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Hepatosplenic Geotrichum capitatum infection in a patient with acute promyelocytic leukemia

Akut promyelositik lösemili bir hastada hepatosplenik Geotrichum capitatum enfeksiyonu

Soyer N[1] Vural F[1] Dönmez A[1] Biçeroğlu S[2] Tombuloğlu M[1] Çağırgan S[1]

[1]Ege Üniversitesi Tıp Fakültesi, Hematoloji Bilim Dalı, İzmir, Türkiye
[2]Ege Üniversitesi Tıp Fakültesi, Radyoloji Anabilim Dalı, İzmir, Türkiye

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

Geotrichum capitatum, immün yetmezliği olan hastalarda nadir görülen invaziv oportunistik bir infeksiyondur. Akut promyelositik lösemi seyrinde hepatosplenik Geotrichum capitatum infeksiyonu gelişen bir olguyu sunmaktayız. Hastanın lösemi tedavisi sırasında alkalin fosfataz artışı ve antibiyotik tedavisine dirençli ateşi gelişti. Batın ultrasonografisi ve bilgisayarlı tomografisinde karaciğer ve dalakta çok sayıda fokal lezyonların varlığı ve kan kültüründe G. capitatum saptanması ile hastaya hepatosplenik kandidiasis tanısı kondu. Liposomal amphoterisin B ile hasta başarıyla tedavi edildi.

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).

Yazışma Adresi: Nur SOYER
Ege Üniversitesi Tıp Fakültesi, İç Hastalıkları Anabilim Dalı, İzmir, Türkiye

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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/ mm^3, neutrophil count (PNL): 230/ mm^3, hemoglobin 8.5gr/ dL, platelet count (PLT):13800/ mm^3). 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/m^2 and induction therapy with FLAG-ida regimen (fludarabine 25 mg/m^2 for 5 days, cytosine arabinoside 1 gr/m^2 for 6 days, idarubicine 10 mg/m^2 for 3 days and granulocyte growth factor). Ten days later, she developed fever (39.2 $^{\circ}$C) while she was neutropenic (WBC: 200/ mm^3, PNL: <100/mm^3 and PLT: 3000/mm^3). Blood, urine specimens were obtained for cultures and emprical 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/ mm^3 and PNL: 100/mm^3). Blood and urine cultures were obtained and empiric antimicrobial regimen was started again. *Escherichia coli* was isolated in the blood cultures. Three days later, she was still febrile (38.2 $^{\circ}$C) and neutropenic (WBC: 340/mm^3 and PNL: 200/mm^3). 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 heterogenity 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/mm^3, PNL: 700/mm^3, hemoglobin: 12.7 gr/dL, PLT: 28500/mm^3) 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/m^2/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. A *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.

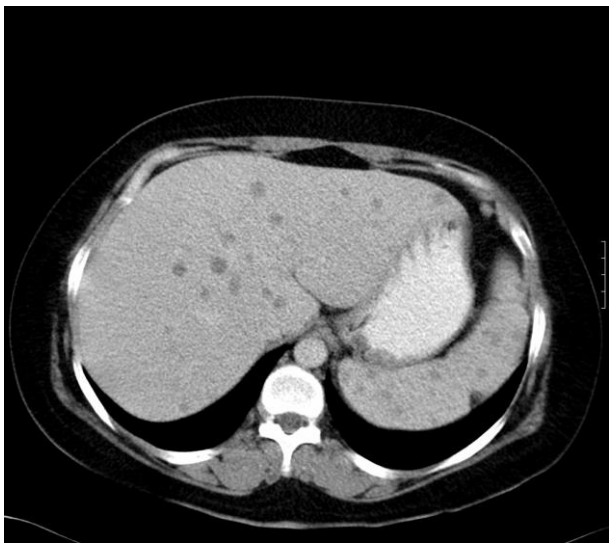

Figure-1. Computerized tomographic (CT) scan of liver and spleen showing numerous hypodense rounded areas, consistent with fungal focal lesions.

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 voricanozole 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 fluconazole 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

1. 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.
2. Bouza E and Munoz P. Invasive infections caused by Blastoschizomyces capitatus and Scedosporium spp. Clin Microbiol Infect 2004; 10(Suppl.1): 76-85.
3. Christakis G, Perlorentzou S, Aslanidou M, et al. Fatal Blastoschizomyces capitatus sepsis in a neutropenic patient with acute myeloid leukemia:first documented case from Greece. Mycoses 2005; 48: 216-220.
4. Perez-Sanchez I, Anguita J, Martin-Rabadan P et al. Blastoschizomyces capitatus infection in acute leukemia patients. Leukemia Lymphoma 2000 ; 391:209-212.

5. Mahul p, piens MA, Guyotat D, et al. Disseminated Geotrichum capitatum infection in a patient with acute myeloid leukaemia. Mycoses 1989; 32: 573-577.
6. Cofrancesco E, Viviani MA, Boschetti C, et al. Treatment of chronic disseminated Geotrichum capitatum infection with high cumulative dose of colloidal amphotericin B and itraconazole in a leukaemia patient. Mycoses 1995; 38: 377-384.
7. Amft N, Miadonna A, Viviani MA, Tedeschi A. Disseminated Geotrichum capitatum infection with predominant liver involvement in a patient with non Hodgkin's lymphoma. Haematologica 1996; 81: 352-355.
8. 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.
9. Groll AH, Walsh TJ. Uncommon opportunistic fungi: new nosocomial threats. Clin Microbiol Infect 2001; 7 (Suppl.2): 8-24.
10. Buchta V, Zak P, Kohout A, Otcenasek M. Disseminated infection of Blastoschizomyces capitatus in a patient with acute myelocytic leukaemia. Mycoses 2001; 44: 505-512.
11. DeMaio J, Colman L. The use of adjuvant interferon-gamma therapy for hepatosplenic Blastoschizomyces capitatus infection in a patient with leukemia. Clin Infect Dis 2000; 31: 822-824.
12. Fianchi L, Montini L, Caira M, et al. Combined voriconazole plus caspofungin therapy for the treatment of probable Geotrichum pneumonia in a leukemia patient. Infection 2008; 36: 65-67.
13. Centers for Disease Control and Prevention; Infectious Disease Society of America; American Society of Blood and Marrow Transplantation. Guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients. MMWR Recomm Rep 2000 ; 49(RR-10): 1-125, CE1-7.