Combined Voriconazole Plus Caspofungin Therapy for the Treatment of Probable *Geotrichum* Pneumonia in a Leukemia Patient

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Abstract
Infections by *Geotrichum capitatum*, occurring in leukemia patients, are rarely reported and generally are characterized by a poor prognosis. Here we reported a case of *G. capitatum* pneumonia in a patient with plasma cell leukemia, successfully treated with antifungal combination with voriconazole and caspofungin and supportive therapy.

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Introduction

In the last years the number of invasive fungal infections registered among patients with hematological malignancies has dramatically increased particularly in subjects suffering from acute leukaemia [1–3]. Pulmonary infections are the major problem in these patients, representing the main cause of infective death associated with bloodstream infections [4, 5]. Pneumonia is usually caused above all by moulds (e.g. *Aspergillus* spp or Zygomycetes), while the observation of pneumonia due to other fungi is generally occasional. However, the spectrum of infecting species appears to be increasing, and many moulds and yeasts have emerged as possible causes of invasive infection [6].

Among the emerging fungi, *Geotrichum capitatum* is a rarely described yeast that produces severe systemic infection with generally a poor prognosis in such patients [7, 8]. Here, we describe a case of *G. capitatum* pneumonia occurring in a patient with plasma cellular leukaemia, a lymphoproliferative disease characterized by bone marrow proliferation and circulation in significant number of a clonal population of terminally differentiated B cells, plasma cells [9], successfully treated with antifungal combination therapy including voriconazole and caspofungin.

Case Report

In February 2006, a 69-year-old female was admitted to the Hospital with a diagnosis of plasma cell leukemia. Four months previously, the patient had been empirically treated with specific antibiotic therapy and steroids for a presumptive tubercular pneumonia and pleuro-pericarditis. She received an induction chemotherapy with cyclophosphamide (2 g/sqm on days 1 and 3) and methyl-prednisolone (500 mg/smq from day 1 to day 4). After 2 days from the end of therapy while neutropenic (neutrophils value 0.02×10^9/l), the patient, experienced fever, productive cough and thorax pain. Blood and sputum samples for microbiological examination were collected. She had not an iv catheter. Chest X-rays showed a bilateral and diffuse interstitial infiltrate. Broad-spectrum antibiotic therapy with ceftazidime and amikacina was started and subcutaneous granulocyte colony-stimulating factor (G-CSF) was added. After 5 days of antibiotic treatment fever persisted, blood cultures and bacterial cultures of sputum resulted negative while sputum direct examination showed the presence of fungal hyphae. At chest CT scan alveolar infiltrates, multiple bilateral nodules and parenchymal consolidation areas were documented and liposomal-Amphotericin B (L-AmB) therapy (3 mg/Kg/day) was started. At day 3 of L-AmB therapy clinical conditions did not improve and from microbiological examination of sputum *G. capitatum* was identified. Bronchoscopy with broncho-alveolar lavage was performed and quantitative culture of the broncho-alveolar lavage fluid yielded 10^4 cfu/ml, thereby confirming fungal infection by *G. capitatum*. Despite L-AmB therapy and recovery from neutropenia (neutrophils value 5.7×10^9/l) fever persisted and clinical condition of patient deteriorated. After a total of 5 days L-AmB was stopped and voriconazole iv therapy (two doses of 6 mg/kg then 4 mg/kg every 12 h) was started.

At day 9 on voriconazole therapy, her clinical conditions dramatically worsened: she presented agitation, intense dyspnea and inability to remove secretions and she was transferred to intensive care unit (ICU) where she received invasive mechanical ventilation. Chest X-rays was repeated confirming interstitial infiltrates and showing the presence of parenchymal consolida-

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tion areas documented at CT scan. In vitro antifungal susceptibility testing, performed by use of the CLSI M27-A2 broth microdilution method [10], showed that the *G. capitatum* isolates were susceptible both to voriconazole (MIC 0.12 μg/ml) and caspofungin (MIC 0.25 μg/ml), as well as to amphotericin B (MIC 0.25 μg/ml).

Considering the deteriorated clinical conditions a combination antifungal treatment was started: caspofungin (70 mg/day the first day and then 50 mg/day) was added to voriconazole therapy. After 5 days of combination therapy, the patient showed a clinical improvement of respiratory failure so as the sedative agent was stopped and she was ready to be weaned from the ventilator. The weaning trial from the ventilator with a gradual reduction in the level of pressure support ventilation was started. In the sixth day of stay in ICU, the endotracheal tube was removed and the patient started a spontaneous breathing with a supply of humidified oxygen by face mask. In the tenth day of stay, she was discharged from the ICU with clinical stable conditions.

After 12 days of combination therapy, fever and clinical conditions improved. Chest CT scan was repeated showing an improvement of pulmonary lesions and sputum examination resulted negative for fungal infections. Combination antifungal therapy was prolonged for 21 days and patient was discharged from hospital with oral voriconazole therapy.

Patient in complete remission from leukemia was submitted to consolidation treatment after 2 months from *Geotrichum* infection. She received secondary oral voriconazole prophylaxis during post-chemotherapy aplasia with no evidence of active fungal disease.

At present the patient was alive after 5 months without no sign of fungal infection.

Discussion

Geotrichum capitatum has been emerging as a rare fungal pathogen in recent years, particularly in severely immunocompromised hosts [3, 7, 8]. The invasive fungal infection caused by this agent is often characterized by a multiorgan involvement with a fatal course despite antifungal therapy.

In pulmonary involvement lung infiltrates are usually visible on chest radiography, resembling classic images of pulmonary mycetoma. This finding, however, could be lacking in neutropenic patients where the radiological pattern is often unspecific as happened in our patient.

Several studies collecting cases of *G. capitatum* infections in haematological patients has showed a 30-day attributable mortality ranging between 40% and 75% [8, 11–14]. In a report by Martino et al, which represents the largest series of patients with probable or definite invasive infection with *G. capitatum*, the heterogeneity of drug combinations used did not allow for any evidence-based suggestions about the drugs of choice for treating this infection [13]. Twelve of thirteen patients who were cured in this study had received AmB therapy, either alone (five patients) or in combination with other drugs (seven patients). Among the azoles, voriconazole and itraconazole appear to be active in vitro [15–18]. On the contrary caspofungin, which has a good fungistatic and fungicidal activity against a variety of yeasts, does not show activity against *G. capitatum* and the other fungi of *Trichosporon* species in limited in vitro data [19, 20]. On the other hand clinical experience with caspofungin in the treatment of *G. capitatum* infection is scanty and an in vitro versus in vivo correlation is not at present available.

In our patient, L-AmB and voriconazole were not clinically effective when used as sole antifungal agents. By contrast, the combination therapy with caspofungin and voriconazole resulted effective in the clinical improvement of the patient.

There are not available data but we retain that for this kind of infections the combination therapy with drugs acting synergistically on different cell targets might be useful to overcome the problem of lack of fungicidal activity of antifungal agents when used alone and could represent the treatment of choice to reduce its high mortality rate.

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