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Multifocal pulmonary aspergillomas: case series and review

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Multifocal lung parenchymal cavities containing multiple aspergillomas are not well-recognized features of chronic pulmonary aspergillosis (CPA). We identified five patients with multiple cavities containing fungal balls from our accumulated cohort of ∼300 patients with CPA. Corticosteroid exposure and radiological and serological characteristics were assessed. The patients, aged 19–55 years, developed 3–11 cavities (or nodules in one case) with thin walls, usually within the lung parenchyma, with very limited pleural involvement. Four had asthma (severe in three) and one had cystic fibrosis; three had allergic bronchopulmonary aspergillosis. All patients had received corticosteroids orally or by inhalation. Four patients had elevated *Aspergillus* IgG antibodies; one had elevated *Aspergillus*-specific IgE. Three patients developed azole resistance on antifungal therapy, after benefit, one of whom underwent a successful bilateral lung transplant, later complicated by a fatal mycotic cerebral aneurysm. Multiple aspergillomas is a new distinct manifestation of CPA. The lack of inflammatory response and the distribution of the cavities in the lungs are remarkable. *Aspergillus* nodules could evolve into cavities with aspergillomas. The management and development of azole resistance in these patients is problematic.

Keywords: fungal infection; chronic pulmonary aspergillosis; *Aspergillus fumigatus*; fungal ball; chronic necrotizing pulmonary aspergillosis

Introduction

Daily exposure to airborne *Aspergillus* is an inescapable fact of life. Human lungs are usually not sterile with respect to fungi.[1–3] It is therefore not surprising that either structural pulmonary or immunological deficiency allows this rapidly growing filamentous fungus to infect localized areas of lung. Indeed patients with allergic bronchopulmonary aspergillosis (ABPA)[4,5] and those with severe asthma are usually colonized in the airways by *Aspergillus fumigatus*,[6] as are many patients with asthma.[6]

In 1842, John Hughes Bennett, a medical microscopist of great renown, found what he thought was a vegetable (resembling *Aspergillus*) in the sputum of a patient.[7] He noted; "the left lung was found studded with cavities of different sizes, some of which communicated, by fistulous openings, with the cavity of the pleura. Several of the smaller cavities were partly filled with soft tuberculous matter, readily separable from the lining membrane." This was the first description of chronic pulmonary aspergillosis (CPA), indeed the first description of any form of pulmonary aspergillosis. CPA is generally a slowly progressive destructive lung disease characterized by pulmonary and/or systemic symptoms, cavitation of the lung, and positive *Aspergillus*-specific IgG antibodies detectable in serum.[8–10] Existing cavities increase the likelihood of *Aspergillus* infection, and preceding diseases include tuberculosis and sarcoidosis, among others.[11] We, and others years before, have also observed new cavity formation during the course of untreated chronic pulmonary aspergillosis; thus, a preexisting cavity is not a sine qua non of this disease. Cavities may or may not contain an aspergilloma.

The first formal description of an aspergilloma was in 1938 by Deve, who referred to it as a "mega-mycetoma."[12] An aspergilloma is a usually spherical mass of tangled hyphae often with a

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necrotic core, visualized radiologically;[13] the vast majority are caused by *A. fumigatus*. Radiological features preceding the development of an aspergilloma include irregular cavity walls or loose material within a cavity that does not resemble a fungal ball. Most patients with aspergillomas have disease localized to one upper lobe of the lung or, rarely, both upper lobes. In this report, we describe multifocal nodules and cavities as an unusual manifestation of chronic pulmonary aspergillosis, many of the cavities containing aspergillomas. We attempt to infer the radiological progression of these manifestations of aspergillosis from patients' images and clinical course.

Patients and method

Patients were identified from the database of >500 individuals referred to the National Aspergillosis Centre (in the UK). We identified five patients with at least three multiple cavities and/or nodules in the parenchyma of the lung (Table 1), which were unusual in appearance compared with the normal appearance of chronic pulmonary aspergillosis and simple aspergilloma.

Medline and *Aspergillus*-related website searches in January 2011 using terms *multiple* and *aspergilloma* and *nodule* identified only reports of immunocompromised patients. A detailed trawl through >100 papers going back to 1938 and describing aspergilloma and chronic pulmonary aspergillosis identified six papers describing multiple aspergillomas.

Laboratory methods

Aspergillus IgG and IgE and total IgE were tested by ImmunoCap® (Phadia, Sweden), with cut-offs of 40 mg/L, 0.4 KIU/mL, and 100 KIU/mL. *Aspergillus* precipitin titers were measured by an in-house precipitins IgG assay.[14] Sputum was cultured for fungi using standard UK methods; DNA extraction from sputum and real-time PCR was performed as described previously.[15] Minimum inhibitory concentrations (MICs) to triazoles were determined by EUCAST methodology with a lower final inoculum concentration (0.5×10^5 as opposed to $1–2.5 \times 10^5$ cfu/mL) as the only methodological variation.[16] Antifungal therapeutic drug monitoring for all triazole therapy was as described elsewhere.[17]

Case histories

Patient 1

A 34-year-old female had poorly controlled asthma in 2008. Before her asthma deterioration, she was fit, attending the gym, and long distance swimming. She had had an accident at age 15 resulting in spinal cord transection and as a result is wheelchair bound. Following the West Country floods in January 2008, there was much external mold contamination, although none in the patient's house. In 2008, she was on oral antibiotics much of the year and received three courses of oral prednisolone (40 mg daily) for a week, with partial improvement, in addition to high dose inhaled steroids. In November 2008, a chest X-ray (CXR) was abnormal, the first radiological sign of CPA. Abnormal CXRs showed two possible balls in a bronchiectatic cavity in her left upper lobe (LUL), with a further smaller ball in her right upper lobe (RUL). On referral her total IgE was 300 mg/L, *A. fumigatus* IgE 3.3 KIU/L, but her *Aspergillus* IgG was >200 mg/L. A CT of her thorax (Fig. 1) confirmed multiple cavities containing "balls," and a pulmonary embolus for which she was started on warfarin, which was changed to dalteparin after an episode of hemoptysis. She was also started on voriconazole 200 mg twice daily (bd), which was well tolerated after the initial symptoms of visual disturbance and nausea, with satisfactory trough levels (4.7, 5.24 mg/L). Her *Aspergillus* IgG fell to 144 over the next year and she remained well, competing in long-distance races. In May 2011, she had a flare of her ABPA that required another course of corticosteroids and ended up being treated with nebulized Pulmicort® 1 mg bd and prednisolone 10 mg daily. An embolization procedure was then required for hemoptysis, suggesting therapeutic failure. Her *Aspergillus* IgG climbed to 529 mg/L and a strong *Aspergillus* PCR signal was detected in sputum, despite therapeutic voriconazole levels, confirming therapeutic failure and presumptive voriconazole resistance. Culture was negative.

Patient 2

This 19-year-old female was referred in 2009 after her sputum tested culture positive for *A. fumigatus* despite taking itraconazole. Her primary underlying diagnosis was cystic fibrosis (CF) complicated by diabetes mellitus and pancreatic insufficiency. She had been colonized with *A. fumigatus* from early teenage years and had serological

Table 1. Clinical details of the patients

No	Age sex	Underlying conditions	Presentation	Lobes affected	Asp IgG (max)	IgE (max)	Asp IgE (max)	Sputum culture	Drug Tx	Outcome
1	34/F	Asthma, ABPA, bronchiectasis	Abnormal CXR during an chronic asthma exacerbation	LUL, RUL, RLL	>200	1500	13.2	*A. fumigatus*	Initially itra, then vori 200 mg bd, (levels 4.7 and 5.24)	Clinically stable, but new hemoptysis and strong *Aspergillus* PCR signal on therapy, culture negative, resistance
2	19/F	CF, ABPA, diabetes pancreatic insufficiency	Persistently positive sputum culture positive and abnormal CT	LUL, RUL	161	110	3.7	Triazole-resistant *A. fumigatus*	Resistant to all azoles, anaphylaxis with Ambisome, maintained on voriconazole prior to lung transplant	Lung transplant May 2011, with intra-operative pleural torulidine, i.v. micafungin and inhaled AmB
3	47/F	Severe asthma requiring intensive care in 90s with fungal sensitization	R pneumothorax, cavitating lesions in both lungs	RLL, RUL, LUL	15	79	2.6	*A. fumigatus*	Vori 300 mg bd then 150 mg bd then 250 bd based on TDM	Stable, asthma controlled with fluticasone 500 bd.
4	55/M	Severe asthma, osteoporosis	Progressive SOB (three years), brown mucus plugs	RUL, LUL	78	639	18.3	Negative	Vori 200 mg bd (intolerant), 3 weeks course i.v. AmBisome® then itra (300 mg)	Chest stable
5	49/F	Moderate asthma, smoker	Right sided pleuritic chest pain, with consolidation that did not clear on antibiotics	RUL, LUL, RLL	165	2500	45.3	*A. fumigatus*	Pred 20 mg for 5 months with improvement, but deteriorated drastically when stopped; confirmed by CT (five new cavitating lesions on CT)	Asthma controlled on fluticasone and itra 200 mg bd (good levels)

ABPA, allergic bronchopulmonary aspergillosis; CPA, chronic pulmonary aspergillosis; CXR, chest X-ray; LUL, left upper lobe; RUL, right upper lobe; LLL, lower left lobe; RLL, right lower lobe; CT, computer tomography; CF, cystic fibrosis; ARDS, acute respiratory distress syndrome; PET, positron emission tomography; ANCA, antineutrophil cytoplasmic antibodies.

markers consistent with ABPA, which fluctuated. She was treated with a course of prednisolone, inhaled corticosteroids, occasional courses of prednisolone (once or twice annually), and itraconazole for many years. Due to her severe CF she had extensive bronchial dilatation particularly in the upper lobes, with many dilated bronchi and cavities containing aspergillomas (Fig. 2). A fungal

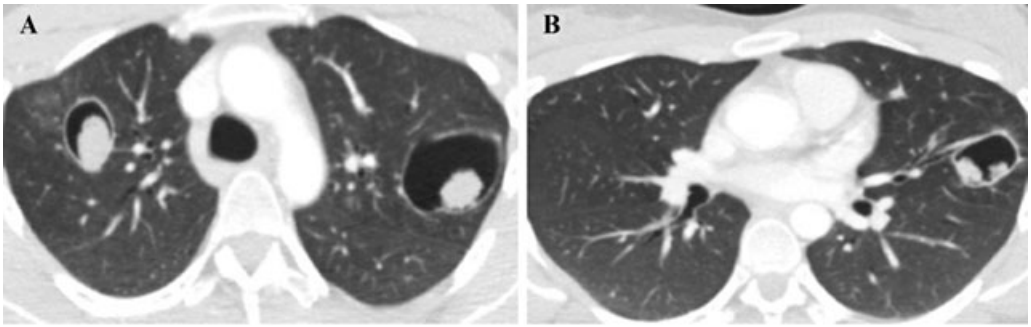

Figure 1. **Patient 1. CT scan showing mild bronchiectasis with two thin-walled cavities bilaterally. In the right lung A is a section of the upper lobe, with B in the lower lobe showing the same cavity. Note that there are three separate aspergilloma in this cavity alone. Fungal balls measured 19 mm (left upper lobe, LUL), 28 mm (left upper lobe, LUL), 20, 18, and 9 mm (in same right upper lobe (RUL) cavity) and two others 20 mm and 23 mm.**

culture (December 2009) grew two isolates of *A. fumigatus* that showed triazole resistance (itraconazole MIC >8 mg/L, voriconazole MIC >8 mg/L, posaconazole MIC 1 mg/L; and itraconazole MIC >8 mg/L, voriconazole MIC 2 mg/L, posaconazole MIC 0.5 mg/L). During a prior admission she had suffered urticarial rash and hypotension with AmBisome®, and so was skin tested and then challenged with conventional amphotericin B. She was successfully transplanted in May 2011, with a heart-lung bypass and did well initially. Her lungs were resected successfully without difficulty because there were few adhesions caused by the aspergillomas, as they were mostly intrapulmonary or bronchial, with little pleural involvement. Histopathology confirmed the presence of multiple fungal balls bilaterally. She was treated with daily micafungin and aerosolized amphotericin B postoperatively but grew two strains of *A. fumigatus*, one fully susceptible and one triazole resistant. Her first biopsy after transplantation showed moderately severe rejection that was treated with pulse steroids, and after a second biopsy (which did not show rejection) she developed severe ARDS and spent a month ventilated. She recovered from this and was discharged to a hospital near home. Unfortunately she suffered an intracranial hemorrhage two months posttransplantation related to a presumed mycotic aneurysm from which she did not recover. A coroner's autopsy was performed.

Patient 3

A 57-year-old female with chronic asthma that had been unusually difficult to control had been followed since an ICU admission involving allergy to *Aspergillus* in the 1990s. She had been markedly steroid dependent, requiring multiple courses of prednisolone as well as 2 g fluticasone via a dry powder inhaler for asthma control. The long duration and symptomatic history are suggestive of long standing ABPA or severe asthma with fungal sensitization (SAFS) that had progressed to CPA. In August 2010 she suffered a right pneumothorax with cavitating lesions found bilaterally; this was confirmed with a CT of the thorax (Fig. 3). At referral, she was *Aspergillus* precipitins positive, her *Aspergillus* IgE was 13 kIU/L, and her total IgE was 890 kIU/L. She is currently on Seretide® 500 1 puff and voriconazole 250 mg both twice daily, which is well tolerated, with much better control of her asthma. There has been no significant change in her imaging over 12 months.

Patient 4

Patient 4 is a 55-year-old male who presented with progressive dyspnoea over three years, with an occasional productive cough of brown mucus "plugs," suggestive of ABPA. He had a 25-year history of steroid-dependant severe asthma, controlled by prednisolone 3.5 mg daily, that was complicated by osteoporosis and spondylosis (he remains on this dose despite efforts to decrease the minimum effective dosage). An investigation revealed an abnormal CXR; a CT showed multiple nodules bilaterally in the upper lobes, some cavitating (see Fig. 4). A CT-guided biopsy showed fungal hyphae and no evidence of malignancy; a subsequent lavage cultured *A. fumigatus*. His serology showed maximum levels of total IgE of 639 mg/L, *A. fumigatus* IgE of 18.3 KIU/L, and *Aspergillus* IgG of 78 mg/L. Testing for gamma interferon production in response

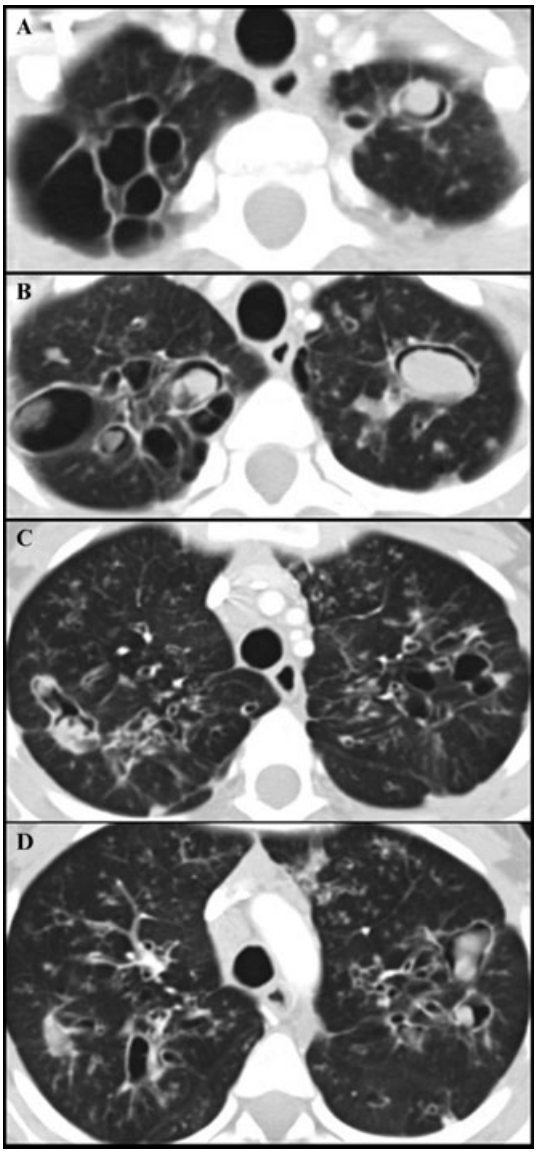

Figure 2. Patient 2. The figures above are images taken from a single CT scan at varying points in the upper lobes of this CF patient. (A) and (B) are two images in upper lobes of the lung, showing multiple thin-walled cavitations. Classic aspergilloma of clear halo and with no cavitation presents within the cavities bilaterally. (C) and (D) show widespread bronchiecstasis and cavitation. In the right lung is a single cavity displaying two fungal balls, however this may also occur in a vertical plane. Eleven fungal balls were visualized by imaging.

to multiple stimuli showed greatly reduced production but a normal response pathway, and he has since been started on gamma-IFN supplementation. Azole-resistant *A. fumigatus* (itraconazole MIC >8 mg/L, voriconazole MIC >8 mg/L, posaconazole MIC 1 mg/L) was grown; he was given a three-week course of Ambisone for hemoptysis, which has now resolved. While there has been little change in his serology over two years, there has been increasing cavitation in his middle zone lesions, but none in his right upper lobe nodular lesions.

Patient 5

A 49-year-old female smoker initially presented with right-sided pleuritic chest pain (2006) and consolidation that did not clear on antibiotics. She was diagnosed with asthma in 1999, which was initially difficult to control but then settled; she currently takes fluticasone + salmeterol regularly. She worked next to a demolition site with, presumably, a higher risk of *Aspergillus* exposure. On referral she had at least three nodules, the largest being 3.5 cm in her right upper lobe. Several scans showed multiple aspergillomas in both upper lobes and right lower lobe. A PET scan showed low uptake. Her serology at referral was *Aspergillus* IgG 165 mg/L, total IgE 2500 kIU/L, and *A. fumigatus* IgE 45.3 kIU/L. Further follow-up revealed eosinophilia and a negative ANCA result. Last year she was treated with prednisolone 20 mg for five months due to radiological progression of aspergilloma to which she had a good response. However, soon after stopping treatment she had a dramatic deterioration in CT, showing five cavitating lesions (Fig. 5). Despite no prior history of hemoptysis recently some blood has been seen mixed with sputum, accompanied with left-sided pleuritic chest pain upon deterioration. Subsequent sputum culture was positive for *A. fumigatus.* She is currently being treated with itraconazole 200 mg BD, with satisfactory levels and well tolerated.

Results and discussion

The term *pulmonary aspergilloma* refers to the presence of solid mass of intertwined *Aspergillus* hyphae within an intrathoracic cavity, usually in the parenchyma of the lung, rarely in the pleura or bronchus.[11] Aspergillomas form when *Aspergillus* conidia adhere to the wall of a cavity, germinate, and gradually grow to form an amorphous mass.[18,19] Often, an affected pulmonary cavity wall has a cobblestone or shaggy appearance, sometimes with ulceration, prior to the overt formation of an aspergilloma.[19] Radiologically, an aspergilloma will have a distinct "halo" or crescent of air round part of the ball as it sits in a cavity. Sometimes

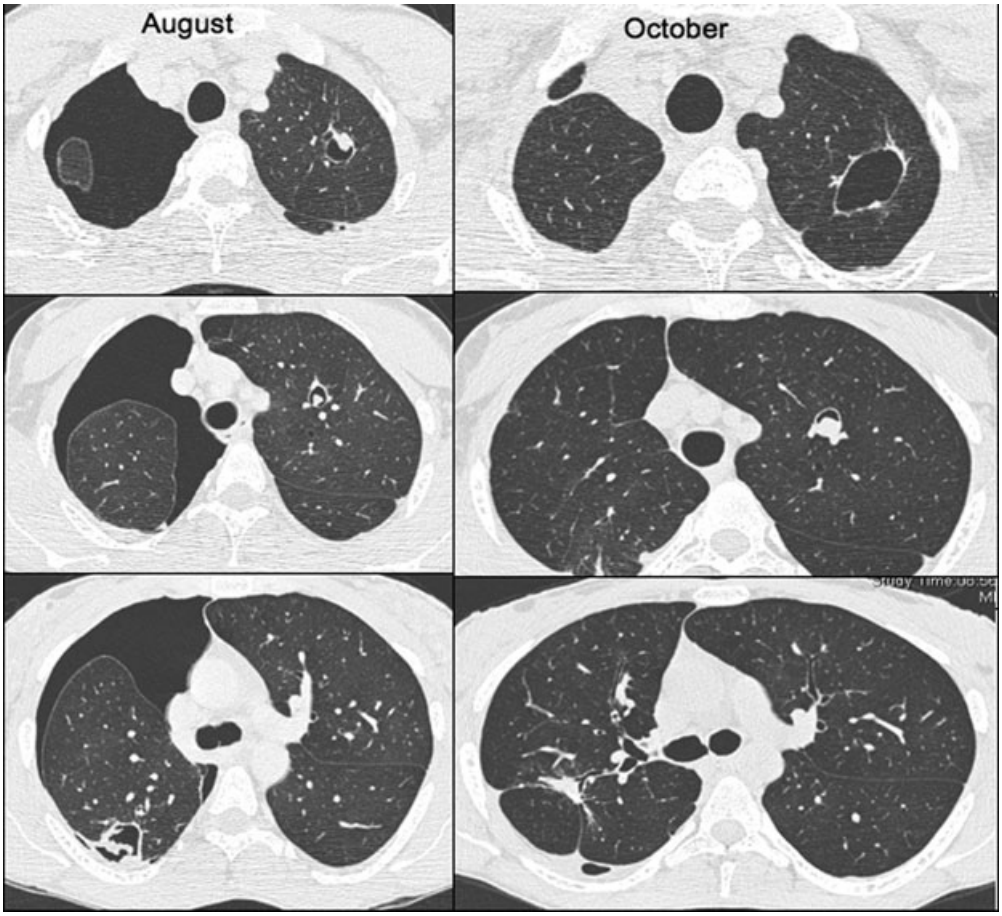

Figure 3. **Patient 3. Images demonstrating pneumothorax, as a result of a right-sided cavity with a fungal ball perforating into the pleural cavity. Two other cavities with intraluminal material are present in the left upper lobe. Significant progression is seen in the three months to October.**

aspergillomas are closely adherent to the cavity wall, but often they are mobile in the cavity.

What distinguishes the cases we describe above is the involvement of multiple lobes bilaterally with small to medium sized thin-walled cavities, typically without the usual pleural thickening and peripheral location. There was also a higher frequency of lower lobe disease than is usual with chronic pulmonary aspergillosis and aspergillomas. In one case (patient 4) the disease was more nodular, another relatively underreported manifestation of CPA.[20]

Any bullous or cavitary pulmonary disease may be complicated by CPA.[11] Occasionally, patients with acute or subacute invasive aspergillosis (otherwise termed *chronic necrotising pulmonary aspergillosis*) develop into CPA. Aspergillomas are found in about 25% of patients with CPA,[21] including occasional simple (single) aspergillomas in a pre-existing cavity. The frequency of CPA following tuberculosis is 15–22% in patients with persistent pulmonary cavities,[11,22] and an estimation of the global five-year period prevalence is 1,174,000 of such patients, or 18/100,000 in the population.[3] However, as an isolated radiological finding on chest radiographs, aspergillomas are rare with a reported prevalence of 0.13%.[23]

The finding of multiple aspergillomas is therefore rare, which is reflected in the lack of associated literature. There were two early reports of individual patients with multiple aspergilloma.[24,25] When CT scanning was introduced, workers at the Brompton Hospital in London noted that 4 (16%) of 26 patients with aspergillomas had bilateral lesions.[18] High-resolution CT of the thorax may facilitate

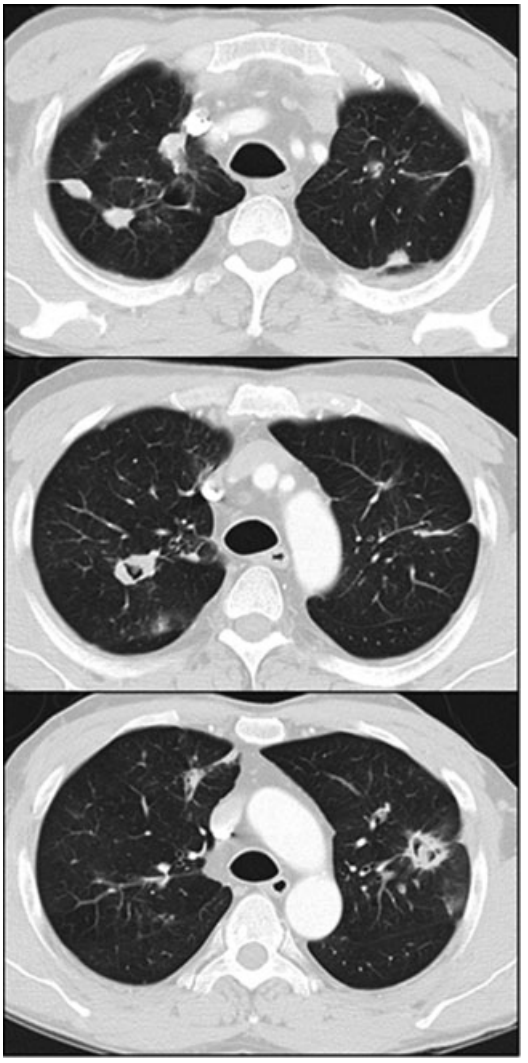

Figure 4. Patient 4. Sections showing multiple well-defined nodules in the upper lobes bilaterally. There were also two cavities inferiorly in the right upper and left upper lobes.

increased diagnosis. More recently four other reports[19,26–28] described bilateral aspergillomas. Shah *et al.* found six patients with multiple fungal balls occurring in the dilated and fusiform bronchial tree, among 41 patients undergoing autopsy or surgical resection.[29] However, little is written about the pathogenesis, diagnosis, and management of this complex presentation. The events that lead up to and result in multiple aspergilloma are yet to be described. This may be in part due to the often-late presentation of aspergilloma, with patients being largely asymptomatic in the earlier stages of the disease.

Aspergillomas have been classified as simple and complex. Simple aspergillomas have smooth edges and sit in a thin-walled cavity. Aspergillomas in a thick-walled cavity, often with surrounding inflammatory disease, have been termed *complex aspergilloma*,[30,31] although this term has also been broadened to include multicavity disease (often containing one or more aspergillomas). Patients 1, 2, and 5 above clearly have multiple, simple aspergillomas, in the sense that they are discrete and thin walled. Singh *et al.*[23] noted that only 10% of their aspergillomas were thin walled, a figure rarely quoted in series. Perhaps these thin-walled cavities have arisen within bronchi causing massive bronchial dilatation, with almost no parenchymal reaction? This is what appears to have occurred in case 3 of Lageze *et al.*,[32] as the presence of multiple bronchi entering and leaving the large cavity suggests this. Such appearances are in stark contrast to those described by the majority of other reports, although Shah's patients might have had a similar disease in some instances.

Patient 2 above may set the record for the largest number of aspergillomas ($n = 11$), with up to six having been seen previously.[33] The architecture of the lungs of patient 2 was one of gross multiple thin-walled cavitation, notably in the upper lobes. Aspergilloma occurrence in CF was reported in three patients from Dublin,[34] and it is likely that most of these fungal balls arose within bronchi. This would be the most likely explanation for the multiple lesions in patient 2, and possibly accounts for the thin walls of each aspergilloma and lack of pleural involvement. As there was so little parenchymal and pleural involvement, the transplant option was deemed best for her, given her dismal overall lung function. Rupture of a cavity with a pneumothorax (patient 3) is also a rare event,[35–37] although this could be the pathogenesis for *Aspergillus* empyema.

Multiple nodules that do not display a thin-walled cavity, or the characteristic crescent sign of an aspergilloma, were also seen in the right upper lobe of patient 4, which may represent another manifestation of chronic pulmonary aspergillosis.[14] Such nodular lesions vary in size and can be cavitating or not, but crucially they also display fungal hyphae on biopsy. While malignancy and other nodular radiological appearances should not be excluded, this presentation should be further examined in CPA patients. These lesions may evolve into

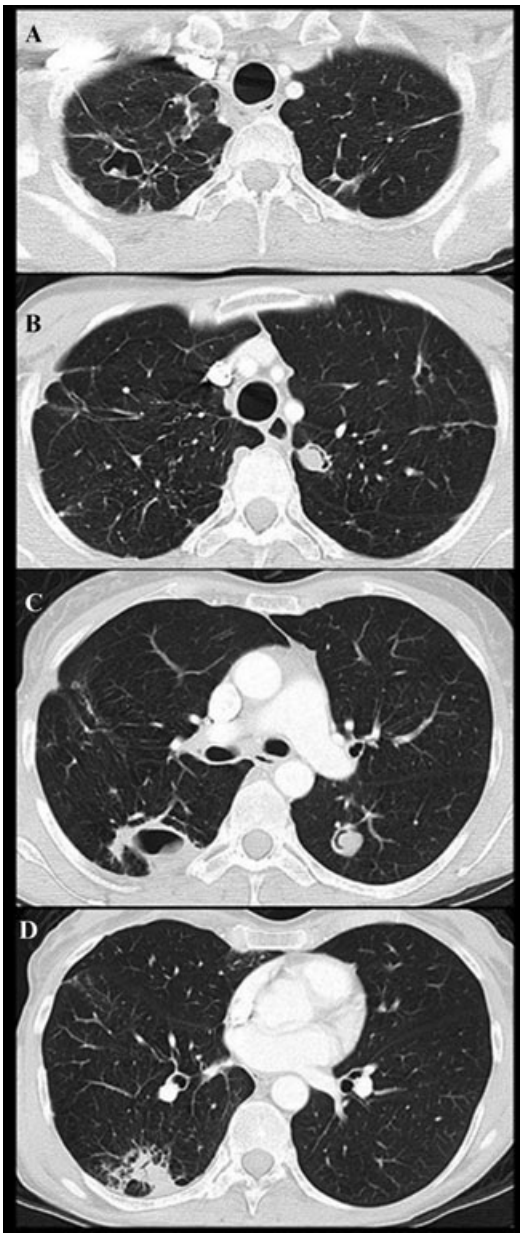

Figure 5. Patient 5. Four CT thorax sections in September 2010 showing four cavities, two containing aspergillomas. The highest section (A) shows a right sided thin-walled cavity with a small amount of material probably adherent posteriorly to the wall. (B) A second cavity on the left side medially almost completely filled with a fungal ball and an air crescent sign. (C) Two further cavities, one on each side, with that on the left with a slightly thicker wall and also almost completely filled with a fungal ball, with an air crescent sign. On the right, posteriorly abutting the pleura, is a thick-walled cavity with associated pleural thickening and two small areas of consolidation laterally. (D) The right-sided cavity is shown to extend several centimeters inferiorly, and change its shape slightly, but without intracavitary material.

cavities with or without fungal balls. Prior to this, lung cancer is the major diagnostic consideration, and surgical resection or biopsy is appropriate to make a histological diagnosis of aspergillosis.[38] Imaging techniques such as PET scanning have also demonstrated the ambiguous nature of an aspergilloma radiologically.[16] Further longitudinal study is required to understand the development of this form of aspergillosis. Other fungal differential diagnoses for pulmonary nodules in nonimmunocompromised patients include coccidioidomycosis[39] and cryptococcosis.[40]

Aspergillus precipitins (IgG antibody) are detectable in over 95% of patients with aspergilloma.[41] About 40% of patients are sensitized to *A. fumigatus* by specific IgE and skin prick testing.[42] Serology was used in all patients to aid diagnosis of aspergilloma or fungal infection. Patient 3 had only *Aspergillus* IgE antibodies detectable, an unusual serological pattern.

While approximately 10% of aspergillomas are reported to lyse spontaneously,[22,43] in the context of multiple lesions this is probably irrelevant to the progression of disease. Most patients with CPA have a progressive downward course, with general ill health including weight loss and fatigue, many pulmonary symptoms of breathlessness, productive cough, chest discomfort, and hemoptysis. In the first six months after diagnosis, 30% succumb to this and the closely related subacute invasive aspergillosis, often with multiple contributory factors.[44] Hemoptysis and pneumonia are the common causes of death. Corticosteroids may provide temporary relief and improvement in general symptoms but ultimately lead to progression of infection,[8,45] as demonstrated in several patients in this series. Long-term medical management is clearly required for these patients as surgery has a limited role with multiple lesions, though the emergence of antifungal resistance in three patients (demonstrated in patients 2 and 4 and inferred in patient 1) is a concern. Azole resistance is an emerging problem in the context of allergic and chronic aspergillosis.[3,16,21,46]

In summary, we have analyzed the characteristics of patients with multiple aspergillomas, which is a rare manifestation of chronic pulmonary aspergillosis. A single aspergilloma is typcially seen radiologically as a spherical mass in a thin-walled cavity displaying a crescent of air or cavitating nodules. Management is challenging and needs additional study.

Conflicts of interest

The authors declare no conflicts of interest.

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