An aspergilloma caused by Aspergillus flavus

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Chronic pulmonary aspergillosis is a broad term encompassing chronic cavitary, chronic fibrosing pulmonary aspergillosis and aspergilloma. All affect patients with structural lung diseases and many have subtle genetic immune defects. Almost all cases are caused by Aspergillus fumigatus. Here we report a patient with an aspergilloma which had Aspergillus flavus recovered from a surgical specimen and serum containing detectable precipitating antibody.

Keywords Aspergillus, mycoses, fungal infections, CCPA, CNPA, aspergilloma

Introduction
Chronic pulmonary aspergillosis is an umbrella term embracing several subcategories, which are distinguished mainly on the basis of their dominant clinical and radiological manifestations. One of these disease manifestations is a single aspergilloma. Most of the patients give a previous history of tuberculosis, or atypical mycobacterial infection although primary bullae in the lung may be implicated [1]. Although Aspergillus flavus is the second leading cause of both invasive and non-invasive aspergillosis [2], aspergillomas have rarely been associated with this species, the vast majority of cases being due to Aspergillus fumigatus. Here we describe a patient with an aspergilloma who had A. flavus recovered from a surgical specimen. The implications of these findings are discussed.

Case report
A 47-year-old woman presented initially with haemoptysis in June 2006, when a chest X-ray showed a small nodule in the upper lobe of the right lung (Fig. 1). She was an ex-smoker (10–15 cigarettes a day for over 30 years) with normal lung function (FEV1 of 2.94 litres, 114% of predicted). Serum inflammatory markers were raised (C-reactive protein 39 µg/ml; ESR 24 mm/h), and serum precipitins were negative against A. fumigatus. Computed tomography (CT) scan confirmed the presence of a single cavitary lesion in the right upper lobe containing soft tissue (Fig. 1). Positron emission tomography (PET) scan showed low intensity FDG uptake in this area, suggesting a non-malignant condition (Fig. 2).

She underwent right thoracotomy and upper lobe wedge resection in September 2006. Gross pathology revealed the presence of a cavity measuring 50 mm in diameter filled with necrotic material. Microscopy showed a cyst lined by bronchial epithelium and filled with dichotomously branching septate fungal hyphae, with no evidence of malignancy. The cyst was formed from a dilated bronchus with focal squamous metaplasia. Fungal hyphae consistent with Aspergillus were seen in the lumen but no invasive component was identified. A moderate number of eosinophils were present in the bronchial submucosa. Tissue culture showed growth of A. flavus fully susceptible to amphotericin B, itraconazole, and voriconazole (MICs of 0.5, 0.125, and 0.5 µg/ml, respectively). A. flavus was identified based on its typical macroscopic and microscopic features. Serum precipitin antibody against A. flavus was detectable in blood (weakly positive). The patient recovered well from the surgery and required no antifungal therapy post-operatively. Serum precipitin antibody against A. flavus reverted to negative 3 months later.

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Discussion

Chronic pulmonary aspergillosis (CPA) is an evolving entity, as reflected by its periodic terminology changes. Previous nomenclatures included semi-invasive aspergillosis, chronic invasive pulmonary aspergillosis, symptomatic pulmonary aspergilloma, progressive chronic pulmonary aspergillosis, simple/complex aspergilloma, and Aspergillus pseudotuberculosis [1]. Simple aspergilloma is characterized by a single cavity containing a fungal mass, which is relatively stable over time, occurring in non-immunocompromised patients. In contrast, chronic cavitary pulmonary aspergillosis (CCPA) is characterized by chronic and progressive formation and expansion of lung cavities affecting not obviously immunocompromised individuals. These cavities may or may not contain aspergillomas (fungal balls). Haemoptysis is the most common clinical problem associated with aspergillomas, although recurrent (presumed bacterial) infections may also occur. In contrast, long-term untreated CCPA usually culminate in extensive lung fibrosis (therefore the term CFPA, chronic fibrosing pulmonary aspergillosis).

The terminology and natural history of simple aspergilloma differs from CCPA. The former manifest very little or no radiological progression over time. As occurred in this report, these patients usually present with a simple cavity containing an aspergilloma on CT scan and histology, with a thin wall. Often they are asymptomatic. However, patients usually show some

Fig. 1 Chest radiograph (on the left) revealing a soft tissue density mass which projects over the anterior tip of the right first rib. Computed tomography scan (on the right) confirms the presence of a well-circumscribed sausage-shaped thin-walled cavity in the right upper lobe containing soft tissue and measuring 2.6 × 1.2 cm. No other parenchymal pathology is noted in the lungs.

Fig. 2 Positron emission tomography (PET) scan showing areas of focal FDG uptake in the upper lobe of the right lung. The uptake level in these areas was below that usually associated with malignancy. A linear area of equally low uptake extending towards the chest wall was observed.

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evidence of active infection, as determined by clinical symptoms (i.e., fatigue and haemoptysis), positive Aspergillus precipitins, and raised inflammatory markers. Aspergillomas may regress spontaneously. Intracavitary Aspergillus colonisation and saprophytic aspergillosis are inappropriate terms in this context, since they do not differentiate infection from colonisation. In fact, the suffix ‘phyte’ in ‘saprophyte’ means ‘plant’, and there is no plant involved in this condition. The expression ‘mycetoma’ is also inappropriate, and it should be reserved for chronic granulomatous infections usually of subcutaneous tissue and caused by traumatic inoculation in tropical and subtropical regions.

CPA patients are generally regarded as immunocompetent individuals, in frank contrast to the severe immunocompromising states observed for patients with invasive aspergillosis. However, recent studies have shown that subtle immune abnormalities are particularly frequent among CCPA patients. These include a deficiency of mannose-binding lectin (which binds Aspergillus species avidly in vitro) [3], genetic polymorphisms in the collagen region of surfactant proteins A2 (SP-A2) [4] and cytokine abnormalities [5]. Although differences in natural history and pathogenesis between patients with simple aspergillomas and CCPA may be genetically determined, this assumption remains speculative. In addition to the genetic features just described, the development of CPA also depends on structural defects involving the lung architecture [6]. Although Aspergillus species can colonize lung cavities caused by different conditions, the occurrence of an aspergilloma in a patient with a congenital bronchogenic cyst as described in this report is however a particularly rare finding [7–9].

A. fumigatus causes the vast majority of these cases of CPA. In a series of 53 CPA patients treated surgically [10], 89.1% of cases confirmed by culture were caused by A. fumigatus, followed by A. flavus in 3 cases (1 simple aspergilloma and 2 CCPA cases), and A. niger in 1. One case was associated with a mixed infection (A. fumigatus and A. terreus), and no serologic test was performed. In the series by Campbell and Clayton [11] A. fumigatus was recovered from the sputum of 82.6% of patients with CPA, while serum precipitins against A. fumigatus occurred in 91.3% of cases (1 patient had positive precipitins against A. nidulans). No case was attributable to A. flavus. In another series involving 16 patients with CPA [12] A. fumigatus caused 83.3% of cases confirmed by culture, followed by A. niger and A. terreus (8.3% both). Again, no case occurred due to A. flavus. In a study describing 14 patients with CPA [13], all cases were due to A. fumigatus. In a review of 59 CPA cases from Japan (including cases of simple aspergillomas and CCPA), only 2% of patients demonstrated positive sputum to A. flavus [14]. Experience from our group in a previous publication [1] also revealed that all CCPA cases were caused by A. fumigatus.

In addition to these case series, very few reports have associated A. flavus with CPA. The reason for this low frequency is unknown. Staib et al. reported the recovery of A. flavus from both sputum and a fungus ball removed at autopsy in a patient with an aspergilloma [15]. Serology was also positive to A. flavus in this case. Guleria et al. [16] reported the isolation of A. flavus from the sputum of a 34-year-old man from India diagnosed with an aspergilloma. This patient also tested positive for A. flavus serology. Another case occurred in Korea [17], where percutaneous aspiration of the intracavitary content in a patient with a giant aspergilloma revealed A. flavus. Serology was not performed. An apparently immunocompetent 18-year-old Saudi woman was diagnosed with CCPA and had associated enlarged mediastinal lymph nodes which tested positive for A. flavus [18]. Another case of aspergilloma was described in a Sudanese series of 6 cases of A. flavus infection [19]. All patients had positive precipitins against A. flavus and not to other Aspergillus species, including 3 patients with invasive aspergillosis and 2 patients with ABPA. Curiously, many of the reports just mentioned came from regions with dry and hot climate. In a comprehensive review of the literature [2], A. flavus was found to be over-represented in these areas of the globe, in comparison to other Aspergillus species. As far as we can ascertain, only one report showed A. oryzae (a member of the Aspergillus flavus complex) as the agent of an aspergilloma [20].

The clinical presentation of CPA caused by A. flavus does not seem to differ from CPA caused by other Aspergillus species, although it is possible that those few patients infected with A. flavus more commonly present with simple aspergillomas. Systemic oxalosis has mostly been associated with A. niger aspergillomas in diabetic patients, and it is considered rare with A. flavus [21]. However in one investigation 4 out of 25 patients (16%) with CPA due to A. flavus had crystals in the sputum [22]. All these four patients had radiographic evidence of cavitary changes over time (suggesting CCPA was the diagnosis), and a fungus ball was observed in one of these patients (questionable in two others).

In summary, recovery of A. flavus from CPA patients is rather infrequent, and that is probably not explained only by underdiagnosis. It is possible that CPA cases
due to *A. flavus* are more prevalent in circumstances of dry and hot climate, but that remains speculative. As shown in this report, negative serum precipitins against *A. fumigatus* do not exclude the diagnosis of an aspergilloma. Cases of CPA caused by *A. flavus* seem to occur mostly as simple aspergillomas and serology may be a useful diagnostic tool. Genetic factors might also account for these differences and deserves further investigation.

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**References**