



Treatment Failure of Disseminated *Trichosporon asahii* Infection with Voriconazole in a Patient with Acute Myeloid Leukemia

Yaygın *Trichosporon asahii* İnfeksiyonu Olan Akut Miyeloid Lösemili Bir Hastada Vorikonazol Tedavi Başarısızlığı

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SUMMARY

Infection with Trichosporon asahii is a major cause of deep-seated and disseminated trichosporonosis, that have a very poor prognosis in patients with persistent neutropenia. We report a 20-year-old girl with acute myeloid leukemia who developed disseminated Trichosporon asahii infection. Antifungal susceptibility was determined. No clinical improvement was seen despite the use of voriconazole and voriconazole plus liposomal amphotericin-B combination treatment, contrarily multiple hepatic and splenic lesions were seen under antifungal therapy. Bone marrow aspiration showed that acute myeloid leukemia was on remission. In this case it was concluded that voriconazole treatment may not be useful in the treatment of disseminated Trichosporon asahii infection and best treatment modality of Trichosporon asahii still remains controversial.

Key Words: *Trichosporon asahii, voriconazole, acute leukemia.*

ÖZET

Trichosporon asahii derin ve yaygın trikosporonozis infeksiyonun en önemli etkenlerinden biridir. Uzun süren nötropenide prognozu oldukça kötüdür. Bu olgu sunumunda 20 yaşında yaygın Trichosporon asahii infeksiyonu gelişen akut miyeloid lösemili bir hastada antifungal tedavi başarısızlığı bildirildi. Antifungal duyarlılığına göre vorikonazol ve "vorikonazol + lipozomal amfoterisin-B kombinasyon" tedavisi verilmesine rağmen hastada herhangi bir klinik düzelme izlenmedi. Antifungal tedavi altında hastada karaciğer ve dalakta lezyon tespit edildi. Kemik iliği değerlendirmesinde akut löseminin remisyonunda olduğu görüldü. Bu olgu sunumunda yaygın Trichosporon asahii infeksiyonunda literatürün aksine vorikonazol tedavisinin etkin olmayabileceği ve en iyi tedavi yönteminin halen net olmadığı sonucuna varıldı.

Anahtar Kelimeler: *Trichosporon asahii, vorikonazol, akut lösemi.*

INTRODUCTION

Trichosporonosis is seen in immunocompromised patients, particularly those with hematologic malignancies who are undergoing chemotherapy. The genus *Trichosporon* spp. can cause a disseminated invasive infection known as trichosporonosis (1,2). By using the new molecular techniques *Trichosporon* genus has been revised and eight species are associated with human infection: *T. asahii*, *T. asteroides*, *T. cutaneum*, *T. inkin*, *T. mucoides*, *T. ovoides*, *T. pullulans*, and *T. lobubieri* (3,4). The *Trichosporon* spp., particularly *T. asahii*, may constitute a part of normal flora of the human skin, oral cavity urinary tract and lower gastrointestinal tract (5). Therefore, the presence of *Trichosporon* spp. in the sputum, feces, and urine specimens does not indicate true infection. However detection of *Trichosporon* spp. in aseptic specimens, such as blood, spinal fluid, or pleural effusion, is clinically important (6). We report a case of disseminated *Trichosporon asahii* infection in a patient with acute leukemia who did not respond to voriconazole and voriconazole plus liposomal amphotericin-B combination treatment.

CASE REPORT

A 20-year-old female was admitted to Dedeman Oncology Hospital. She had symptoms of fever and progressive fatigue. The diagnosis of acute myeloid leukemia was established. Antracyclin and cytarabine was started as induction chemotherapy. She became neutropenic and subsequently developed fever exceeding 39°C. The blood cultures were negative for fungus and bacteria. The clinical isolates from sputum and urine samples also did not yield any culture positivity. On initial evaluation galactomannan, beta-D-glucan, and CMV PCR levels were in normal limits. Despite use of various antibiotics, including meropenem and teicoplanin intermittent fever with a temperature up to 39°C persisted. Bone marrow aspiration showed that acute myeloid leukemia was on remission. There was no pathological sign on abdominal, thoracic and cranial CT scans. *Trichosporon* species grew on blood cultures three weeks after initiation of chemotherapy. The fungi spp. growth on sabura-dextrose agar and yeast colonies showed white to cream colors. The fungi spp. was identified with the use of the API 20C Aux yeast identification system (bioMérieux). The isolate was classified as *Trichosporon asahii* with an approximately 80% certainty (API 20C Aux 6745776). Antifungal susceptibilities were determined by using RPMI 1640 media, and the following MICs were found: amphotericin B, 0.50 µL/mL; voriconazole, 0.125 µL/mL; and it

was resistance to caspofungin. The patient was started on voriconazole therapy at a loading dose of 6 mg/kg for day one followed by 4 mg/kg twice a day.

Blood cultures (BacT/Alert; bioMérieux, Durham, N.C.) were positive in two consecutive blood cultures after initiation of antifungal therapy. Beta-D glucan level was higher than 523 pg/mL and remained high in six consecutive blood samples, but simultaneous galactomannan levels were negative. Culture from the indwelling catheter-tip showed no growth. Other diagnostic evaluations including transthoracic echocardiogram, computed tomography of paranasal sinus, chest, abdomen, and pelvis performed at that time were unrevealing. CMV PCR levels were also negative. The patient developed abdominal pain and liver function tests (LFTs) were elevated, with the following peak values: alkaline phosphatase, 876 U/liter; aspartate aminotransferase, 276 U/liter; alanine aminotransferase, 369 U/liter; total bilirubin, 4.5 mg/dL; and direct bilirubin, 2.8 mg/dL. Abdominal pain worsened and fever persisted despite the use of voriconazole. Hepatosplenomegaly was detected on physical examination. There were no skin lesions. Contrast-enhanced abdominal computed tomography and MRI revealed multiple hypodense liver and spleen lesions and hepatosplenomegaly (Figure 1).

Given the need for further treatment and according to the radiological findings, the patient underwent a liver biopsy. Histopathological examination revealed submassive tissue necrosis with fungal element markers including septate hyphae (Figure 2). A follow-up computed tomography and MR revealed progression of the hepatic lesions and enlargement. Amphotericin-B lipid complex at a dose of 5 mg/kg/day was added to her



Figure 1. Multiple hypodense liver and spleen lesions.

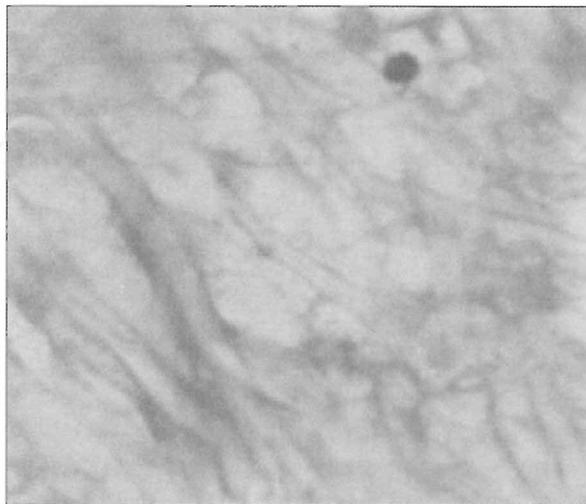


Figure 2. Submassive tissue necrosis with fungal element markers including septate hyphae.

therapy. She continued to be symptomatic; due to the severity of illness and decreased performance status, a decision was made to go on antifungal and antibiotic treatment. The patient died on september 2008.

DISCUSSION

Invasive trichosporonosis is a rare, emerging, life-threatening fungal infection that may develop rapid clinical symptoms (3,7). In a previous multicenter study performed in Italy it was detected that the incidence of trichosporonosis in acute leukemia patients was 0,4% (3). The prognosis of disseminated trichosporonosis is usually poor in neutropenic patients with a mortality rate of approximately 80% (8-10). Early attempts to treat this infection with amphotericin B has controversial results in trichosporonosis and sometimes combined therapy may be unsuccessful (11,12). Echinocandins have no reliable activity against *Trichosporon* spp. and are not recommended for trichosporonosis treatment (10,13,14). With the new advances in triazole antifungal compounds, successful treatment of trichosporonosis became possible. Fluconazole, itraconazole, ketoconazole and voriconazole have all been reported to be effective in the treatment of *Trichosporon* spp. infection (11,15-17). The recent in vitro study suggested that the new azoles (voriconazole, posaconazole, ravuconazole) are superior to amphotericin-B. In some other studies therapeutic failure was seen after fluconazole, voriconazole and liposomal amphotericin-B treatment (18,19). The in vivo and in vitro efficacy of the antifungal drugs does not correlate all the time (4).

The review of the literature revealed that clinical manifestations were fever (90%), cutaneous lesions (43%), lung involvement (30%), hepatic abscesses (6%), splenic abscesses (4%), bone/joint (3%), retinal lesions (3%) (1). In our case the frequent features such as cutaneous lesions and lung involvement were not seen. Although hepatic and splenic abscesses were revealed in the literature to our knowledge there was no report about coexistence of both hepatic and splenic abscesses in disseminated *Trichosporon* spp. infection. In our case both hepatic and splenic abscesses were seen.

White blood cell recovery is a very important factor for a favourable outcome in these patients; although bone marrow aspiration showed that acute myeloid leukemia was on remission progression was seen in our patient. In a case serum galactomannan increment was seen, there was no increase in galactomannan levels in our case but there was a significant increase in Beta-D glucan levels (16). In a recent study it was shown that only in a few patients 1,3-beta-d-glucan levels were elevated before positive blood culture. In the cases that do not respond to antifungal therapy should be evaluated about *Trichosporon* spp. infection and its antifungal susceptibility (20).

Combination therapy of amphotericin-B and voriconazole was not effective in the treatment of our patient. In addition hepatic and splenic lesions were detected and progression was seen under antifungal therapy. Certainly, *Trichosporon* spp. infection is the second most seen agent of disseminated yeast infection that should be considered in the differential diagnosis of immunosuppressive patients who develop signs of septicemia or local infection, especially patients who are already receiving chemotherapy due to hematological malignancies. Combination therapy seems to be effective according to the literature but treating patients with trichosporonosis still remains a challenge.

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