Clinical microbiological case: chronic disseminated candidiasis unresponsive to treatment

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CASE REPORT

A 24-year-old male patient with acute myeloid leukemia (AML), who had been in remission for 18 months following the completion of chemotherapy, presented with fatigue and nasal bleeding. He was found to have pancytopenia, and bone marrow aspiration showed relapsed AML. He was given high-dose sequential chemotherapy consisting of cytosine arabinoside, 500 mg/m^2 per day as a 24-h continuous infusion, idarubicin, 12 mg/m^2 per day on days 1–3, etoposide, 200 mg/m^2 per day as a 24-h continuous infusion on days 8–10, and granulocyte colony-stimulating factor (G-CSF), 5 μg/kg per day subcutaneously, starting from day 12 until absolute neutrophil recovery above 1000/mL. The patient became neutropenic, with a count below 100/mL, on the 5th day of chemotherapy. He was pyrexial on the next day, with a temperature of 39 °C, without any localizing symptoms or signs of infection. Blood cultures were taken, and chest X-ray was normal. Empirical antibiotic therapy with piperacillin–tazobactam was commenced, and vancomycin was added 48 h later, when no response was obtained. Examination revealed widespread oral mucositis on the fourth day of the febrile neutropenic episode. Blood cultures, which had been taken every other febrile day, revealed extended-spectrum β-lactamase-producing *Escherichia coli* on the seventh day of pyrexia, and meropenem and amikacin were substituted for piperacillin–tazobactam. Total parenteral nutrition was also commenced on the same date, as the patient now suffered from severe dysphagia and could not tolerate any oral intake. Fever and dysphagia continued, and an endoscopy was performed, revealing esophageal candidiasis on the 12th day of pyrexia. Fluconazole, 6 mg/kg per day, was commenced intravenously. A non-*albicans Candida* sp. was grown in both esophageal and blood cultures on the 14th day of pyrexia, and fluconazole was changed to amphotericin B deoxycholate, 0.7 mg/kg per day, due to continuing pyrexia and the possibility of a fluconazole-resistant *Candida* sp. Surprisingly, two different non-*albicans Candida* species were identified later, with esophageal cultures revealing *C. krusei*, whereas blood cultures yielded *C. kefyr* with a fluconazole MIC of 4 mg/L and an amphotericin B deoxycholate MIC of 0.25 mg/L. Fundoscopic examination was negative for candida retinitis. The patient's neutrophil count rose above 500/mL on the 19th day of pyrexia (25th day following chemotherapy). Mucositis and dysphagia gradually resolved with a subsequent increase in the oral intake, and parenteral nutrition was terminated. However, pyrexia reaching 39 °C continued. Amphotericin B deoxycholate was replaced with liposomal amphotericin B, 100 mg, daily due to hypokalemia refractory to intravenous replacement therapy, and meropenem, amikacin and vancomycin treatment was terminated on the 26th day of pyrexia. The patient remained febrile, and liver transaminase levels were found to be elevated. Abdominal CT on the 33rd day of pyrexia demonstrated numerous, prominent hypodense lesions within the spleen, and few lesions in the liver and kidneys, consistent with abscesses. A diagnosis of chronic disseminated candidiasis (CDC) was made. A bone marrow aspirate at this stage confirmed that the patient's AML was still

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in remission. He remained febrile with no change in his clinical condition after a total of 45 days of therapy (24 days and 1.2-g total dose of amphotericin B deoxycholate, and 21 days and 2.1-g total dose of liposomal amphotericin B). A control abdominal CT on the 55th day of pyrexia revealed no improvement of the lesions.

QUESTIONS

1. How would you proceed at this stage?
2. What is the role of different forms of amphotericin B in the management of CDC?
3. What is the role of fluconazole in the management of CDC?