

A case of pulmonary aspergillosis with lack of response to caspofungin

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Summary Currently, susceptibility testing of *Aspergillus* isolates towards caspofungin is hampered by a lack of interpretative cut-off values. Nevertheless, caspofungin has been widely recommended for the treatment of invasive aspergillosis. This antifungal, however, could lead to therapy failure as demonstrated by the case in this report of a 55-year-old patient, who eight months after the diagnosis of leukemia and successful allogenic hematopoietic stem cell transplantation (HSCT), succumbed to a fatal pulmonary aspergillosis infection, which resisted treatment with caspofungin.

Key words *Aspergillus fumigatus*, Invasive aspergillosis, Antifungal, Caspofungin, Treatment, Resistance

Un caso clínico de aspergilosis pulmonar que no respondió al tratamiento con caspofungina

Resumen Las pruebas actuales de estudio de la sensibilidad in vitro a la caspofungina de los aislamientos de *Aspergillus* están limitadas porque se carece de puntos de corte para su interpretación. Sin embargo, se ha recomendado utilizar caspofungina en el tratamiento de la aspergilosis invasora. Esta actuación puede conducir a un fallo terapéutico como en el caso de una paciente de 55 años que, ocho meses después de ser diagnosticada de leucemia y ser sometida con éxito a un trasplante alogénico de precursores hematopoyéticos, sufrió una aspergilosis pulmonar con desenlace fatal que no respondió al tratamiento con caspofungina.

Palabras clave *Aspergillus fumigatus*, Aspergilosis invasora, Antifúngico, Caspofungina, Tratamiento, Resistencia

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Invasive pulmonary aspergillosis is an ominous infection in patients with hematologic malignancies. In such patients, fever of unknown origin and pulmonary infiltration are suggestive of mycosis, and preemptive antimycotic therapy is mandatory [2]. Sometimes, these patients do not tolerate amphotericin or triazoles due to liver or kidney toxicities. In such cases, the antifungal agent of choice at present is caspofungin, the first clinically available candidin [4]. The aspergilli are in general considered to be amenable to the fungistatic effect of caspofungin; however, no respective interpretative cut-off values for susceptibility testing have yet been recommended. It is probable that in vitro testing yields conflicting results which prevent a straight forward reading of minimal inhibitory concentrations (MIC) [3]. Here, we present a case in which such an uncertainty possibly contributed to a fatal outcome.

Case history

A 55-year old woman was diagnosed with acute myeloid leukaemia, and during bone marrow aplasia in the course of remission induction therapy she developed fever, which was refractory to antibiotic treatment. Coincidentally, multiple hepatic and splenic lesions and a positive *Candida* serology were detected. Thus, the patient was diagnosed to be suffering from hepatosplenic candidiasis [9]. She was treated successfully with liposomal amphotericin B and received voriconazole after discharge. She experienced a relapse of the acute myeloid leukaemia and finally received an allogenic hematopoietic stem cell transplantation, eight months after the antifungal treatment. With her white blood cell counts nearly normalized at 3,200 cells/ μ l, we were surprised to see her again hospitalized earlier this year. She had abdominal pain, due to kidney stones, and, subsequently, she developed dyspnoea and a pulmonary infiltrate on the right side of her chest. Liver and spleen showed residual lesions of previous candidiasis. However, in the further course of disease, there was no sign of a reactivation of candidiasis. Upon admission, the patient received a systemic immunosuppression with mycophenolate mofetil and cortisone for a cutaneous and intestinal graft versus host reaction. Because of the pulmonary infiltrate, which was suggestive of aspergillosis, the antibacterial chemotherapy was supplemented with caspofungin. The triazole voriconazole, which would have been the antifungal of choice, was not used due to elevated bilirubin and liver enzymes during previous voriconazole administration, indicating drug-induced liver damage. Though only limited data of caspofungin as first line treatment of pulmonary aspergillosis are available, its efficiency has been confirmed in neutropenic patients [1].

At the beginning of antifungal therapy, serum was tested for *Aspergillus* galactomannan antigen (Platelia EIA, BioRad, Germany), resulting in an index value of 0.66. This value was still considered to be in the normal range according to the manufacturer, but is deemed suspicious of aspergillosis in transplant patients according to Marr et al. [5]. During continuous antifungal therapy, the patient's condition initially slightly improved and she did not exhibit clinical signs of a progressive infection. On day seven of antifungal therapy *Aspergillus* galactomannan antigen index values had risen slightly to 0.77 and 0.74, then the patient's conditions deteriorated rapidly and she ultimately died from respiratory failure.

Upon necropsy, the pathologist suspected extensive fungal pneumonia and initiated the investigation of cons-

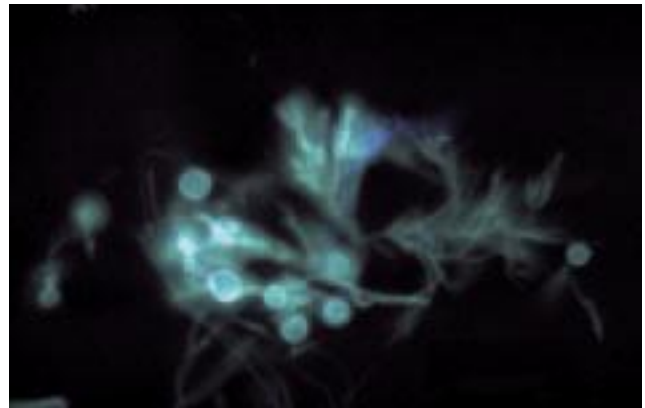


Figure 1. Hyalohyphomycete after maceration from the patient's pulmonary tissue and staining with an optical brightener, showing atypical chlamyospore-like elements (magnification 300x). The fungus was subsequently identified as *A. fumigatus*.

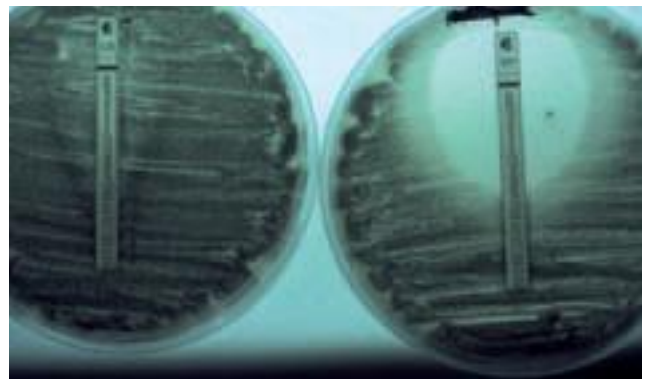


Figure 2. The patient's *A. fumigatus* isolate upon E-test against caspofungin or voriconazole after 48 h 37 °C on RPMI-agar. No definite inhibition by caspofungin was observed, as compared with a stable zone of inhibition due to voriconazole.

picuous tissue. This confirmed mould pneumonia after fluorescent staining of fresh tissue with an optical brightener and simultaneous maceration by KOH [8]. However, fungal elements displayed chlamyospore-like swollen structures in many places (Figure 1). Such structures had been observed already upon exposure of *Aspergillus fumigatus* to the related antifungal micafungin [6]. Such abnormalities suggested damage to the fungal cell wall as was expected due to the drug-related inhibition of glucan synthase. Most surprisingly, fungal hyphae grew from the infected tissue already after 18 h at 37 °C; after 30 h, there was already lush sporulation of the fungus on Sabouraud glucose agar. The isolate grew at 45 °C and was identified as *A. fumigatus*.

The isolate was subjected to susceptibility testing towards caspofungin and voriconazole. While the latter caused a regular zone of inhibition in the E-test (Viva Diagnostika, Germany), the corresponding test against caspofungin suggested an initial inhibition of the fungus (MIC 0.25 μ g/ml). In the course of 24 h, though, the fungus achieved maximum growth which reached the caspofungin test strip, leaving no certain zone of inhibition (Figure 2). A comparable conflicting result has already been communicated [3]. Re-testing of colonies from the outside or within the initial inhibition ellipse on the agar surface disproved the presence of two distinct fungal populations since the phenomenon could be reproduced at will with fungi from either origin.

Discussion

Invasive pulmonary aspergillosis is a highly dreaded fungal infection in haematologic patients. Definite diagnosis is difficult, but may be supported by monitoring galactomannan antigen; however, the interpretation of cut-off values of the resulting indices is under discussion [5].

At the same time, besides amphotericin B, new therapeutic options for invasive pulmonary aspergillosis have become available, such as voriconazole and caspofungin [4]. The latter has an excellent safety profile, but currently its clinical use is hampered by a lack of interpretative cut-

off breakpoints obtained from susceptibility testing and problems with the reproducibility of such testing [7]. This obviously was confirmed by the case of invasive pulmonary aspergillosis, presented here, that was caused by a resistant isolate of *A. fumigatus* and led to a lethal outcome. Resistance of the isolate to caspofungin was also observed in broth dilution according to NCCLS-M38 (result not shown). The properties of this isolate are at present under investigation.

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