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Case report

Successful treatment of *Aureobasidium pullulans* central catheter-related fungemia and septic pulmonary emboli

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ABSTRACT

Introduction: *Aureobasidium pullulans* is a saprophytic fungus that is widely distributed in the environment, and in the right host can be an opportunistic human pathogen.
Presentation of Case: A 66-year-old man with Crohn's disease with a single kidney, and requiring total parenteral nutrition via a Hickman catheter, was admitted with a 10-week history of progressive shortness of breath, fevers and weight loss. Chest imaging demonstrated new multifocal lung parenchymal opacities compatible with septic pulmonary emboli. Blood culture grew a yeast-like organism that transformed into a black mold on subculture, eventually identified as *A. pullulans*. Due to triazole resistance, the patient was treated with liposomal amphotericin and micafungin. Serum (1,3)-β-d-glucan level was used to monitor therapy, initially measured at > 500 pg/mL and decreasing to 66 pg/mL after one year of therapy.
Discussion: We describe the successful treatment of a case of catheter related fungemia and septic pulmonary emboli due *A. pullulans*. While initially appearing as an oval yeast on blood culture, subsequent growth as a black mold led to identification of the fungus as *A. pullulans*. The infection was cured with a combination of antifungal agents, even though the foreign body could not be safely removed. Nephrotoxicity required dosing adjustment of the amphotericin to biweekly during the maintenance phase of treatment. The serum (1,3)-β-d-glucan level proved to be useful in monitoring response to therapy.
Conclusion: We report here successful treatment of a disseminated *A. pullulans* infection with an induction and maintenance approach to liposomal amphotericin dosing, and monitoring response to therapy with serum (1,3)-β-d-glucan levels.

Introduction

Aureobasidium pullulans is a saprophytic fungus that is widely distributed in the environment and used in a wide range of industrial applications [1]. Like many saprophytic fungi, in the right host *A. pullulans* can be an opportunistic human pathogen [2], and has been reported to cause hypersensitivity pneumonitis [3], subcutaneous infection [4], peritonitis [5], and rarely disseminated infection [6]. Most human disease has been caused by *A. pullulans* var. *melanigenum* rather than *A. pullulans* var. *pullulans* [7]. Because of the rarity of this infection, the optimal therapy is unknown. Here we report a case of *A. pullulans* fungemia in an individual with a chronic indwelling central venous catheter who was successfully treated with a prolonged course of liposomal amphotericin B and micafungin. We also report the successful use of serum β-D-glucan to monitor the progress of treatment.

Case report

A 66-year-old man with Crohn's disease who was not on systemic therapy was admitted with a 10-week history of progressive shortness of breath, decreased exercise tolerance, night sweats, fevers to 102°F, and unintentional weight loss. About one month prior to the onset of his illness he was spelunking in an Arizona cave. The week prior to admission he was treated for five days with azithromycin without resolution of his symptoms. During this admission he received i.v. azithromycin and ceftriaxone for one day with some improvement and was

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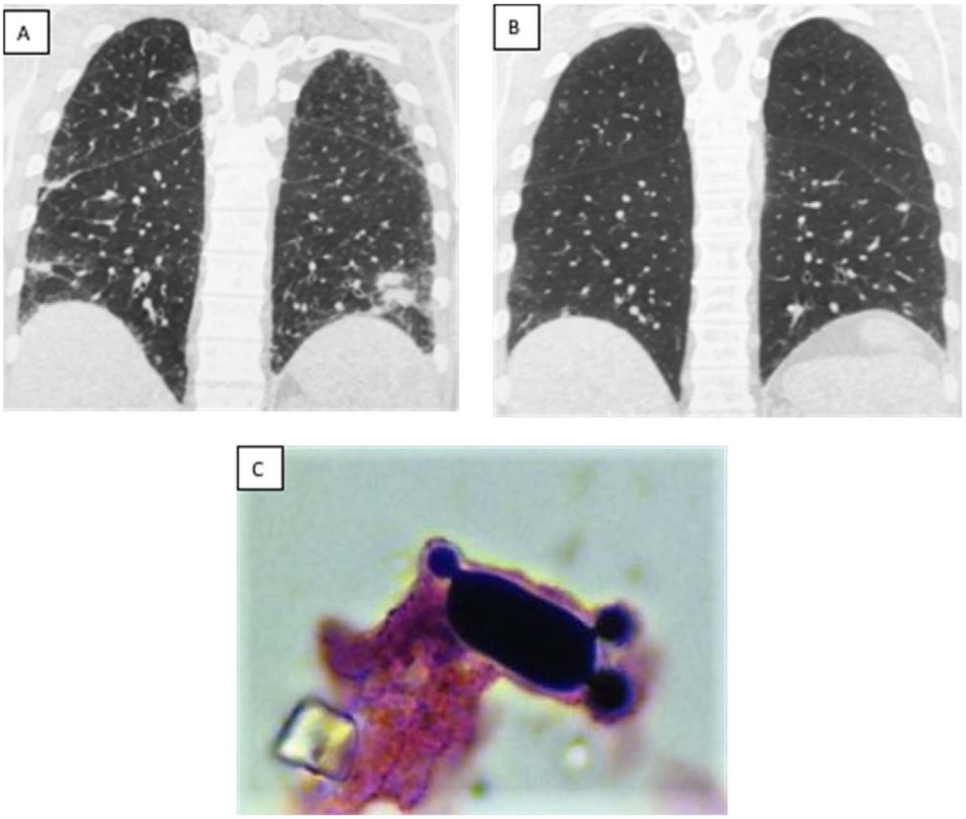

Fig. 1. A. CT thorax, coronal rendering. Scan done on admission shows multifocal sub-pleural and peripheral nodular opacities consistent with septic pulmonary emboli. B. Scan done after completion of therapy shows near complete clearing of multifocal pulmonary nodules. C. Gram stain of blood culture showing oval, multiple budding yeast.

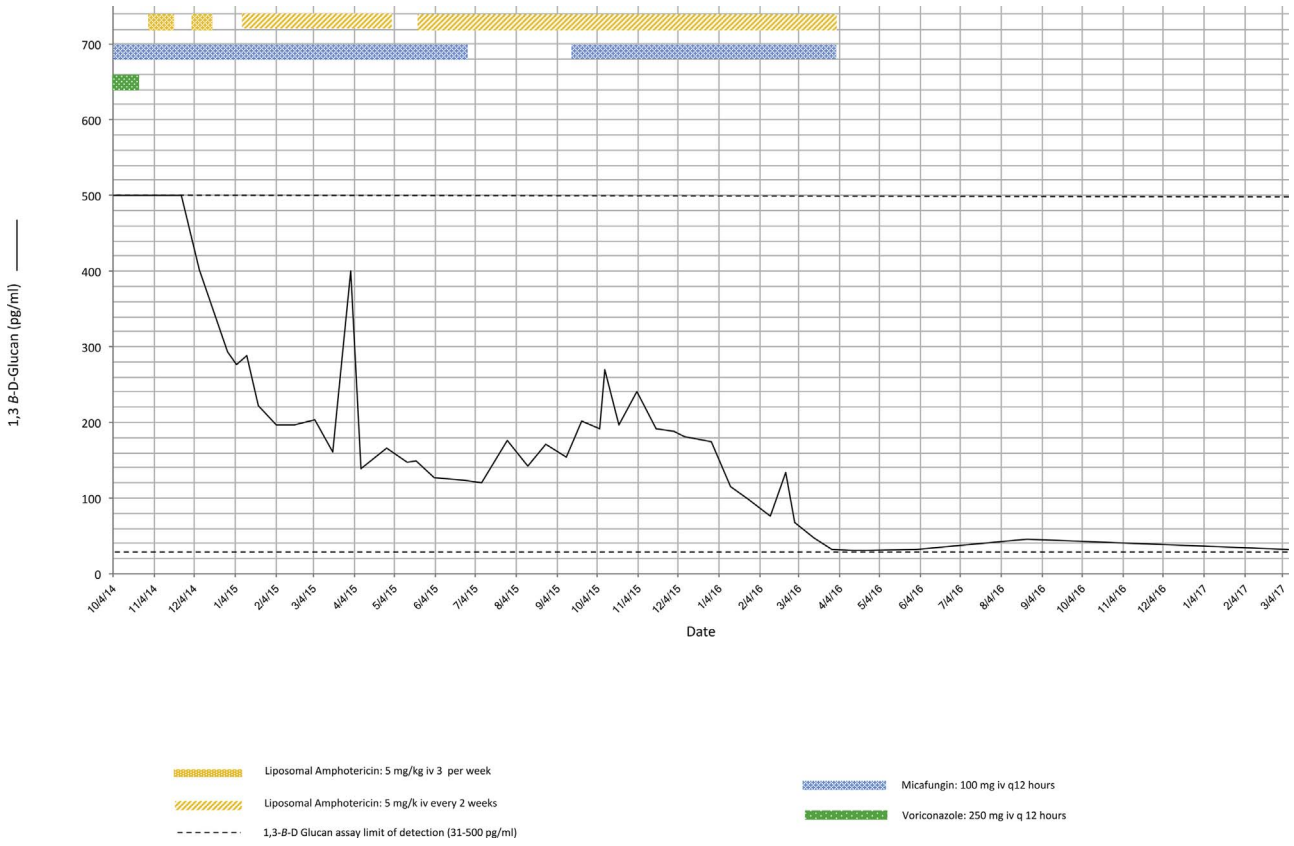

Fig. 2. Serum (1,3)-β-D-glucan levels over the treatment course.

discharged the next day to continue that treatment at home via his Hickman catheter. After discharge, 4/4 blood culture bottles grew a coagulase-negative Staphylococcus (CNS) and he was told to return to the hospital. A chest radiograph and CT scan showed new multifocal lung parenchymal opacities compatible with septic pulmonary emboli (Fig. 1A). He was placed on antibacterials and his Hickman catheter was replaced over a guidewire. That catheter had been in place for 4 years, but the patient had been using central lines for infusion of total parenteral nutrition for 22 years for malabsorption due to previous surgical resections of his distal small bowel and proximal colon. Over that period, despite meticulous care, he had 9 episodes of catheter related bacteremia, always with CNS, all managed with vancomycin and catheter changes. Due to his malabsorption, he had also formed an obstructing oxalate stone and developed pyelonephritis necessitating a nephrectomy. His admission serum creatinine (Cr) was 0.91 and his estimated glomerular filtration rate (EGFR) was 64 mL/min/1.73 m^2.

Repeat blood cultures revealed yeast in the two aerobic bottles after 5 days of incubation. The gram stain of the blood culture revealed oval yeast (Fig. 1C) not identified with the bioMerieux® Vitek YST card (Marcy-l'Etoile, France). With further incubation, the yeast-like colonies began to transform into a mold that eventually turned black. It was identified as *A. pullulans* both by Matrix Assisted Laser Desorption/Ionization-Time Of Flight (MALDI-TOF, Bruker) (Billerica, MA) and by DNA sequencing done at ARUP Laboratories. Sensitivity testing done at ARUP Laboratories showed the isolate was resistant to triazoles (MIC > 16). The MIC for amphotericin B was 1 μg/mL and the MEC for caspofungin and micafungin were 1 μg/mL and 2 μg/mL respectively. The serum (1,3)-β-D-glucan level was > 500 pg/mL. Prior to receiving sensitivity results he was treated with intravenous micafungin and voriconazole. Based on the sensitivity results, treatment was changed to liposomal amphotericin B 5 mg/kg (325 mg) and micafungin 100 mg/day, both administered through his Hickman catheter. Amphotericin was started as three doses/week for 2 weeks then decreased to twice/week after the β-D-glucan level fell to < 500 and his serum Cr doubled. After discharge, with pharmacy assistance, we decided to give infusions once every two weeks in the infusion center. Micafungin was given daily from the end of September 2014 thru the end of June 2015, and resumed in mid-September 2015 because of rising serum β-D-glucan levels. Fig. 2 shows the serum β-D-glucan values over time. He received a total of 14.125 gm of liposomal amphotericin B and 47.3 gm of micafungin. At the end of treatment his serum Cr and EGFR were 1.56 mg/dL and 44 L mL/min/1.73 m^2 respectively. One year after treatment ended they were 1.23 and 66 L. Fig. 1B shows near total resolution of pulmonary infiltrates in April 2016, about 1 month after treatment was ended.

Discussion

We describe the successful treatment of a case of catheter related fungemia and septic pulmonary emboli due *A. pullulans*. Because our patient's catheter was co-infected with a CNS that was faster-growing than the fungus, the fungemia did not become apparent until antibiotics suppressed the growth of the bacteria in the blood cultures. The finding of very high levels of serum β-D-glucan confirmed the diagnosis of a systemic fungal infection and provided an object way to measure his fungal burden. We used normalization of (1,3)-β-D-glucan (< 60 pg/mL) [8] to decide when to stop therapy, and his blood cultures remain negative one year later.

We were initially misled by the appearance of the oval yeast in the blood culture, thinking it was a *Candida* sp., but it was identified as *A. pullulans* by MALDI-TOF and subsequently grew as a black mold at room temperature. While classified as a dematiaceous fungus, *A. pullulans* has significant morphologic variability, affected by carbon source, colony age, temperature, light, and substrate, which can make microbiologic diagnosis very difficult [2,9–11]. *A. pullulans* grows well on potato dextrose agar at 10–35 °C, with optimal growth at 30 °C. Colonies initially appear yeast-like with a cream or light pink color, then evolve to black with time. Morphologically, the fungus grows as a hyphomycete with septate hyaline hyphae that darken with age, forming chains of thick walled arthroconidia. In addition, primary conidia develop on short denticles from the hyphae that are smooth-walled, single-celled, ellipsoidal, with the overall appearance of yeast. Secondary conidia are much smaller, and give the appearance of a budding yeast. Thus, our observation of an irregular yeast-like organism in the blood may have been a form of adventitious sporulation [12].

It took over 1 year to cure this infection, possibly because it was on a foreign body that could not be removed safely. We do not know whether both antifungal agents we used were necessary, but when we stopped micafungin there was a rise in the β-glucan titer so we resumed that drug and the concentration declined, implying it was active in vivo. Given triazole resistance, we relied on amphotericin B as the second drug, even though he had only 1 kidney, utilizing a biweekly regimen to balance efficacy with nephrotoxicity. As the majority of the administered amphotericin B remains bound to tissues, it has a two week terminal half-life [13]. Furthermore, for some chronic fungal infections the total but not the daily dose of amphotericin B correlates best with cure [14]. So after induction, we chose a regimen of 3 mg/kg on alternate weeks, which we believed provided continuing effective therapy while largely preserving his renal function.

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