Medical Mycology Case Reports 46 (2024) 100666

Contents lists available at ScienceDirect

Medical Mycology Case Reports

journal homepage: www.elsevier.com/locate/mmcr

Primary treatment of chronic pulmonary aspergillosis with weekly liposomal amphotericin B: A case report from Uganda

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ARTICLE INFO

Handling Editor: Dr Adilia Warris

Keywords:
Aspergilloma
Liposomal amphotericin B
Treatment outcome
Resource limited settings

ABSTRACT

Chronic pulmonary aspergillosis (CPA) treatment in Africa remains unexplored. We present a 23-year-old Ugandan male, previously treated thrice for pulmonary tuberculosis, developing CPA. Imaging showed lung fibrosis, bronchiectasis, and a fungal ball. He received weekly 600mg (10mg/kg) of liposomal amphotericin B for six weeks, leading to marked clinical improvement. Weekly liposomal amphotericin B may be a viable treatment option for CPA in resource-limited settings.

1. Introduction

Chronic pulmonary aspergillosis (CPA) is a spectrum of progressive parenchymal diseases of varying severity that complicates several respiratory disorders such as pulmonary tuberculosis (PTB), fibrocavitary sarcoidosis, and chronic pulmonary obstructive disease [1]. Radiologically, CPA has 5 distinct phenotypes, namely, *Aspergillus* nodules, simple aspergillomas, chronic necrotizing pulmonary aspergillosis, chronic cavitary pulmonary aspergillosis, and chronic fibrosing pulmonary aspergillosis [2]. The annual global incidence of CPA currently stands at over 1.8 million cases with approximately 340,000 deaths [3]. In Uganda, CPA is estimated at 26,765 annual cases and 63,574 5-year-period prevalent cases [4].

International guidelines recommend oral itraconazole or voriconazole for at least 6 months as alternative first-line agents for the treatment of CPA [1,5]. However, both drugs are not on the essential medicine list in Uganda and their cost has continually been prohibitive. Intravenous amphotericin B, with a response rate of about 60 % is used as 4th line therapy for CPA in patients who are intolerant or pan-azole resistant and those who may not have access to the echinocandins [1,5]. Amphotericin B is widely available in Uganda, despite the lipid formulation being available only in selected centers, and covered by government payment. Here, we report a case of CPA related to PTB successfully treated with liposomal amphotericin B.

2. Case presentation

A 23-year-old male presented with a history of persistent symptoms including productive cough, moderate hemoptysis of about 75mls in 24hours, chest pain, difficulty in breathing, evening fevers, weight loss, and drenching night sweats (day 0). He was negative for HIV and did not smoke cigarettes. He was treated three times for bacteriologically confirmed PTB in 2017, 2021 and 2023. In August 2017, the patient was diagnosed with rifampicin-resistant PTB, treated and declared cured in September 2018. However, he relapsed, and was diagnosed with drug-susceptible PTB in 2021, which was successfully treated with an outcome of cure. In July 2023, he was again diagnosed with PTB, on clinical and radiological grounds with two negative sputum GeneXpert results. After 4 months of anti-TB treatment, he clinically failed to respond.

His vital signs on day 0 were as follows: Blood pressure 121/92 mmHg (normal), pulse rate 119bpm (increased), respiratory rate 26 breaths per minute (increased), oxygen saturation 92 % on room air (low), temperature 37.5 °C (normal), body weight 60 kg, height of 175 cm and BMI of 19.6 kg/m^2 (normal).

General examination revealed a young man in a fair general

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https://doi.org/10.1016/j.mmcr.2024.100666
Received 31 July 2024; Received in revised form 11 August 2024; Accepted 23 August 2024
Available online 27 August 2024

condition. He had mild pallor and grade III digital clubbing, with no cyanosis, jaundice, or edema. On respiratory examination, there were reduced breath sounds in the right axillary and posterior lung zones, with a dull percussion note. Coarse breath sounds were noted in the left subclavicular region. The cardiovascular examination revealed a regular rhythm with normal heart sounds (S1 and S2) and no additional heart sounds. Abdominal examination showed a normally full abdomen with no tenderness or organomegaly. Neurologically, he was alert and oriented, with no focal deficits. His musculoskeletal examination was unremarkable. His skin was intact with no rashes or lesions.

Chest imaging revealed lung fibrosis and bronchiectasis in the right lung, along with an intracavitary fungal ball in the left upper zone, Fig. 1A–C. Serum *Aspergillus* IgG-IgM was positive (Fig. 1D) and serum *Aspergillus* galactomannan was negative. A diagnosis of CPA was made. CT phenotype was consistent with a simple aspergilloma.

Throughout the treatment period, the patient's full hemogram, renal function, electrolytes, and liver function were monitored. His hemoglobin levels increased from 9.2 g/dL on Day 0–11.4 g/dL on Day 37, while platelet and white cell counts remained within the normal range, fluctuating between 300 and 456 x 10^3/μL and 4.5 to 7.2 x 10^3/μL, respectively. Renal function tests showed minor fluctuations but remained within normal limits, with urea nitrogen levels ranging from 7 to 10.1 mg/dL, and creatinine levels between 0.46 and 0.78 mg/dL. Electrolytes remained normal, with serum sodium ranging from 135 to 148 mmol/L and serum potassium from 4.2 to 4.7 mmol/L. His liver function also remained normal.

2.1. Treatment

The patient could not afford 6 months course of oral itraconazole. He was therefore offered a treatment option of weekly amphotericin B, of which he and his family accepted after carefully providing them with the information regarding liposomal amphotericin B and its side effects.

On day 2 we commenced him on weekly "AmBisome®" at a dose of 600mg, with a preload of 20 mEq of potassium chloride in 500mls of 0.9 % normal saline infusion. He was given 1,200mg of potassium chloride tablets twice daily for three days, and a slow magnesium tablets of 1,070mg once daily for three days. In total, 1.5 L of 0.9 % normal saline were administered: 500mls with KCl and 500mls of plain 0.9 % normal saline as preload and 500mls as a post-load following the liposomal amphotericin B infusion. Additionally, he was given 1g of paracetamol. He received the same doses of the drugs on a weekly basis over a 6-week period on days 2, 9, 16, 23, 30, and 37.

2.2. Follow up

The patient underwent weekly follow-up laboratory analyses, including full hemograms, renal and liver function tests. Throughout the early days of treatment, he reported no significant changes in clinical symptoms. By day 9, he noted the absence of hemoptysis, but still experienced a productive cough, chest pain, and mild difficulty in breathing. By day 16, there was a marked reduction in cough frequency, although he still experienced some chest pain and difficulty in breathing. Day 23 showed no notable changes. However, by day 30, he reported no difficulty in breathing and only mild chest pain, though a mild cough persisted. On day 37, he reported no chest pain, only a lingering cough.

2.3. Health-related quality of life

Furthermore, we assessed the patient's health-related quality of life on day 2 and day 37 using the EuroQol Five Dimensions (EQ-5D-5L) and the St. George's Questionnaires (SGRQ). On day 2, his EQ-5D-5L health index was 21224, indicating slight problems with walking, no problems with self-care, slight problems with doing usual activities, slight pain or discomfort, and severe anxiety or depression, and with an EQ VAS score of 65 %. In addition, he had a high SGRQ total score of 61.64, indicating a moderate impairment in his quality of life due to respiratory symptoms and their impact on his daily activities and well-being. His overall self-rated QoL was 70 %. On day 37, his EQ-5D-5L score improved to 11112, indicating no problems with walking, self-care or doing usual activities, and no pain or discomfort. However, he still reported slight anxiety or depression. His EQ-5D-5L visual analogue scale and SGRQ total scores improved to 95 % and 85.00, respectively. His overall self-rated QoL improved to 90 %.

2.4. Patient's perspectives and experiences with AmBisome®

The patient expressed initial fear and uncertainty about his condition, followed by a sense of relief upon receiving a definitive diagnosis.

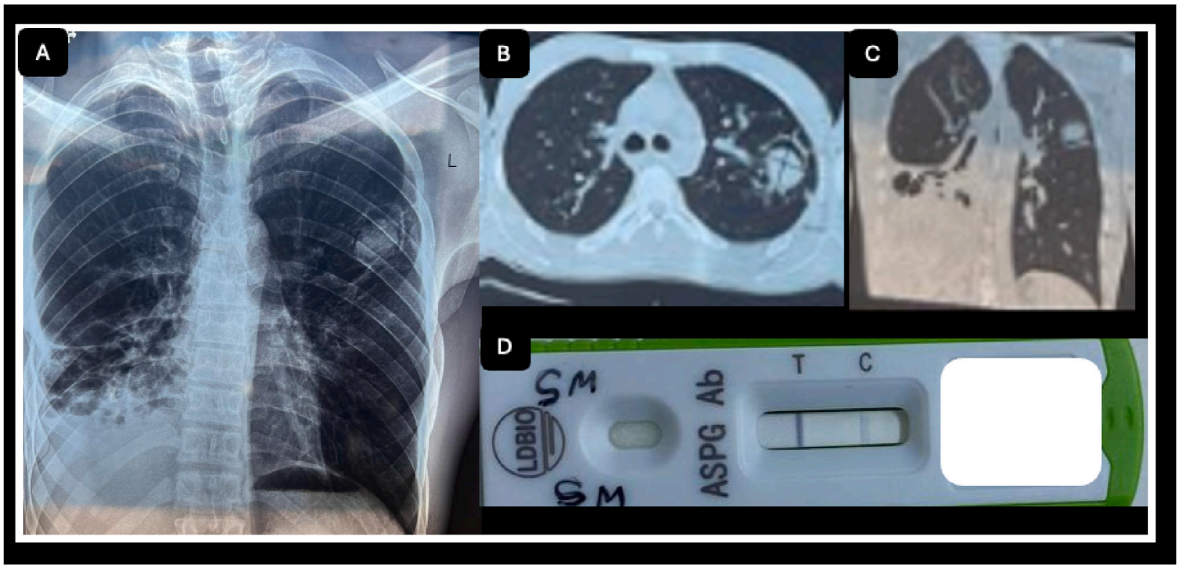

Fig. 1. Chest x-ray showing lung fibrosis and bronchiectasis in the right lung, along with an intracavitary fungal ball in the left upper zone (1A), a chest CT showing intra-cavitary fungal ball in the left upper lung zone, with fibrosis and bronchiectasis in the right lower lung zone (1B & C), and a positive LD Bio *Aspergillus* IgG-IgM lateral flow assay (1D).

"I thought I was going to die when I started coughing up so much blood despite taking my anti-TB drugs diligently, but when I was finally told what I was suffering from, I was relieved to know that the doctors had found what was causing my illness."

He reported a positive experience with AmBisome® as the weekly dosing did not require inpatient treatment and he did not experience any side effects, which collectively encouraged his adherence to the regimen.

"When the doctors told me about the possible side effects of the drug (amphotericin B), I was scared, but I felt that it was better for me to be treated than to die."

*"This medicine [..*AmBisome®*] didn't treat me badly at all. I was receiving it only once a week as an outpatient, and I would have bed rest for about 2 hours before going home. It did not give me any side effects."*

Reflecting on the outcome of his treatment, he reported significant improvement in his health and overall quality of life.

"After my treatment, I felt better. I can now play well with my mates, not like before where I could not play for too long before feeling breathless. In fact, I no longer cough up any blood."

3. Discussion

We report the first case of CPA related to PTB treated with weekly liposomal amphotericin B with significant clinical improvement.

CPA presents a spectrum of clinical manifestations, ranging from asymptomatic incidental findings to severe life threatening hemoptysis [6]. The diagnosis of CPA involves radiological findings of pulmonary cavities with a fungal ball, direct evidence of aspergillosis using microscopy or culture, and immunological detection of aspergillus antibodies [2]. An aspergilloma comprises of *Aspergillus* hyphae along with mucus and cellular debris [7]. CPA poses diagnostic and therapeutic challenges, especially among individuals in resource limited settings. While antifungal azoles, such as voriconazole and itraconazole, are recommended as first-line therapy, their accessibility may be limited due to cost constraints in such settings. Liposomal amphotericin B, though traditionally reserved for severe fungal infections, offers a viable alternative therapeutic option. Its efficacy in treating pulmonary CPA, as demonstrated in this case, suggests its potential utility in resource-limited settings where cost-effective alternatives are imperative. Liposomal amphotericin B has a longer terminal half-life of up to 7 days, enabling less frequent dosing schedules and improving patient compliance [8,9].

There is limited data on the primary use of intravenous amphotericin B among patients with CPA, however, some studies have demonstrated its effectiveness. In 1973, Hammaerman and colleagues reported significant radiological improvement in 23 CPA patients treated with intravenous amphotericin B [8]. Fujita and colleagues noted significant radiological and laboratory improvements in two out of three patients treated with a twice-weekly regimen of intravenous liposomal amphotericin B for one week, with minimal adverse effects including fatigue and brief periods of fever [10]. A multicenter trial in Japan found efficacy rates of 49.0 % and 52.9 % at two weeks and the end of therapy, respectively, with AmBisome® (2.5–5.0 mg/kg once daily for a week), compared to 59.3 % and 67.8 % with voriconazole, but similar adverse effect occurrences (54.2 % for AmBisome® and 59.0 % for voriconazole) [11]. Furthermore, a retrospective study in the UK demonstrated a significant response (76.6 %) and quality of life improvement (91.7 %) in CPA patients treated with intravenous AmBisome® for less than 6 weeks, while long-term treatment (3–4 times weekly for at least 2 months) resulted in a response in all patients [12]. However, 50 % of patients developed an increased risk of AKI, with 25 % experiencing AKI after their first treatment [12]. Similarly, a recent systematic review revealed an overall response rate of 58 % for intravenous AmBisome® at 3 mg/kg for 2–3 weeks, with only 25 % experiencing renal function loss [13].

Furthermore, several studies have reported successful weekly use of amphotericin B, in conjunction with surgical intervention or intracavitary administration rather than as a primary treatment or after the failure of azole therapy [1]. For instance, a recent publication reported a case of a 60-year-old male in India with pulmonary aspergilloma who was admitted to the intensive respiratory care unit and responded positively to intravenous liposomal amphotericin B coupled with intercostal drainage [14]. Additionally, in a case involving a 3-year-old with CPA where systemic azole treatment was unsuccessful due to intolerances, liposomal amphotericin B was administered following lung lobectomy, resulting in a favorable outcome within approximately three weeks [15].

These findings collectively highlight the importance and efficacy of liposomal amphotericin B in managing CPA in diverse patient populations, particularly when conventional azole therapy is either contraindicated or inaccessible. However, we acknowledge the scarcity of data regarding the exploration of the weekly use of intravenous amphotericin B in the primary management of pulmonary aspergillomas, necessitating further research into this knowledge gap, especially in resource limiting settings.

This case also highlights the significant impact CPA on the health-related quality of life of affected individuals, significantly impairing their physical functioning and activities of daily living. Consequently, the use of liposomal amphotericin B showed significant improvement of quality of life. Therefore, this case further emphasizes the need for the adoption of a holistic approach to the management of patients with pulmonary aspergillomas, recognizing the multidimensional impact of the disease and prioritizing interventions that promote both physical and psychological well-being.

4. Conclusion

We report the first case of CPA related to PTB treated with weekly liposomal amphotericin B with significant clinical improvement. This case emphasizes the successful weekly use of liposomal amphotericin B in managing CPA in a tuberculosis patient leading to clinical improvement and improvement in the overall health related quality of life. Thus, more tailored therapeutic approaches are necessary in the treatment of fungal diseases in similar resource limited settings.

Ethical form

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

CRediT authorship contribution statement

Winnie Kibone: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Conceptualization. **Felix Bongomin:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Conceptualization. **David W. Denning:** Writing – review & editing, Writing – original draft, Visualization. **David B. Meya:** Writing – review & editing, Writing – original draft, Visualization, Conceptualization.

Declaration of competing interest

All authors declare that they have no conflict of interest.

Acknowledgements

The authors acknowledge the administration of Mulago National

Referral Hospital as well as the doctors and clinical care nurses.

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