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Chronic Pulmonary Aspergillosis Misdiagnosed as Smear-Negative Pulmonary Tuberculosis in a TB Clinic in Nigeria

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Authors' contributions

This work was carried out in collaboration between all authors. Author TGB designed and wrote the manuscript. Author FB designed and wrote the manuscript and author NI contributed to the final version of the manuscript. Author AON contributed to the final version of the manuscript. Author ROO conceived the study and was involved in the planning and supervised the work. All authors read and approved the final manuscript.

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Case Study

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ABSTRACT

The clinical manifestations of chronic pulmonary aspergillosis (CPA) and pulmonary tuberculosis (PTB) are practically indistinguishable. We present a case of CPA in a 35-year-old HIV-negative trader, who had had three unsuccessful treatment courses for smear-negative PTB. He presented with a five-year history of recurrent symptoms suggestive of TB (haemoptysis, weight loss and productive cough). His sputum smear was acid-fast bacilli negative and GeneXpert analysis was negative for Mycobacterium tuberculosis. Chest X-rays revealed bilateral apical cavities and bullae. His *Aspergillus*-specific IgG tests were positive (>40 mg/L). He was managed with itraconazole 200mg twice daily with marked improvement in his clinical presentation and his quality of life after 4 months of therapy. However, he significantly deteriorated after discontinuing itraconazole for 1 month; he had adherence counselling and was re-commenced on long-term itraconazole therapy.

Keywords: Chronic pulmonary aspergillosis; smear-negative TB; itraconazole Aspergillus IgG.

1. INTRODUCTION

Chronic pulmonary aspergillosis (CPA) is an umbrella term that comprises four entities: chronic cavitary pulmonary aspergillosis (CCPA), simple aspergilloma, *Aspergillus* nodule and – the most severe form – chronic fibrosing pulmonary aspergillosis (CFPA) [1]. Patients are usually immunocompetent or subtly immunocompromised, middle-aged, with prior or current structural underlying lung conditions presenting with prominent systemic and pulmonary symptoms which are clinically indistinguishable from pulmonary tuberculosis (TB) [2,3]. The global prevalence of CPA is estimated at about 3 million cases, 1.2 millions of whom have had prior TB [4]. Other underlying conditions predisposing patients to CPA include pulmonary sarcoidosis, pneumothorax, emphysema, chronic obstructive pulmonary disease, allergic bronchopulmonary aspergillosis (ABPA) and others [5]. Herein, we present a case of CPA in a 35-year-old HIV-negative trader, who had had three unsuccessful treatment courses for smear-negative PTB.

2. CASE REPORT

A 35-year-old immunocompetent male presented at the Tuberculosis (TB) clinic in the National Institute for Medical Research (NIMR), Lagos in April 2016 with a five-year history of intermittent haemoptysis, productive cough with occasional breathlessness and weight loss. His past medical history showed previous diagnosis of TB and he had completed treatment for TB in 2011 and 2012. Diagnosis in 2011 and 2012 was done with Chest X-ray and sputum tests for Acid-Fast Bacilli (AFB). At presentation, his sputum smear was negative for AFB and GeneXpert negative for Mycobacterium tuberculosis. His complete blood count and serum electrolytes and urea were within normal ranges. However, he had a raised erythrocyte sedimentation rate (ESR) at 35mm/hr. He had a body mass index (BMI) of 15.4 (weight: 50 kg; height: 180 cm). His chest X-rays (CXR) findings in October 2015 and February 2016 were suggestive of PTB. A month after presentation, he was commenced on TB treatment as per National guidelines. He completed anti-Koch's treatment in October 2016 and there was no improvement in his symptoms. Repeat CXR in December 2016 revealed enlarging thick walled cavities and bullae (Fig. 1).

In January 2017, a diagnosis of chronic pulmonary aspergillosis was made based on his *Aspergillus* IgG result (>40 mg/L), clinical presentation and radiological findings. He had a normal liver function test (LFT); he was subsequently placed on itraconazole 200 mg twice daily. A month after commencement of itraconazole, he reported reduced episodes of haemoptysis but a persistent cough; he was encouraged to continue therapy. Two months into itraconazole treatment, he reported cough was subsiding, and a weight gain- 55 kg (BMI 17) was observed. His LFT values remained within normal range and he did not report any adverse events related to itraconazole therapy. Five months into treatment, our patient discontinued his medications for about a month, he was misled by his family members to use an imported herbal medicine which they hoped would be a quick remedy. He presented with a significant weight loss to 49 kg (BMI 15.1) and worsening haemoptysis. He received adherence counselling and continued on long-termitraconazole therapy with improvement in his clinical symptoms and quality of life.

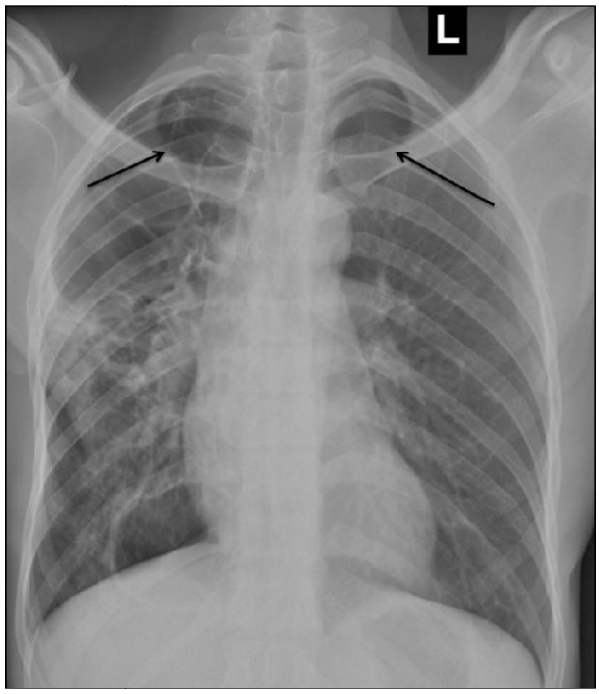

Fig. 1. A plane chest x-ray done on our patient in December 2016 showing bilateral thick-walled apical cavities without fungal balls consistent with chronic cavitary pulmonary aspergillosis

Important to state is that, because this patient is living in a resource-limited setting, some more specific diagnostic tests that may be helpful in the management of this patient were not available.

3. DISCUSSION

CPA is a neglected disease in resource-limited settings and most cases match the World Health Organization diagnostic criteria for smear-negative TB [6]. CPA is recognized as a significant global health burden estimated to affect 3 million people worldwide with significant morbidity and mortality. It occurs in individuals with underlying respiratory pathology that results in the formation of air-filled cavity or bullae. Globally, the most common predisposing factor for CPA is previously treated tuberculosis TB. CPA complicates previous PTB in 15-90% of the cases [7]. In Nigeria, 120, 753 cases of CPA with a very high prevalence rate (78/100,000) have been estimated primarily as a sequel of PTB [8]. The spectrum of CPA ranges from the most common form; CCPA (which if untreated may progress to CFPA to the less common manifestations such as *Aspergillus* nodule and single aspergilloma [2]. The three entities are found in non-immunocompromised patients with prior or current lung disease. Subtle immune defects in the cells of the innate and adaptive immunity have recently been described [9]. Our patient had CCPA without evidence of an aspergilloma.

In resource rich-settings, CPA is diagnosed based on the criteria proposed by Denning *et al*[2] and require the presence of: 1) underlying pulmonary disease, 2) symptoms, 3) radiological findings, and 4) microbiological evidence of aspergillosis, *A. fumigatus* IgG antibody-positive or culture from sputum of a non-*fumigatus* species of *Aspergillus* in patients with a compatible radiological findings. *Aspergillus* IgG is positive in over 95% of the cases. However, many nations in the resource-limited settings do not have access to high-resolution chest CT scans or *Aspergillus* assays. At the 2nd Global Fungal Infection Forum in Liverpool, UK in October 2015, diagnostic criteria for CPA in resource limited-settings have been proposed. CPA was defined as an illness of at least three months and a combination of symptoms, radiographic appearances and documentation of *Aspergillus* infection: 1) symptoms of weight loss; a persistent cough and hemoptysis; 2)chest imaging showing progressive cavitary infiltrates, and/or a fungal ball and/or pericavitary fibrosis or

infiltrates or pleural thickening; and 3) a positive *Aspergillus* IgG antibody assay or other evidence of *Aspergillus* infection. Mycobacterial infection should be ruled out according to national guidelines. This revised definition is anticipated to improve patient care and catalyse research in resource-limited settings [10].

The optimal regimen and duration of treatment of CPA is not standardised. The American and European aspergillosis guidelines recommend a minimum of 6 months of oral triazole therapy [1,11,12]. Long-term Itraconazole and voriconazole therapy, with therapeutic drug monitoring, are the first-line oral agents of choice, posaconazole and isavuconazole can be used as alternative therapies in patients who are intolerant of or have adverse events to first-line agents [1,12]. Clinical benefits are observed at 6-12 months of continuous triazole therapy [13,14]. Key challenges to long-term therapy are adverse events and development of resistant species of *Aspergillus* [13,15]. About 10% of patients who develop pan-azole resistance or cross-azole intolerance will require intravenous antifungals, either cyclical liposomal amphotericin B or an echinocandin [13]. Haemoptysis and respiratory failure due to volume loss are the main complications of CPA; however, rare complications such as massive and tension pneumothorax have recently been reported [16].

4. CONCLUSION

CPA is a slowly destructive pulmonary syndrome characterised by progressive cavitation, fibrosis, and pleural thickening as does occur in TB. Patients who present with symptoms similar to TB and are sputum AFB negative should be further investigated for CPA, especially when they have previously been treated for TB and re-presenting with a recurrence of symptoms. *Aspergillus* IgG assay is an essential tool for the diagnosis of CPA and should always be considered in patients presenting with a similar scenario to this case study.

CONSENT

As per international standard or university standard written patient consent has been collected and preserved by the authors.

ETHICAL DISCLAIMER

As per international standard or university standard written ethical permission has been collected and preserved by the authors.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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