Geotrichum capitatum septicemia in a hematological malignancy patient with positive galactomannan antigen: case report and review of the literature

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SUMMARY Özkaya-Parlakay A, Cengiz AB, Karadağ-Öncel E, Kuşkonmaz B, Sarıbaş Z, Kara A. Oğuz B. *Geotrichum capitatum* septicemia in a hematological malignancy patient with positive galactomannan antigen: case report and review of the literature. Turk J Pediatr 2012; 54: 674-678.

***Geotrichum capitatum*, formerly known as Trichosporon capitatum, is an uncommon but frequently fatal invasive fungal infection in immunocompromised patients, especially in hematological malignancies. We report a seven-year-old patient with acute myeloid leukemia with *Geotrichum septicemia* with involvement of the lungs, liver, spleen, and kidneys, who had a favorable outcome after therapy. Alteration of antifungal treatment to liposomal amphotericin B resolved the fever with favorable clinical response.**

Key words: Geotrichum capitatum, septicemia, child.

Invasive fungal infections are unfortunately encountered commonly in immunocompromised patients, especially those with hematological malignancies and severe neutropenia. Over the past two decades, invasive fungal infections have increased significantly in both number and frequency and as causes of morbidity and mortality. The possible reasons for the increase in the incidence of the mycoses are increased use of intensive cytotoxic therapy, immunosuppressive treatment, allogenic blood stem cell transplantation, and more invasive medical management with broader spectrum antibiotics. The rate of sepsis due to fungal organisms in the United States (USA) increased by 207% during the period 1979–2000, which was the largest increase observed due to any group of organisms. Most of these fungal infections are caused by Candida spp., Aspergillus spp. and Mucor spp. *Geotrichum capitatum*, originally known as Trichosporon capitatum, has occasionally been reported especially in acute leukemia patients[1]. Increase in the use of prophylaxis and early empiric antifungal therapy result in clinical infection with this mycosis.

G. capitatum is considered in the phylum Ascomycota. It produces arthroconidia and annelloconidia. Trichosporon also produces arthroconidia, and biochemical tests and carbohydrate assimilation patterns are generally used to differentiate *G. capitatum* from Trichosporon [2]. This organism can be encountered in foods and soil as well as human mucosa and skin[3]. As virulence of this fungus is low, it is not expected to cause infection in immunocompetent patients. When it is the causative organism in non-neutropenic patients, local infections have been reported in the literature.

Possible routes for entrance of *G. capitatum* could be the respiratory and digestive tract. Clinical findings of *G. capitatum* infection cannot be differentiated from invasive candidiasis and aspergillosis[4,5].

We conducted a MEDLINE search for Geotrichum, Blastoschizomyces and Trichosporon capitatum between 1965 and September 2011, and found 202 reports, of which 186 were invasive. Outcomes of the disease is usually unfavorable, with a mortality rate over 50%[2,5,6]. To the best of our knowledge, our case is the second youngest (both of them

are 7 years old[7]) patient in whom *G. capitatum* was isolated. Galactomannan antigen positivity was an interesting finding in our case, similar to the reports of Giacchino et al.[7] and Bonini et al.[8]. Enzyme-linked immunosorbent assay (ELISA) is widely used throughout the world in diagnosing invasive aspergillosis, but a major problem with the detection of circulating galactomannan antigen is the occurrence of false-positive results, which in some cases, have been shown to be related to cross-reactivity with other opportunistic fungi, as also seen in our case. In this report, it was aimed to emphasize the importance of investigating not only aspergillus but also other rarely encountered fungi such as *G. capitatum* in galactomannan antigen positivity and resistant fever in hematological malignancies.

Case Report

A seven-year-old boy who was under treatment for acute myelogenous leukemia and had received cytarabine 20 days prior to his complaints admitted to a local hospital with a complaint of rectal pain and fever. He was hospitalized because of neutropenia, with 200/mm^3 absolute neutrophil count.

His physical examination yielded a perirectal hyperemic abscess measuring 3x2 cm. The clinical exam was otherwise normal. He also had thrombocytopenia (7000/mm^3); other laboratory examinations in that hospital were normal.

Meropenem, vancomycin, fluconazole, metronidazole, and amikacin were initiated in that hospital with a diagnosis of neutropenic fever and perirectal abscess. He was referred to our hospital as he was febrile despite 14-day antimicrobial treatment.

On the day of admittance to our hospital, he had weakness and rectal pain. The physical examination revealed hyperemic perirectal abscess in the 4 o'clock position, measuring 2x2 cm and covered with crust.

Leukocyte count was 500/mm^3 with no polymorphonuclear leukocytes or blast cells, hemoglobin was 11 g/dl and platelet count was 49000/ mm^3. Radiologic examination of the thorax did not show any pathologic findings. Imipenem, vancomycin, ornidazole, and caspofungin were initiated as empiric antimicrobial therapy. Blood, urine and throat cultures did not reveal any microorganisms.

As his fever did not resolve, bone marrow aspiration was studied, which was hypocellular with an increase in histiocytes. On the fifth day after admittance to our hospital, his thorax tomography showed consolidation in the right middle lobe and left lingular segment. Since the patient's fever persisted on day 7 after initiation of antimicrobial therapy in our hospital, abdominal ultrasonography, chest X-ray and culture studies were repeated. Ultrasonography showed hypoechoic nodules in the spleen. As there was suspicion of fungal infection, voriconazole was added to the therapy.

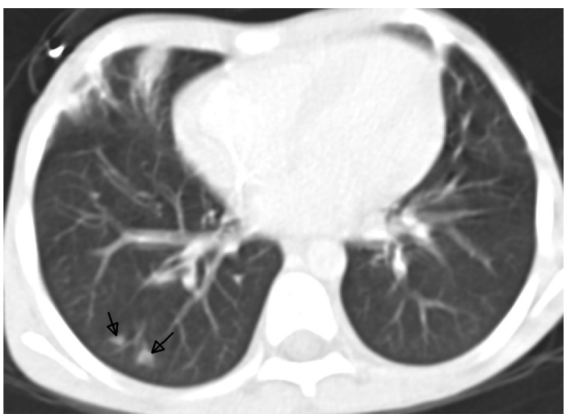

Fig. 1. (a). Thorax CT image showed two nodules in the lower lobe of the right lung *(arrows)* and subsegmental atelectasia in the right middle lobe.

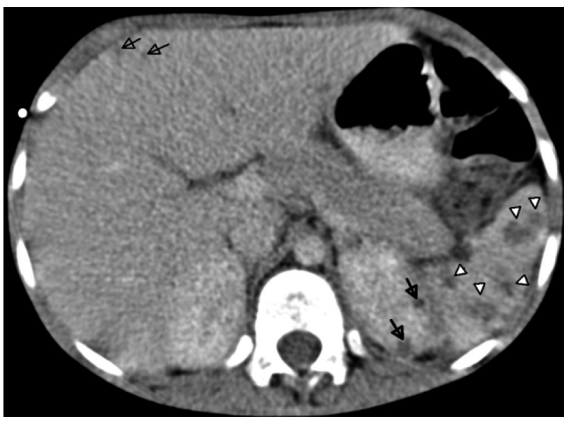

Fig. 1. (b). At the same time, abdominal CT image showed hypodense multiple nodules in the spleen *(arrowheads)*, in the left kidney *(long arrows)* and in the liver *(short arrows)*. These findings were compatible with fungal infection.

Fig. 2. Culture of *Geotrichum capitatum* on Sabouraud dextrose agar.

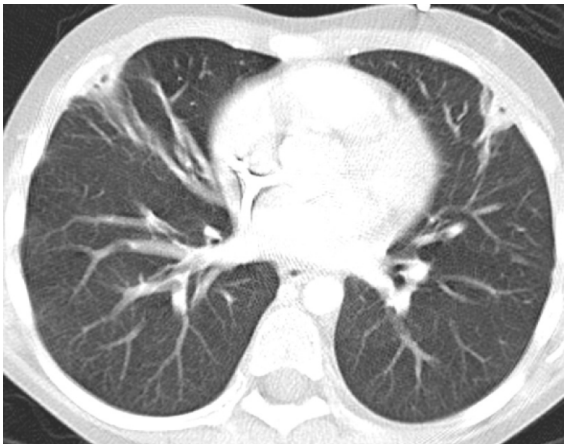

Fig. 3. Thorax CT taken after treatment showed disappearance of the nodules.

On day 10, galactomannan antigen increased to 10 TU/ml, while it was 2.7 TU/ml on day 4 (0-1 TU/ml: negative, 1-1.5 TU/ml board). Blood cultures were reported as positive by BACTEC automated blood culture system on the ninth day after initiation of antimicrobial therapy. On day 18, as the fever was still present, thoracoabdominal tomography was repeated, and two new nodules with a diameter of 1 cm were present in the lower zones of the lungs and multiple millimetric nodules were present in the kidneys, liver and spleen (Fig. 1). Identification of the yeast isolate was performed by assimilation tests (ID32C; BioMérieux, Marcy l'Etoile, France) and morphological examination on corn meal Tween 80 agar[9] (Fig. 2 shows microorganism on Sabouraud dextrose agar). Susceptibility testing for fluconazole, voriconazole and caspofungin was performed according to the Clinical and Laboratory Standards Institute (CLSI) M27-A3 guide[10]. Broth microdilution susceptibility testing was performed, and minimum inhibitory concentrations (MICs) were read after 24 and 48 hours (h) incubation. MIC-2 values were 2 μg/ml (24 h) and 4 μg/ml (48 h) for fluconazole; 0.06 μg/ml (24 h) and 0.125 μg/ml (48 h) for voriconazole; and 2 μg/ml (24 h) and 4 μg/ml (48 h) for caspofungin. Susceptibility testing for amphotericin B was performed by Etest (AB Biodisk, Sweden) according to the manufacturer's recommendations. Antibiotic medium 3 with 2% glucose was used, and MICs were the lowest concentration on the Etest strip at which there was 100% inhibition. Amphotericin B MIC values were 0.064 μg/ml in 24 h and 0.094 μg/ml in 48 h[11,23]. Candida krusei ATCC 6258 was used as the quality control strain in each test. Antimicrobial susceptibility test interpretive categories are not defined for *G. capitatum*. According to the antifungal susceptibility testing results, caspofungin and voriconazole treatment was changed to liposomal amphotericin B (5 mg/kg/day) and voriconazole. The patient's fever and general status responded well to the treatment alteration. His blood culture on day 31 did not yield any microorganisms, and on day 51, follow-up tomography was conducted, and revealed two nodules with a diameter of 4 mm, which was smaller compared to the older tomography. Voriconazole therapy was stopped in six weeks while amphotericin B was continued for eight weeks, and the patient was discharged with a plan of bone marrow transplantation, having 2700/mm^3 absolute neutrophil count. Thoracal tomography on day 98 taken after treatment showed disappearance of the nodules (Fig. 3), and abdominal ultrasonography showed multiple hypoechoic nodules with a diameter of 6 mm, but no nodules were present in the spleen or kidneys. No kidney involvement was present based on ultrasonography, urine analysis and culture.

Discussion

G. capitatum septicemia is rare in hematological malignancies[12]. Prolonged neutropenia, use of corticosteroids, vascular catheterization, chemotherapy, and broad-spectrum antibiotics

are the same risk factors as for other invasive fungal infections[13].

All fungal infections could have fungal colonization of the respiratory, urogenital or gastrointestinal tract preceding systemic infection as a common finding[6,14]. *G. capitatum* can be found in the normal microbial flora of the human digestive and respiratory tracts, such that discrimination between colonization and infection is difficult. However, in many studies, it has been proven that the isolation of these yeasts from superficial sites is significantly correlated with the development of invasive infection[2]. The probable portal of entry is the gastrointestinal[6,15] and respiratory[6,9] systems or skin[6,14], and nosocomial transmission has been suggested in a number of cases[11]. All of these pathways could be the possible routes in our patient.

Patients with *G. capitatum* septicemia can present similarly to those with other fungal infections[2-6]. Typically, which was very demonstrative in our patient, fever with abrupt onset that is unresponsive to antibiotics is observed in patients with severe neutropenia, and almost all organs can be involved[2,6,13].

In non-neutropenic patients, *G. capitatum* infections can be local, such as endocarditis[14,16], meningitis[4], and osteomyelitis and intervertebral discitis[17]. Neutropenic patients are more likely to have disseminated infection[2,5,6].

Blood culture is positive in more than 70% of invasive geotrichosis infections, with a high yield ratio, whereas for Candida, it is <50%[18], for Aspergillus 10%[19] and for Fusarium 56%[20], and 60–80% of patients with *G. capitatum* develop deep organ involvement[2,5]. In our patient, there was involvement of the lungs, spleen, liver, and kidneys.

Pulmonary involvement in cases from the literature is common in *G. capitatum* septicemia[2,6,9]. Similar to invasive pulmonary aspergillosis, the halo sign and the air crescent sign are also present in *G. capitatum* infection[21]. However, these findings were not present in our patient.

Skin involvement of acute disseminated *G. capitatum* infection may be seen, likewise in fusarial infections, and lesions that are initially present as purpuric nodules might progress to centrally necrotic lesions, which can involve the oral and pharyngeal mucosae. The fungus can be found in biopsy and/or culture[4,6], but in many cases, the skin biopsy is sterile[6]. Fusariosis causes skin involvement in 70% of patients, yielding red or grey macules, which may develop central ulceration and black eschar[22]. It is possible that the etiologic agent of perirectal abscess was *G. capitatum*, but as no biopsy was obtained from that region, it was not proven.

To date, no optimal curative therapy for systemic *G. capitatum* infections has been established.

As the fever in our case did not resolve with caspofungin and voriconazole, treatment with liposomal amphotericin B instead of caspofungin was initiated, as in the cases found in the literature [2,3,5,12,15], in whom conventional amphotericin B, either alone or together with other antifungal agents, was the most frequently used drug as first-line therapy. Giacchino et al.[7] obtained a good result with voriconazole and amphotericin B in a seven-year-old patient, similar to our case.

In several studies, investigators have proposed amphotericin B together with flucytosine for geotrichosis[2,6] , but there is no evidence that this drug combination is more effective than single drug regimens. There are a few cases reported in which voriconazole or caspofungin was used as first-line therapy of geotrichosis[5]. However, outcomes of these cases were worse compared to amphotericin B alone or in combination with voriconazole.

Girmenia et al. [23] investigated the in-vitro activities of amphotericin B, flucytosine, fluconazole, itraconazole, and voriconazole against 23 isolates of *G. capitatum*. The results confirmed previous observations on the high activity of amphotericin B against this species[6,9,15] and the poor susceptibility of some strains to flucytosine, fluconazole and itraconazole[15,24], and showed voriconazole to be a very active drug against this fungus[20]. Our patient had a favorable outcome with six weeks voriconazole and eight weeks amphotericin B therapy, whereas there are successful results with shorter therapies (6 weeks amphotericin B duration)[3].

Mortality of disseminated *G. capitatum* infection is unfortunately high; prognosis is further

aggravated by neutropenia and other immune deficiencies, and also underlying disease[2,4-6].

G. capitatum infection is a very rare but potentially fatal infection. If early diagnosis, effective antifungal treatment and marrow regeneration are achieved, the outcome might be more favorable. Galactomannan antigen positivity, a useful tool to diagnose aspergillosis, should also be detected for other rare causes of fungal infections. In patients with resistant fever and underlying hematological malignancy, fungal infection and *G. capitatum* should be kept in mind, and early initiation of appropriate antifungal treatment must be overviewed.

REFERENCES

1. Gadea I, Cuenca-Estrella M, Prieto E, et al. Genotyping and antifungal susceptibility profile of Dipodascus capitatus isolates causing disseminated infection in seven hematological patients of a tertiary hospital. J Clin Microbiol 2004; 42: 1832–1836.
2. Girmania C, Pagano L, Martino B, et al. Invasive infections caused by Trichosporon species and *Geotrichum capitatum* in patients with haematological malignancies: a retrospective multicenter study from Italy and review of the literature. J Clin Microbiol 2005; 43: 1818–1828.
3. El Omri H, Fathallah-Mili A, Ben Youssef YB, et al. *Geotrichum capitatum* septicemia in neutropenic patient, case report and review. J Mycol Méd 2005; 15: 242–246.
4. Koll BS, Brown AE. Changing patterns of infections in the immuno-compromised patient with cancer. Hematol Oncol Clin North Am 1993; 7: 753–769.
5. Martino R, Salavert M, Parody R, et al. *Blastoschizomyces capitatus* infection in patients with leukemia: report of 26 cases. Clin Infect Dis 2004; 38: 335–341.
6. Martino P, Venditti M, Micozzi A, et al. *Blastoschizomyces capitatus*: an emerging cause of invasive fungal disease in leukemia patients. Rev Infect Dis 1990; 12: 570–582.
7. Giacchino M, Chiapello N, Bezzio S, et al. Aspergillus galactomannan enzyme-linked immunosorbent assay cross-reactivity caused by invasive Geotrichum capitatum. J Clin Microbiol 2006; 44: 3432-3434.
8. Bonini A, Capatti C, Parmeggiani M, et al. Galactomannan detection in *Geotrichum capitatum* invasive infections: report of 2 new cases and review of diagnostic options. Diagn Microbiol Infect Dis 2008; 62: 450-452.
9. Larone DH. Medically Important Fungi. A Guide to Identification (2nd ed). Washington DC: American Society for Microbiology; 1993: 25.
10. CLSI. Reference method for broth dilution antifungal susceptibility testing of yeasts; approved standard (3rd ed). CLSI document M27-A3. Wayne, PA: Clinical and Laboratory Standards Institute; 2008.
11. Wanger A, Mills K, Nelson PW, Rex JH. Comparison of Etest and National Committee for Clinical Laboratory Standards broth macrodilution method for antifungal susceptibility testing: enhanced ability to detect amphotericin B-resistant Candida isolates. Antimicrob Agents Chemother 1995; 39: 2520-2522.
12. Fouassier M, Joly D, Cambon M, Peigue-Lafeuilleh H, Condat P. [*Geotrichum capitatum* infection in a neutropenic patient. Apropos of a case and review of the literature]. Rev Med Interne 1998; 19: 431–433.
13. Gadea I, Cuenca-Estrella M, Prieto E, et al. Genotyping and antifungal susceptibility profile of Dipodascus capitatus isolates causing disseminated infection in seven hematological patients of a tertiary hospital. J Clin Microbiol 2004; 42: 1832–1836.
14. Arnold AG, Gribbin B, Deleval M, MacArtney F, Slack M. *Trichosporon capitatum* causing fungal endocarditis. Thorax 1981; 36: 478–480.
15. Shiemann R, Glasmacher A, Bailly E, et al. *Geotrichum capitatum* septicaemia in neutropenic patients: case report and review of the literature. Mycoses 1998; 41: 113–116.
16. Polacheck I, Salkin IF, Kitsez-Cohen R, Raz R. Endocarditis caused by *Blastoschizomyces capitatus* and taxonomic review of the genus. J Clin Microbiol 1992; 30: 2318–2322.
17. D'Antonio D, Piccolomini R, Fioritoni G, et al. Osteomyelitis and intervertebral discitis caused by *Blastoschizomyces capitatus* in a patient with acute leukemia. J Clin Microbiol 1993; 32: 224–227.
18. Armstrong D. Problems in management of opportunistic fungal diseases. Rev Infect Dis 1989; 11: 1591–1599.
19. Girmenia C, Nucci M, Martino P. Clinical significance of Aspergillus fungaemia in patients with haematological malignancies and invasive aspergillosis. Br J Haematol 2001; 114: 93–98.
20. Boutati EI, Anaissie EJ. Fusarium, a significant emerging pathogen in patients with hematologic malignancy: ten years' experience at a cancer center and implications for management. Blood 1997; 90: 999–1008.
21. Caillot D, Casasnovas O, Bernard A, et al. Improved management of invasive pulmonary aspergillosis in neutropenic patients using early thoracic computed tomographic scan and surgery. J Clin Oncol 1997; 15: 139–147.
22. Nucci M, Anaissie E. Cutaneous infection by Fusarium species in healthy and immunocompromised hosts: implications for diagnosis and management. Clin Infect Dis 2002; 35: 909-920.
23. Girmenia C, Pizzarelli G, D'Antonio D, Cristini F, Martino P. In vitro susceptibility testing of *Geotrichum capitatum*: comparison of the E-Test, disk diffusion, and Sensititre colorimetric methods with the NCCLS M27-A2 broth microdilution reference method. Antimicrob Agents Chemother 2003; 47: 3985–3988.
24. D'Antonio D, Mazzoni A, Iacone A, et al. Emergence of fluconazole-resistant strains of Blastoschizomyces capitatus causing nosocomial infections in cancer patients. J Clin Microbiol 1996; 34: 753–755.