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Pseudallescheria boydii with *Aspergillus fumigatus* and *Aspergillus terreus* in a Critically Ill Hematopoietic Stem Cell Recipient with ARDS

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Abstract *Pseudallescheria boydii* is a fungal organism known to affect immunocompromised patients. This organism is known to cause, in severe cases, invasive infection of various organs such as the central nervous, cardiovascular, and respiratory systems. We report an unusual case of pulmonary *P. boydii* pneumonia in an immunocompromised critically ill patient with a co-infection of *Aspergillus fumigatus* and *Aspergillus terreus* with ARDS. This case highlights the importance of a high index of suspicion for superimposed fungal infections in patients who are critically ill and immunocompromised. Uncommon fungal pathogens should be considered in the differential diagnosis of respiratory failure, especially if diagnostic markers such as galactomannan (from BAL and serum) or 1,3-beta-D-glucan are elevated. Further diagnostic interventions are warranted when insufficient clinical improvement is observed to prevent treatment failure and adverse outcomes.

Keywords *Pseudallescheria boydii* · Critically ill · *Aspergillus terreus* · *Aspergillus fumigatus*

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Introduction

Pseudallescheria boydii is a fungal organism known to affect immunocompromised patients. This organism, a soil and water natural inhabitant, is known to cause madura foot and, in severe cases, invasive infection of various organs such as the central nervous, cardiovascular, and respiratory systems. We report an unusual case of pulmonary *P. boydii* pneumonia in an immunocompromised critically ill patient with a co-infection of *Aspergillus fumigatus* and *Aspergillus terreus* with ARDS. This case highlights the importance of including uncommon fungal pathogens in the differential diagnosis in critically ill hematopoietic stem cell recipients with respiratory failure.

Case

A 69-year-old male patient was admitted to our intensive care unit because of an acute respiratory failure. A few days before the patient received a high-dosage chemotherapy with melphalan followed by an autologous hematopoietic stem cell transplantation because of a history of multiple myeloma.

On admission, the patient was afebrile but neutropenic with an elevated respiratory rate of 24/min under 10 l of oxygen. Oxygen saturation was 94 %, blood pressure was hypotensive with 90/50 mmHg, and heart rate was elevated up to 130 bpm. An

initiated computed tomogram (CT) of the chest revealed only in the right lobe pulmonary infiltrates.

Laboratory findings demonstrated an elevated procalcitonin level of 124 ng/ml (<0.1 ng/ml), a C-reactive protein of 40.9 mg/dl (<0.5 mg/dl), and a leukocyte count of <0.1 G/l (4–9 G/l). Furthermore, the patient presented an acute kidney injury with anuria.

Within a few hours, the patient developed septic shock and intubation and high-dosage norepinephrine therapy was necessary. Beside bronchoscopy with bronchoalveolar lavage (BAL) for standard microbiological testing, galactomannan from BAL as well from serum and additional 1,3-beta-D-glucan testing, was performed (see Table 1). The initiated antibiotic regime from the normal ward of meropenem, linezolid, and clarithromycin and the antimycotic therapy with liposomal amphotericin B were continued.

Within another 24 h later, the patient developed severe acute respiratory distress syndrome (ARDS) which makes an ECMO (extracorporeal membrane oxygenation) necessary.

Referred to the findings in Table 1, the initiated antibiotic regime was expanded to oseltamivir and ribavirin for influenza B and respiratory syncytial virus, respectively. After the new findings of *Aspergillus terreus* and *P. boydii*, the antimycotic therapy was switched to voriconazole. However, after 19 days the patient died due to ARDS. An autopsy was denied from the patient by testament.

Discussion

Pseudallescheria boydii and its asexual anamorph, *Scedosporium*, are ubiquitous filamentous fungi found in soil, water, and sewage [1]. It is a frequent pathogen in near-drowning victims, especially in areas where *P. boydii* is endemic [1, 2]. This organism has septated, thin-walled, branching hyphae and an angioinvasive tendency. Clinically, *P. boydii* infection has an insidious onset and is often fatal in immunocompromised hosts as reported in our case [2, 3]. The spectrum of pulmonary diseases caused by *P. boydii* is remarkably similar to that due to Aspergillus infection, including allergic bronchopulmonary pseudallescheriasis, pseudallescherioma, pneumonia, and invasive infection [3].

Central nervous system abscesses, rhinosinusitis, endophthalmitis, pneumonia, and skin lesions (madura foot) may be present [3]. *Aspergillus* tracheobronchitis has been reported most commonly in patients with hematologic malignancies as seen in our patient, recipients of solid organ transplants, and patients with HIV infection [4].

The diagnosis of both *P. boydii* and *Aspergillus* spp. is challenging as clinical findings and tomographic imaging are nonspecific as we have seen in our case.

It is important that *P. boydii* be differentiated from *Aspergillus* spp. because most invasive infections are caused by members of the *A. fumigatus* species complex. In a report of 218 infections in 24 transplant

Table 1 Mycological and other findings with time course

	Mycological findings	Other findings
Initial BAL	*Candida albicans*	Legionella species
	Galactomannan 7.28	Influenza B
	(index <0.5)	Respiratory syncytial virus
Initial diagnostic from serum	Galactomannan 3.09	
	(index <0.5)	
	1,3-beta-D-glucan 947 pg/ml	
	(cutoff <60 pg/ml)	
BAL after 7 days	*Pseudallescheria boydii*	Respiratory syncytial virus
	Aspergillus terreus	
	Galactomannan 6.48	
	(index <0.5)	
BAL after 14 days	*Pseudallescheria boydii*	
	Aspergillus fumigatus	
	Aspergillus terreus	
	Candida albicans	

centers in the USA, 67 % were caused by members of the *A. fumigatus* complex, followed by *A. flavus* (13 %), *A. niger* (9 %), and *A. terreus* (7 %) [4–6].

Chest CT abnormalities may display pulmonary cavitations or noncavitary masses, tree-in-bud nodules, ground-glass opacities, bronchial thickening, and mediastinal lymphadenopathy [7].

Culture of the organism, in combination with evidence of tissue invasion on histopathology, or culture from a normally sterile site provides the most certain evidence. During histopathological diagnosis *P. boydii* may be confused with *Aspergillus*, because both form color-less, septated hyphae with dichotomous branching (hyalohyphomycoses) [9]. Histopathological findings of septate, branching, hyaline hyphae are similar to those of aspergillosis on direct microscopy [4, 8, 9].

Furthermore, performing a biopsy is not feasible in some patients due to bleeding risk or risk of other complications, which was the situation in our patient because of an outraged thrombocytopenia. In patients with risk factors and clinical and/or radiographic features that are suggestive of invasive aspergillosis, culture of *Aspergillus* spp. from respiratory secretions provides adequate evidence of invasive disease. *Aspergillus* is a rapidly growing fungus in the laboratory and is often visible in culture within a few days of incubation [4]. However, identification of the species requires sporulation in order to microscopically examine spore-bearing structures. The positive predictive value was highest in BAL cultures and is dependent upon both the host and the clinical presentation [10]. In a study that evaluated the predictive value of lower respiratory tract cultures in different patient populations with probable or proven invasive pulmonary aspergillosis, the positive predictive value was highest in hematopoietic cell transplant recipients, patients with hematological malignancies, and granulocytopenic patients [11, 12].

In contrast, a range of diagnostic molecular methods such as pan-fungal or multiplex PCR have been employed to diagnose *P. boydii*, but are not yet validated and should be used only as an adjunct to conventional laboratory tests. Particularly within the *P. boydii* complex, identification is complicated by low interspecies diversity and high intraspecies variability.

However, galactomannan, a polysaccharide that is a major constituent of *Aspergillus* spp. cell walls, is highly specific, reacting with antigens from *Aspergillus* spp. but not with antigens from a large number of clinically important fungi, including *Candida species, Cryptococcus neoformans*, *Fusarium solani*, *Penicillium marneffei*, and *P. boydii* as reported in our case. Even more recent assays that use a double-sandwich enzyme immunoassay (EIA) have higher sensitivity and are available for use on serum samples as an adjunctive test for the diagnosis of aspergillosis [12, 13]. The galactomannan EIA is performed with an optical readout that is interpreted as a ratio relative to the optical density (OD) of a threshold control provided by the manufacturer, which is called the OD index [13]. The assay has a suggested threshold OD index of 0.5; thus, an OD index $\geq$0.5 is considered to be a positive result. As reported in our patient, the index was 3.09. When combining proven and probable cases, the sensitivity and specificity were 61 % (95 % CI 59–63 %) and 93 % (95 % CI 92–94 %), respectively [11–13]. Subgroup analyses suggested that the assay performs better in patients who have a hematologic malignancy or who have received hematopoietic cell transplant as reported in this case.

The galactomannan EIA detects fungal antigens even when the organism does not grow in the laboratory, providing an indication of potentially invasive disease. The galactomannan EIA performed on BAL fluid provides additional sensitivity compared with culture, estimated in most studies to exceed 70 %, and the specificity was 91 %, whereas an OD index threshold $\geq$0.5 resulted in a sensitivity of 93 % and a specificity of 87 %. As seen in our patient, the OD index was highly elevated to 7.28. As noted above, an OD index of $\geq$0.5 was positive for galactomannan EIA in both serum and BAL fluid [11–13].

The 1,3-beta-D-glucan, another cell wall component of many fungi, is detected by the beta-D-glucan assay [14]. The output of the serum assay currently is based on spectrophotometer readings, in which optical density is converted to beta-D-glucan concentrations; the results are interpreted as negative (range <60 pg/ml), indeterminate (60–79 pg/ml), or positive (>80 pg/ml) [14, 15]. Our patient has a beta-D-glucan level of 947 pg/ml. Importantly, these cutoffs were defined in the clinical context of identifying breakthrough invasive fungal infections (primarily, invasive candidiasis) in people who were undergoing treatment for hematologic malignancies, which was reported above with an massive elevated beta-D-glucan level. Precise cutoffs to optimize the performance of the

assay as an aid to diagnose invasive aspergillosis have not been defined and may be different [15]. A meta-analysis that included six cohort studies of patients with hematologic malignancies noted a lower sensitivity (50 %, 95 % CI 34–65 %) and a higher specificity (99 %, 95 % CI 97–100 %) on probable invasive aspergillosis than previously reported [16]. Despite the substantial heterogeneity among different studies, the beta-D-glucan assay has good accuracy for distinguishing patients with proven or probable invasive fungal infections from patients without invasive fungal infection [16, 17]. The beta-D-glucan assay may be used for detecting invasive fungal infections early in the course of infection, prior to the onset of overt clinical findings. Although the best results using the 1,3-beta-D-glucan assay are in diagnosing invasive candidiasis and aspergillosis, there are also small reports in detecting uncommon fungal diseases such as *Scedosporium* spp. [18].

Another important point in isolating the fungus is the variable susceptibility of these fungi to amphotericin B and other antifungal agents.

The fungi *P. boydii* and *A. terreus* show resistance to amphotericin B but are sensitive to the azole drugs [19, 20]. The antifungal treatment varies according to immunologic status. Voriconazole is the mainstay of treatment in immunocompromised hosts. *P. boydii* is generally sensitive to azoles [20–22]. Various reports indicate an intrinsic *P. boydii* resistance to polyenes. Moreover, the optimum duration of treatment is unknown.

Conclusion

This case highlights the importance of a high index of suspicion for superimposed fungal infections in patients who are critically ill and immunocompromised. Uncommon fungal pathogens should be considered in the differential diagnosis of respiratory failure, especially if diagnostic markers are elevated. Further diagnostic interventions are warranted when insufficient clinical improvement is observed to prevent treatment failure and adverse outcomes.

Compliance with Ethical Standards

Conflict of interest None.

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