Emergence of Resistance to Amphotericin B During Therapy for Candida glabrata Infection in an Immunocompetent Host

Resistance in Candida species to amphotericin B, a polyene macrolide antimicrobial agent, is rare [1]. Almost all described cases of resistance to amphotericin B have occurred in immunocompromised hosts [1–4]. Additional risk factors include extensive chemotherapy with cytotoxic agents, granulocytopenia, and long-term treatment with both antibacterial and polyene antibiotics [1]. Primary resistance to amphotericin B has been described in immunocompetent patients who developed fungemia due to Candida lusitaniae [4] and Candida albicans [5] after receiving prolonged antibiotic therapy. Emergence of resistance to amphotericin B during therapy for infection due to C. albicans [1], C. lusitaniae [3], and Candida guilliermondii [6] has been documented in immunocompromised hosts. We report the in vivo development of amphotericin B resistance in an immunocompetent host infected with Candida glabrata.

A 79-year-old woman with a 4-year history of calcium oxalate kidney stones developed recurrent urinary tract infections. She had a history of glucose intolerance (diet controlled) and stage I endometrial cancer for which she had undergone total abdominal hysterectomy; there was no history of chemotherapy or cirrhosis. She was seronegative for antibodies to HIV.

After 1 year of recurrent urinary tract infections, the patient underwent retrograde ureterography and cystoscopy, which showed a left ureteral stricture and pus draining from the ureterovesical junction. A ureteral stent was placed. Within hours, she developed sepsis. Two cultures of blood and a culture of urine all yielded C. glabrata. She was treated with intravenous fluconazole (400 mg daily) for 7 days, and her condition clinically improved; therapy was then switched to oral fluconazole (100 mg daily). Fluconazole therapy was discontinued after several weeks, and her dysuria quickly recurred. Cultures of urine again yielded C. glabrata, and a study of the left renal pelvis with contrast medium given via nephrostomy showed multiple filling defects in the pelvis, which were consistent with mycetomas.

Fluconazole therapy was restarted. Within days, amphotericin B (0.5 mg/[kg·d]) was substituted for fluconazole. However, the level of serum creatinine rose above 3.3 mg/dL after 10 days of therapy, so amphotericin B was discontinued and fluconazole therapy (100 mg/d) was restarted. Her symptoms resolved, the mycetomas cleared, urine cultures became negative, and the patient’s level of serum creatinine dropped to 0.8 mg/dL. Fluconazole was stopped after 6 weeks.

Within 8 days, urine cultures yielded C. glabrata, and fluconazole therapy was immediately resumed. Seven weeks later, she developed fever and chills; despite ongoing fluconazole therapy, cultures of urine continued to yield C. glabrata. Obstruction of the right ureter at the ureterovesical junction, caused by local inflammatory edema, was documented. Ketoconazole (400 mg iv daily) therapy was substituted for fluconazole, and bilateral ureteral stents were placed. A 2-week course of ketoconazole did not produce any response, and that drug was replaced with amphotericin B. Drug susceptibility testing of the C. glabrata isolate from the patient’s urine revealed that the MIC of amphotericin B for the organism was 0.06 μg/mL. Nonetheless, despite the fact that she had received a total amphotericin B dose of 2.6 g over 59 days, her urine failed to clear, and she had repeated bouts of sepsis associated with urologic manipulations; bacterial and fungal cultures of blood were negative.

A left nephrectomy was performed because of the intractable ureteral stricture, but the procedure failed to eradicate the infection. Treatment with amphotericin B was continued without interruption. On day 78 of amphotericin B therapy (cumulative dose, 3.5 g), susceptibility testing of the fungal isolates from her urine continued to show that the MIC of amphotericin B was 0.06 μg/mL. On day 129 of amphotericin B therapy (cumulative dose, 5.1 g), a right nephrectomy was performed in the hope of eradicating the persistent source of fungal infection. She appeared to respond but died suddenly 2 weeks after the second nephrectomy. In vitro testing of C. glabrata isolated from the excised right kidney showed that the MIC of amphotericin B was 4.0 μg/mL.

In vitro susceptibility testing of amphotericin B was performed at SmithKline Beecham Clinical Laboratories (Tucker, GA). Isolates were grown in yeast nitrogen broth. Susceptibility testing was performed via the microtiter plate technique with use of the antibiotic medium 3 FDA [7]. Each isolate was run simultaneously against reference strain C. glabrata ATCC (American Type Culture Collection) 90030, for which the MIC of amphotericin B was 0.06–0.25 μg/mL. The patient’s isolates were not tested in parallel against each other.

There is one prior report of the development of amphotericin B resistance during treatment of a candida infection in an immunocompetent host [2], but the patient had defective leukocyte function and diabetes mellitus. In the patient reported herein, inadequate natural drainage of the kidneys secondary to strictures and persistent foci of infection in her renal stones and prosthetic stents contributed to the refractory nature of the C. glabrata infection. The prolonged C. glabrata infection and concomitant exposure to amphotericin B may have contributed to the development of resistance [1]. The decrease and eventual loss of ergosterol is the proposed mechanism of resistance to polyene antibiotics [1–3, 6]. In addition, C. glabrata is haploid (unlike C. albicans, which is diploid) and therefore more prone to mutation and the development of resistance [8].

The MICs of antifungals may vary greatly according to differing test conditions [9], and there is no generally accepted cutoff MIC for antifungal resistance. However, the increase in the MIC for this patient’s C. glabrata isolate, as determined using a medium that reliably detects amphotericin B resistance [10], coupled with the failure to eradicate the infection, suggests that resistance to amphotericin B did in fact develop.

The findings in this case demonstrate that resistance to amphotericin B can develop during prolonged courses of therapy, even in immunocompetent hosts. Susceptibility testing of Candida species, especially non-albicans species, should be performed in cases like...
ours and in the previously mentioned settings where the possibility of resistance to polyene antibiotics is increased.

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References

Pseudomonal Necrotizing Enterocolitis in a Patient with Polymyositis

Necrotizing enterocolitis is a rare condition characterized by necrosis of the bowel related to bacterial or fungal invasion of the ileal or colonic wall [1]. It usually affects neonates, but it has also been occasionally described as occurring in adults who are neutropenic as a result of acute leukemia, aplastic anemia, cyclic neutropenia, Felty’s syndrome, or chemotherapy [2–4]. We recently observed a nonneutropenic adult in whom severe necrotizing enterocolitis developed while she was receiving steroid therapy for polymyositis.

A 71-year-old woman was admitted to the hospital because of abdominal pain of recent onset. She was treated with prednisolone (8 mg daily) for polymyositis, diagnosed 5 months earlier. Non-insulin-dependent diabetes mellitus, which had developed as a consequence of obesity and corticotherapy, had been diagnosed recently.

Ten hours prior to admission, she started to complain of sudden periumbilical pain and nausea and was referred to our hospital. On physical examination, diffuse abdominal tenderness to palpation and peritoneal signs were noted. Her temperature was 35.3°C; blood pressure, 110/80 mm Hg; and pulse rate, 120.

Laboratory investigations revealed the following values: leukocytes, 9,700/mm³, with 86% polymorphonuclear neutrophils; hemoglobin, 16.3 g/dL; platelets, 273,000/mm³; glucose, 201 mg/dL; lactate dehydrogenase, 970 U/L (normal, <480 U/L); and liver enzymes (aspartate aminotransferase, glutamate-pyruvate transaminase, gamma-glutamyl transferase, and alkaline phosphatase) and creatinine phosphokinase, all normal.

A plain film of the abdomen was unremarkable, but abdominal ultrasonography and CT scanning showed a thickening of the bowel wall in the right and left gutters, with a small amount of free abdominal fluid.

As the clinical status rapidly deteriorated in relation to septic manifestations (hypotension, hypothermia, and cyanosis), surgery was undertaken. The presumptive diagnosis was ischemic colitis.

At surgery, 500 mL of ascitic fluid was removed. The colon was grossly necrotic from the cecum to the sigmoid, and spots of necrosis (3 cm in diameter) were found in the terminal (50 cm) ileum. Mesenteric vasculature appeared normal. An ileocolic resection with ileostomy was performed. Culture of peritoneal fluid yielded Pseudomonas aeruginosa.

Pathological examination of the colon and terminal ileum revealed extensive necrosis in the mucosa, edema and congestion in the submucosa, and focal areas of necrosis and hemorrhage in the muscular layers, with localized granulocyte infiltration. Numerous colonies of gram-negative bacteria were present within the bowel wall in the cecum and right colo.

The immediate postoperative course was characterized by septic manifestations and acute renal failure. Because P. aeruginosa was repeatedly isolated from cultures of abdominal drainage fluid and blood, a second-look laparotomy was performed 3 days later. New spots of small-bowel necrosis were found in previously healthy areas. A 95-cm resection was performed. Besides spots of necrosis, vascular congestion with pericapillary gram-negative bacilli infiltration was observed histologically.

During the next 2 weeks, her condition improved progressively with systemic antibiotic therapy (ceftazidime, amikacin, and ornidazole), renal support, and ventilatory assistance. On day 18, however, her respiratory status deteriorated, and progressive hypoxemia associated with bilateral pulmonary infiltrates developed. Endotracheal aspirates yielded Aspergillus fumigatus, and therapy with amphotericin B was started. During the next 48 hours, major hemodynamic difficulties were encountered, and she ultimately died of refractory shock 20 days after admission.

At postmortem examination, angioinvasive pulmonary aspergillosis complicated by myocardial and renal microabscesses was