Eur Radiol (2015) 25:3100–3107
DOI 10.1007/s00330-015-3690-7

CHEST

# Chronic Aspergillosis of the Lungs: *Unravelling the Terminology and Radiology*

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Received: 11 September 2014 / Revised: 17 February 2015 / Accepted: 23 February 2015 / Published online: 20 March 2015


**Abstract**
The propensity for *Aspergillus* spp. to cause lung disease has long been recognised but the satisfactory classification of these disorders is challenging. The problems caused by invasive disease in severely neutropenic patients, saprophytic infection of pre-existing fibrotic cavities and allergic reactions to *Aspergillus* are well documented. In contrast, a more chronic form of *Aspergillus*-related lung disease that has the potential to cause significant morbidity and mortality is under-reported. The symptoms of this form of *Aspergillus* infection may be non-specific and the radiologist may be the first to suspect a diagnosis of chronic pulmonary aspergillosis. The current review considers the classification conundrums in diseases caused by *Aspergillus* spp. and discusses the typical clinical and radiological profile of patients with chronic pulmonary aspergillosis.

*Key Points*
- *The classification of Aspergillus-related lung disease is mired in confusion.*
- *The chronic form of Aspergillus infection is associated with significant morbidity and mortality.*
- *Progressive consolidation and cavitation with intracavitary material is the radiological hallmark.*

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**Keywords** Aspergillosis · Chronic necrotising pulmonary aspergillosis · Imaging, diagnostic · Tomography, x-ray computed · Nomenclature

## Introduction

In a paper published well over a century ago, Sluyter was one of the first to report the potential for *Aspergillus* to cause lung disease in humans [1]. Since that early description it has become apparent that *Aspergillus* spp. can cause a wide spectrum of pulmonary disorders. The variable manifestations are thought to result from the interplay between fungal virulence, host immunity (or hypersensitivity) and the presence of pre-existing lung disease [2, 3]. However, despite the wealth of knowledge about *Aspergillus*-related lung diseases, the categorisation of these conditions has proved difficult. A key issue is the different approaches to classification taken by pathologists, clinicians and radiologists.

The problem of invasive *Aspergillus* infection in severely neutropenic patients (well-covered in recent review articles by Georgiadou et al. [4] and Marom and Kontoyiannis [5]) is not within the scope of this article. To date, comparatively little has been written about the more indolent and chronic forms of *Aspergillus* infection. This is surprising given the global burden of chronic pulmonary aspergillosis, particularly in developing nations where prevalence rates of over 40 per 100,000 population have been estimated [6]. In this review, the terminological confusion related to diseases caused by *Aspergillus* spp. will first be examined. The entity of chronic pulmonary aspergillosis and a classification proposed by Denning and colleagues will then be discussed. Finally, there follows a discussion of the key imaging features, which highlights the role of radiologists in alerting clinicians to the possible diagnosis of chronic pulmonary aspergillosis.

## *Aspergillus*-related lung disease: classification issues

The genus *Aspergillus* comprises a large group of fungi of about 300 species [7], only a minority of which cause human lung disease. Of these, *Aspergillus fumigatus* is the most commonly implicated [2]. A list of names of chronic pulmonary diseases caused by *Aspergillus*, culled from the literature, is shown in Table 1. Attempts at classifying these diseases have been severely hampered by terminological variation and overlap (exemplified in Table 1) [8]. The challenge in bringing some order to the classification of *Aspergillus*-related diseases can be highlighted by examining some examples of these terms.

An obvious example is the variability with which the term aspergilloma is used. In one of the earliest reports from the mid-1940s, Hemphill referred to a mobile "loose body within a cavity", comprised of fungal elements [9]. It seems highly likely that the author was describing the entity later given the generic moniker "mycetoma". Nevertheless, this view of a mass of fungal hyphae and cellular debris in a pre-existing fibrotic cavity is at apparent odds with the opinion of pathologists who, as recently as 2008, advocated that the term mycetoma "accurately applies to soft tissue infections and should not be applied to intracavitary fungal mycelial growth" [2]. Another good example of semantic confusion—covered in more detail later in this review (see the section "Chest radiography" in "Imaging of chronic pulmonary aspergillosis")—relates to terms used to describe a key radiological sign of an aspergilloma. Thus, where radiologists would probably use the words "crescent sign" and "air crescent sign" interchangeably, the author of one review is at pains to highlight apparent differences [10].

The division between what constitutes invasive and non-invasive *Aspergillus* disease is often blurred. For instance, a "pneumonia" caused by *Aspergillus* [11] and allergic bronchopulmonary aspergillosis (ABPA) [12] have been reported in patients with a pre-existing mycetomas. The converse scenario, where aspergillomas develop in patients with ABPA has also been described [13–15]. Indeed, features of tissue invasion are seen in *Aspergillus*-related diseases that are otherwise not regarded as being overtly "invasive" [15–17]. Thus, in one report of a patient with clinical/serological features of ABPA and steroid-dependent asthma, an ultimately fatal invasive aspergillosis developed [17]. In this case, it was thought that APBA preceded invasive disease and that immunosuppression from low dose corticosteroid treatment was a contributory factor [17].

**Table 1** Various terms in the literature describing chronic lung disease caused by (or associated with) *Aspergillus* spp.

| |
|---|
| "Simple" aspergilloma |
| "Complex" aspergilloma |
| Tracheobronchial aspergillosis |
| *Aspergillus* bronchitis |
| *Aspergillus* pseudotuberculosis |
| Semi-invasive aspergillosis |
| Subacute invasive pulmonary aspergillosis |
| Chronic necrotising pulmonary aspergillosis |
| Chronic necrotising bronchopulmonary aspergillosis |
| Chronic cavitary pulmonary aspergillosis |
| Chronic fibrosing pulmonary aspergillosis |
| Allergic bronchopulmonary aspergillosis |

## Chronic *Aspergillus* infection: clinical and classification considerations

The traditional view which broadly divides pulmonary *Aspergillus* infection into invasive and non-invasive types is arguably too rigid [16, 18–20]. In their report from the early 1980s, Gefter et al. described a different form of *Aspergillus* infection (with histopathological and radiographic features somewhere between invasive and non-invasive disease), and coined the term "semi invasive" pulmonary aspergillosis [21]. In essence, they were reporting a more indolent yet slowly progressive infection caused by *Aspergillus*. In this paper, the characteristic finding on serial imaging was of slowly progressive large thick-walled upper lobe cavities containing intracavitary material often associated with thickening of the adjacent pleura. The authors made the important observation that, in contrast to a "classical" mycetoma, there was *no* pre-existing cavity. The implication was that *Aspergillus* infection might itself cause cavities to form. To support their hypothesis, it was noted that previous chest radiographs were normal (or near normal) in four out of five patients. Secondly, the clinical presentation and radiological findings resembled those seen in tuberculosis. Finally, with the exception of one patient, there was mild immunosuppression (variably caused by cancer, general debility or alcoholism) and/or evidence of pre-existing but minor lung damage related to chronic obstructive pulmonary disease or radiation-induced fibrosis.

In 2003, Denning and colleagues proposed their new nomenclature for chronic *Aspergillus*-related lung disease [22], which is now frequently cited. However, it is worth noting that this classification was based largely on the analysis of radiological findings in only 18 patients. The authors identified three broad patterns of behaviour and termed these chronic cavitary, chronic fibrosing and chronic necrotising aspergillosis. The unifying radiological theme was consolidation with one or more cavities. In the cavitary form there was, in some patients, progressive fibrosis and marked volume loss. The tendency to cause severe fibrosis was less apparent in the necrotising pattern of aspergillosis. Irrespective of the initial appearances, intracavitary material was seen on imaging in six cases and prompted the authors to propose that an

"aspergilloma" should also be considered in the ambit of chronic *Aspergillus* infection in the lung [22].

Constitutional symptoms (most commonly including weight loss, cough and haemoptysis) were prominent and generally prolonged (i.e. typically over 3 months) [22]. *Aspergillus* precipitins were present in the serum of all patients. Total immunoglobulin E (IgE) levels were elevated in most cases and *Aspergillus*-specific IgE was raised in approximately two-thirds of patients [22]. As in Gefter's series [21], overt immunosuppression was not a feature but there was mild immunodeficiency caused by alcohol abuse, diabetes and steroid treatment in some cases. More recently, there has been interest in the role of defective interferon-γ production by T lymphocytes (caused by genetic variations) in chronic pulmonary aspergillosis [23, 24].

A pre-existing lung abnormality (most often mycobacterial infection or chronic obstructive airways disease) was common in Denning's report [22], and this has been borne out in larger series [25]. The response to treatment with itraconazole was surprisingly good, with around 70 % of patients showing improvement [22] (Fig. 1). However, data from other studies suggests that the outlook for some patients is less than favourable: in two small series (85 patients in total), the reported mortality approached 50 % [26, 27]. In this setting, the impact of co-morbid conditions is likely to be important [26–28]: a low body mass index and an increased Charlson co-morbidity index have been independently linked with an adverse outcome [28].

The original observations made by Denning and colleagues [22] have, to a greater or lesser extent, been substantiated [3, 6, 25–27, 29, 30] and, on the basis of the relatively small number of published reports, a stereotype of the typical patient with chronic pulmonary aspergillosis emerges (Table 2). However, despite the attraction and seeming convenience of "splitting" the different subtypes of chronic infection, as proposed by Denning, it is apparent the histopathological and radiological features overlap considerably [31]. Therefore, at least for clinical and radiological purposes, we now propose the use of the generic term 'chronic pulmonary aspergillosis' to encompass this type of *Aspergillus* infection.

## Chronic pulmonary aspergillosis: histopathological features

Chronic inflammatory infiltration, cavitation and fibrosis (which, in some patients, is prominent and associated with marked volume loss) are the cardinal findings in chronic pulmonary aspergillosis. The macroscopic and microscopic features vary but, as mentioned above, almost certainly overlap. In one small study of 10 patients, Yousem described three recognisable histopathological patterns [30]: a necrotising granulomatous pneumonia with branching septate hyphae in the central nidus (invading small vessels and leading to coagulative necrosis and cavitation) was the main finding in four patients. Bands of dense fibrosis were seen and, importantly, there was marked pleural fibrosis overlying the necrotising pneumonia. In a second pattern, there were airway-centred cavities, bounded by a fibrous capsule that was contiguous with the submucosa of the adjacent bronchiectatic airway. Interestingly, there were invasive features with tongues of acute inflammation penetrating the fibrous cavity and infiltrating the adjacent lung. Marked pleural fibrosis was seen in one case. Finally, the least common pattern (seen in two subjects) was a bronchocentric granulomatous inflammation with replacement of airway mucosa and filling of the lumen with inflammatory cells and *Aspergillus* hyphae [30].

Regardless of the initial histopathological appearances, the end result in many patients is the development of a single or multiple cavities containing a mass of fungal hyphae, cellular debris, fibrin and mucus [3]. The term aspergilloma (appended by some to "complex aspergilloma", in an attempt to mark the distinction with the colonisation of a *pre-existing* fibrotic cavity) has been given to this pathological-radiological entity. Another characteristic feature, also highlighted in Yousem's series [30], is pleural fibrosis and thickening. Indeed, the propensity to involve the pleura seems to be feature of *Aspergillus*-related lung disease in general [32, 33]. For instance, progressive thickening of the cavity wall and/or adjacent pleural surface (which sometimes regresses in the absence of treatment) is a recognised finding in patients with mycetomas [34, 35]. There is also an intriguing parallel with the relatively new but rare

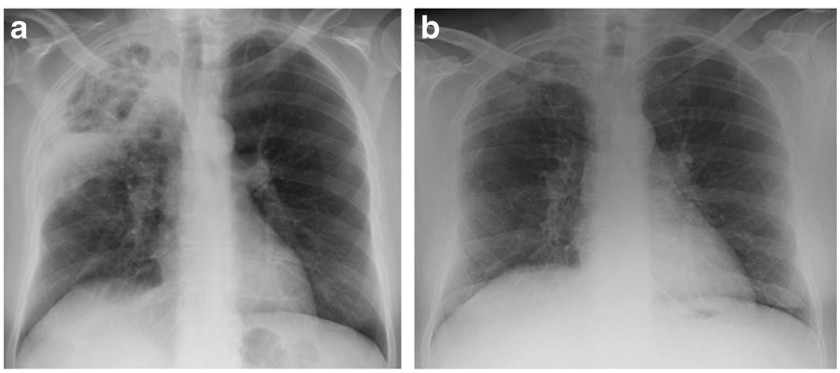


**Fig. 1** Treatment response in chronic pulmonary aspergillosis. **a** Chest radiograph shows consolidation and a thick-walled cavity in the right upper lobe. There is pleural thickening and some intracavitary material. **b** Follow-up chest radiograph, after 8 months of itraconazole therapy, shows considerable (albeit incomplete) resolution

**Table 2** Typical clinical, serological and radiological profile of patients with chronic pulmonary aspergillosis [3, 6, 21, 22, 25–30, 35, 46, 47]

| Clinical characteristics | |
|---|---|
| Age | 4th–8th decade |
| Gender | M > F |
| Symptoms | Weight loss, productive cough ± haemoptysis, dyspnoea & low grade pyrexia (>3 months) |
| Predisposing factors | COPD, diabetes, cystic fibrosis, corticosteroid treatment, connective tissues diseases, alcoholism, low body mass index & cancer |
| Co-existing lung disease | Mycobacterial infection (esp. non-tuberculous mycobacteria) |
| Immune status | Mildly suppressed; genetic variants of interferon-γ |
| Blood/serological | |
| Inflammatory markers (ESR, CRP) | Raised |
| *Aspergillus*-specific IgG | Raised |
| Total & *Aspergillus*-specific IgE | Raised |
| Radiological features (CXR & CT) | |
| Consolidation | Usually upper lobes |
| Cavities | Single or multiple (thin or thick-walled) ± intracavitary material |
| Pleural thickening | Progressive (NB: may resolve spontaneously or on treatment) |
| Volume loss | Progressive—may be marked |

entity of pleuroparenchymal fibroelastosis (PPFE), which is characterised by dense intra-alveolar fibrosis, florid alveolar wall elastosis and fibrous thickening of the pleura [36, 37]. A possible link between PPFE and low-grade *Aspergillus* infection has been highlighted in at least two recent publications [38, 39]. In the larger of the two, Reddy and colleagues found that there was a history of recurrent infections in just over half of their 12 patients, one of whom had tested positive for *Aspergillus* IgG antibody [38]. Another patient, with typical CT features (but ultimately excluded from the study because of inconclusive histopathological findings), also had allergic bronchopulmonary aspergillosis and an aspergilloma.

## Imaging of chronic pulmonary aspergillosis

A diagnosis of chronic pulmonary aspergillosis may first be suspected on the basis of findings on chest radiography and/or CT alone. Hence, a detailed discussion of the radiological findings is relevant. In the sections below, the typical chest radiographic and computed tomographic features of chronic aspergillosis are explored.

### Chest radiography

A review of serial chest radiographs is arguably the most important step in making or suggesting a diagnosis of chronic

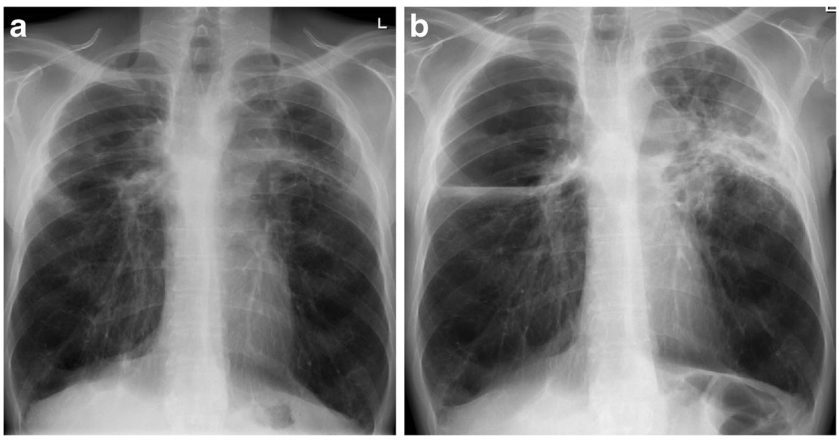


**Fig. 2** Progressive disease caused by chronic pulmonary aspergillosis and non-tuberculous mycobacterial co-infection. **a** Chest radiograph showing bilateral upper zone volume loss. There is ill-defined opacification in the left upper zone and some smooth pleural thickening laterally. Serum *Aspergillus* precipitins and *Aspergillus*-specific IgE were elevated but there was no clinical evidence of mycobacterial infection. **b** Follow-up radiograph, on oral itraconazole treatment, 4 months later showing progressive opacification in the left upper zone and an air-fluid level on the right. Sputum cultures were positive for *Mycobacterium xenopi* and *Mycobacterium kansasii* (serum *Aspergillus* precipitins remained high) and, despite the addition of anti-tuberculous therapy, the patient died 15 months later

pulmonary aspergillosis. Persistent consolidation progressing to cavitation (with or without intracavitary material) and volume loss over time are the principal findings. In most patients, there is consolidation which is usually centred in the upper lobes [22, 28]. Not surprisingly, because of an upper lobe predilection and the similarity of constitutional features, a presumptive radiological diagnosis of reactivation tuberculosis is often made. Indeed, pulmonary mycobacterial infections of various sorts are one of the more commonly identified disorders associated with chronic pulmonary aspergillosis [22, 25–28]. It is worth emphasising that, in clinical practice, aspergillosis and non-tuberculous mycobacterial infection may co-exist [40–44] and this combination confers a worse prognosis (Fig. 2) [41, 44]. In the absence of treatment, consolidation caused by chronic pulmonary aspergillosis may progress, rarely causing complete opacification of a lung and volume loss [22] (Fig. 3).

Cavitation in consolidated lung is a characteristic finding and single or multiple cavities can develop. Cavity walls in chronic aspergillosis may be thin or irregularly thickened and the size of individual cavities can vary significantly [22]. In the earliest stages, there may be a crescent of air density, the so-called air crescent sign. As previously discussed, a little too much has perhaps been made of the potential different meanings of this radiological sign [10, 22, 31]. Indeed, regardless of the exact pathophysiological mechanism or the clinical setting in which it is seen, it is important to realise that this radiological sign simply indicates the presence of a rim of air in a cavity, separating its wall from the inner solid components [45]. In other words, an air crescent is not specific to mycetomas that form in pre-existing fibrotic cavities and may be seen in other situations including angioinvasive aspergillosis or with de novo cavitation in chronic aspergillosis (Fig. 4).

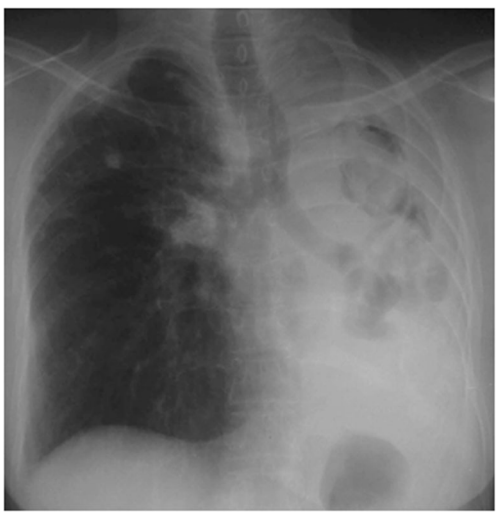

**Fig. 3** Chest radiograph in advanced and destructive chronic pulmonary aspergillosis showing widespread consolidation and marked volume loss on the left. There is evidence of cavitation and an air crescent in the upper zone

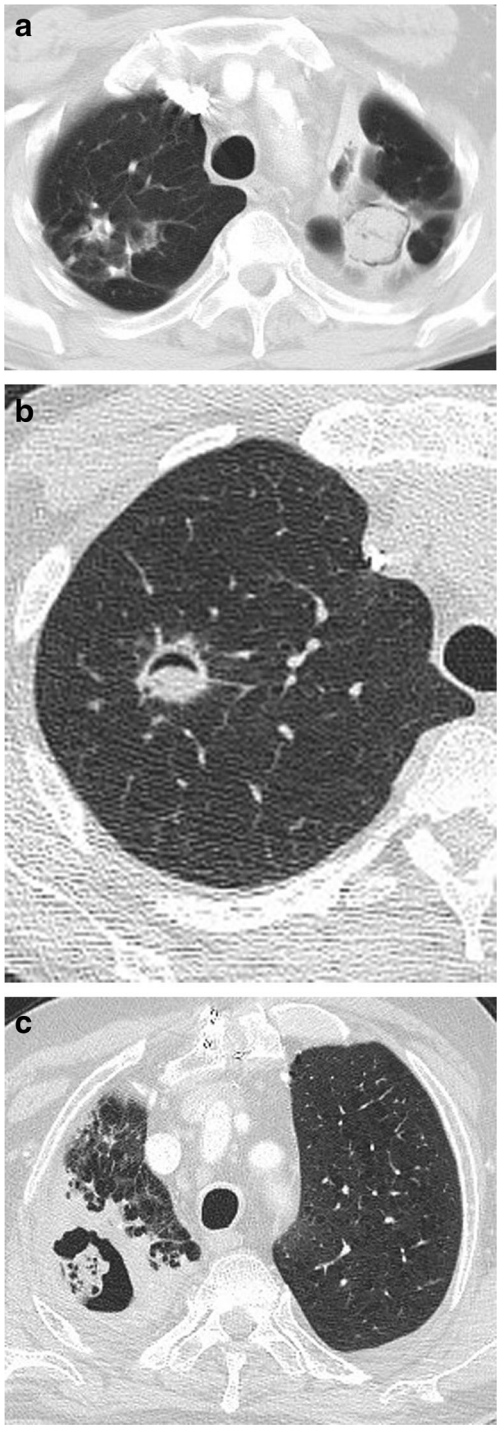


**Fig. 4** Three different causes of a CT air crescent sign. **a** Mycetoma: image through the upper lobes shows a fungal ball in a pre-existing fibrotic cavity (chronic sarcoidosis) at the left apex; **b** angioinvasive aspergillosis: targeted image of the right upper lobe in a severely neutropenic patient with a focal nodule (note that there is no evidence of pre-existing fibrocavitary disease) and **c** chronic pulmonary aspergillosis in a patient with chronic obstructive pulmonary disease and diabetes—the key features being adjacent consolidation and pleural thickening

Thickening of the pleura, adjacent to consolidation or cavities, is a helpful radiological finding in chronic aspergillosis.

In Denning's review, there was radiographic pleural thickening in the majority [22]. Florid thickening was seen in three out of six patients with an aspergilloma but this feature was also present in patients without obvious intracavitary material. An important observation is that, on chest radiographs, the development of the pleural thickening can precede the appearance of an obvious aspergilloma [10]. The key message is that new or progressive thickening of the pleura, in a patient with upper lobe consolidation or cavitation, should alert the radiologist to the diagnosis of chronic pulmonary aspergillosis, regardless of whether there is obvious intracavitary material (Fig. 5).

The lung remote from regions of chronic aspergillosis is frequently abnormal [25–28]. In Smith and Denning's series of 126 patients, one third had evidence of previous mycobacterial infection [25]. In a more recent but smaller retrospective review of 44 patients, chronic obstructive airways disease was present in one third of cases [28]. There was bronchiectasis in another third and a quarter had evidence of previous mycobacterial infection.

## Computed tomography

The CT features of chronic pulmonary aspergillosis mirror those seen on chest radiography. However, because of the superior contrast resolution and the absence of anatomical superimposition, an advantage of CT is that the different radiological patterns and the extent of abnormal lung are more readily appreciated.

To date, published descriptions of CT appearances in chronic pulmonary aspergillosis have been limited to case reports and relatively small series [22, 26, 28, 35, 46–48]. In two large studies [26, 28], with a combined total of 87 patients, single or multiple cavities—most often in the upper lobes—were the most prevalent findings (Fig. 6). Consolidation (frequently cavitating) and pleural thickening are also important CT features of chronic pulmonary aspergillosis. Consolidation uncommonly involves the whole lobe and is more often segmental. In Franquet's series, histopathological examination showed that consolidation on CT corresponded with the presence of intra-alveolar haemorrhage, tissue necrosis and microabscesses [46]. *Aspergillus* organisms were also present in the alveoli. There were similar histopathological features reported by Kim et al., in their study of six patients with chronic pulmonary aspergillosis [47]. As on chest radiography, pleural thickening in regions of consolidation/cavitation is a

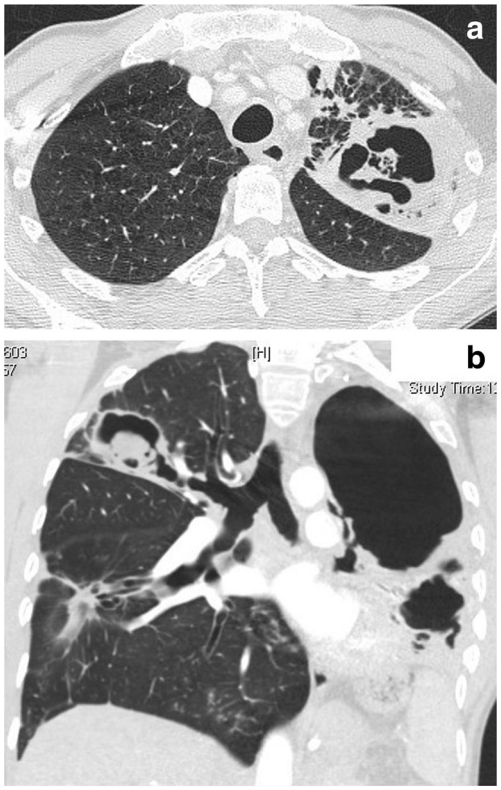


**Fig. 6** Cavitation in chronic pulmonary aspergillosis. **a** Single left upper lobe cavity containing fungal 'debris'. Minor volume loss is present as judged by the relatively anterior position of the oblique fissure. **b** Coronal CT reconstruction in another patient with more advanced chronic pulmonary aspergillosis showing multiple cavities and associated consolidation in the left lung. There is also an aspergilloma in the right upper lobe; the changes in the right lower lobe are likely to reflect overspill of disease from the upper lobes

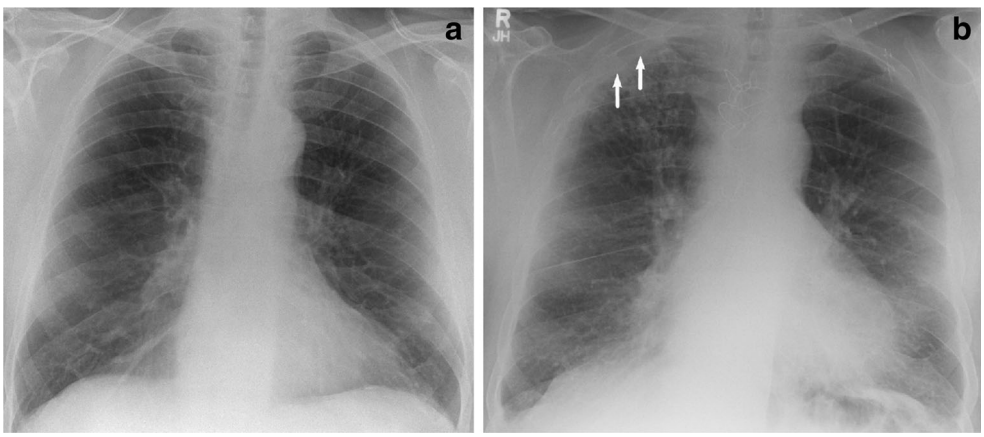


**Fig. 5** Pleural thickening caused by chronic pulmonary aspergillosis. **a** Chest radiograph (the same patient illustrated in Fig. 4c), with features suggesting chronic airflow obstruction but no other significant abnormality. **b** Chest radiograph 5 years later showing ill-defined consolidation in the right upper lobe with thickening of the adjacent pleura (*arrows*)

characteristic finding. The thickening may be florid and circumferential but, as has already been pointed out, can reverse spontaneously [35]. Intracavitary material is seen in around one half of patients [26, 28].

The radiological response to antifungal chemotherapy is variable [26, 49]. In one study of 43 patients [26], the clinical and CT features, before and after more than 3 months of treatment, were compared. The authors found that whilst there was a symptomatic response in fewer than 60 % of patients, CT appearances had improved in less than one half. Indeed, a combined clinical and radiological response was seen in only 38 % of cases with an identical percentage showing no improvement. A more recent study has also confirmed that the discontinuation of antifungal drugs is associated with recurrence in around one third of cases [49].

## Conclusion

Chronic pulmonary aspergillosis is an important manifestation of infection caused by *Aspergillus* spp. Disentangling the classification of *Aspergillus*-related lung disease and specifically the form of chronic infection discussed in the current review remains challenging. Given the considerable overlap in histopathological and radiological features between putatively different manifestations, we suggest that the generic term 'chronic pulmonary aspergillosis' is used. The clinical, serological and radiological phenotype of patients with chronic pulmonary aspergillosis is broadly recognisable such that, in clinical practice, the radiologist may be the first to alert clinicians to the possibility of the diagnosis.

**Acknowledgements** Professor David M. Hansell is the recipient of a National Institute of Health Senior Investigator Award. The scientific guarantor of this publication is Dr. Sujal R. Desai. The authors of this manuscript declare no relationships with any companies whose products or services may be related to the subject matter of the article. The authors state that this work has not received any funding. No statistical methods were necessary for this paper. Institutional review board approval was not required because the submitted manuscript is a review article. Methodology: not applicable. The submitted manuscript is a review article.

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