



## Letters to the Editor

### Zygomycosis in Children: Disseminated Infection Caused by *Cunninghamella bertholletiae*\*

#### Zigomicosis en niños: infección diseminada por *Cunninghamella bertholletiae*

Dear Editor,

Infections by *Cunninghamella bertholletiae* are infrequent but particularly severe and have high associated mortality. Gomes et al.<sup>1</sup> reported 6 pediatric cases, 4 with pneumonia and 2 with disseminated disease. In said study, hematologic disease was the majority risk factor. Three patients with lung affection who underwent surgery and antifungal treatment survived. Our case is a 17-year-old patient who was diagnosed in 2006 with acute lymphoblastic leukemia-B and admitted for unrelated allogeneic transplantation in 2011 and had received prophylaxis with amphotericin B (AMB) liposomal, acyclovir and trimethoprim/sulfamethoxazole. Antibiotic prophylaxis (+6) was started with meropenem due to neutropenia with no fever. Vancomycin (+10) was associated after daily fever and increased acute-phase reactants coinciding with the leukocyte transplantation. On day +41, the patient was hospitalized due to persistent diarrhea with no microbiological confirmation that was treated with meropenem and ganciclovir. The pathology study of the colon suggested grade I graft-versus-host disease (GVHD), which evolved to grade III in a later study. On day +64, the subject presented a single painful erythematous lesion in the left hypochondriac region suggestive of septic embolism. The biopsy report identified angioinvasive mycosis suggestive of mucormycosis. On thoracoabdominal-pelvic CT, a nodular lesion was observed in the left lung compatible with a fungal infection. Pathology studies were done of the skin, bone marrow and lungs. The skin and lung studies revealed angioinvasive mycosis compatible with zygomycosis. From the culture of the lung nodule, *Cunninghamella* spp. was isolated and with pan-fungal CRP (ISCI) it was identified as *C. bertholletiae*. Blood cultures were negative. Liposomal AMB was administered at high doses (10 mg/kg/day) along with terbinafine (TER) and posaconazole (PSC). The MIC of these antifungal preparations was 4, 8, and 2 µg/ml, respectively. The lung nodule and skin lesion were resected (+72). During post-op in the pediatric ICU, vancomycin and amikacin were added to meropenem due to an increase in acute-phase reactants with negative blood cultures. A series of radiological controls detected a left lung infiltrate with pleural effusion. Given the respiratory deterioration, a new pulmonary CT showed an increase in the effusion and nodular lesions in the

right lung suggestive of fungal dissemination in the refractory acute grade IV GVHD. The patient died (+100) due to irreversible respiratory deterioration.

There are few studies about invasive zygomycosis in children. Zaoutis et al.<sup>2</sup> reviewed 157 pediatric cases where neutropenia is the most common predisposing factor (18%) and skin affection is the most frequent localized form (27%). Disseminated infection (32%) has an associated mortality of 88%; this factor together with an age <1 year and the absence of antifungal and surgical treatment, are independent risk factors for death. In said study, 52% of cases were diagnosed only by histology and 47% by histology and culture, as in our case. The characterization of the genus is done by microscope: wide hyphae, non-septated and ramifications at 90°. The interspecies variation requires the study of specific fungal elements. The therapeutic strategy in children is similar to that of adults. Out of 81 patients with anti-fungal therapy, 73% received AMB alone and the rest received a combination with other antifungal medication.<sup>2</sup> *In vitro*, AMB is active, although the MIC in *C. bertholletiae* is higher.<sup>3</sup> The lipid formulations associate higher rates of clinical response.<sup>4</sup> The combination of AMB at high doses of 10 mg/kg/day<sup>5</sup> and surgery significantly reduces mortality (92% and 84%, respectively), together with the premature correction of risk factors.<sup>2</sup> This therapeutic attitude in our case was perhaps not effective given the underlying clinical severity. PSC and TER have been shown to be effective *in vitro*. *In vivo*, AMB and PSC have similar activity, the latter being a therapeutic alternative.<sup>6</sup>

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M. José González-Abad,\* Mercedes Alonso Sanz

Sección de Microbiología, Servicio de Análisis Clínicos, Hospital Infantil Universitario Niño Jesús, Madrid, Spain

\* Corresponding author.

E-mail address: mjglezabad@yahoo.es (M.J. González-Abad).

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