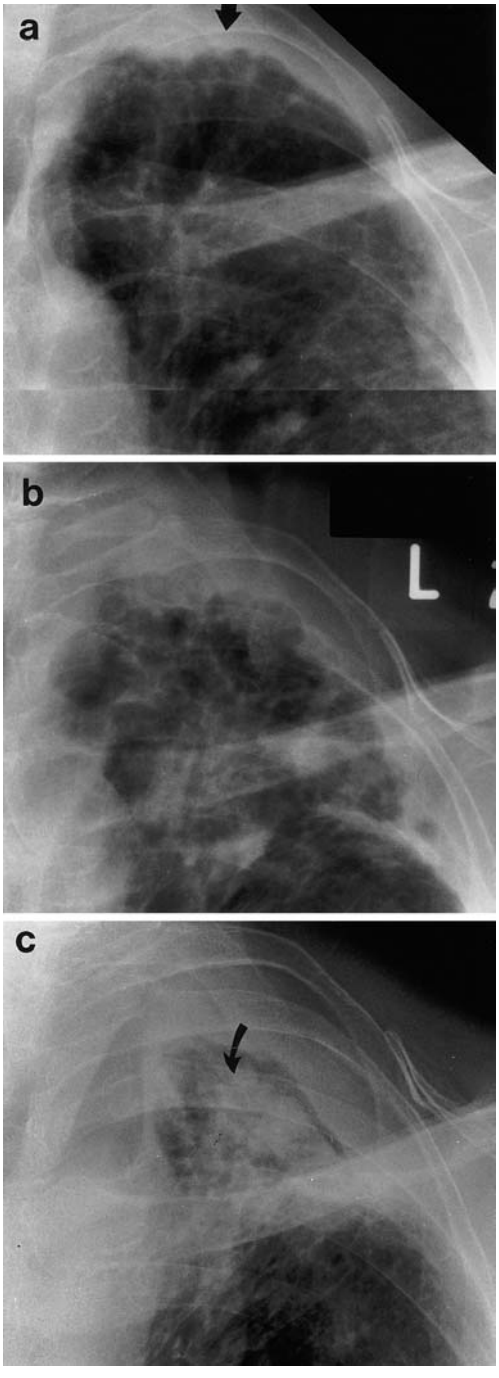


Fig. 3a–c Evolution of aspergilloma on chest radiography. **a** Minimal pleural thickening at the left apex (*arrow*) in a patient with fibrotic lung disease. **b** Five years later, there is lateral pleural thickening but no obvious aspergilloma. **c** Ten years after **a**, there is an intracavitary aspergilloma (*arrow*) compatible and more extensive pleural thickening

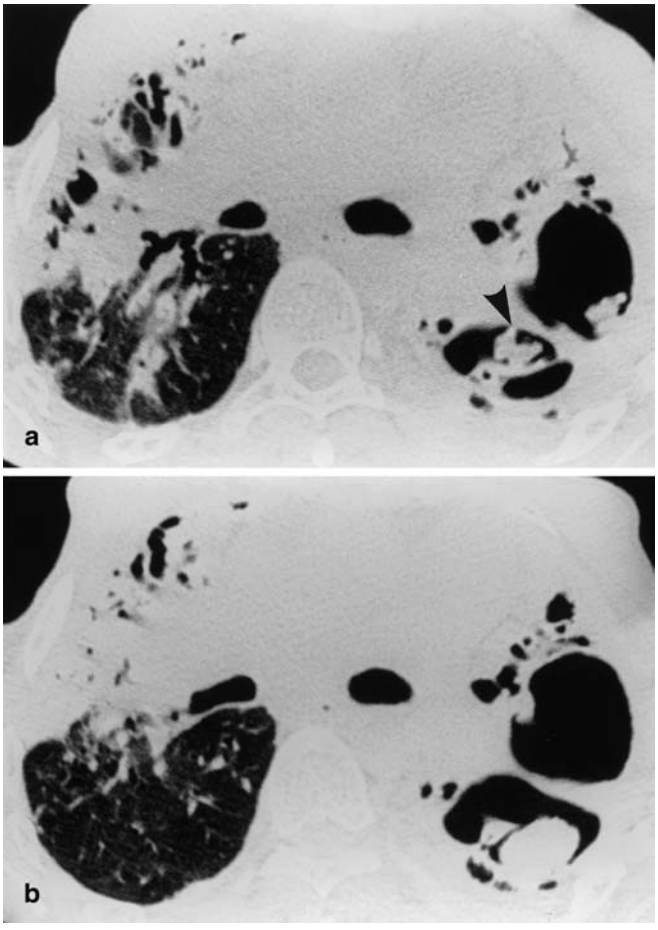


Fig. 4a, b The development of aspergilloma shown on CT. **a** Left apical cavity with pleural thickening and fronds and finger-like projections arising from the cavity wall (*arrowhead*) in a patient with severe fibro-cavitary disease. **b** Fourteen months later, the fronds have broken away from the wall and formed a mature fungus ball

angioinvasive aspergillosis, where it corresponds pathologically to a space caused by retraction of an area of retracted infarcted lung (Fig. 2) [39].The diagnosis of aspergilloma is usually presumptive and made on radiographic findings. An early sign of aspergilloma formation in a cavity is pleural thickening which often antedates the radiographic features of an obvious intracavitary fungus ball [40]. An increase in wall thickness of the lateral aspect of a fibrotic cavity, reflecting a combination of pleural and cavity wall thickening, may be a helpful sign of radiographically cryptic aspergilloma (Fig. 3) [41]. This feature is a reactive phenomenon, with regression of the aspergilloma leading to a normalisation of the pleural thickness [42]. Thin-section CT can demonstrate the early stages of aspergilloma much more readily than chest radiography. Fungal fronds can be seen arising from the cavity wall, often intersecting each other (Fig. 4a). These fronds coalesce and break away from the cavity wall to form a mature fungus ball (Fig. 4b), which may contain small foci of high attenuation, presumably representing calcifications [43]. Not surprisingly, CT also demonstrates additional smaller aspergillomas that are not evident on chest radiograph. Computed tomography is a useful adjunct in cases where an aspergilloma is suspected but the chest radiograph is inconclusive, and in assessment prior to resection (to evaluate the extent of the aspergilloma, and to assess the integrity of the remaining lung). In a few patients aspergillomas appear to regress, sometimes following a superadded bacterial infection [27], but apparently spontaneous resolution has also been reported [44]. The treatment options are dependent on symptomatology, the severity of underlying lung disease and the general condition of the patient. Surgical resection in specialist centres provides the best overall result, but because most patients have advanced diffuse lung disease, few patients are suitable surgical candidates [26, 29, 45]. Other treatment strategies are palliative and involve control of haemopytsis with bronchial embolisation or intracavitary anti-fungal therapy (under CT guidance or fluoroscopy) [46, 47, 48].

Invasive aspergillosis

The term *invasive aspergillosis* is often used in the context of aggressive disease in immunocompromised patients; however, this form of *Aspergillus* infection may be more indolent and occurs in patients with mycetoma or ABPA, and in patients with chronic debilitation [1, 7, 49]. By definition, the hyphae invade the adjacent lung parenchyma, first bronchial wall and subsequently the accompanying arterioles. There are two main forms: angioinvasive (predominantly involving invasion of the pulmonary artery branches) and airway invasive (predominantly involving the bronchi and bronchioles); however, given the anatomic proximity of the bronchi and pulmonary arteries, it is not surprising that the two forms co-exist in the same patient, and that it is not always possible to distinguish between the two types. As well as blood dissemination, *Aspergillus* is seen rarely to invade locally into the adjacent mediastinum or pleura (Fig. 5) [25, 50, 51].

Angioinvasive aspergillosis

Angioinvasive aspergillosis is the classical form of invasive aspergillosis which is characterised clinically by haemorrhagic bronchopneumonia. The hallmark is hyphal invasion of blood vessels with consequent infarction and necrosis [52]. Associated extrapulmonary foci are found in 10–25% of patients at autopsy, with the gastrointestinal tract, brain, heart, liver, spleen and thyroid

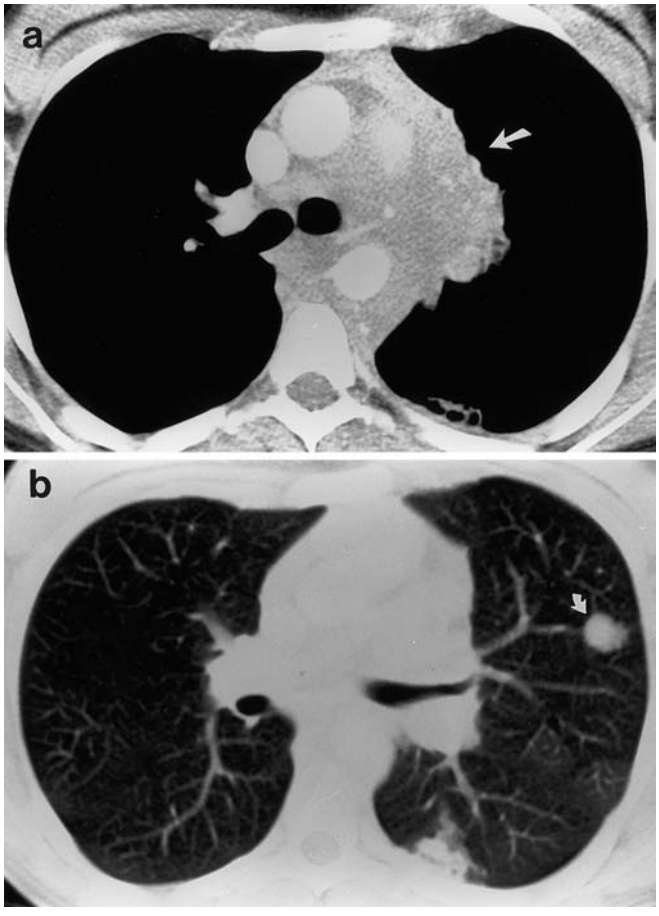


Fig. 5 Invasive mediastinal aspergillosis. A 19 year old girl presented with a hoarse voice and difficulty swallowing. **a** The CT shows a large mediastinal mass infiltrating around the great vessels (*arrow*), and left hilum. **b** Lung windows demonstrate the presence of parenchymal nodules (*arrow*). Biopsy performed under CT showed invasive aspergillosis, and this was confirmed by medastinal biopsy. There was no history of asthma, and despite extensive investigations no immunodeficiency was found. The patient responded to antifungal therapy, and remained well at 2 year follow-up

the most frequently affected organs [23]. Florid angioinvasive aspergillosis is seen almost exclusively in severely immunocompromised patients (particularly those with neutropaenia), most commonly after bone marrow transplant for haematological malignancy, after solid organ transplant, following cytotoxic chemotherapy inducing a neutropaenia, and in a few patients with AIDS.

There have been a few cases described in which the patient had no known prior immunodeficiency. Orr et al. documented two patients with normal host defences dying of disseminated aspergillosis at post-mortem studies (one patient had a previous history of coronary heart disease, and the other acute renal failure following gangrenous appendicitis) [52].

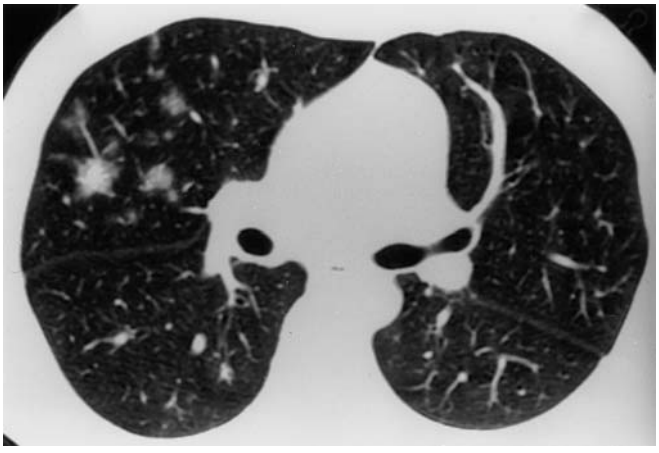


Fig. 6 The "halo" sign of invasive aspergillosis. Multiple nodular opacities clustered in the right upper lobe with surrounding ground-glass attenuation (halo) in an immunocompromised patient following recent bone marrow transplant (which resolved completely on antifungal therapy)

In up to 25% of patients with invasive aspergillosis, the chest radiograph may appear normal [23]. Radiographic abnormalities include: single or multiple nodular infiltrates; segmental or subsegmental consolidation; diffuse ground-glass pattern (often progressing to consolidation); and cavitation (air-crescent sign) [23, 39]. The air-crescent sign in angioinvasive aspergillosis is seen in up to 48% of patients (with biopsy-proven invasive aspergillosis) in the recovery phase [53], and relates to hyphal invasion of blood vessels leading to an area of infarcted lung (sequestrum), in which resorption of necrotic tissue in the periphery or retraction of the sequestrum from viable lung parenchyma leads to a crescent of air surrounding the sequestrum [39]. Cavitation is more likely to occur in larger areas of consolidation or nodules [53], and is associated with a higher risk of massive haemopytsis which may require prophylactic lobar/segmental resection [53, 54]. Cavitation is more frequently seen during the recovery phase of neutropaenia, and it has been postulated that potent proteolytic enzymes are released by the influx of neutrophils, causing tissue destruction with subsequent air-crescent formation [54].

High-resolution CT shows nodules surrounded by areas of ground-glass attenuation (halo sign; Fig. 6), and areas of segmental and non-segmental consolidation with or without a halo [55, 56, 57]. The halo sign represents haemorrhage around a nodule [57, 52, 50] and is seen much earlier (on average 1–2 weeks), and with greater frequency, than the air-crescent sign [56]. In early reports much was made of the sensitivity of the halo sign [55, 56, 57, 58] in immunocompromised patients, and in the appropriate clinical setting it is highly suggestive of angioinvasive aspergillosis; however, this feature has been described in the same group of patients found to

have mucormycosis, *Candida*, cytomegalovirus (CMV) infection, herpes infection, organizing pneumonia and pulmonary haemorrhage [59]. It may also be seen in non-immunocompromised patients with Wegener's granulomatosis, Kaposi's sarcoma and metastatic angiosarcomas [60]. Concomitant infections are not infrequently seen in these patients and include viral infection (CMV, hepatitis B, herpes simplex particularly in the AIDS patients), bacterial infection and other fungal infection (e.g. *Candida*) emphasising the need for diagnostic confirmation by more definitive means such as bronchoalveolar lavage (BAL) and/or biopsy in patients not responding to empirical systemic antifungal therapy.

i) Airway invasive aspergillosis

The pathological definition of airway invasive aspergillosis is the presence of *Aspergillus* organisms deep to the basement membrane of the bronchial tree [5]. This form of aspergillosis is divided into: (a) acute airway invasive aspergillosis; and (b) chronic airway invasive aspergillosis (also known as semi-invasive aspergillosis or chronic necrotising aspergillosis [1, 7])

Acute airway invasive aspergillosis

Acute airway invasive aspergillosis occurs most frequently in the same group of immunocompromised patients as angioinvasive aspergillosis, but accounts for less than one-third of all cases of invasive aspergillosis [52]. Acute airway invasive aspergillosis causes a spectrum of disease from acute tracheobronchitis, exudative bronchiolitis and a bronchopneumonia. The radiographic findings in biopsy of autopsy-proven cases include patchy consolidation of lower lobe predominance, ill-defined nodules, and a normal chest radiograph [5]. The HRCT findings mirror the pathogenesis of the disease and include peribronchiolar consolidation, centrilobular micronodules (<5 mm), ground-glass attenuation and lobar consolidation (reflecting an exudative bronchiolitis and air-space infiltration; Fig. 7). *Aspergillus* is seen deep to the basement membrane of the bronchioles at histology, and is usually seen within the airway lumen [5]. It is noteworthy, but perhaps unsurprising, that positive yield from BAL is more likely in airway- than in angioinvasive aspergillosis (8 of 10 vs 2 of 10, respectively in one study [58]). Occasionally, *Aspergillus* can invade the trachea and cause pseudomembranous necrotising tracheal aspergillosis which has a high mortality [61]. Imaging features include opacification of paratracheal fat on CT, tracheal narrowing, and pneumomediastinum in immunocompromised patients (including AIDS patients) [61, 62].

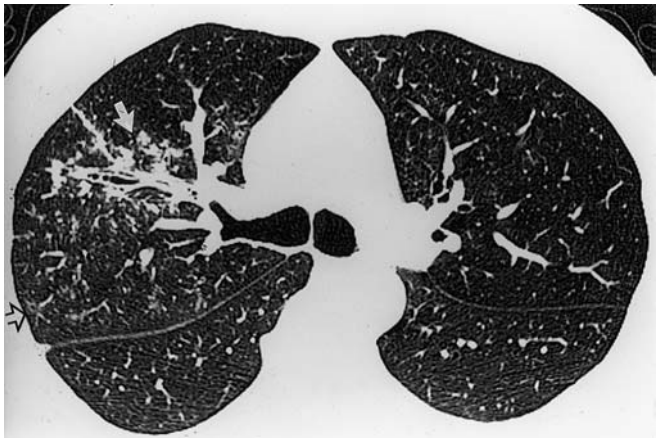


Fig. 7 Acute airway invasive aspergillosis. High-resolution CT demonstrates peribronchial nodular thickening (*white arrow*), with adjacent tree-in-bud pattern (*black arrow*)

Table 2 Pulmonary and systemic factors predisposing to chronic airway invasive aspergillosis. *COPD* chronic obstructive pulmonary disease (Adapted from [14])

Pulmonary factors	Systemic factors
COPD	Corticosteroid therapy
Interstitial lung disease	Alcoholism
Asthma (includes ABPA)	Rheumatoid arthritis
Pneumonia	Diabetes mellitus
Thoracic resection	Ankylosing spondylitis
Influenza	Chemotherapy/radiotherapy
	Debilitation
	Chronic granulomatous disease

ii) Chronic airway invasive aspergillosis

Chronic airway invasive (chronic necrotising/semi-invasive) aspergillosis is a relatively rare condition characterised by an indolent granulomatous cavitatory *Aspergillus* infection [6] which may mimic reactivation tuberculosis radiographically [1, 6]. The diagnosis relies on biopsy specimens showing local tissue invasion with *Aspergillus*, and thus it can be argued that this entity should correctly be called the chronic airway invasive form. Tissue necrosis and granulomatous inflammation then ensues. This entity was first described in the early 1980s by Gefter et al. [1] and Binder et al. [7]. Since then, over 100 cases have been reported [1, 7, 14]. Patients present with a variety of symptoms including haemoptysis, sputum production, weight loss and fever.

Over one-third of patients have multiple risk factors (some of which are shown in Table 2) [14]. Radiographically, chronic airway invasive aspergillosis starts as a focus of consolidation (usually in the upper lobes), which progresses with time to cavitation, and subsequent aspergilloma formation with associated adjacent pleural thick-

ening. The process progresses slowly often over months [1, 7, 63]. Patients are treated with systemic antifungals (itraconazole orally, or intravenous amphotericin B), surgery and, in a few cases, intracavity amphotericin B. Mortality is between 10 and 34% (often from the underlying disease of the patient rather than the *Aspergillus* infection itself) [14]. An interesting observation is the coexistence of chronic airway invasive aspergillosis in a few patients with atypical mycobacterial infection, as the same risk factors apply to both infections [64].

Allergic bronchopulmonary aspergillosis

The complex pathology that characterises ABPA results in tenacious secretions, inflammatory bronchial wall damage and eventually bronchiectasis and fibrosis. It is most often encountered in patients with a history of asthma (of variable severity) [65, 66], but also occurs in patients with cystic fibrosis [67, 68]. Familial occurrence has also been reported [69, 70]. The criteria for a secure diagnosis of ABPA ([71, 72, 73]) are: (a) bronchial asthma; (b) blood eosinophilia (>1000/ul); (c) immediate cutaneous reactivity to *Aspergillus* fumigatus antigen; (d) precipitating antibodies to *Aspergillus* fumigatus antigen; (e) elevated serum immunoglobulin IgE concentration; (f) a history of transient or fixed pulmonary infiltrates; (g) central bronchiectasis; and (h) elevated serum IgG and IgE to *Aspergillus* fumigatus antigen. The diagnosis is usually made on the basis of clinical history, immune criteria, and central bronchiectasis. Only rarely do patients with ABPA exhibit all the diagnostic criteria at any given time (Table 3) [71].

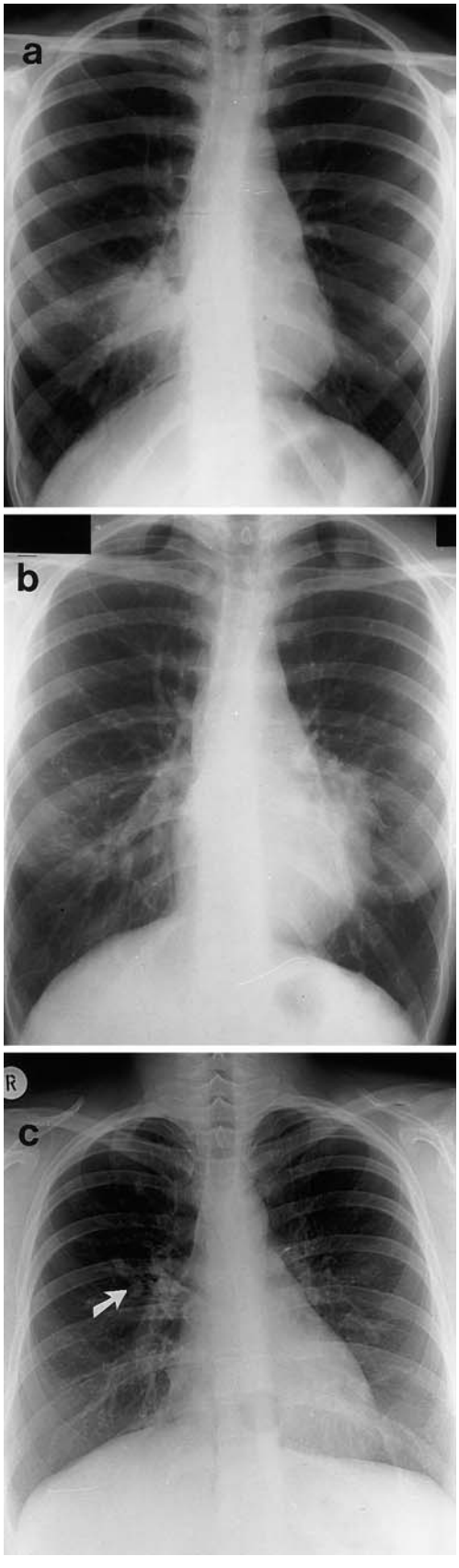
ABPA has been classified into five clinical subgroups [74]: (a) acute stage (classic signs, symptoms, and laboratory findings present at diagnosis); (b) remission (clearing of radiographic abnormalities, a decline in total serum IgE, control of respiratory symptoms, and a discontinuation of steroid therapy over 6 months without exacerbation); (c) recurrent exacerbation (exacerbation of the acute stage, or a twofold rise in serum IgE in association with a new radiographic abnormality); (d) corticosteroid-dependent asthma with exacerbations of ABPA (patients require continuous steroids to control their asthma, and/or control of recurrent exacerbations of ABPA); and (e) fibrotic lung disease (extensive changes on the chest radiograph, which are irreversible). In the early stages of the disease (stages 1–3) the disease is still potentially reversible, but in the later stages (stages 4–5) irreversible parenchymal changes have occurred in the form of central bronchiectasis and fibrosis [75]. The terminology "ABPA-CB" is used when central bronchiectasis is present and "ABPA-Serologic" when it is not [71], but this presupposes that all patients with suspected ABPA undergo an HRCT examination.

Up to 10% of patients with cystic fibrosis have ABPA [67]. In these patients the diagnosis is made from clinical history, positive sputum cultures of *Aspergillus*, and immune criteria (specific serum positivity to *Aspergillus* fumigatus, *Aspergillus*-fumigatus-specific IgE and precipitating antibodies to *Aspergillus* fumigatus) [68].

The classical radiographic findings of ABPA comprise: fleeting air-space shadows (pathologically, these are probably areas of eosinophilic pneumonia, often with elements bronchocentric granulomatosis; Fig. 8a,b) [18, 76]; tubular—sometimes branching—densities, also known as "toothpaste" and "gloved-finger" shadows (representing mucoid impaction in bronchi; Fig. 8c); "pseudohilar adenopathy" caused by mucous plugging of central bronchi; tram-line shadows; parallel shadows and ring shadows of bronchiectasis [76, 77]. The development of atelectasis and cavitation was shown to occur in 46 and 20% of patients with ABPA, respectively, in one series [78]. Cavitation was observed to occur in patients with a chronic infiltrate, often in the absence of secondary bacterial infection, and was assumed to represent necrosis within the eosinophilic pneumonia [78]. The de-

Table 3 Summary of the clinical, laboratory and serological findings in ABPA patients. (Adapted from [71])

Studies	Diagnostic value
Clinical or laboratory findings	
Asthma	ABPA possible
Eosinophilia	ABPA possible
Fleeting pulmonary infiltrates	ABPA probable
Central bronchiectasis	ABPA almost certain
Serological assessment	
Precipitins against *A. fumigatus* positive	All four tests positive: diagnosis is established
IgE antibody to *A. fumigatus* >2 times asthmatic control	Three tests positive; diagnosis very likely
IgG antibody to *A. fumigatus* >2 times asthmatic control	
Total serum IgE >1000 ng/ml	Two tests positive; diagnosis possible
Outcome following treatment	
Total serum IgE declines by 50–75% after treatment with prednisone	Consistent with ABPA



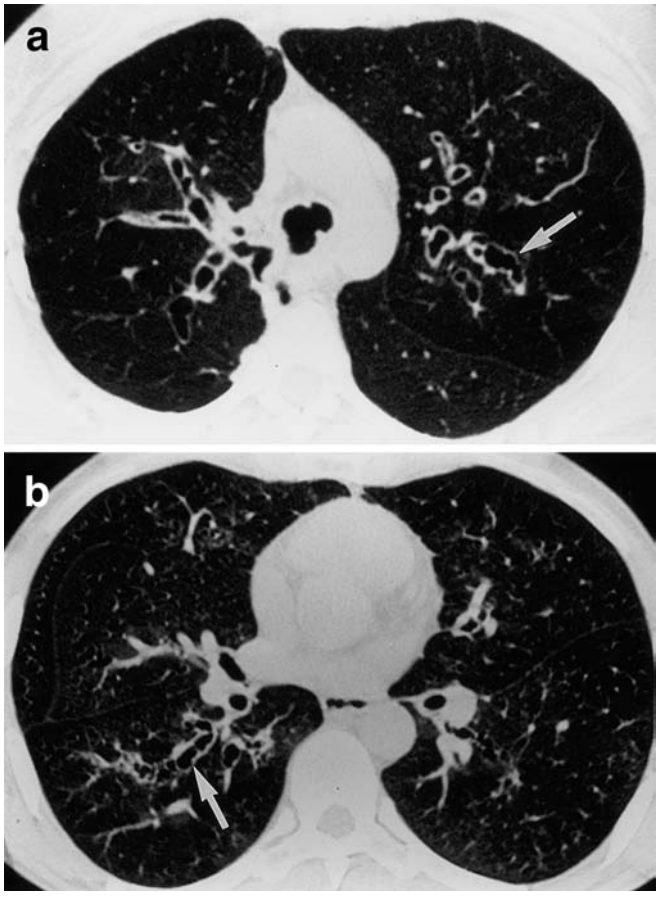


Fig. 9 High-resolution CT of allergic bronchopulmonary aspergillosis. Two patients with typical proximal varicose bronchiectasis (*arrows*) in the mid and upper zones

velopment of aspergillomas is uncommon but well described and reported in up to 7% of patients with ABPA. Usually, mycetoma occurs in patients with longstanding ABPA with extensive lung destruction [76, 79], although this is not always the case and rapid formation of mycetoma in early ABPA has been described [80].

Central bronchiectasis with normal tapering of distal bronchi was the hallmark in the era of bronchography [81].

High-resolution CT is well suited to showing the distribution, extent, and progression of bronchiectasis in ABPA [82, 83, 84]. In patients with an established clinical and radiological diagnosis of ABPA, HRCT most often demonstrates central bronchiectasis in 95% (central and upper lobe predominance; Fig. 9), although a mix-

Fig. 8a–c Radiographic features of allergic bronchopulmonary aspergillosis (ABPA). Fleeting air-space consolidation in the right middle lobe (**a**), and several years later in the lingular (**b**). Note the overinflated lungs in this asthmatic patient. **c** "Gloved-finger" appearance corresponding to mucoid impaction of proximal bronchi (*arrow*), with bronchial wall thickening and dilatation elsewhere in the upper lobes compatible with bronchiectasis

ture of central and peripheral is often seen, and occasionally a pattern of lower-lobe cylindrical bronchiectasis, similar to that seen in idiopathic bronchiectasis, is encountered [85]. Other findings on HRCT include centrilobular nodular opacities (tree-in-bud pattern), mucoid impaction, parenchymal consolidation, parenchymal scarring and pleural abnormalities (effusions and minor pleural thickening) [83, 84, 86]. High-attenuation mucous plugging on CT has been described in up to 30% of cases [87], but in practice this is not a conspicuous feature. The cause of high-attenuation mucoid impaction is thought to relate to calcium salts and metal ions within mucoid material, as has been shown in paranasal soft tissue masses related to aspergillosis [88]. In asthmatics a combination of three or more lobes affected with central bronchiectasis (especially the upper lobes), the presence of centrilobular nodules, and mucoid impaction is highly suggestive of ABPA [84].

In a large prospective study by Eaton et al. 20% of asthmatic patients had skin-prick testing positivity to *Aspergillus* fumigatus; of these, HRCT findings compatible with ABPA were found in 25% [89], emphasising the role of HRCT in the diagnostic work-up in asthmatic patients with possible ABPA.

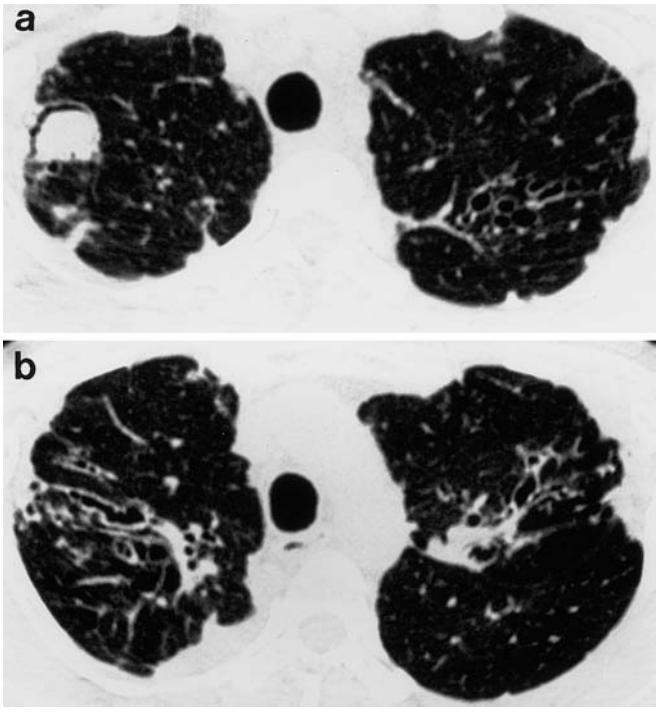


Fig. 10a, b Co-existent aspergilloma in a patient with longstanding allergic bronchopulmonary aspergillosis shown on HRCT. **a** An aspergilloma in the right upper lobe, with typical proximal bronchiectasis seen in **b** ABPA on an adjacent section

Aspergillus *hypersensitivity pneumonitis*

Aspergillus can occasionally produce a hypersensitivity pneumonitis (extrinsic allergic alveolitis). This particular entity is often seen as a consequence of contaminated water sources (particularly hot tubs), but also can be the main antigen in some cases of farmer's lung. It presents in exactly the same manner as other cases of extrinsic allergic alveolitis, with fever, chills, acute shortness of breath, or with progressive shortness of breath in the sub-acute and chronic phases. The radiological picture is that of ground-glass opacity or diffuse small nodules on the chest radiograph, and on CT is that of centrilobular nodules with patchy areas of ground-glass attenuation, and focal patchy air trapping on expiration. Fibrosis is seen in the later phases [90].

Issues of classification and overlap

The degree of overlap between what are often regarded as discrete clinicopathological entities may appear, at first sight, surprising. Although aspergillomas are thought of as an indolent saprophytic growth, cases of subsequent invasive aspergillosis are well described [91, 92]. Another linkage is the development of ABPA following the formation of an aspergilloma [93].

ABPA is set apart from the *Aspergillus* infections by the observation that the fungal hyhae are confined to the bronchial lumen. In longstanding ABPA the bronchi show marked bronchiectatic change and aspergillomas may form within them. In one series of 111 patients with ABPA radiographic evidence of mycetomas was evident in 8 (probably an underestimate) [76], and 7 of these were located in the midzone of the lung (Fig. 10). The development of aspergillomas can also be seen early in the disease process of ABPA (before bronchiectasis) [80] implying that in some patients they form from direct parenchymal invasion in much the same way as mycetomas resulting from chronic airway invasive aspergillosis. The invasive propensity of *Aspergillus*, in the context of ABPA, has been carefully described by Riley et al. [94]: the chest radiograph of a patient with longstanding ABPA showed chronic fibrocystic changes in the right upper lobe; the lobe was resected and macroscopically the specimen showed pleural fibrosis, a contracted lobe with gross bronchiectasis and also numerous intrapulmonary nodules and several cavities. Histological examination showed granulomas throughout the lobe both close and distant to the major bronchi; of these, 10% had branching hyphae of *Aspergillus* within them [94]. This patient had a chronic airway invasive infection with *Aspergillus* co-existent with ABPA, and this has been described subsequently (Fig. 11) [14]. Not only can hypha invade the lung locally in ABPA, but blood-borne dissemination is also possible (Fig. 12) [95]. This complica-

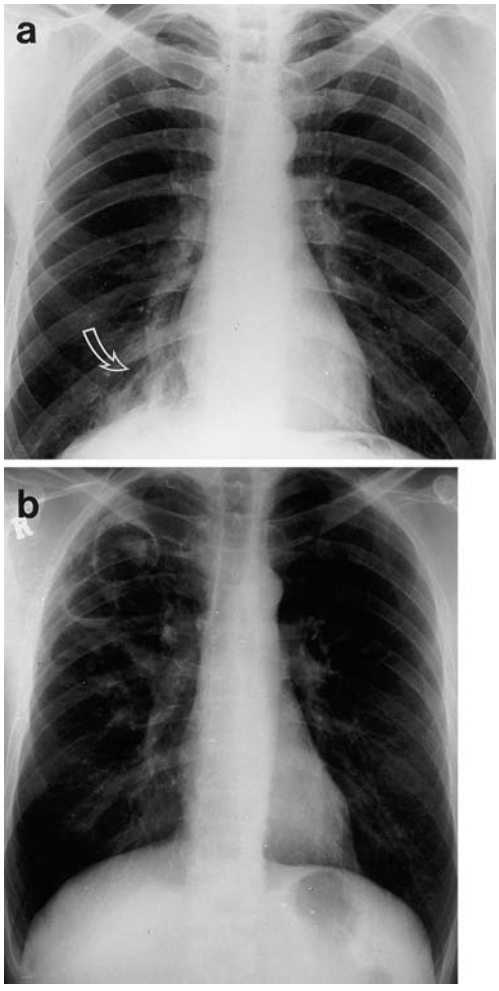


Fig. 11a, b Chronic airway invasive, and invasive aspergillosis in allergic bronchopulmonary aspergillosis. **a** Consolidation in right lower zone (*arrow*) of a patient with longstanding ABPA during an acute exacerbation. **b** One year later, there are two large thin-walled cavities (containing a fluid level and aspergilloma) with minor patchy consolidation in the right upper lobe, which worsened with steroid treatment. Open-lung biopsy of the affected lung showed chronic airway invasive aspergillosis

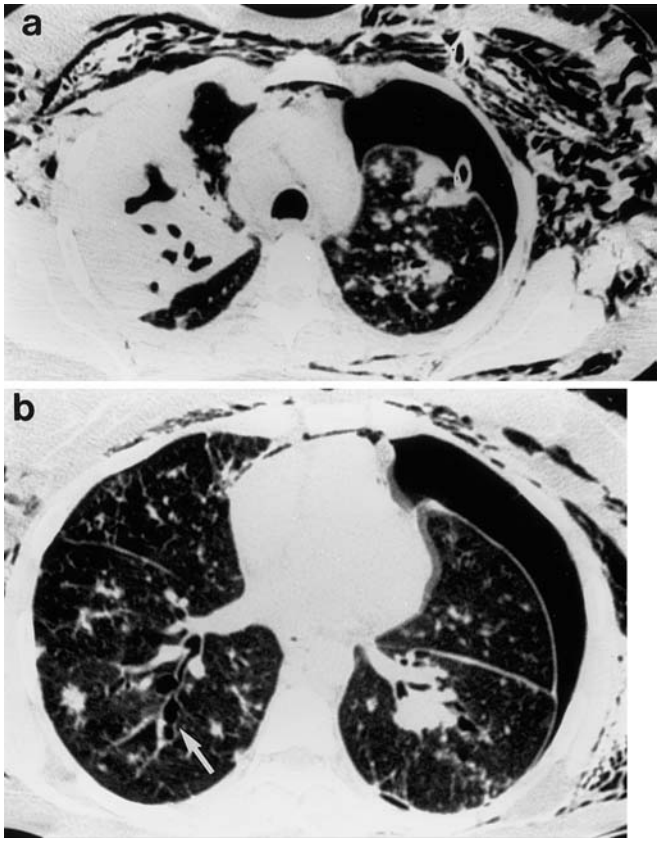


Fig. 12a, b Allergic bronchopulmonary aspergillosis with invasive aspergillosis. A patient with longstanding ABPA presented with a persistent right upper lobe infiltrate which progressed despite steroid and antifungal therapy. **a** The CT scan shows dense consolidation containing bronchiectatic airways and probable cavitation in the right upper lobe, and multiple nodules in the left upper lobe. There is a pneumothorax on the left with extensive surgical emphysema and a chest drain in situ. **b** An image from a lower cut shows the proximal bronchiectasis (*arrow*) typical of allergic ABPA and more parenchymal nodules. The patient deteriorated despite systemic antifungals and the post-mortem examination showed invasive pulmonary aspergillosis, with dissemination to the mediastinum, liver and spleen

tion has a very high mortality and identification at an early stage is therefore highly desirable. The propensity for *Aspergillus* to become invasive in ABPA presumably relates to the interplay between degree of pre-existing bronchial wall damage from longstanding ABPA, the amount of *Aspergillus* fungus in the bronchial tree, and systemic immune factors (including the use of high-dose steroids). Table 4 summarises the overlap between the different forms of *Aspergillus* infection.

Generally, invasive aspergillosis occurs in immunocompromised patients, as previously described; however, there have been several reports documented in patients with no known prior immunodeficiency, and in patients with only minor immunodeficiency [22, 23, 24, 25].

Table 4 Coincident forms of *Aspergillus* in the lung

Overlap	Reference
Mycetoma→invasive aspergillosis	[91]
Mycetoma→ABPA	[93]
ABPA→mycetoma	[76]
ABPA→chronic airway invasive aspergillosis	[94]
ABPA→angioinvasive aspergillosis	[95]

Lake et al. described a case of fatal disseminated aspergillosis in an asthmatic patient in whom the only immunosuppression was a short course of corticosteroids [96]. Chronic airway invasive aspergillosis starts as an infil-

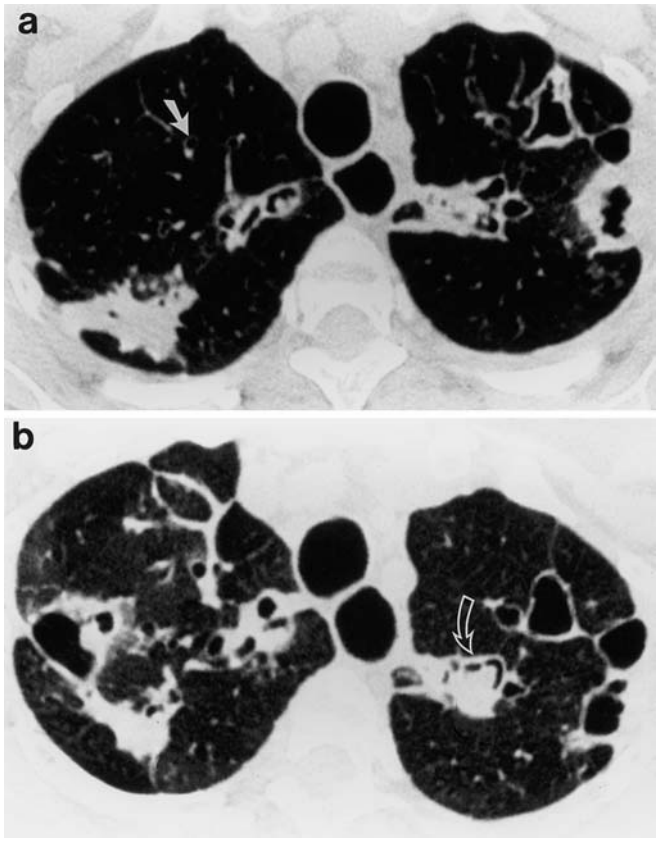


Fig. 13a, b Chronic airway invasive aspergillosis in an elderly woman with co-existing mycobacterium avium intracellulare. **a** The CT shows cavitating lesions, pleural thickening and bronchiectasis (*arrow*), and at this time mycobacterium avium intracellulare and *Aspergillus* were both isolated. **b** The patient deteriorated and a repeat CT 4 months after initial CT shows cavitation, but also an aspergilloma (*arrow*) in one of the left upper lobe cavities. The patient continued to deteriorate despite treatment for both atypical mycobacterial infection and chronic airway invasive aspergillosis but died 6 months later

trate with local tissue invasion of *Aspergillus* which then cavitates, and subsequent aspergilloma formation within the cavity. This form is usually seen in frail patients with a debilitating illness (see Table 2) and is only made following the exclusion of other infections and positive cultures for *Aspergillus*. Recently, Hafeez et al. described four cases of non-tuberculous mycobacterium infection (three patients were infected with mycobacterium malmoense, and one with mycobacterium avium intracellulare) in whom chronic airway invasive aspergillosis was co-existent [64]. As the same patients' risk factors predispose to both atypical mycobacterial infection and chronic airway invasive aspergillosis, it is not surprising that the two can co-exist. Radiographically, the appearances are similar to chronic airway invasive aspergillosis alone showing consolidation and cavitation in the upper lobes (Fig. 13). Chronic airway invasive aspergillosis should therefore be considered in any patient with a non-tuberculous mycobacterial infection who fails to respond to appropriate therapy [64, 97]. It is interesting that three of the four patients improved on treatment with corticosteroids, and the authors postulate that a local type-III hypersensitivity reaction may contribute to the lung destruction in chronic airway invasive aspergillosis [64].

The form *Aspergillus* pulmonary infection takes is dependent on local and systemic host immunity, and the presence of underlying lung pathology, both of which can change in any given patient with time and so modify the manifestation of *Aspergillus* infection. Figure 14 summarises the possible combinations of *Aspergillus* involvement in the lung.

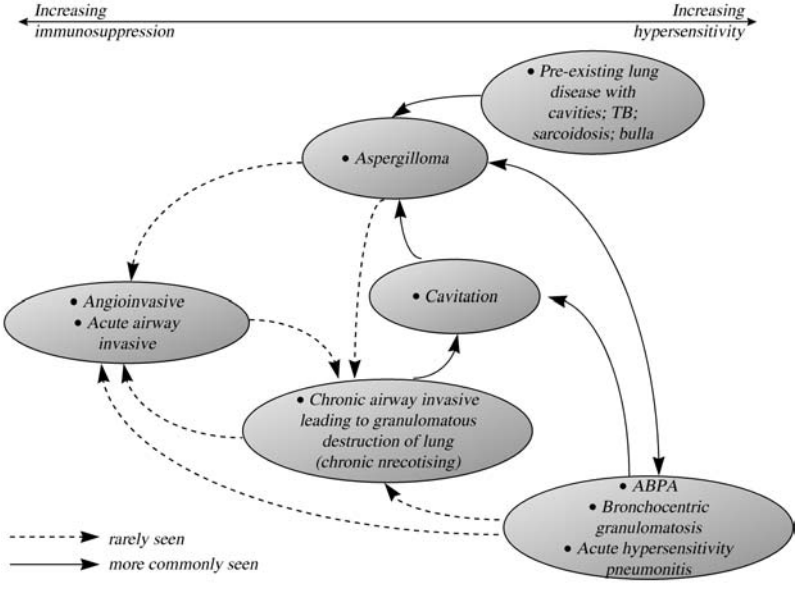


Fig. 14 Flow diagram summarising the possible coincident forms of *Aspergillus* in the lung

Conclusion

The spectrum of disease caused by *Aspergillus* in the lung is wide ranging from hypersensitivity in ABPA, to invasive aspergillosis in the immunocompromised patient, and it is clear that local and systemic host immune factors play an integral role. In practice, most patients can be categorised as having an aspergilloma, ABPA, or invasive aspergillosis. Nevertheless there is a tendency for patients with ABPA, in particular, to develop aspergillomas, and occasionally chronic airway invasive and angioinvasive aspergillosis (see Table 4).

Chronic airway invasive aspergillosis is the preferred term in our classification for the previously described entities of semi-invasive and chronic necrotising aspergillosis as it best fits the underlying pathological process (of local parenchymal invasion with *Aspergillus*, and hyphae found deep to the basement membrane).

References

1. Gefter WB, Weingrad TR, Epstein DM, Ochs RH, Miller WT (1981) "Semi-invasive" pulmonary aspergillosis: a new look at the spectrum of *Aspergillus* infections of the lung. Radiology 140:313–321
2. Greene R (1981) The pulmonary aspergilloses: three distinct entities or a spectrum of disease. Radiology 140:527–530
3. Klein DL, Gamsu G (1980) Thoracic manifestations of aspergillosis. Am J Roentgenol 134:543–552
4. Franquet T, Müller NL, Gimenez A, Guembe P, de La TJ, Bague S (2001) Spectrum of pulmonary aspergillosis: histologic, clinical, and radiologic findings. Radiographics 21:825–837
5. Logan PM, Primack SL, Miller RR, Müller NL (1994) Invasive aspergillosis of the airways: radiographic, CT, and pathologic findings. Radiology 193:383–388
6. Gefter WB (1992) The spectrum of pulmonary aspergillosis. J Thorac Imaging 7:56–74
7. Binder RE, Faling LJ, Pugatch RD, Mahasaen C, Sinder GL (1982) Chronic necrotizing pulmonary aspergillosis: a discrete clinical entity. Medicine 00:109–124
8. Hinson KFW, Moon AJ, Plummer NS (1952) Bronchopulmonary aspergillosis. Thorax 7:317–333
9. Stevens DA, Kan VL, Judson MA, Morrison VA, Dummer S, Denning DW, Bennett JE, Walsh TJ, Patterson TF, Pankey GA (2000) Practice guidelines for diseases caused by *Aspergillus*. Infectious Diseases Society of America. Clin Infect Dis 30:696–709
10. Wheaton SW (1890) A case of primary tubercle, in which a fungus (*Aspergillus*) grew in the bronchi and lung, simulating actinomycosis. Trans Path Soc Lond 41:34–37
11. Hemphill RA (1946) Mycotic lung infection. Am J Med:708–709
12. Twinning EW, Kerley P (1951) A textbook of X-ray Diagnosis. 441-
13. Finegold SM, Will JF, Murray JF (1959) Aspergillosis. A review and report of twelve cases. Am J Med 27:463–482
14. Saraceno JL, Phelps DT, Ferro TJ, Futerfas R, Schwartz DB (1997) Chronic necrotizing pulmonary aspergillosis: approach to management. Chest 112:541–548
15. Waldorf AR (1989) Pulmonary defense mechanisms against opportunistic fungal pathogens. Immunol Ser 47:243–271
16. Greenberger PA.(1997) Immunologic aspects of lung diseases and cystic fibrosis. J Am Med Assoc 278:1924–1930
17. Robinson BW, Venaille TJ, Mendis AH, McAleer R (1990) Allergens as proteases: an *Aspergillus* fumigatus proteinase directly induces human epithelial cell detachment. J Allergy Clin Immunol 86:726–731
18. Bosken CH, Myers JL, Greenberger PA, Katzenstein AL (1988) Pathologic features of allergic bronchopulmonary aspergillosis. Am J Surg Pathol 12:216–222
19. Ward S, Heyneman LE, Flint JD, Leung AN, Kazerooni EA, Müller NL (2000) Bronchocentric granulomatosis: computed tomographic findings in five patients. Clin Radiol 55:296–300
20. Miller WT (1996) Aspergillosis: a disease with many faces. Semin Roentgenol 31:52–66
21. Schatz M, Patterson R, Fink JN (1979) Immunologic lung disease. N Engl J Med 300:1310–1230
22. Cook DJ, Achong MR, King DE (1990) Disseminated aspergillosis in an apparently healthy patient. Am J Med 88:74–76
23. Herbert PA, Bayer AS (1981) Fungal pneumonia (part 4): invasive pulmonary aspergillosis. Chest 80:220–225
24. Cooper JA, Weinbaum DL, Aldrich TK, Mandell GL (1981) Invasive aspergillosis of the lung and pericardium in a nonimmunocompromised 33 year old man. Am J Med 71:903–907
25. Ahmad M, Weinstein AJ, Hughes JA, Cosgrove DE (1981) Granulomatous mediastinitis due to *Aspergillus* flavus in a nonimmunosuppressed patient. Am J Med 70:887–890
26. Regnard JF, Icard P, Nicolosi M, Spagiarri L, Magdeleinat P, Jauffret B, Levasseur P (2000) Aspergilloma: a series of 89 surgical cases. Ann Thorac Surg 69:898–903
27. Aspergilloma and residual tuberculous cavities: the results of a resurvey (1970) Tubercle 51:227–245
28. Wollschlager C, Khan F (1984) Aspergillomas complicating sarcoidosis. A prospective study in 100 patients. Chest 86:585–588
29. Jewkes J, Kay PH, Paneth M, Citron KM (1983) Pulmonary aspergilloma: analysis of prognosis in relation to haemoptysis and survey of treatment. Thorax 38:572–578
30. Schouwink JH, Weigel HM, Blaauwgeers JL, Schreurs AJ (1997) Aspergilloma formation in a pneumatocele associated with *Pneumocystis carinii* pneumonia. AIDS 11:135–137
31. Aslam PA, Eastridge CE, Hughes FA Jr (1971) Aspergillosis of the lung: an eighteen-year experience. Chest 59:28–32
32. Le Thi HD, Wechsler B, Chamuzeau JP, Bisson A, Godeau P (1995) Pulmonary aspergilloma complicating Wegener's granulomatosis. Scand J Rheumatol 24:260-
33. Cubillo-Herguera E, McAlister WH (1969) The pulmonary meniscus sign in a case of bronchogenic carcinoma. Radiology 92:1299–1300
34. Nomori H, Horio H, Hasegawa T, Naruke T (1996) Retained sponge after thoracotomy that mimicked aspergilloma. Ann Thorac Surg 61:1535–1536
35. Bard R (1975) Crescent sign in pulmonary hematoma. Radiology 32:247–251
36. Bahk YW, Shinn KS, Choi BS (1978) The air meniscus sign in sclerosing hemangioma of the lung. Radiology 128:27–29
37. Evans WA (1943) Echinococcus cyst of the lung. Radiology 40:362–366
38. Stivelman BP (1938) Rasmussen aneurysm: its roentgen appearance; report of case with necropsy. J Am Med Assoc 110:1829–1831

39. Curtis AM, Smith GJ, Ravin CE (1979) Air crescent sign of invasive aspergillosis. Radiology 133:17–21
40. Libshitz HI, Atkinson GW, Israel HL (1974) Pleural thickening as a manifestation of *Aspergillus* superinfection. Am J Roentgenol Radium Ther Nucl Med 120:883–886
41. Sansom HE, Baque-Juston M, Wells AU, Hansell DM (2000) Lateral cavity wall thickening as an early radiographic sign of mycetoma formation. Eur Radiol 10:387–390
42. Franquet T, Gimenez A, Cremades R, Domingo P, Plaza V (2000) Spontaneous reversibility of "pleural thickening" in a patient with semi-invasive pulmonary aspergillosis: radiographic and CT findings. Eur Radiol 10:722–724
43. Roberts CM, Citron KM, Strickland B (1987) Intrathoracic aspergilloma: role of CT in diagnosis and treatment. Radiology 165:123–128
44. Hammerman KJ, Christianson CS, Huntington I, Hurst GA, Zelman M, Tosh FE (1973) Spontaneous lysis of aspergillomata. Chest 64:679–679
45. Chatzimichalis A, Massard G, Kessler R, Barsotti P, Claudon B, Ojard-Chillet J, Wihlm JM (1998) Bronchopulmonary aspergilloma: a reappraisal. Ann Thorac Surg 65:927–929
46. Ueda H, Okabayashi K, Ondo K, Motohiro A (2001) Analysis of various treatments for pulmonary aspergillomas. Surg Today 31:768–773
47. Giron J, Poey C, Fajadet P, Sans N, Fourcade D, Senac JP, Railhac JJ (1998) CT-guided percutaneous treatment of inoperable pulmonary aspergillomas: a study of 40 cases. Eur J Radiol 28:235–242
48. Lee KS, Kim HT, Kim YH, Choe KO (1993) Treatment of hemoptysis in patients with cavitary aspergilloma of the lung: value of percutaneous instillation of amphotericin B. Am J Roentgenol 161:727–731
49. Ganassini A, Cazzadori A (1995) Invasive pulmonary aspergillosis complicating allergic bronchopulmonary aspergillosis. Respir Med 89:143–145
50. Hruban RH, Meziane MA, Zerhouni EA, Wheeler PS, Dumler JS, Hutchins GM (1987) Radiologic–pathologic correlation of the CT halo sign in invasive pulmonary aspergillosis. J Comput Assist Tomogr 11:534–536
51. Luce JM, Ostenson RC, Springmeyer SC, Hudson LD (1979) Invasive aspergillosis presenting as pericarditis and cardiac tamponade. Chest 76:703–705
52. Orr DP, Myerowitz RL, Dubois PJ (1978) Patho-radiologic correlation of invasive pulmonary aspergillosis in the compromised host. Cancer 41:2028–2039
53. Kim MJ, Lee KS, Kim J, Jung KJ, Lee HG, Kim TS (2001) Crescent sign in invasive pulmonary aspergillosis: frequency and related CT and clinical factors. J Comput Assist Tomogr 25:305–310
54. Albelda SM, Talbot GH, Gerson SL, Miller WT, Cassileth PA (1985) Pulmonary cavitation and massive hemoptysis in invasive pulmonary aspergillosis. Influence of bone marrow recovery in patients with acute leukemia. Am Rev Respir Dis 131:115–120
55. Kuhlman JE, Fishman EK, Burch PA, Karp JE, Zerhouni EA, Siegelman SS (1988) CT of invasive pulmonary aspergillosis. Am J Roentgenol 150:1015–1020
56. Kuhlman JE, Fishman EK, Burch PA, Karp JE, Zerhouni EA, Siegelman SS (1987) Invasive pulmonary aspergillosis in acute leukemia. The contribution of CT to early diagnosis and aggressive management. Chest 92:95–99
57. Kuhlman JE, Fishman EK, Siegelman SS (1985) Invasive pulmonary aspergillosis in acute leukemia: characteristic findings on CT, the CT halo sign, and the role of CT in early diagnosis. Radiology 157:611–614
58. Brown MJ, Worthy SA, Flint JD, Müller NL (1998) Invasive aspergillosis in the immunocompromised host: utility of computed tomography and bronchoalveolar lavage. Clin Radiol 53:255–257
59. Won HJ, Lee KS, Cheon JE, Hwang JH, Kim TS, Lee HG, Han J (1998) Invasive pulmonary aspergillosis: prediction at thin-section CT in patients with neutropenia—a prospective study. Radiology 208:777–782
60. Primack SL, Hartman TE, Lee KS, Müller NL (1994) Pulmonary nodules and the CT halo sign. Radiology 190:513–515
61. Vail CM, Chiles C (1987) Invasive pulmonary aspergillosis: radiologic evidence of tracheal involvement. Radiology 165:745–746
62. Miller WT Jr, Sais GJ, Frank I, Gefter WB, Aronchick JM, Miller WT (1994) Pulmonary aspergillosis in patients with AIDS. Clinical and radiographic correlations. Chest 105:37–44
63. Franquet T, Müller NL, Gimenez A, Domingo P, Plaza V, Bordes R (2000) Semiinvasive pulmonary aspergillosis in chronic obstructive pulmonary disease: radiologic and pathologic findings in nine patients. Am J Roentgenol 174:51–56
64. Hafeez I, Muers MF, Murphy SA, Evans EG, Barton RC, McWhinney P (2000) Non-tuberculous mycobacterial lung infection complicated by chronic necrotising pulmonary aspergillosis. Thorax 55:717–719
65. Grammer LC, Greenberger PA, Patterson R (1986) Allergic bronchopulmonary aspergillosis in asthmatic patients presenting with allergic rhinitis. Int Arch Allergy Appl Immunol 79:246–248
66. Basich JE, Graves TS, Baz MN, Scanlon G, Hoffmann RG, Patterson R, Fink JN (1981) Allergic bronchopulmonary aspergillosis in corticosteroid-dependent asthmatics. J Allergy Clin Immunol 68:98–102
67. Laufer P, Fink JN, Bruns WT, Unger GF, Kalbfleisch JH, Greenberger PA, Patterson R (1984) Allergic bronchopulmonary aspergillosis in cystic fibrosis. J Allergy Clin Immunol 73:44–48
68. Skov M, Koch C, Reimert CM, Poulsen LK (2000) Diagnosis of allergic bronchopulmonary aspergillosis (ABPA) in cystic fibrosis. Allergy 55:50–58
69. Shah A, Khan ZU, Chaturvedi S, Malik GB, Randhawa HS (1990) Concomitant allergic *Aspergillus* sinusitis and allergic bronchopulmonary aspergillosis associated with familial occurrence of allergic bronchopulmonary aspergillosis. Ann Allergy 64:507–512
70. Graves TS, Fink JN, Patterson R, Kurup VP, Scanlon GT (1979) A familial occurrence of allergic bronchopulmonary aspergillosis. Ann Intern Med 91:378–382
71. Patterson R, Greenberger PA, Harris KE (2000) Allergic bronchopulmonary aspergillosis. Chest 118:7–8
72. Greenberger PA, Patterson R (1988) Allergic bronchopulmonary aspergillosis and the evaluation of the patient with asthma. J Allergy Clin Immunol 81:646–650
73. Rosenberg M, Patterson R, Mintzer R, Cooper BJ, Roberts M, Harris KE (1977) Clinical and immunologic criteria for the diagnosis of allergic bronchopulmonary aspergillosis. Ann Intern Med 86:405–414
74. Zhaoming W, Lockey RF (1996) A review of allergic bronchopulmonary aspergillosis. J Investig Allergol Clin Immunol 6:144–151
75. Ricketti AJ, Greenberger PA, Mintzer RA, Patterson R (1984) Allergic bronchopulmonary aspergillosis. Chest 86:773–778
76. McCarthy DS, Simon G, Hargreave FE (1970) The radiological appearances in allergic broncho-pulmonary aspergillosis. Clin Radiol 21:366–375
77. Mintzer RA, Rogers LF, Kruglik GD, Rosenberg M, Neiman HL, Patterson R (1978) The spectrum of radiologic findings in allergic bronchopulmonary aspergillosis. Radiology 127:301–307

78. Gefter WB, Epstein DM, Miller WT (1981) Allergic bronchopulmonary aspergillosis: less common patterns. Radiology 140:307–312
79. Safirstein BH, D'Souza MF, Simon G, Tai EH, Pepys J (1973) Five-year follow-up of allergic bronchopulmonary aspergillosis. Am Rev Respir Dis 108:450–459
80. Israel RH, Poe RH, Bomba PA, Gross RA (1980) The rapid development of an aspergilloma secondary to allergic bronchopulmonary aspergillosis. Am J Med Sci 280:41–44
81. Scadding JG (1967) The bronchi in allergic bronchopulmonary aspergillosis. Scand J Respir Dis 48:372–377
82. Panchal N, Pant C, Bhagat R, Shah A (1994) Central bronchiectasis in allergic bronchopulmonary aspergillosis: comparative evaluation of computed tomography of the thorax with bronchography. Eur Respir J 7:1290–1293
83. Panchal N, Bhagat R, Pant C, Shah A (1997) Allergic bronchopulmonary aspergillosis: the spectrum of computed tomography appearances. Respir Med 91:213–219
84. Ward S, Heyneman L, Lee MJ, Leung AN, Hansell DM, Müller NL (1999) Accuracy of CT in the diagnosis of allergic bronchopulmonary aspergillosis in asthmatic patients. Am J Roentgenol 173:937–942
85. Reiff DB, Wells AU, Carr DH, Cole PJ, Hansell DM (1995) CT findings in bronchiectasis: limited value in distinguishing between idiopathic and specific types. Am J Roentgenol 165:261–267
86. Neeld DA, Goodman LR, Gurney JW, Greenberger PA, Fink JN (1990) Computerized tomography in the evaluation of allergic bronchopulmonary aspergillosis. Am Rev Respir Dis 142:1200–1205
87. Goyal R, White CS, Templeton PA, Britt EJ, Rubin LJ (1992) High attenuation mucous plugs in allergic bronchopulmonary aspergillosis: CT appearance. J Comput Assist Tomogr 16:649–650
88. Logan PM, Müller NL (1996) High-attenuation mucous plugging in allergic bronchopulmonary aspergillosis. Can Assoc Radiol J 47:374–377
89. Eaton T, Garrett J, Milne D, Frankel A, Wells AU (2000) Allergic bronchopulmonary aspergillosis in the asthma clinic. A prospective evaluation of CT in the diagnostic algorithm. Chest 118:66–72
90. Patel RA, Sellami D, Gotway MB, Golden JA, Webb WR (2000) Hypersensitivity pneumonitis: patterns on high-resolution CT. J Comput Assist Tomogr 24:965–970
91. Leggat PO, De Kretser DM (1968) *Aspergillus* pneumonia in association with an aspergilloma. Br J Dis Chest 62:147–150
92. Degott C, Potet F, Werner P, Lesobre R (1973) Diffuse pulmonary aspergillosis occurring 4 years after removal of an aspergilloma. Ann Med Interne (Paris) 124:135–140 [in French]
93. Ein ME, Wallace RJ Jr, Williams TW Jr (1979) Allergic bronchopulmonary aspergillosis-like syndrome consequent to aspergilloma. Am Rev Respir Dis 119:811–820
94. Riley DJ, Mackenzie JW, Uhlman WE, Edelman NH (1975) Allergic bronchopulmonary aspergillosis: evidence of limited tissue invasion. Am Rev Respir Dis 111:232–236
95. Anderson CJ, Craig S, Bardana EJ Jr (1980) Allergic bronchopulmonary aspergillosis and bilateral fungal balls terminating in disseminated aspergillosis. J Allergy Clin Immunol 65:140–144
96. Lake KB, Browne PM, Van Dyke JJ, Ayers L (1983) Fatal disseminated aspergillosis in an asthmatic patient treated with corticosteroids. Chest 83:138–139
97. Jouannic I, Desrues B, Lena H, Quinquenel ML, Donnio PY, Delaval P (1996) Exogenous lipoid pneumonia complicated by *Mycobacterium fortuitum* and *Aspergillus* fumigatus infections. Eur Respir J 9:172–174