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Letter to the editor

Geotrichum capitatum fungemia in patients treated for acute leukemia

Fongémie à Geotrichum capitatum compliquant une leucémie aiguë

Keywords: *Geotrichum capitatum*; Acute leukemia; Amphotericin B

Mots clés : *Geotrichum capitatum* ; Leucémie aiguë ; Amphotéricine B

1. Introduction

Patients treated for hematological malignancies are at risk of invasive fungal infections. Most of these opportunistic infections are due to *Candida* and *Aspergillus* species.

Geotrichum capitatum originally known as *Trichosporon capitatum* is an uncommon yeast affecting immunocompromised patients presenting with hematological malignancies and prolonged neutropenia [1–3]. The virulence of *G. capitatum* is low in immunocompetent patients but this opportunistic fungus is associated with unfavorable outcome in patients presenting with severe neutropenia in the hematological ward. Despite appropriate antifungal treatment, the case fatality is high (approximately 50–70%) [4,5].

We report four cases of patients treated with chemotherapy for acute leukemia who presented with *G. capitatum* invasive infection.

2. First case patient

A 35-year-old man was diagnosed with acute lymphoblastic leukemia (pro B ALL). He was treated according to the French protocol GRAALL05 and received induction chemotherapy and four consolidation blocks. He was planned to undergo allogeneic stem cell transplantation but presented with pulmonary tuberculosis delaying bone marrow transplantation. The patient experienced relapse seven months later. He received chemotherapy consisting of high-dose cytarabine (2000 mg/m^2 twice daily for four days) and idarubicin (12 mg/m^2/day for three days). He was febrile on day 1 of chemotherapy and received piperacillin-tazobactam and colistin empirically. On day 10 he presented with diarrhea leading to a change in antibiotics to use imipenem and amikacin. Fever persisted despite antibiotic administration. The use of an antifungal treatment with deoxycholate amphotericin B (1 mg/kg/day) was therefore recommended as of day 13. Peripheral blood cultures and galactomannan antigenemia were both negative. The chest X-ray was normal.

On day 15, while he was still febrile, the patient presented with skin lesions consisting of small erythematous papules and nodules on the back and legs. Cutaneous biopsy did not show blast cells. Vancomycin was started but fever did not resolve. Procalcitonin was positive (6.77 ng/mL).

Blood cultures performed on day 14 and 16 were positive for yeasts. Caspofungin was initiated on day 17 until identification of the yeast. During this period the patient remained febrile with extension of the cutaneous papules, and the procalcitonin level increased to 11 ng/mL. On day 20 *Trichosporon mucoides* was identified. Caspofungin was discontinued and replaced by voriconazole. On day 26 blood cultures were positive for *G. capitatum*. *G. capitatum* was susceptible to fluconazole and amphotericin B. The antifungal treatment was modified to prescribe fluconazole starting from day 26. The full-body CT scan showed multiple pulmonary hepatic and splenic nodules. The outcome was favorable with disappearance of skin lesions and decreased procalcitonin level. Fever persisted due to the discontinuation of the antituberculosis treatment. It should be noted that blood cultures were negative from day 20. The patient was in remission after this course of chemotherapy but relapsed one month later and died from leukemia.

3. Second case patient

A 40-year-old man presenting with biphenotypic acute leukemia was hospitalized in our hematology department for induction therapy. He received induction therapy consisting of idarubicin (12 mg/m^2/day on days 1–3) and cytarabine (200 mg/m^2/day on days 1–7). Piperacillin-tazobactam was initiated as the empirical antimicrobial therapy following hospital admission. On day 10 the patient experienced a second fever episode and teicoplanin was initiated. Deoxycholate amphotericin B was added to the antimicrobial treatment from day 12 because of fever persistence. As the patient was still febrile on day 14, piperacillin-tazobactam was replaced by imipenem and amikacin. Procalcitonin level was elevated to 15 mg/L on day 17 leading to the use of fosfomycin. The patient remained febrile despite this extended-spectrum antibiotic therapy. The chest X-ray was normal and galactomannan antigen was negative. The CT scan performed on day 19 showed hepatosplenomegaly with micronodules of the spleen. The blood culture taken on

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day 19 yielded *G. capitatum*. The strain was susceptible to fluconazole and flucytosine. Voriconazole was not tested. The patient remained febrile despite receiving antifungal therapy with amphotericin B and voriconazole. He became dyspneic and died of respiratory failure.

4. Third case patient

A 39-year-old man was admitted to our hematology department for acute myeloid leukemia. We started an induction course with idarubicin (12 mg/m^2/day on days 1–3) and cytarabine (200 mg/m^2/day on days 1–7). On day 4 the patient presented with isolated fever treated empirically with piperacillin-tazobactam and colistin. Treatment was switched to imipenem on day 9 because of diarrhea. Deoxycholate amphotericin B was started empirically on day 15. The day-18 blood culture isolated *G. capitatum*. The strain was susceptible to amphotericin B and fluconazole. The patient presented with respiratory failure despite the use of amphotericin B and was transferred to the intensive care unit. He died of a septic shock on day 23.

5. Fourth case patient

A 45-year-old man was diagnosed with acute myeloid leukemia. He received an induction therapy with idarubicin (12 mg/m^2/day on days 1–3) and cytarabine (200 mg/m^2/day on days 1–7). On day 19, while he was receiving successive empirical antibiotic therapy (imipenem for 7 days, vancomycin for 2 days, and deoxycholate amphotericin B for 8 days), he presented with fever and nodular skin lesions on the legs and back. As the skin lesions were similar to those observed in patients presenting with disseminated candidiasis, fluconazole was initiated. The blood culture performed on day 19 was positive for *G. capitatum*. In vitro susceptibility tests showed susceptibility to amphotericin B, fluconazole, and flucytosine. Favorable outcome was observed. The patient had 14 days of fluconazole treatment after blood culture became sterile.

6. Discussion

Geotrichum capitatum (*Blastoschizomyces capitatus*) is an emerging yeast that has been reported to cause invasive infections in immunocompromised patients. This yeast is commonly found in the environment, the normal flora of human digestive and respiratory tracts and skin [3,4,6]. Because of the increased use of intensive chemotherapy and stem cell transplantation, the incidence of *G. capitatum* infections and invasive fungal infections is increasing.

Risk factors for *G. capitatum* infection are the same as for other invasive fungal infections including severe and prolonged neutropenia, broad-spectrum antibiotics, use of corticosteroids, chemotherapy, and vascular catheterization [5,6]. Most cases have been reported in patients treated for hematological malignancies who had received cytotoxic chemotherapy and experienced deep and prolonged neutropenia.

Our four patients were at risk of *G. capitatum* infection: they were treated for acute leukemia (two acute myeloid leukemia cases, 1 ALL, and 1 biphenotypic leukemia), they had chemotherapy causing grade 4 neutropenia and were receiving broad-spectrum antibiotics.

In neutropenic patients, *G. capitatum* produces an infection similar to that of candidiasis and other invasive fungal infections. Overall, 60–80% of patients develop deep organ involvement [5]. One patient (no. 1) had probable pulmonary localization on CT scan even though lung biopsy was not performed. *G. capitatum* is frequently isolated from the respiratory tract, and the lung colonization may lead to the infection.

Skin involvement of disseminated *G. capitatum* infection is frequent and the skin can be a portal of entry. Lesions can present as erythematous nodules just like in *Candida* infections and *Fusarium* infections. Skin biopsy may identify the fungus. Two of our patients had skin nodules. A skin biopsy was performed in these two patients and fungal localization was found in only one patient.

The diagnosis is usually made by blood culture, which is positive in more than 70% of patients [3] *G. capitatum* was detected by blood culture in all our patients. We used biochemical identification for detecting *G. capitatum*. It should be noted that the taxonomy has been subjected to revision on the basis of molecular data and this pathogen has undergone extensive reclassification.

G. capitatum antigens may be cross-reactive in the *Aspergillus* galactomannan assay and galactomannan may be detected in some patients [7,8]. None of our patients had positive galactomannan.

There is no sufficient data and evidence-based recommendations to assess the optimal treatment for *G. capitatum* infection, but it seems that amphotericin B with or without flucytosine is an efficient treatment [10]. Voriconazole and itraconazole seem to be active against *G. capitatum* [9,10].

All our patients showed susceptibility to fluconazole and amphotericin B. Only the infection of the two patients treated with fluconazole was controlled whereas the other two patients died. The lipid formulation of amphotericin B is not available in Tunisia; deoxycholate amphotericin B is used instead. The emergence of the infection in patients receiving amphotericin B treatment may be due to the use of the deoxycholate formulation as low doses must be administered due to the renal toxicity of this type of amphotericin B.

7. Conclusion

G. capitatum infection is a rare fungal infection with a clinical presentation similar to that of candidiasis. It occurs in the hematology and intensive care settings leading to high case fatality in neutropenic patients. Our study underlines the difficulty of treating *G. capitatum* infection.

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Contribution of authors

H.BN wrote the article and managed the four patients.
M.B and B.M managed the patients.
M.H and O.B performed the microbiological analysis.
A.K and K.K performed the identification and the antifungal susceptibility test at the mycology laboratory.

Disclosure of interest

The authors declare that they have no competing interest.

References

[1] Durán Graeff L, Seidel D, Vehreschild MJ, Hamprecht A, Kindo A, Racil Z, Demeter J, et al. Invasive infections due to Saprochaete and Geotrichum species: report of 23 cases from the FungiScope Registry. Mycoses 2017;60(4):273–9.
[2] Martino R, Subira M. Invasive fungal infections in hematology: new trends. Ann Hematol 2002;81(5):233–43.
[3] Vaux S, Criscuolo A, Desnos-Ollivier M, Diancourt L, Tarnaud C, Vandenbogaert M, et al. Multicenter outbreak of infections by Saprochaete clavata, an unrecognized opportunistic fungal pathogen. M Bio 2014;5(6):1–10.
[4] Girmenia C, Pagano L, Martino B, et al. Invasive infections caused by Trichosporon Species and Geotrichum capitatum in patients with hematological malignancies: a retrospective multicenter study from Italy and review of the literature. J Clin Microbiol 2005;43(4):1818–28.
[5] Martino R, Salavert M, Parody R, Thomas J, et al. Blastoschizomyces capitatus infection in patients with leukemia: report of 26 cases. Clinical Infect Dis 2004;38:335–41.
[6] Bouza E, Munoz P. Invasive infections caused by Blastoschizomyces capitatus and Scedosporium spp. Clin Microbiol Infect Dis 2004;10(supp 1):76–85.
[7] Bonini A, Capatti C, Parmeggiani M, Gugliotta L, et al. Galactomannan detection in Geotricum capitatum invasive infections: report of 2 new cases and review of diagnostic options. Diagn Microbiol Infect Dis 2008;62:450–2.
[8] Giacchino M, Chiapello N, Bezzio S, Fagioli F, Saracco P, et al. Aspergillus galactomannan enzyme-linked immunosorbent assay cross reactivity caused by invasive Geotrichum capitatum. J Clin Microbiol 2006;44(9):3432–4.
[9] Fianchi L, Montini M, Caira M, Voso MT, Maviglia R, Posteraro B, Pagano L. Combined voriconazole plus caspofungin therapy for the treatment of probable Geotrichum capitatum pneumonia in a leukemia patient. Infection 2008;36(1):65–7.
[10] Ikuta K, Torimoto Ikuta K, Torimoto, Yamamoto, Okamura N, Hosoki T, Sato K, et al. Successful treatment of systemic Geotricum capitatum infection by liposomal amphotericin B, itraconazole and voriconazole in a Japanese man. Internal Med 2010;49:2499–503.

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