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Endobronchial amphotericin B to treat hemoptysis in an inoperable patient with aspergillosis

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ABSTRACT

A 37-year-old man presented with chronic cavitary pulmonary aspergillosis and hemoptysis refractory to systemic antifungal therapy with voriconazole and bronchial artery embolization. Surgical excision was unfeasible due to the patient's refusal of blood transfusions. Ten sessions of intracavitary instillation of amphotericin B via flexible bronchoscopy were then performed. Hemoptysis cessation and aspergilloma resolution were achieved, with no toxicity or side effects, and the clinical benefits were sustained at six months of follow-up.

1. Introduction

Chronic cavitary pulmonary aspergillosis (CCPA) presents in immunocompetent individuals with underlying lung abnormalities (usually cavities from previous tuberculosis) [1,2]. It usually develops over the course of several months, and common symptoms include weight loss, fever, productive cough, and hemoptysis. Chest computer tomography (CT) shows large, thick-walled cavities, often containing aspergillomas. Diagnosis can be confirmed by positive serum IgG or precipitins for *Aspergillus*, positive galactomannan antigen in serum or bronchoalveolar lavage (BAL), fungal growth in sample culture, or hyphae visible on microscopy, without parenchymal invasion [1]. CCPA requires systemic therapy, and itraconazole or voriconazole are the preferred first line agents, with posaconazole reserved for cases of failure, toxicity or resistance [3–5]. Both CCPA and simple aspergilloma can cause hemoptysis, and surgical resection is usually the first line of treatment [6]. When surgery is unfeasible or is refused by the patient, alternatives to manage hemoptysis include bronchial artery embolization (BAE) and antifungal instillation into the cavity [7]. We report our experience with direct intracavitary bronchoscopic instillation of amphotericin B to treat an inoperable patient with CCPA and hemoptysis refractory to BAE.

2. Case

A 37-year-old man, born in Angola, presented to a tertiary care hospital in Lisbon with productive cough, hemoptysis, and 12 kg loss in body weight in the previous six months. He travelled to Portugal to pursue medical care in accordance with the International Cooperation Agreement between the two countries. He was a non-smoker, and previous medical history was relevant for pulmonary tuberculosis at 23 years of age (treated with a first line regimen), and several hospitalizations due to hemoptysis since then. As a Jehovah's Witness, he refused blood transfusions. On physical examination, he was hemodynamically stable, afebrile, had a normal pulse oximetry, and normal pulmonary and cardiac auscultation. A chest CT performed on admission (day 0) revealed a 6 cm wide, thick-walled cavity in the apical segment of the right upper lobe, containing a dense, round structure compatible with an aspergilloma (Fig. 1), as well as bronchiectasis in the right lower lobe.

Tuberculosis was suspected, but acid-fast bacillus (AFB) stain and nucleic acid amplification tests (NAAT) of sputum (days +1, +2 and + 5) were negative. Flexible bronchoscopy was performed on day +8, and culture of BAL fluid was positive for *Pseudomonas aeruginosa*, but AFB stain and NAAT were also negative. However, BAL and serum galactomannan antigen titers were positive, supporting a diagnosis of CCPA. Voriconazole was started on day +8, with a loading dose of 6 mg/kg or 400 mg twice daily (q12h) on the first day and then a maintenance dose of 4 mg/kg or 300 mg q12h. Piperacillin-tazobactam to treat *P. aeruginosa* infection was also started and maintained for 21 days. BAE was performed on day +26 due to persistent hemoptysis, but proved ineffective. On day +42, the Thoracic Surgery team was consulted and proposed a right upper lobectomy to control the bleeding, but surgery

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was unfeasible due to the patient's refusal of blood transfusions. The Interventional Pulmonology team was consulted and another flexible bronchoscopy was proposed to ascertain whether the cavity was accessible. If so, antifungals would be administered directly inside; otherwise, a percutaneous catheter would be inserted, under CT guidance, to instill the medication. On day +60, after obtaining the patient's informed consent and Pharmaceutical Committee approval, the inhabited cavity was accessed with a standard 5 mm flexible videobronchoscope through an orifice adjacent to the right B1 bronchus (Fig. 2), and 50 mg of liposomal amphotericin B, diluted in 20 mL of glucose 5 % solution, was instilled through the working channel. Afterwards, the patient was placed on right lateral decubitus for 1 h, to keep the solution inside the cavity. Ten procedures were scheduled over five weeks, with intermediate CT reevaluation after five sessions. In most sessions, a balloon catheter was used to seal the cavity entrance during instillation. However, even without the balloon, amphotericin loss due to cough was minimal. The bronchoscopies were performed under conscious sedation with midazolam and fentanyl, and were well tolerated.

Samples were taken and sent for microbiological studies in every session. Due to persistent *P. aeruginosa* growth in BAL fluid culture (resistant to piperacillin-tazobactam), the patient was started on ciprofloxacin and inhaled colistin on day +61. Culture of aspergilloma fragments was positive for *Aspergillus fumigatus*, and fungal hyphae were visible on microscopy (Fig. 3). As treatment progressed, the fungal ball's dimensions decreased. The intermediate chest CT on day +76 showed the aspergilloma had become smaller and significantly less dense. During the last bronchoscopy (day +98), it disintegrated and the fragments were removed with forceps. Only a small stem remained adherent to the cavity wall, which was not removed to avoid bleeding. No systemic toxicity or local side effects resulted from amphotericin instillation.

Hemoptysis gradually ceased, allowing hospital discharge on day +100. One month after discharge, the patient reported small amounts of hemoptoic sputum that resolved spontaneously. He was kept on voriconazole and inhaled colistin, with monthly follow-up visits to monitor toxicity. Six months after discharge, his overall status improved, with an almost 10 kg recovery in body weight, and no relapse of hemoptysis occurred. A chest CT performed at this time (Fig. 4) showed no signs of aspergilloma resurgence.

3. Discussion

Management of CCPA is complex and often requires a multidisciplinary team of specialties such as Infectious Diseases, Pulmonology and Thoracic Surgery. If untreated, CCPA can cause fibrosis and destruction of the affected lung. Hemoptysis is a potentially life-threatening complication that requires prompt intervention. Our patient presented with hemoptysis refractory to BAE, and surgery would be the optimal treatment. Unfortunately, his refusal of blood transfusions made surgery unfeasible, which presented a challenge to our Interventional Pulmonology team.

The main forms of intracavitary antifungal delivery described in literature are percutaneous and endobronchial administration. Regarding the former, a retrospective study of 40 patients who underwent CT-guided transthoracic injection of amphotericin B paste (50 mg mixed with contrast and emulsifying wax) showed good short-term control of moderate hemoptysis [8]. A more recent article described 20 cases of amphotericin B instillation (50 mg in 20 mL of glucose 5 %), through a percutaneous catheter inserted in the cavity. This study showed good rates of short-term hemoptysis control and aspergilloma clearance, but pneumothorax occurred in 26 % of patients, and a third experienced hemoptysis recurrence on follow-up [9].

As for the endobronchial approach, it was first reported in 1964 [10]. More recently, a retrospective study of 82 patients treated with endobronchial voriconazole (400 mg in 20 mL of normal saline) showed two thirds had hemoptysis cessation after two sessions, but a third experienced recurrence, and aspergilloma reduction only occurred in half the cases [11]. A randomized trial comparing bronchoscopic instillation of voriconazole with medical therapy alone in 60 patients with inoperable aspergilloma found a greater reduction in hemoptysis severity, cough and aspergilloma size in the intervention group [12]. A recent retrospective study included 42 patients with pulmonary aspergillosis treated with endobronchial amphotericin B (10 mg in 10 mL of water), and found 31 cases (74 %) of improvement on imaging studies, with no systemic toxicity or significant adverse effects [13].

In our patient, the endobronchial approach was deemed more advantageous, since percutaneous catheter placement carried a risk of hemorrhage, and the patient did not consent to transfusions. We decided to use amphotericin B instead of voriconazole because hemoptysis persisted after two months of systemic treatment with this agent, and also due to our team's experience with amphotericin B in lung transplant recipients. We treated our patient before Yang and colleagues published their work [13], and decided to use the same formulation and dose demonstrated to be safe and effective for percutaneous catheter instillation by Kravitz et al. [9] Furthermore, we noted an adequate absorption of the instilled volume (20 mL) by the fungus ball, minimizing extravasation and cough.

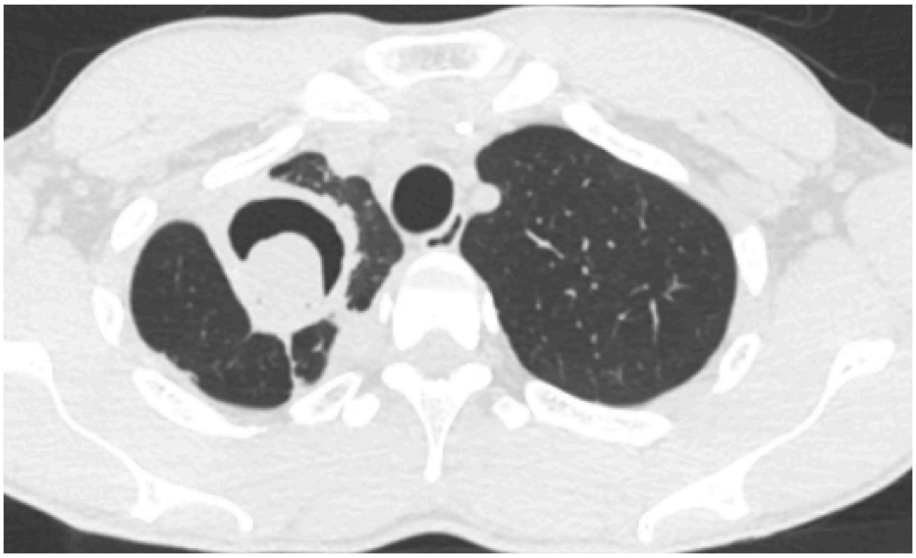

Fig. 1. Chest CT on admission, showing right upper lobe cavity with aspergilloma.

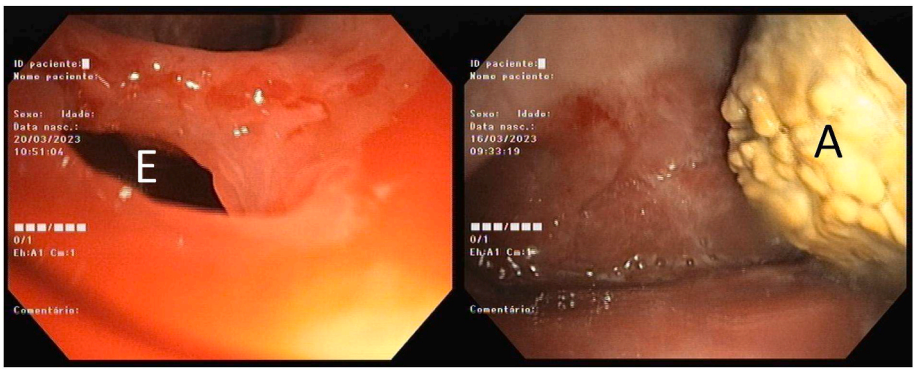

Fig. 2. Left: Cavity entrance (E) adjacent to the right B1 bronchus. Right: Aspergilloma (A) before treatment, within cavity.

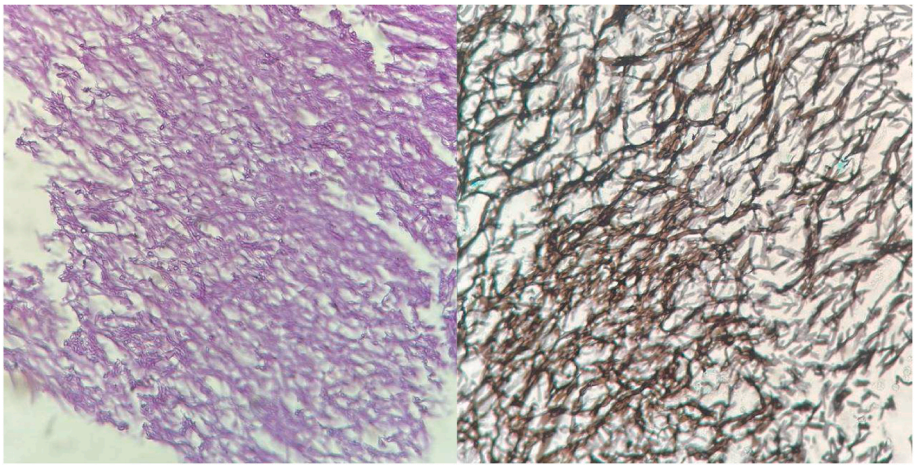

Fig. 3. Fungal hyphae. Left: Periodic Acid Schiff stain at 400x. Right: Grocott stain at 400x.

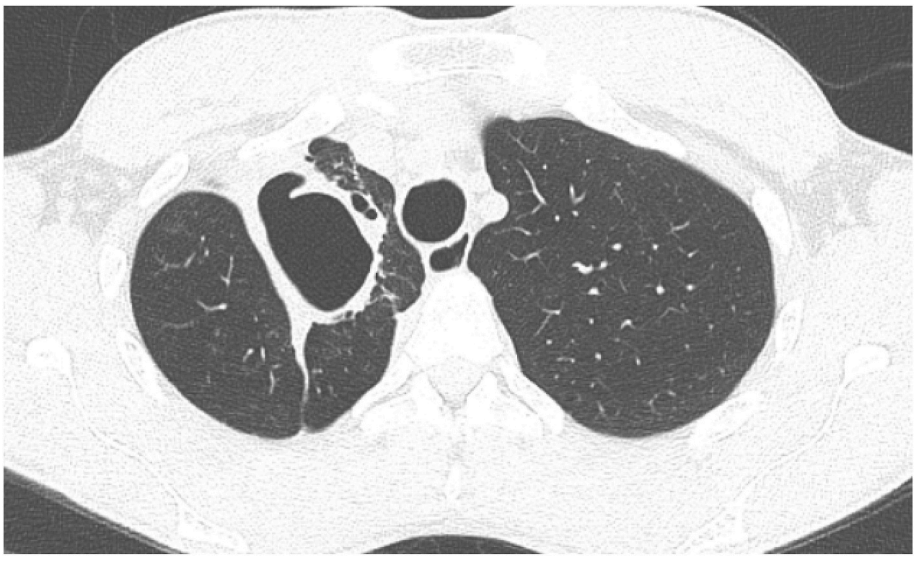

Fig. 4. Chest CT at six months after discharge, showing empty cavity.

The long term results of our intervention remain to be seen, but results at six months were promising, with significant clinical improvement, complete cessation of hemoptysis, and no aspergilloma recurrence. It is important to note that this procedure should be considered an adjuvant to systemic antifungal therapy, which is essential to treat CCPA and often maintained for several months. In vitro antifungal susceptibility testing of *Aspergillus* isolates is not available in our hospital, but may be useful to exclude resistance when patients fail to respond to systemic therapy. Lastly, our patient's bronchiectasis and chronic co-infection by *P. aeruginosa* may have contributed to hemoptysis as well.

Ethics statement

No sources of funding or conflicts of interest to declare.

Written and signed consent to publish the case report has been obtained from the patient.

The statements on funding, conflict of interest and consent were also submitted via the Ethical Form.

CRediT authorship contribution statement

Mário Pinto: Conceptualization, Investigation, Writing – original draft, Visualization. **João Rodrigues:** Conceptualization, Investigation. **Marta Silva:** Conceptualization, Investigation. **Dionísio Maia:** Investigation, Resources, Writing – review & editing, Supervision. **António Miguel:** Supervision, Project administration.

Declaration of competing interest

There are none.

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