Hepatosplenic Geotrichum capitatum infection in a patient with acute promyelocytic leukemia

Akut promyelositik lösemili bir hastada hepatosplenik Geotrichum capitatum enfeksiyonu

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Summary
Geotrichum capitatum infection is a rare, opportunistic fungus which causes invasive disease in immunocompromised patients. We report a case of hepatosplenic infection with Geotrichum capitatum in a patient with acute promyelocytic leukemia. After chemotherapy, the patient developed fever unresponsive to antibiotic treatment, elevated serum alkaline phosphatase. Blood cultures revealed a G. capitatum infection and ultrasound and abdominal computed tomography showed multiple focal lesions in the liver and spleen. We treated the patient successfully with amphotericin B.

Key Words: Geotrichum capitatum, fungal infection, leukemia.

Özet

Anahtar Sözcükler: Geotrichum capitatum, mantar infeksiyonu, lösemi.

Introduction
Invasive fungal infections have serious complications in immunocompromised patients, especially in those with acute leukemia. Whereas Aspergillus spp. and Candida spp. are the most common causes of fungal infections, uncommon opportunistic fungi have been reported to cause life-threatening invasive infections in patients with leukemia. It has been reported that Geotrichum capitatum is a cause of systemic fungal infection in immunocompromised patients (1). This pathogen is a yeast-like fungus. It forms round, creamy-colored colonies macroscopically, and microscopically produces hyphae and annelloconidia. It is urease-negative and non fermentative and is resistant to cycloheximide (2).

It can be widely distributed in soil. It is also found as part of the normal flora of the human respiratory and digestive tracts and skin (1, 2). Since the most important predisposing factor is neutropenia, invasive G.capitatum infection affects patients with hematological malignancies.

We report a case of hepatosplenic G. capitatum infection that was treated successfully with amphotericin-B in a patient with acute promyelocytic leukemia.

Case
In July 2002, a 35-year old woman had been diagnosed with acute myeloid leukemia in a hospital. The patient had been treated with the standard induction regimen 7-3 (cytosine arabinoside and idarubicin) and achieved complete hematological remission. She received three cycles of consolidation therapy and was monitored. In February 2003, the patient was admitted to our hospital because of petechiae and ecchymosis. Her
complete blood count showed pancytopenia (white blood cell count (WBC):1180/ mm³, neutrophil count (PNL): 230/ mm³, hemoglobin 8.5gr/ dl, platelet count (PLT):13800/ mm³). There were 22% blasts in blood smear examination. Histological examination of the bone marrow and presence of t(15;17)(q22;q21) in the cytogenetic analysis of bone marrow resulted in the diagnosis of acute promyelocytic leukemia (AML-M3). Biochemistry analysis and coagulation tests were normal. The patient was treated with all-trans-retinoic acid (ATRA) 25 mg/m² and induction therapy with FLAG-ida regimen (fludarabine 25 mg/m² for 5 days, cytosine arabinoside 1 gr/m² for 6 days, idarubicine 10 mg/m² for 3 days and granulocyte growth factor). Ten days later, she developed fever (39.2 °C) while she was neutropenic (WBC: 200/mm³, PNL: <100/mm³ and PLT: <3000/mm³).

Blood, urine specimens were obtained for cultures and empirical antibiotic treatment (cefepime and amikacin) was started. Fever was controlled with broad spectrum antibiotics and urine and blood cultures were negative. Antibiotic treatment was stopped ten days later. On day 26, she developed fever again and was still neutropenic (WBC: 250/mm³ and PNL: 100/mm³). Blood and urine cultures were obtained and empiric antimicrobial regimen started again. *Escherichia coli* was isolated in the blood cultures. Three days later, she was still febrile (38.2 °C) and neutropenic (WBC: 340/mm³ and PNL: 200/mm³). Blood and urine cultures were obtained while she was febrile. Amphotericin B lipid complex (Abelcet) was added to her treatment at a dose of 4 mg/kg per day. Fungus was isolated in blood cultures which were taken when she was febrile and *G. capitatum* was identified. Abdominal ultrasonography and computerized tomography showed multiple focal lesions in the liver and spleen. Laboratory tests such as serum alkaline phosphatase (ALP), gamma glutamil transferase (GGT), aspartate aminotransferase (AST), alanine aminotransferase (ALT) were elevated. On the third day of antifungal therapy, fever control was achieved. On day six of antifungal therapy, the neutrophil count was recovered. Both hematological and molecular remissions were obtained. Therapy was maintained for three weeks. Laboratory tests improved. After the parenteral antifungal treatment was completed, maintenance therapy was initiated with oral fluconazole. Abdominal ultrasonography for control showed only heterogeneity in the liver and the spleen was normal. Thereafter, autologous peripheral blood stem cell transplantation was performed with fluconazole prophylaxis without recurrence of *G. capitatum* infection. She was followed up while in remission until September 2006 and there was no sign of fungal infection. Then, pancytopenia in her complete blood count (WBC: 1660/mm³, PNL: 700/mm³, hemoglobin: 12.7 gr/dL, PLT: 28500/mm³) 18% blasts in blood smear was noted. Histological examination and cytogenetic analysis of bone marrow established the diagnosis of AML-M3. As the arsenic trioxide was not available in our country at that time, we treated the patient with ATRA 45mg/m²/day as a case of relapsed AML-M3. In March 2007, a myeloablative allogeneic transplantation from a HLA full match sibling donor was performed. Molecular remission was obtained again. After 1.5 months, she was admitted to the hospital with diarrhea and a skin rash. *Cytomegalovirus* (CMV) antigenemia test was positive (52 cells/ 200000 cells). Skin biopsy revealed acute graft versus host disease. We treated the patient with prednisolone and gancyclovir. In July 2007, the patient was hospitalized because of CMV antigenemia positivity. After gancyclovir treatment, a CMV antigenemia test became negative, but fever, dispnea and hypoxemia persisted. Computerized tomography showed a halo sign in both upper lobes of lung parenchyma. Urine, blood and bronchoalveolar lavage fluid cultures were all negative. Despite all treatment, she died of acute respiratory distress syndrome.

Discussion

*G.capitatum* infections primarily affect patients with hematological malignancies and especially in patients with profound neutropenia. After 1980, *G.capitatum* infections have been reported in immunocompromised patients as a fatal invasive infection (3). The most common clinical manifestation of infection is fever that is unresponsive to antibiotic treatment (2). Others are maculopapular skin lesions, catheter-related sepsis,
pulmonary infiltrates, meningitis, encephalitis, focal intracerebral lesions, osteomyelitis, endocarditis, renal, pancreatic, gastrointestinal and hepatosplenic involvements that cannot be distinguished clinically and radiologically from hepatosplenic candidiasis (1-6). An increase in serum ALP is an early sign of liver involvement with fungal infections (6). Hepatosplenic involvement is detected by ultrasound and/or computed tomography. Positive blood cultures are present in more than 90% of cases during acute disseminated infection (2,4,7). If blood cultures are negative, liver biopsy should be performed for definitive diagnosis. Deep organ infection has been reported in 60-80% of the patients with G.capitatum (8). Cure rates with antifungal therapy are 20-30%. The 30-day mortality was reported to be 60% and rapid removal of the central venous catheter, a good performance status and initiation of antifungal therapy before the onset of infection are associated with lower 30-day mortality (8). Amphotericin B alone, or in combination with other drugs such as voriconazole or 5-flucytosine, is the most common antifungal therapies (2). On the other hand, removal of the central venous catheter and recovery of the neutrophil count are essential in addition to antifungal therapy (2). In some reports, decreased susceptibility of G.capitatum to amphotericin B has been reported (8,9). Other studies reported successful results with amphotericin B therapy, either alone or in combination with other drugs (2,8). Resistance to fluconazole has been reported in some publications (8-10). In some cases, treatments with interferon gamma and granulocyte infusion seem to be effective (11). The duration of therapy varies from 14 to 60 days in patients treated with amphotericin B as reported in previous literature (8). In a case report, one patient was reported to be successfully treated with voriconazole and caspofungin combination therapy for 21 days (12). However, the optimal anti-fungal agent choice and the duration of therapy still need to be elucidated. In our case, 21 days of amphotericin B lipid complex followed by peroral fluconazole was sufficient for a clinical and microbiological cure.

Martino et al. reported 21 patients with evidence of G.capitatum that 12 were infected, four were possibly infected and five had evidence of G.capitatum colonization. Eight infected patients presented with hepatic involvement and fungemia was detected in 11 of 16 patients. In these series, three patients were treated for G.capitatum infection and there was no sign of fungal infection in their follow up examination (1). Perez-Sanchez et al. (4) reported four patients with G.capitatum infection who had hematological malignancy. One patient who was treated with voriconazole was alive and others who were treated with amphotericin B died.

Korinek et al. (7) reported a patient with acute leukemia who had liver involvement by G.capitatum infection. She was treated with amphotericin B and 5-flucytosine but died of fungemia and polymicrobial sepsis despite antifungal therapy.

Martino et al. (8) reported 26 cases with G. capitatum infection. Thirteen patients were cured with antifungal therapy. Twelve patients received amphotericin B therapy, either alone or in combination with other drugs.

The risk factors for development of fungal infection in our patient were profound neutropenia, damage of mucosal membranes resulting from chemotherapy and underlying hematological malignancy. Our patient did not receive any prophylactic antifungal therapy such as fluconazole or itraconazole but she had a good performance status. As the fever was not controlled with empiric antibiotic therapy, we suspected fungal infection and started antifungal treatment empirically and then, through positive blood cultures, radiographic and laboratory tests, confirmed G.capitatum fungemia and hepatosplenic involvement. She totally recovered from the fungal infection with this treatment and autologous peripheral blood stem cell transplantation was performed with standart fluconazol prophylaxis for hematopoietic stem cell transplantation as recommended in the literature (13).

Although the outcome of G.capitatum infection is often fatal, early diagnosis of fungal infection and early antifungal treatment should decrease the mortality rate. Amphotericin B therapy is recommended by the authors. Combination regimens with amphotericin B and other antifungal agents such as voriconazole, caspofungin and 5-flucytosine were also recommended. In conclusion, removal of the central venous catheter quickly and early antifungal treatment may improve survival in patients with G.capitatum infection.

References