Aspergillus-related lung disease in people with cystic fibrosis: can imaging help us to diagnose disease?

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Abstract

In people with cystic fibrosis (PwCF), viscous sputum and dysfunction of the mucociliary escalator leads to early and chronic infections. The prevalence of *Aspergillus fumigatus* in sputum is high in PwCF and the contribution of *A. fumigatus* to the progression of structural lung disease has been reported. However, overall, relatively little is known about the contribution of *A. fumigatus* to CF lung disease. More knowledge is needed to aid clinical decisions on whether to start antifungal treatment. In this review, we give an overview of *A. fumigatus* colonisation and infection in PwCF and the different types of pulmonary disease caused by it. Furthermore, we discuss the current evidence for structural lung damage associated with *A. fumigatus* in PwCF on chest computed tomography and magnetic resonance imaging. We conclude that radiological outcomes to identify disease caused by *A. fumigatus* can be important for clinical studies and management.

Introduction

Cystic fibrosis (CF) is a multi-system disease caused by a mutation in the gene that encodes for the cystic fibrosis transmembrane conductance regulator (CFTR) protein [1–3]. The CFTR protein defect leads to an abnormal composition of the epithelial lining fluid, viscous sputum and dysfunction of the mucociliary escalator [3–5]. As a result, most people with CF (PwCF) suffer from early and chronic airway infections caused by a wide range of microorganisms, especially *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Aspergillus fumigatus* [6–10].

There is a huge amount of knowledge available about bacterial infections in PwCF, but relatively little is known about the contribution of *A. fumigatus* infection. The prevalence of *A. fumigatus*-positive sputum cultures in adult PwCF ranges from 27% to 57% [11]. The prevalence of *A. fumigatus* in paediatric PwCF was thought to be relatively low under the age of 8 years, and more common in children older than 10 years [12]. However, the incidence may be significantly underestimated in children [13]. In 2018 and 2019, studies using bronchoalveolar lavage (BAL) samples taken from children up to the age of 6 years found the median age of colonisation with *Aspergillus* species (mainly *A. fumigatus*) in PwCF to be 3.2 years [14], and *A. fumigatus* to be present in up to 28% of patients from the age of 3 years onwards [15].

Previous research has indicated that *A. fumigatus* is not an innocent bystander but can contribute substantially to structural lung damage [11, 15–23]. However, it is not clear how to distinguish *A. fumigatus*-related lung damage from lung damage caused by other CF-related microorganisms. Diagnostic imaging techniques can be important to make this distinction and to aid clinical decision-making on whether to start antifungal

treatment. The threshold to start such treatment in PwCF with positive cultures for *A. fumigatus* is high, as antifungal drugs can have substantial side effects. Furthermore, there are no well-conducted trials available in CF to guide treatment and anti-fungal drugs are known to have a high number of drug–drug interactions with other CF medications. Therefore, it is important to identify within the larger group of *A. fumigatus*-positive PwCF those individuals that require antifungal treatment to avoid accelerated progression of structural lung damage and lung function decline. For those subjects, negative consequences of antifungal treatment will likely be outweighed by the advantages, because halting or slowing down the progression of structural lung damage will have a direct effect on their life expectancy and quality of life.

For this review, we will first give an overview on how *A. fumigatus* colonisation and infection in PwCF can develop and discuss the different types of pulmonary disease caused by *A. fumigatus*. Next, we will elaborate on the role imaging can play in the detection of *A. fumigatus*-related structural lung damage and in the differentiation between the different types of pulmonary disease it can cause in PwCF.

Background of *A. fumigatus*
Sources of Aspergillus
Although over 150 species of *Aspergillus* have been described, only a few can cause disease in humans [24]. The most important *Aspergillus* species associated with pulmonary disease is *A. fumigatus* [20, 25]. Commonly, *A. fumigatus* grows ubiquitously in soil, on carbon-rich substrates or as a contaminant of starchy foods such as bread and potatoes (figure 1a). Furthermore, studies have shown that patients colonised with *A. fumigatus* may become the source of patient-to-patient transmission *via* cough aerosols or sputum [26, 27]. *A. fumigatus* has different stages in its life cycle with different morphological forms. Conidia, which are tiny hydrophobic particles, are easily dispersed by air and are inhaled on a daily basis by humans (figure 1b). Conidia are the infective form of the *Aspergillus*, while hyphae are the invasive form causing invasive disease (figure 1c, d). Conidia in the airways of PwCF can become metabolically active and secrete antigens which can provoke an allergic response. Once conidia land in a suitable environment with sufficient nutrients, such as the lungs, they can start to germinate and form hyphae which can cause an invasive infection (figure 1d) [28, 29].

Inhalation
People inhale on average between 100 and 1000 conidia per day [28, 30, 31]. The mass median aerodynamic diameter of the conidia is in the order of 2 to 3 µm, with extremes up to 3.5 µm [31, 32].
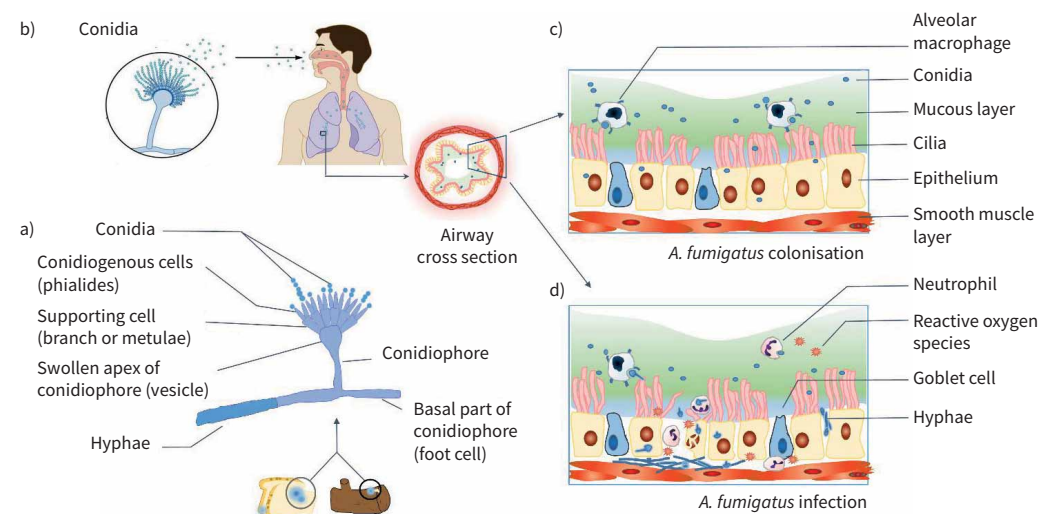

FIGURE 1 *Aspergillus fumigatus* from transmission to colonisation or infection. a) Microscopic morphology of *Aspergillus* which can grow on dead wood or starchy foods [29]. b) Inhalation of conidia into airways. Panel b) is reproduced and modified from [29] with permission. c) Colonisation of *A. fumigatus* in the airways in people with cystic fibrosis, where due to impaired mucociliary clearance of the thick mucus layer, the inhaled conidia are not eliminated. d) *A. fumigatus* infection in which germination of conidia leads to hyphal growth and tissue invasion triggering neutrophil recruitment and the release of reactive oxygen species which mediate a multitude of inflammatory pathways causing damage to the airways.

Hence, conidia are in the respirable range, meaning that they are small enough to bypass the upper airways to get deposited into the peripheral airways and even into the alveoli [33–35]. In healthy subjects, mucociliary clearance will be able to clear inhaled conidia effectively. Furthermore, alveolar macrophages as the first line of defence can eliminate conidia at an early stage, thereby avoiding germination [11, 16, 36–38]. In PwCF, the mucociliary clearance is severely compromised and CFTR-defective alveolar macrophages are less effective in the elimination of conidia. Therefore, inhaled conidia have a higher chance to germinate. Furthermore, it has been shown that dysfunction of epithelial cells in CF influences the interaction with *A. fumigatus* and leads to inflammation of the lungs [16, 39].

Colonisation

Colonisation by *A. fumigatus* is defined as the presence of this fungus in laboratory cultures of the respiratory tract without clinical symptoms or deterioration in lung function (table 1 [13, 40, 41]) [16, 25, 42]. The exact prevalence of colonisation in PwCF is not well known and reports vary at between 3.4% and 57% [11, 38, 43].

Rates of colonisation are associated with levels of exposure [11, 44]. Certain climate factors, such as temperature, wind speed and humidity alter the load of *A. fumigatus* in the air [45], which may influence rates of colonisation in PwCF. For example, most reports show that higher concentrations of airborne conidia are detected in warmer weather, especially during summer and autumn, but without significant differences both in colonisation rate and airborne counts [46–49].

TABLE 1 Differences between *Aspergillus fumigatus* colonisation/infection and disease diagnosis and presentation in people with cystic fibrosis [13, 40, 41]

	Colonisation/infection	Disease		
		Aspergilloma	*Aspergillus* bronchitis/bronchiolitis	ABPA
Diagnostic tests				
Fungal airway culture	+	+[#]	+	+
Positive RT-PCR	+	+	+	+
Serology				
Total IgE	=	↑	=/↑	↑↑
A. fumigatus-specific IgE/IgG	=	↑	−/↑	↑
Galactomannan	−	↑	↑	↑
Signs and symptoms				
Clinical symptoms (productive cough, tenacious sputum, breathlessness or haemoptysis)	=	=/↑	=/↑	↑↑
Pulmonary function	=/↓	=/↓	↓	↓
Most common imaging features				
CR	None/aspecific	Spherical/ovoid mass within a cavity (Monod sign[¶])	Bronchopneumonia pattern with alveolar or peribronchial opacity	Transitory alveolar opacities, central mucus plugs (finger in glove sign)
CT	BWT, low attenuation regions increased, some mucus plugs	Fungal ball in pre-existing cavity	Bronchiolits pattern with centrilobular nodules, tree-in-bud, BWT, BE, GGO, peribronchial consolidation	Central BE with mucus plugs and mucus with high density (30% of cases, attenuation value >70 HU)
MRI	Low intensity regions (representing trapped air or hypoperfusion), T2 hyperintense plugs	Monod sign[¶]: fungal ball with low T1WI and T2WI signal	BWT, T2WI hyperintense peribronchial consolidation and peripheral mucus plugs (tree-in-bud[+])	BWT and T2 hyperintense mucus plugs (in 30% of cases inverted mucus sign, mucus with high T1WI and low T2WI signal)

−: Absent; +: present; =: normal levels; ↑: increase; ↓: decrease. RT-PCR: real-time polymerase chain reaction; CR: chest radiograph; CT: computed tomography; MRI: magnetic resonance imaging; BWT: bronchial wall thickening; BE: bronchiectasis; GGO: ground glass opacities; HU: Hounsfield Unit; T1WI: T1 weighted images; T2WI: T2 weighted images; ABPA: allergic bronchopulmonary aspergillosis. [#]: Particularly if no other organisms are isolated from repeated sputum cultures. [¶]: Crescentic shape of the mass with surrounding air. [+]: Mucus impaction in branching bronchioles.

Risk factors for *A. fumigatus* colonisation include previous treatment with steroids or antibiotics. Short courses of steroids in PwCF have been associated with an increased risk of positive sputum cultures for *A. fumigatus* [11, 13, 20, 25, 34, 50–55]. Furthermore, long-term antibiotic exposure may also provide a more favourable environment for fungi to grow, causing *A. fumigatus* colonisation to occur [6, 54, 55].

Interactions

Another risk factor for persistent colonisation with *A. fumigatus* is co-infection with *P. aeruginosa*. There is a lot of conflicting literature about the interaction of co-infection between *A. fumigatus* and *P. aeruginosa*. The prevalence of chronic *P. aeruginosa* infection currently ranges from 3.3% to 26% for children and between 41% and 52% for adults with CF [56]. *In vitro* research has shown that the production of cytotoxic elastase by *P. aeruginosa* increases in co-culture with *A. fumigatus*, leading to damage to the human lung epithelial cells [54, 57]. Alternatively, eradication treatment for *P. aeruginosa* could create a microbial environment favourable for *A. fumigatus* colonisation [58]. Data from the Irish CF registry showed that co-colonisation with *P. aeruginosa* and *A. fumigatus* was associated with a 165% increase in hospital admissions, a 112% increase in the number of respiratory exacerbations and a 48% increase in the number of oral antimicrobial courses, compared to patients with negative cultures for both pathogens [59].

Apart from *P. aeruginosa*, interactions between *A. fumigatus* and other bacterial infections, such as *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Klebsiella pneumoniae* and *Stenotrophomonas maltophilia*, do not only lead to superinfection but also increase the chance of *A. fumigatus* infection evolving into pulmonary disease in PwCF [60]. In addition, in PwCF, a positive fungal culture is often associated with a positive culture for nontuberculous mycobacteria [61, 62], a combination that seems to predispose to the development of chronic pulmonary aspergillosis [63, 64]. Therefore, further research is needed on these complex interactions between microorganisms and their effect on clinical outcomes in PwCF.

Recently, the interaction between anti-fungal treatment and CFTR modulators has attracted attention in PwCF, as the treatment of chronic *Aspergillus* infection has become troublesome for those who are also receiving modulator therapy. CFTR modulators, which can enhance the functional expression of specific CFTR mutations, also impact fungal colonisation [65]. On one hand, CFTR modulator studies have shown ivacaftor, lumacaftor and tezacaftor to have a positive effect on the dysregulated host response to *Aspergillus* in PwCF [66], which may reduce airway inflammation from *Aspergillus* infection. On the other hand, CFTR modulators can have drug–drug interactions with antifungal medication. For instance, the cytochrome P450-3A-inducing effect of lumacaftor can make it difficult to reach clinically effective blood levels of orally administered antifungal medications [65].

Infection

A. fumigatus infection occurs when the conidia in the airway trigger the release of harmful factors such as antigenic proteins and toxins, and/or germinate into hyphae becoming invasive (figure 1d), thereby initiating an inflammatory response. Neutrophils are recruited resulting in high levels of reactive oxygen species which mediate a multitude of inflammatory pathways causing even more damage to the airways [67, 68]. Furthermore, *A. fumigatus* produces some secondary metabolites, such as proteolytic enzymes and gliotoxins, leading to epithelial cell detachment and further impaired mucociliary clearance and enhanced inflammation [6, 18, 34, 35, 38]. A mycobiome analysis approach in a non-CF bronchiectasis cohort has been reported, which stated that the pulmonary mycobiome, in which *A. fumigatus* is one of the dominated profiles, is of clinical relevance in the development of bronchiectasis [23]. The multi-omics approach will likely be a benefit for diagnosing *Aspergillus* infection, as the characterisation of the host–fungal interaction and the use of multi-omics strategies may lead to a better understanding of host biology and its interaction with fungal pathogens [69].

In PwCF, pulmonary aspergillosis can be subclassified in three distinct clinical manifestations: aspergilloma, *Aspergillus* bronchitis/bronchiolitis and allergic infection. Insight is lacking why some PwCF do not develop *Aspergillus* disease upon exposure, while others develop hyper-inflammatory disease characterised by a Th1-driven inflammation or Th2-driven allergic hyper-inflammation. Over time, PwCF can present with different *Aspergillus* disease presentations and move between one entity and the other, which is an observation not yet explained.

Pulmonary aspergilloma

An aspergilloma is the development of a fungal ball in a pre-existing cavitary lesion or ectatic bronchus without signs of tissue invasion [70, 71]. Complex aspergilloma is nowadays referred to as chronic cavitary pulmonary aspergillosis, indicating multiple pulmonary cavities containing one or more

aspergillomas [72, 73]. In PwCF, this is a rare complication that can present in those patients colonised with *A. fumigatus* and severe or end-stage pulmonary disease [74, 75], and in patients with large cystic bronchiectasis. Aspergilloma can be discovered on computed tomography (CT) as an accidental finding or after an episode of haemoptysis without any specific other symptoms [37, 76].

Aspergillus bronchitis/bronchiolitis
Invasive pulmonary aspergillosis (IPA) is defined as a condition where the hyphae invade the bronchial wall or adjacent lung parenchyma, such as the pulmonary vasculature [77, 78]. IPA is only seen in the case of immunodeficiency and as a rare entity in CF patients. In PwCF, *Aspergillus* bronchitis/bronchiolitis is the more common infection type. *Aspergillus* bronchitis, first reported in 2006 in a cohort of six CF patients [79], is defined as a chronic superficial infection of the airways [80]. The reported prevalence of *Aspergillus* bronchitis is 9% in PwCF, but likely to be under-reported [81]. *Aspergillus* bronchitis is defined as: a) symptoms related to chronic lower airway disease; b) *Aspergillus* species detected in sputum or BAL by culture or real-time polymerase chain reaction test; and c) *Aspergillus*-specific IgG in serum [80]. Clinical symptoms associated with *Aspergillus* bronchitis are productive cough, tenacious sputum, breathlessness and haemoptysis and can hardly be distinguished from a bacterial exacerbation in PwCF [40, 80].

Allergic pulmonary aspergillosis infection (ABPA)
ABPA is a serious complication in PwCF and the result of a complex immunologic response against *A. fumigatus*. ABPA has a prevalence of 4–9% in children and around 10% in adult PwCF [11, 82–88]. ABPA individuals sensitised to *A. fumigatus* can develop an IgE-mediated allergic inflammatory reaction (type I immediate hypersensitivity) which leads to an acute inflammatory response resulting in mucus impaction and bronchial obstruction after inhaling *A. fumigatus* spores [89–91]. ABPA mice models show that chronic exposure to *A. fumigatus* antigens may lead to fibrosis and irreversible lung damage [10, 89].

The diagnosis of ABPA can be difficult in PwCF because of atypical clinical symptoms such as cough, wheeze and increased sputum production [44, 92, 93]. Patients typically show a drop in forced expiratory volume in the first second that does not respond to regular antibiotic treatment directed against bacteria cultured from their sputum. The diagnosis can be supported by typical immunologic features such as an elevated total IgE concentration (greater than 1000 ng·mL^{-1} or 416 IU·mL^{-1}), increased *Aspergillus* specific IgE antibodies (greater than 1.91 kilo units of antibody per litre), or increased *Aspergillus* specific IgG antibodies (greater than 78 mg·L^{-1}) [25, 37, 40, 89, 94–100]. The basophil activation test, an *in vitro* test to measure the activation of basophils by IgE stimulation with *A. fumigatus* extract and CD63, CD193 and CD203c [101], can be used to discriminate ABPA from *Aspergillus* colonisation and non-ABPA in PwCF [102]. Furthermore, the results of basophil activation tests are not affected by antifungal or corticosteroid treatment; therefore, this test might be used as an additional criterion to identify ABPA and monitor *A. fumigatus*-related clinical status in PwCF [102–104].

Imaging and aspergillosis
Despite the currently available diagnostic tools, it remains challenging to differentiate colonisation *versus* infection with *Aspergillus* according to clinical tests (table 1). In clinical practice, it is also difficult to distinguish progression of CF lung disease due to *Aspergillus* from progression related to other, mainly bacterial, airway pathogens. Therefore, an important goal for clinicians is to find the particular fingerprint for *Aspergillus*-related lung damage (figure 2).

Imaging is an essential tool in the management of patients with pulmonary disease related to *A. fumigatus* [105, 106]. The two most used imaging tools to screen patients at high risk for pulmonary aspergillosis are chest radiography (CR) and CT. Both techniques are used to detect pulmonary disease related to *A. fumigatus* 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 CR [107] in the evaluation of chest lesions and therefore considered the gold standard for an accurate differential diagnosis of different forms of pulmonary aspergillosis. CR, however, because of its high accessibility, low cost and radiation exposure to the patient, is frequently used when high frequency repetitive or bedside imaging of critically ill patients is required. More recently, magnetic resonance imaging (MRI) has been proposed as an imaging tool to diagnose specific subtypes of pulmonary aspergillosis [108–111]. A main advantage of MRI over CT is the ability to follow-up response to treatment with serial imaging without concerns related to radiation exposure. MRI has been increasingly used in those tertiary centres with experience in chest MRI.
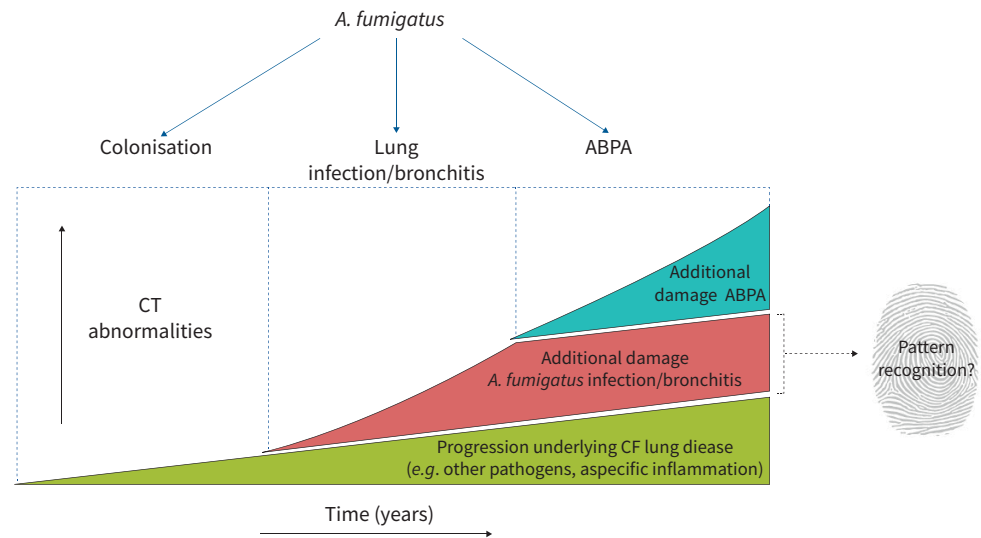
FIGURE 2 The distinction between cystic fibrosis (CF)-related and *Aspergillus fumigatus*-related structural lung damage in people with CF. The figure represents the difficulty of distinguishing "normal" progression of CF-related lung disease on chest computed tomography (CT) from *A. fumigatus* infection/bronchitis-related progression and allergic bronchopulmonary aspergillosis (ABPA)-related structural lung disease on top of this progression, and our goal to find the fingerprint for *Aspergillus*-related lung damage. Note: ABPA and *Aspergillus* bronchitis can either co-exist or occur separately.

In the section below we will discuss the most common radiological hallmarks of *A. fumigatus* colonisation, *Aspergillus* bronchitis and ABPA using CT and MRI in PwCF. Imaging features of each subtype of *Aspergillus* infection in PwCF are summarised in table 1.

Imaging features of A. fumigatus *colonisation*

In theory, one would expect that mere colonisation with *A. fumigatus* would not be related to any identifiable abnormalities on CT. In contrast, the few imaging studies that have looked into the relationship between *A. fumigatus* colonisation and structural lung changes in CF did report significant differences [2, 58]. In particular, PwCF who are colonised with *A. fumigatus* were found to have more low attenuation regions (often referred to as "trapped air") on expiratory chest CT than a control group without colonisation [58]. There are also indications that this process can start early in life. In a study of a 5-year-old PwCF, the presence of *A. fumigatus* in the BAL fluid was associated with low attenuation regions on chest CT [58]. In addition, more severe bronchiectasis and more mucus plugging were observed in a group of *A. fumigatus* colonised PwCF compared to a non-colonised group [2]. Causal associations between *A. fumigatus* and the reported structural lung abnormalities cannot be asserted from these observational studies, but they do strongly suggest that airway cultures positive for *A. fumigatus* may not be an innocent finding in asymptomatic patients. Hence, at least a proportion of patients who are considered to be merely colonised by *A. fumigatus* according to current standards might in fact have an *A. fumigatus* infection.

Imaging features of saprophytic Aspergillus *infection*

Saprophytic aspergillosis or aspergilloma can be identified on chest CT as a fungal ball in a pre-existing pulmonary cavity, cyst or other air-containing space [97, 112]. Single or multiply lesions of aspergilloma can affect both lungs with equal frequency [113]. The mean diameter of aspergillomas is around 4 to 5 cm, with a maximum size of around 10 cm, and rarely shows regression in size without treatment [113].

An early CT finding of aspergilloma in the non-CF population and PwCF is the thickening of the lateral cavity wall, which reflects the saprophytic germination of the fungus onto the cavity wall. When this germination is large enough it will fall from the wall and form the aspergilloma (figure 3). The position of the fungal ball in the cavity on CT may change depending on the posture of the subject [78]. Pleural thickening can also be found on CT in association with *A. fumigatus* infection, which may present as early as 2–3 years before the formation of the fungal ball [78, 114, 115]. On MRI, the characteristic of aspergilloma shows low signal intensity on T1- and variable signal on T2-weighted images caused by
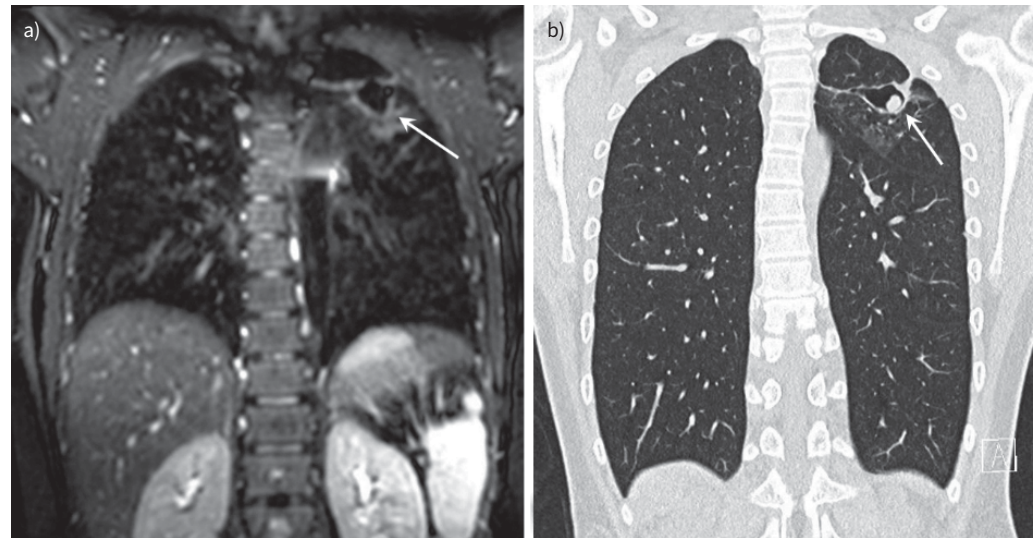
FIGURE 3 Chest imaging of a 13 -year-old boy with cystic fibrosis. a) Magnetic resonance imaging (MRI) scan (isotropic T2-weighted CUBE, coronal reformat) and b) computed tomography (CT) scan (isotropic coronal reformat) performed 10 months after the MRI. Note cavitary lesion in the left upper lobe on MRI (arrow) with wall thickening but without a solid component. On the follow-up CT, there is a new round solid lesion within the cavity, representing an aspergilloma (arrow) not completely filling the cavity (Modod sign).

calcium, air or ferromagnetic elements in the aspergilloma [116]. Air surrounding a fungal ball that does not completely fill up the cavity can be recognised as the Monod sign (figure 3) [78].

Imaging features of Aspergillus bronchitis/bronchiolitis

Histology of patients diagnosed as having *Aspergillus* bronchitis show superficial invasion by *A. fumigatus* of the superficial mucosal layers [21]. Therefore, CT findings in *Aspergillus* bronchitis follow the bronchocentric invasion of the airways. The initial signs of infection are bronchial wall thickening and centric-lobular nodules with ground glass opacities (GGOs) (figure 4a) with development of peri-bronchiolar and lobar consolidations as the infection progresses with consequent filling of airspaces (figure 4b). However, these findings can be non-specific, especially in PwCF [77, 78, 117]. The same holds for bronchiectasis, which has been described on CT in *Aspergillus* bronchitis in patients with non-CF chronic lung disorders, but is non-specific in PwCF [117]. To our knowledge there is only one case report on *Aspergillus* bronchitis in CF with a detailed description of CT findings, reporting signs of bronchitis/bronchiolitis with centrilobular nodules, tree-in-bud, GGO and peribronchial consolidations [118].

Allergic pulmonary aspergillosis

The most common radiological sign in ABPA is central varicose or cystic bronchiectasis in both non-CF patients and PwCF [10, 84, 91, 98, 119], also described as a "string of pearls" [120]. Another imaging sign of ABPA is mucous impaction in the central airways [99]. Furthermore, high attenuation regions on CT, with a mucus density higher than the para-spinal skeletal muscle (generally >70 Hounsfield units), are considered a specific feature for the radiological diagnosis of ABPA in CF [41, 84, 86, 121–125] (figure 5a, b). Nodule or granuloma formation can be detected in the periphery of the lungs [85], as well as large opacities, which tend to affect the upper and middle lobes [90, 126]. In addition, improvement of the imaging abnormalities in response to steroid treatment supports the diagnosis of ABPA in PwCF [89, 126].

General features of CF lung disease and early changes related to ABPA are difficult to differentiate. For the diagnosis and follow-up of ABPA, MRI has advantages over CT as it does not require ionising radiation. Furthermore, MRI allows the collection of morphological and functional information that might allow a more sensitive and specific diagnosis of ABPA-related changes [116]. Some studies with a small sample size have reported MRI findings of ABPA, especially in paediatric patients [108, 109]. These studies indicate that high T1 and low T2 signal intensities of mucus impaction (inverted impaction mucus sign) are both sensitive and specific for the diagnosis of ABPA in CF (figure 5c, d) [108–111]. This high discriminating ability of ABPA by MRI requires further confirmation in a larger number of PwCF.
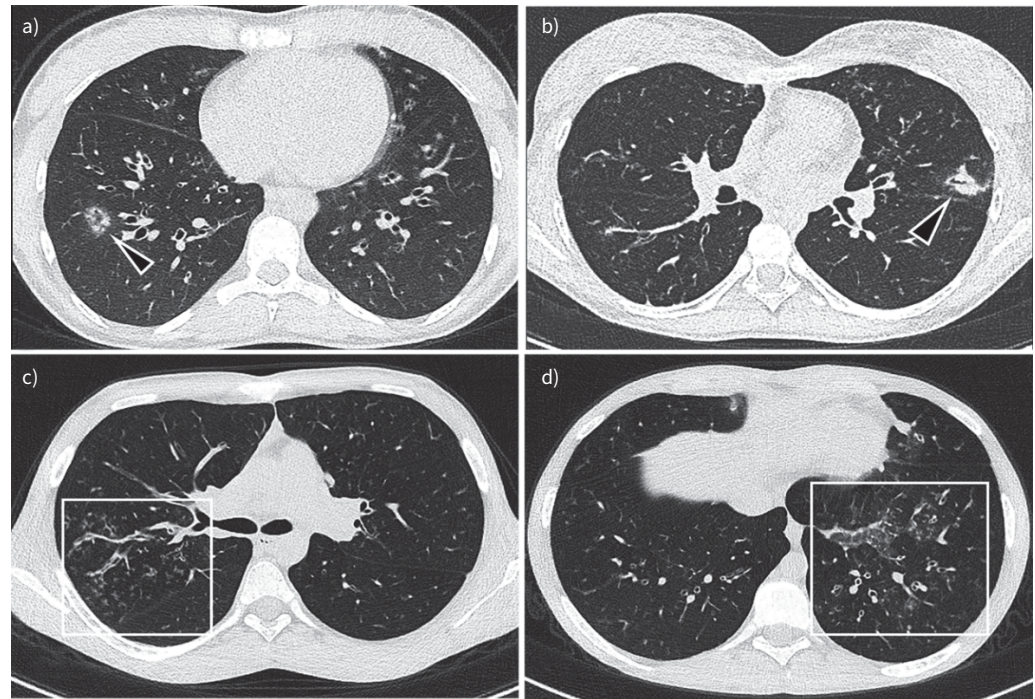
FIGURE 4 *Aspergillus* bronchitis/bronchiolitis example images: a) 18-year-old male non-cystic fibrosis (CF) patient, but with sickle cell disease. Multiple nodules with ground glass opacity around peripheral vessels are shown in the right lower lobe (arrowhead in a). b) Chest computed tomography (CT) image of a 17-year-old girl with CF shows *Aspergillus* bronchopneumonia. Note bronchocentric peri-bronchiolar consolidation on left upper lobe; c and d) Chest CT images of a 15-year-old boy with CF show *Aspergillus* bronchiolitis. Note filling of peripheral airways with a tree-in-bud pattern and bronchial wall thickening (box in c). In d there is also an area of ground glass (box in d).

Without antifungal treatment, *Aspergillus* diseases may move to chronic infections with complex appearances on image exams. The granulomas presenting in chronic *Aspergillus* infection indicate limited tissue invasion, which is often accompanied by enlarged intra-pulmonary lymph nodes (figure 6). On CT imaging, *Aspergillus* granulomas may cause extensive parenchymal consolidations, may lead to bronchiectatic cavities or may remain exclusively bronchogenic. The latter pattern is characterised by multiple nodules with a perilymphatic distribution (subpleural and perivisceral). Adjacent pleura can be invaded as well, which leads to the formation of cavitations, aspergilloma and pleural thickening on CT [73].

The way forward

Based on what is known in the literature, there are strong indications that *A. fumigatus* can contribute to the progression of structural lung damage in PwCF. As *A. fumigatus* can be cultured in a high percentage of PwCF, it is important to differentiate colonisation *versus* infection and to develop state-of-the-art sensitive and specific image analysis systems that are able to identify *A. fumigatus*-associated structural abnormalities on chest CT and/or MRI. This will support differentiation between harmless colonisation and infection with its associated structural lung damage. Such an image analysis system can be used for PwCF and *A. fumigatus*-positive sputum cultures to assist in the early detection and monitoring of *A. fumigatus*-associated structural lung damage and to monitor the effect of antifungal treatment.

Routine biennial chest CTs are used in around half of the European CF Society (ECFS) clinical trial network (CTN) centres. All these ECFS-CTN centres contribute data to the ECFS patient registry. The availability of an automated image analysis system sensitive and specific to detect *A. fumigatus*-associated structural changes opens up the possibility to analyse a large number of chest CTs to add key imaging outcomes to the registry. This will allow a better understanding of *A. fumigatus* induced lung damage. In addition, such a system can play an important role as outcome measures for clinical studies. An example of this is the recently started international cASPerCF study (clinicaltrial.gov identifier NTC 01782131) [127] evaluating the therapeutic effect of posaconazole treatment in children and adolescents with CF and
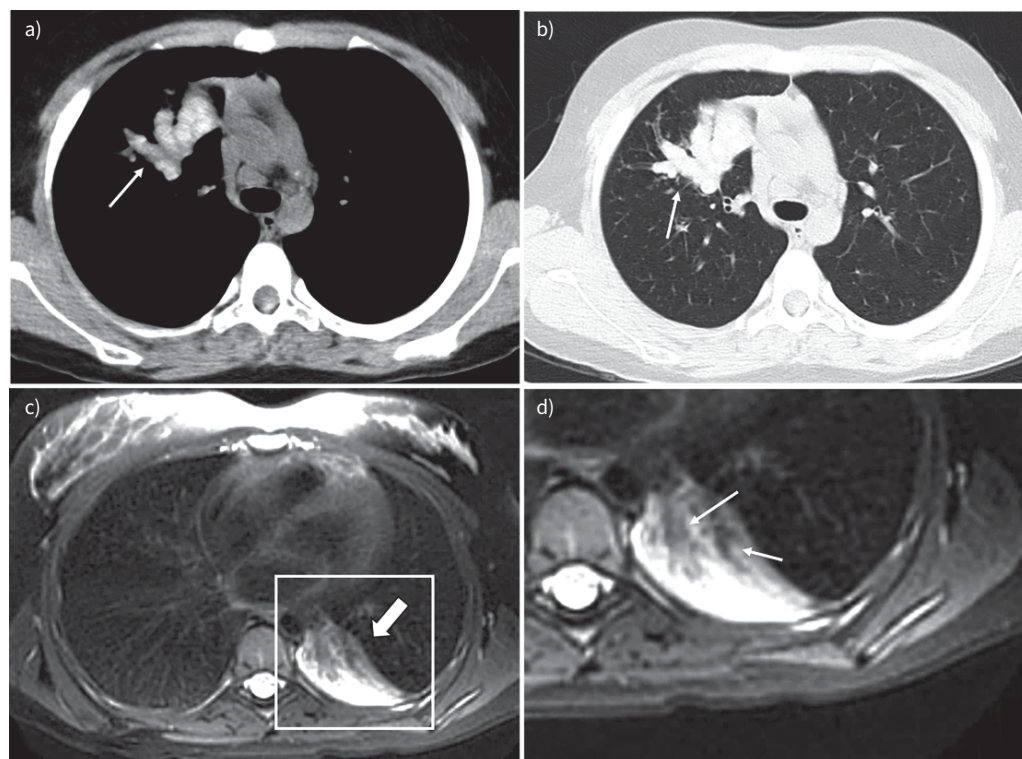
FIGURE 5 Allergic bronchopulmonary aspergillosis example images. a) and b) Chest computed tomography (CT) images of a 12-year-old boy with cystic fibrosis (CF). a) 2.5 mm axial CT soft tissue window and b) 1 mm axial CT lung window at the same level. Note in a), central bronchiectasis filled with high density material (arrow). In b), note mucus plugs with a typical cylindrical shape originating from the hilar region and extending towards the periphery (arrow) showing typical higher density than paraspinal muscles. c) and d) Lung magnetic resonance imaging scans (T2-weighted axial PROPELLER, in plane resolution 1×1 mm, slice thickness 5 mm) of a 15-year-old girl with CF. c) Atelectasis in the left lower lobe (thick arrow). d) Hypo-intense material filling the central airways (arrows).
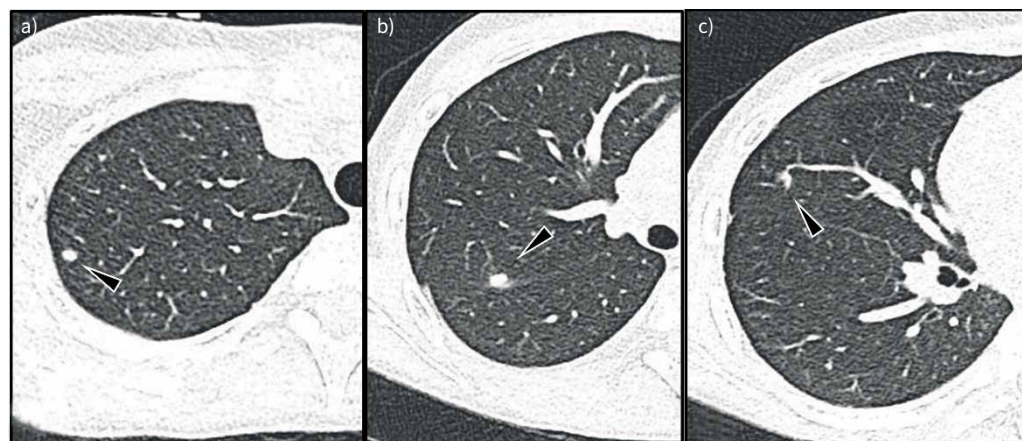

FIGURE 6 Chronic aspergillosis with skin and lung abnormality in a 15-year-old boy with cardiomyopathy. Note sub-pleural (arrowhead in a) and peri-fissural (arrowheads in b and c) nodules. From their location, these nodules are most likely intrapulmonary lymph nodes, which disappeared after 4 months of treatment with antifungal medication (voriconazole).

A. fumigatus infection. The cASPerCF study will explore whether chest CT-related outcomes are sensitive to detect a therapeutic effect.

Furthermore, chest MRI could also play an important role in the differential diagnosis and follow-up of pulmonary aspergillosis. Chest MRI could be used as an imaging tool for short-term follow-up of therapy changes in PwCF. In our centre, we are currently using a short scanning protocol including T2-weighted and proton density-weighted imaging to follow treatment changes in PwCF and *Aspergillus* infection, namely consolidation and large mucus plugs. The complementary role of chest MRI in pulmonary aspergillosis will become clinically relevant when this technique has broader use in clinical practice. Current limitations to the use of MRI in clinical practice are the lack of protocol standardisation between CF centres and major differences in image quality, which hampers its applicability on a large scale. Finally, post-processing tools for chest MRI are not commercially available and most of the time are reported in the literature as in-house developed tools.

Conclusion

Our review provides support that specific structural lung damage on chest CT associated with *A. fumigatus* infection in PwCF can be identified. The development of sensitive and specific image analysis methods for chest CT and MRI are needed to identify whether in PwCF *A. fumigatus*-related structural lung damage can be detected at an early stage to guide treatment. Furthermore, image-related outcomes can be important as outcome measures for clinical studies and for clinical management.

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