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Risk factors in a patient with fungemia caused by fluconazole-resistant *Candida albicans*

Case report

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Abstract: Blood stream infections due to Candida species are becoming increasingly important causes of morbidity and mortality in hospitalized patients. Risk factors that predispose patients to developing invasive *Candida* infections have been documented as, iatrogenic and/or nosocomial conditions and immunosuppression. In the present report, we want to emphasize the risk factors that predispose individuals to the development of candidemia, particularly those that are relevant to our patient. We describe a female patient with diabetes mellitus who had been receiving glucocorticoids for 20 years as replacement therapy for hypopituitarism resulting from hypophysis adenoma surgery. The patient received antibiotic therapy for recurrent wound infections and was hospitalized for a long time, including a period in the intensive care unit and instrumented. The patient eventually succumbed to fungemia caused by a fluconazole-resistant strain of *C. albicans* strain.

Keywords: Fungemia • Risk factors • C. albicans • Fluconazole resistance • Diabetes mellitus • Glucocorticoid

1. Introduction

Over the past several decades, the incidence of nosocomial fungal infections has increased dramatically. Numerous studies have defined the risk factors that predispose patients to developing invasive *Candida* infections. The predominant risk factors are iatrogenic and/or nosocomial conditions and immunosuppression. The factors responsible for the development of these infections are anticipated to become more prevalent over the coming decades, predicting an upward trend in the incidence of invasive fungal infections in the nosocomial setting [1-3].

Recent studies have shown *Candida* spp. to be the third most frequent nosocomial bloodstream isolate. The predominant species in terms of invasive *Candida* infections is *C. albicans*, although there has been a steady increase in invasive non-*albicans* species [1,4].

The present case study concerns a patient with diabetes mellitus who received broad-spectrum antibiotics and corticosteroid therapy, and who subsequently developed fungemia caused by a fluconazole-resistant *C. albicans* strain.

2. Case report

The 55 year old female subject had diabetes mellitus and had been operated on for a hypophysis adenoma 20 years ago. Since that surgery, she had been taking prednisolone, L-tyroxine sodium replacement therapy, and insulin for diabetes mellitus. She was admitted to the Duzce University Hospital with a persistent lesion on her left elbow. The lesion had persisted for 4 months and she had been treated with oral antibiotic therapy (ciprofloxacin and cefadroxil) in a local state hospital. On examination, a 1.0×1.5-cm lesion with purulent discharge was noted on the dorsal aspect of the elbow. The sedimentation rate was 20 mm/hour and there was evidence of mild leukocytosis. *Acinetobacter baumanii*

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was isolated from the cultures, so imipenem (4 × 500 mg) and amikacin sulfate (2 × 500 mg i.v.) infusion therapies were started. By the 13th day of antibiotic therapy, the lesion had healed completely and the patient was discharged.

One month later, the subject was readmitted to the hospital. On examination, she was conscious with blood pressure of 120/80 mmHg, heart rate of 84 beats/min, body temperature of 36.7°C, and sedimentation rate of 24 mm/hour. She exhibited spontaneous respiration and her respiratory sounds were normal with a rate of 22 breaths/minute. She exhibited swelling, redness, pain, and an ulcerated lesion (2.0 × 3.5 cm) on her left elbow. The elbow lesion was excised and debrided, and cultures were obtained. Antibiotic therapy was initiated with sultamicillin at 1.5 g four times per day. On bone scintigraphy, osteomyelitis of the ulna was detected. From the cultures, *A. baumanii* and *C. albicans* were isolated. Therefore, cefazoline sodium (3 × 1 g. iv) and imipenem (4 × 500 mg iv) infusions, and fluconazole (400 mg/day, po) were administered. On the 23rd day of therapy, fungal growth was noted in pure cultures of the blood specimens, and *C. albicans* was identified using the API–20C Aux identification system (bioMérieux, Marcy l'Etoile, France). Antifungal susceptibility testing with the API ATB Fungus system (bioMérieux) revealed resistance to fluconazole (MIC, 128 µg/ml), so antifungal therapy with amphotericin B deoxycholate (0.7 mg/kg/d) was initiated. Despite all these therapies, the condition of the patient was compromised, and she was transferred to the intensive care unit and intubated. Subsequently, multiple blood cultures were positive for *C. albicans* and the patient died in the intensive care unit.

3. Discussion

Invasive fungal infections, such as candidemia caused by *Candida* species, are increasing in incidence and are associated with high mortality. Iatrogenic and nosocomial conditions, such as colonization, use of broad-spectrum antibiotics, central venous catheterization, parenteral nutrition, gastrointestinal or cardiac surgery, prolonged hospital stay, intensive care unit stay, burns, and premature neonatal condition, as well as immunosuppression, which may involve neutropenia, corticosteroid use, HIV infection, and diabetes mellitus, are major risk factors for candidemia [1,5,6].

Diabetes mellitus, Cushing's syndrome, hypoparathyroidism, hypothyroidism, and polyendocrinopathy are endocrine diseases that are associated with increased susceptibility to infection. The mechanisms by which diabetes mellitus increases

infection susceptibility include increased tissue glucose level, altered yeast adhesion, and decreased phagocytosis [7,8]. Although the cellular and immune mechanisms remain controversial, various *in vitro* studies have demonstrated significant defects in T-lymphocyte function, opsonization, natural killer cell activity, and memory CD4+ cell populations. Recent studies have shown abnormalities of signal transduction, in which insulinopenia itself and other factors, such as circulating immune complexes, may be involved [9].

The major form of immunosuppression that predisposes to the development of disseminated candidiasis is a defect in phagocytic activity. Neutropenia and glucocorticoids increase the risk of disseminated candidiasis by suppressing phagocyte function [10,11].

Antibiotic usage is another factor that influences the onset of fungal infections. Antibiotics damage the ecology and niche of microorganisms in the bowel and on body surfaces, thereby permitting the overgrowth of *Candida* and undesirable bacteria [12].

In addition, disruption of normal skin barriers, through burn injury or percutaneous catheter placement, and disruption of gut mucosal barriers, by abdominal surgery, instrumentation, induction of mucositis, or mucosal atrophy from radiation or parenteral nutrition, are major risk factors for invasive *Candida* infections [1].

Prolonged hospital stay is another risk factor; the mean time to onset of disease in a recent, large prospective study was 22 days of hospitalization [13].

The patient described in our case study presented with several risk factors for candidemia, i.e., diabetes mellitus, receiving antibiotic therapy, long hospital stay including a period in the intensive care unit and instrumentation. Furthermore, the patient had been receiving glucocorticoids for 20 years as replacement therapy for hypopituitarism, which was the result of hypophysis adenoma surgery.

Due to the difficulties associated with confirmatory laboratory testing, empirical administration of therapy, usually fluconazole, is often based on a clinical diagnosis of disseminated candidiasis [14]. Although fluconazole-resistant strains of *C. albicans* strains remain rare [15], an increase in the incidence of resistance has been reported recently [16,17]. Our patient received empiric fluconazole therapy. However, after the onset of fungemia, antifungal susceptibility testing revealed fluconazole resistance. Azole therapy for the elbow lesion seems to have led to fluconazole resistance and treatment failure.

In the present report, we want to emphasize the risk factors that predispose individuals to the development of candidemia, particularly those that are relevant to our patient. Fluconazole resistance in *C. albicans* strains is

rare but requires vigilance. For patients with fungemia, evaluation of blood cultures and antifungal susceptibility testing are recommended, to prevent treatment failure and to reduce patient mortality.

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