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Case Report

Pulmonary aspergilloma: An evasive disease

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ABSTRACT

Aspergillomas are often misdiagnosed as tuberculosis (TB) in developing countries where the prevalence of TB is high, hemoptysis is often equated with TB, and most patients are diagnosed clinically. This report describes the case of a patient being treated for smear-negative TB who presented with hemoptysis and was found to have an aspergilloma.

Introduction

Aspergillomas are mass-like fungus balls that are typically composed of *Aspergillus fumigatus*, and represent a non-invasive form of pulmonary aspergillosis. Aspergillomas occur in patients with structurally abnormal lungs, with pre-existing cavities. This case report highlights an evasive clinical condition with profound diagnostic and treatment challenges particularly in developing countries.

Case report

In July 2013, a 38-year-old Ghanaian male on his 3rd week of treatment for smear-negative tuberculosis (TB) was referred to our hospital for further management of massive hemoptysis. He had noticed a small amount of hemoptysis about 1 month prior to his current visit along with weight loss, low-grade fevers, and night sweats. At that time, he reported to a district clinic and was started empirically on rifampicin, isoniazid, pyrazinamide, and ethambutol. He also reported a 5-year history of unproductive cough. Although he had only minimal exposure to cigarettes (<1 pack in his lifetime), he had been exposed to second-hand smoke for 17 years. The patient was originally from Salaga, Ghana, had been living in Niger for nearly 20 years, and traveled frequently through the desert and to Mali and Ghana.

The patient stated that his first experience of pulmonary symptoms occurred 7 years earlier. In April 2006, the patient

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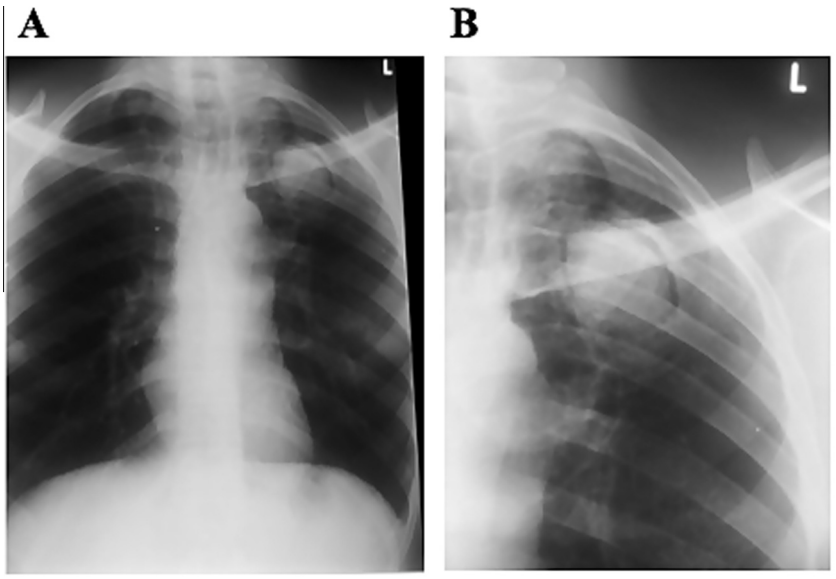

Fig. 1 – (A) Chest radiograph showing fungal ball in the left apical lung taken at initial diagnosis; (B) 5 months into treatment with 200 mg of daily itraconazole showing the aspergilloma.

presented with a 2-month history of a low-grade fever, night sweats, weight loss, and a cough productive of mucoid sputum without hemoptysis. At presentation, the patient weighed 40 kg. He had attempted unsuccessfully to treat his symptoms at home with antitussives, antimalarials, and multivitamins. Human immunodeficiency virus (HIV) screening test result was negative and sputum for acid-fast bacilli (AFB) was negative on three occasions. Chest radiographs were performed, and based on those results he was given a clinical diagnosis of TB. He completed a 2-month course of streptomycin, isoniazid, rifampicin, and pyrazinamide followed by 6 months of isoniazid and thiacetazone. At his follow-up appointment in November 2006, he had a 29-kg weight gain and resolution of his signs and symptoms.

The patient remained well until March 2008 when he presented with a mucopurulent cough, low-grade fever, night sweats, and left-sided chest pain. Radiological findings were suggestive of TB; however, further testing did not support this diagnosis. His sputum smears were negative for AFB and bacterial growth; erythrocyte sedimentation rate and full blood count were both within normal limits. Physical examination was unremarkable and demonstrated a well-appearing middle-aged man with a clinically clear chest. He was ultimately diagnosed with resolving atypical pneumonia, prescribed analgesics for left-sided chest pain, and sent home.

His constitutional symptoms ultimately resolved, but he continued to suffer from a nonproductive cough. In August 2009, he presented for evaluation of persistent cough. Sputum AFB smears were negative, and the patient was reassured that he did not have TB. As the underlying cause for his cough could not be determined, the patient was prescribed 1 week of empiric amoxicillin/clavulanate. Despite the antibiotics, his cough never resolved.

In June 2013, he noticed worsening of his usual cough along with weight loss, low-grade fever, night sweats, and minimal hemoptysis. He reported to a district hospital where he was started on a second course of first-line anti-TB medication (rifampicin, isoniazid, pyrazinamide, and ethambutol).

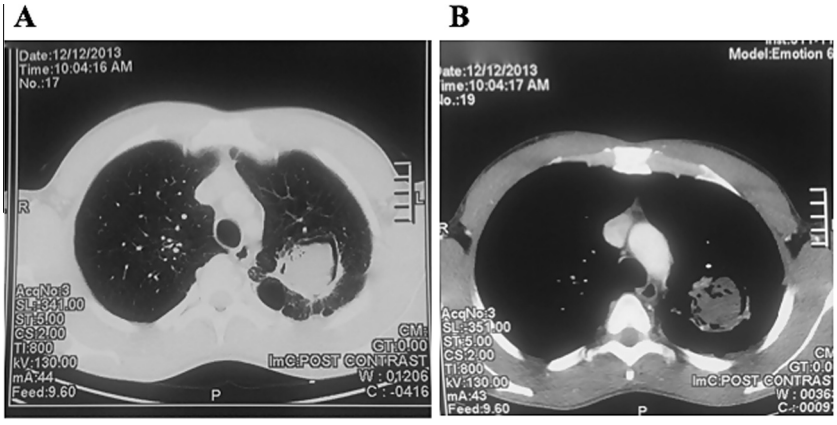

Fig. 2 – Chest computed tomography scan showing bilateral apical post-tuberculosis lung fibrosis and a left apical 5.5 × 5.4-cm^2 thick-walled cavity with a solid intracavity mass with air crescent sign. (A) Lung; (B) mediastinal window.

There was no improvement in his symptoms, and 3 weeks into treatment he was rushed to a private clinic after three episodes of massive hemoptysis (about 200–300 mL of blood during each episode). He was referred to our hospital with a presumptive diagnosis of smear-negative TB and a differential diagnosis of histoplasmosis.

After reviewing the patient's history and obtaining chest radiographs (Fig. 1A), the infectious disease physician at our hospital made a clinical diagnosis of aspergilloma and initiated itraconazole while continuing the anti-TB medications. A medical review 2 weeks later showed marked improvement in the patient's symptoms and cessation of his hemoptysis. After 5 months of itraconazole, chest radiograph still showed a well-circumscribed lesion in the left upper zone (Fig. 1B). Chest computed tomography (CT) scan at that time showed bilateral apical post-TB lung fibrosis and a left apical 5.5 × 5.4-cm^2 thick-walled cavity with a solid intracavity mass with air crescent sign (Fig. 2A and B). After 2 years and 4 months of itraconazole, he had clinically improved except for occasional dry cough and left-sided chest pains.

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

Discussion

Background information

Although it is clear that the global burden of fungal infections – such as those caused by *Aspergillus* spp. – is increasing, the exact magnitude of the problem remains unknown [1–3]. This surge has been attributed to HIV/AIDS, TB, chronic obstructive pulmonary disease, the growing use of immunosuppressive therapies, and a host of other conditions [4]. Globally, it is estimated that 1.2 million people have chronic pulmonary aspergillosis (CPA) as a sequel to TB, with Africa, Western Pacific, and South-East Asia being the most affected [5]. Aspergilloma is one of several disease manifestations of CPA and involves the saprophytic growth of *Aspergillus* spp. such as *Aspergillus fumigatus* in the lung, most commonly in apical lung cavities.

The diagnosis of aspergilloma can be elusive in developing countries with a high prevalence of TB because hemoptysis is often equated with TB without consideration of other differential diagnoses such as aspergilloma [5,6]. For this reason, the actual disease burden of aspergilloma in sub-Saharan Africa as well as its impact on morbidity is unknown [6]. In cases where sputum for AFB is negative or patients fail to improve on standard therapy, patients may be started on treatment for smear-negative or drug-resistant TB. This is especially likely when serology or radiology is unavailable or inaccessible to the patient due to cost. Even when patients are correctly diagnosed, the paucity of evidence-based data to guide aspergilloma treatment in resource-poor settings makes individualizing care challenging.

Primary aspergilloma is rare and tends to occur in immunocompromised patients such as those with neutropenia, long-term glucocorticoid use, or AIDS through bronchial invasion by *Aspergillus* spp. and subsequent cavitation [7]. Secondary aspergilloma occurs in immunocompetent patients with previous lung pathology such as TB, sarcoidosis, lung abscess, bronchogenic cysts, or lung tumor who are exposed to *Aspergillus* spores in dry or very dusty environments, hay barns, or compost sites [8–12]. The most common pre-existing lung pathology is TB [8,10,13] with time interval between diagnosis of TB and aspergilloma ranging from <1 year to 30 years [10].

In the case of our immunocompetent host, his prior history of TB in 2006 was the primary lung pathology that made him susceptible to aspergilloma. This initial clinical diagnosis of smear-negative TB was supported by a 29-kg increase in his weight and resolution of his constitutional symptoms following TB treatment. Chest CT scan in 2013 also demonstrated bilateral apical post-TB lung fibrosis. It is possible that our patient was then exposed to *Aspergillus* conidia during his frequent desert travels, which resulted in seeding of a tuberculous cavity. There was a 6-year interval between the patient's diagnosis of TB and aspergilloma, which could be attributed to diagnostic challenges since he had been symptomatic for a 5-year period.

The natural history of aspergilloma is still largely unknown [3,13]. However, most cases of aspergilloma are asymptomatic and 10% demonstrate spontaneous resolution [6,13,14]. Symptoms are nonspecific and include hemoptysis, cough, chest pain, and fever. Massive hemoptysis, which occurred in our patient, is an uncommon complication and is thought to occur as a result of mechanical or endotoxic irritation vessels or direct invasion by the fungal ball [6]. Development of invasive disease is also a recognized complication [15].

Previously, the only published guidelines for the diagnosis and management of aspergilloma were put forth by the Infectious Disease Society of America (IDSA) in 2000 and updated in 2008. In January 2016, the European Society for Clinical Microbiology and Infectious Diseases (ESCMID) collaborated with the European Respiratory Society (ERS) to review recent data on fungal infections and release new clinical guidelines for the management of CPA (including aspergilloma) [16]. According to ESCMID/ERS, diagnosis of aspergilloma requires radiological imaging consistent with aspergilloma, direct serological or microbiological evidence of *Aspergillus* spp., and exclusion of other diagnoses. Symptoms also need to have been present for 3 months before the criteria are met [16].

Diagnosing aspergillomas

Chest radiographs are often the first imaging ordered and reviewed when there is suspicion for lung pathology. In the case of aspergilloma, they may show fibrosis (especially in the upper lung lobes), cavitation, thickening, or a fungal ball [16]. Fungal ball within a pulmonary cavity is highly suggestive of the diagnosis. A CT scan is preferential for diagnostic purposes, and two distinct signs may aid in diagnosis. Air crescent sign is a crescent-shaped air space separating the fungal ball from the cavity wall. Notably, this may also be found in Wegener's granulomatosis, hydatid cyst, hematoma, and lung abscess [17]. Monod sign, a change in position of the

fungal ball with movement, is unique to aspergilloma and occurs in approximately two-thirds of patients [10,17]. Our patient had fungal ball on chest radiographs (Fig. 1A and B) as well as on CT scan showing bilateral apical post-TB lung fibrosis and a thick-walled cavity with a solid intracavity mass with air crescent sign (Fig. 2A and B). These findings ultimately allowed for diagnosis of aspergilloma in our patient.

If imaging is suggestive of aspergilloma, evidence of an immunological response to *Aspergillus* spp. or direct evidence of *Aspergillus* can help to confirm the diagnosis [16]. Serological testing for precipitins [immunoglobulin G (IgG) antibodies to *Aspergillus*] allows for definitive diagnosis and will be present in >90% of cases [16]. Testing for IgM and IgA antibodies is not recommended, but IgE may be useful in specific contexts [16]. There is also an assay against galactomannan (GM), a polysaccharide component of the cell walls in *Aspergillus* that may be detected in bronchoalveolar lavage fluid and blood. The sensitivity for GM in bronchoalveolar lavage has been shown to be much greater than serum GM [9,18,19]. Moreover, the GM test will be falsely positive in patients taking piperacillin or tazobactam and its clinical utility has been questioned by some researchers [8]. In some cases of aspergilloma, antibody or GM testing may be falsely negative, especially if another species of *Aspergillus* is involved or if the patient is taking corticosteroids [6].

The presence of *Aspergillus* (via microscopy, polymerase chain reaction assay, or culture) from bronchoscopic or sputum specimens may be consistent with the diagnosis of aspergilloma, but these investigations alone are not diagnostic as they are not extremely sensitive or specific for aspergilloma [16]. Ideally, aspergilloma and TB can be distinguished by history, serology/respiratory samples, and radiological differences without lung biopsy [20]. However, biopsy and video thoracoscopy can also play a role in diagnosis [21].

Our patient did not receive any of these laboratory tests as they were not available at our hospital, so his aspergilloma diagnosis was aided by thoracic CT scan. Availability of tests required for definitive diagnosis of aspergilloma is a common challenge in resource-poor settings. The tests needed to thoroughly investigate this differential are often lacking, and even when available, patients may be unable to afford them [5,6]. A host of other conditions such as TB, lung tumor, histoplasmosis, and blastomycosis may also present with similar symptoms and a well-circumscribed upper lobe lesion [7,9,11,12], and diagnostic delays may increase morbidity and mortality. In the developing world, aspergilloma is often misdiagnosed as TB because clinicians rely heavily on presumptive diagnoses and empiric treatment. To further complicate matters, active TB may coexist with aspergilloma in rare cases [22]. In our patient, the initial diagnosis of aspergilloma was likely missed, explaining the patient's lack of response to anti-TB medication and worsening symptoms that ultimately led to massive hemoptysis.

Treatment of aspergillomas

Generally, asymptomatic patients with aspergilloma do not require treatment and can be monitored for the development of symptomatic disease. Symptomatic patients are treated based on whether they have single or multiple aspergilloma as well as the severity of their symptoms. Single symptomatic lesions are best treated by surgical resection [3,10,23]. However, surgery carries significant risks such as bronchopleural fistula, massive hemorrhage, empyema, Horner's syndrome, and death from respiratory failure [10], and so the benefits must be weighed carefully against calculated risks. Despite this, the IDSA and ESCMID/ERS guidelines recommend surgery for all eligible patients with aspergilloma, especially those with severe hemoptysis [16,20]. In our patient, surgical resection was not considered due to availability and cost.

Antifungals can be used as the mainstay of treatment in cases such as with our patient where surgery is not available or feasible [3,8]. Although the drug does not penetrate the cavity of the aspergilloma well [8], some researchers have found itraconazole to be 60–70% effective in stabilizing or improving symptoms and arresting progression [5]. Currently, itraconazole is most widely used [6] but voriconazole and intralesional amphotericin B can be used for secondary treatment [11]. It is not clear whether antifungal therapy as an adjuvant to surgery has a significant impact on postoperative morbidity or long-term survival [12,24]. Radiologic improvement and resolution rarely occurs in symptomatic cases.

Conclusion

This case report serves to sensitize physicians of the need to entertain a broad differential diagnosis in patients presenting with symptoms of TB, especially in cases where sputum for AFB is negative, patients appear to have failed standard TB treatment, or patients have risk factors for developing CPA such as aspergilloma. Improved access to efficacious antifungals and options for surgical treatments are greatly needed and will increase patients' life expectancy and decrease working days lost to sickness. This report also highlights the need for affordable and easy-to-use tools to improve case finding of aspergilloma in developing countries and to determine its contribution to morbidity and mortality.

Conflicts of interest

The authors declare no conflicts of interest.

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