



Successful long-term terbinafine therapy in an asthmatic patient with *Aspergillus* sensitization and bronchiectasis



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ABSTRACT

Severe asthma with fungal sensitization (SAFS) is estimated to affect ~25% of patients with poorly controlled asthma. Tri-azole therapy is effective in only 60–80% and side effects are common. We report a 25-year-old woman with severe asthma, *Aspergillus* sensitization and marked bronchiectasis that developed a rare Achilles-tendinopathy with both itraconazole and voriconazole. She started a trial with terbinafine as salvage therapy that led to a striking improvement and long-term control of her respiratory disease.

1. Introduction

Asthma has emerged as a major public health problem affecting over 300 million individuals worldwide. This condition affects 5–30% of children and 2–30% of adults. Sensitization to fungi is an important factor in patients with allergic respiratory tract diseases, playing a major role in the development, persistence, and severity of lower airway disease, particularly asthma [1–3]. *Aspergillus fumigatus* has a high capacity to colonize the bronchial tract of asthmatic patients, causing severe persistent asthma and low lung function [4,5], and sometimes leading to allergic bronchopulmonary aspergillosis (ABPA). It has been estimated that up to a quarter of all asthmatic patients referred to a specialist doctor due to difficult management has *Aspergillus* sensitization and forty percent of patients with *Aspergillus* sensitization develop ABPA [6].

ABPA is an immunological pulmonary disorder caused by hypersensitivity to *Aspergillus fumigatus* that complicates asthma, primarily in adults [7]. It is rarely seen in children, other than complicating cystic fibrosis. The prevalence of ABPA in adults has been estimated at ~2.5%, although it is probably less common in the USA and more common in India [8]. The global burden has been estimated at 4.8 million ABPA patients in a world-wide asthma population of 193 million. There is a 5% familial incidence. Two randomised controlled trials showed that systemic antifungal therapy in ABPA can offer a therapeutic benefit to 60% of patients [9]; and nebulised amphotericin B are the antifungals most frequently used in ABPA patients, although their use is frequently limited by the appearance of side effects and drug

interactions [10,11]. Terbinafine has recently been shown as an effective alternative therapy in a few CPA patients [12]. Treating ABPA usually leads to improvement of patient's symptoms, lung function and prevention of bronchiectasis.

A. fumigatus is frequently isolated from the respiratory tract of patients with asthma who do not fulfil all the criteria for ABPA [4] and is detected using PCR in SAFS patients compared to severe asthma controls [5]. The term severe asthma associated with fungal sensitivity (SAFS) was coined to illustrate this high rate of fungal sensitivity in patients with severe asthma and response to oral antifungal therapy. It has been estimated that the global prevalence of SAFS is about 6.5 million people worldwide [1]. When compared to other asthmatic patients of similar disease severity, those with IgE sensitivity to *A. fumigatus* have more fixed airflow obstruction and more bronchiectasis [2]. It is speculative whether ABPA represents one florid manifestation of a spectrum of fungus-associated airway disease.

2. Case

A 25 year old woman with a history of peanut and peas allergy and a medical history of severe asthma since the age of seven had required several courses of corticosteroids, different inhaled treatments and some hospital admissions due to recurrent chest infections and asthma exacerbations. She had a family history of atopy and a sister who suffers from hay fever and eczema. In 1998 she was referred from her general practitioner to the “difficult asthma clinic” at University Hospital of south Manchester reporting cough and a high volume of daily sputum

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Fig. 1. High-resolution chest CT without contrast showing mild multilobar cylindrical bronchiectasis in both lower lobes.

with varied consistency and colours. By the time she attended she denied wheezing. On physical examination she was very thin but nothing more remarkable and there was no evidence of airway obstruction on auscultation.

Computed tomography (CT) scan in 1998 found no evidence of bronchiectasis. Pulmonary function tests were near normal. However there was mild bronchial hyperactivity on histamine challenge testing (PC20 = 2.8 mg/ml). She was followed up in clinic without experiencing any improvement on symptoms (persistently productive cough) despite intermittent steroid courses. A CT scan was repeated in 2001 that showed quite extensive mild bronchiectasis, predominant in the lower lobes, without mucus plugging (Fig. 1). Laboratory tests were performed and showed a high total IgE of 110 KUa/L, high *Aspergillus*-specific IgE level of 6 KUa/L (normal 0–0.4KUa/L), normal *Aspergillus* IgG levels and normal eosinophil count. Serum galactomannan was not requested. Repeated sputum cultures showed the presence of normal respiratory tract flora.

She did not fulfil all the criteria for ABPA with a normal eosinophil count (off corticosteroids) and a total IgE \leq 1000 KU/L, but had a high level of *Aspergillus* sensitisation, and the interval development of moderate bronchiectasis. She was diagnosed with asthma with *Aspergillus* sensitization and secondary bronchopulmonary damage. After pregnancy and a period of breast-feeding she started antifungal treatment with itraconazole in 2003 which was followed by a striking improvement on respiratory symptoms. One month after the commencement of itraconazole treatment she suffered profound bilateral Achilles tendinopathy that made her housebound for some weeks; itraconazole was discontinued. She experienced a complete recovery of tendinopathy, but her respiratory symptoms promptly relapsed again with daily productive cough. She was seen at the National Aspergillosis Centre for expert advice on management.

Following evaluation and a successful funding request, she commenced voriconazole therapy at a dose of 200 mg twice a day which was increased to 250 mg due to undetectable voriconazole levels ($<$ 0.2 mg/L). Despite undetectable levels after raising the dose, she experienced significant improvement in her lung symptoms and as a result treatment was continued despite low serum voriconazole concentrations. After five months of treatment she again developed bilateral Achilles tendinopathy and voriconazole was stopped. The heel pain resolved completely during the following month after discontinuing the drug. Unfortunately, her respiratory symptoms relapsed again after some weeks without treatment. In this patient a drug-related association appears to be a triazole class-related side effect of Achilles tendinitis.

In April 2004, she was commenced (as a rescue approach) on a trial with oral terbinafine therapy at a dose of 500 mg daily. She had a prompt improvement in her respiratory symptoms and a significant decrease on the rate of infective exacerbations. She stayed on long-term

therapy because of the rapid relapses after discontinuing azoles. Follow up lung function testing in 2007 was completely normal and a lung CT undertaken in 2009 showed unchanged bronchiectasis compared to 2001. In February 2005 the dose was reduced to 250 mg daily without experiencing any symptomatic deterioration. She continues on terbinafine therapy and has remained completely asymptomatic without any toxicity, has normal liver function tests and continues with an annual clinic follow up.

3. Discussion

The incidence of fungal diseases has risen rapidly over the last two decades, and fungal allergy is one of the commonest manifestations worldwide. The definition of fungal sensitization includes immune-mediated response to a fungus usually documented by an elevated fungal-specific IgE [11]. This entity arises from a combination of host genetic factors and both indoor/outdoor environmental exposure and potentially airway colonisation.

A. fumigatus is a viable organism found within airway mucus plugs that causes an intense and local immune reaction, together with marked remodelling of the airway, leading to fixed airflow obstruction with bronchiectasis [2]. *Aspergillus* sensitization is associated with worse asthma control and significant morbidity [1,8]. IgE sensitization to *A. fumigatus* is associated with abnormalities of the airways and changes in mucus production and properties may contribute to the development of ABPA in patients with asthma. This disorder is best detected and treated before bronchiectasis develops because the occurrence of bronchiectasis is associated with poorer outcomes, including progressive destruction of the lung parenchyma and loss of lung function and the recurrent cycle of bacterial infection, chronic mucus production and further airway damage [7].

The diagnosis of ABPA is based on clinical and immunologic reactivity to *A. fumigatus* [11]. The recently proposed diagnostic criteria have been debated several times about the relative merits of the radiological, microbiological and immunological tests utilized, and how to best differentiate *Aspergillus* colonisation, *Aspergillus* sensitization and ABPA as clinical entities [4,7]. In 2006, Denning et al. coined the term “severe asthma and fungal sensitization” (SAFS) to describe severely asthmatic patients who are sensitive to fungi, do not meet the criteria for ABPA, and respond to antifungals [1] which is usually a diagnostic of exclusion.

Here we report a case that did not fulfil all the classical criteria for ABPA as her total IgE level was less than 1000 μ L and her eosinophil count was within normal limits despite being off steroids [11]. However, *A. fumigatus* specific IgE levels have recently been suggested as better criteria for ABPA diagnosis [13] and the evidence of *A. fumigatus* in the airways has been strongly associated with *Aspergillus* IgE-sensitization and worse lung function in these patients [4]. SAFS is

an alternative diagnosis but the development of bronchiectasis has been considered a criterion of ABPA and it is not a part of the SAFS definition [4]. Despite the SAFS definition not including lung damage as a diagnostic criterion, in our patient it is likely that *Aspergillus* sensitization has led to progressive allergic airway inflammation, remodelling and ultimately bronchiectasis [2]. Therefore, as cited previously, ABPA and SAFS could be simply the severe end of the same spectrum of disease [14,15].

The management of ABPA consists of glucocorticoids as an anti-inflammatory to suppress immune reactivity combined with antifungal agents to attenuate the fungal load in the airways reducing the need for glucocorticoids. Management of SAFS patients is similar and antifungals are also effective, although more studies are needed to specify the dose and the duration of treatment [16]. Itraconazole and nebulised amphotericin B are the antifungals most frequently used in ABPA and SAFS patients, although their use is frequently limited by the appearance of side effects and drug interactions [9–11]. The newer triazoles (voriconazole and posaconazole) and terbinafine have also shown promise as second and third line treatments in patients with ABPA and SAFS, primarily in cystic fibrosis, but latterly in asthma [3,12,17,18].

Many drugs for therapeutic interventions can cause unexpected toxicity in tendon tissue, often leading to significant morbidity and disability. Our patient developed a rare tendinopathy after two different azole therapies (itraconazole and voriconazole). The temporal relationship with the drugs and the significant improvement of symptoms after discontinuation, support their association. To the best of our knowledge this is the first reported case of tendinopathy precipitated by azole therapy as a class related side effect.

Terbinafine is an allylamine antifungal agent, available in both topical and oral preparations, with fungicidal activity due to the inhibition of ergosterol biosynthesis through interfering with squalene epoxidase enzyme [19]. Several studies have demonstrated the in vitro and in vivo efficacy of this drug against various emerging non-dermatophytic fungal infections, including moulds. Indeed, it has shown potent activity against clinical isolates of *Aspergillus* spp. equivalent to amphotericin B or itraconazole [20]. Terbinafine has been used before to treat ABPA and CPA patients with successful outcomes. A recent small randomised multicenter clinical trial of terbinafine versus itraconazole for chronic pulmonary aspergillosis has shown more successful rates (91.7% vs 70%) and lower proportion of adverse events with terbinafine [12].

In conclusion, as azole therapy is being increasingly used in chronic fungal infections, we consider essential that clinicians recognize tendinopathy as a possible azole class-therapy adverse event. Moreover, more effective drug treatments with convenient dosing regimens and a low level of adverse events are needed to reduce morbidity and mortality of patients with chronic *Aspergillus*-related infections. As previously described, our case suggests that the use of terbinafine as a salvage therapy could be an option as a long-term treatment for patients with *Aspergillus* sensitization and secondary lung damage.

Conflict of interest

There are none financial or personal conflicts of interests.

Ethical form

We have obtained verbal and written consent to publish the case report from the patient.

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There are none.

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