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Treatment of Candidal Cholangitis with Caspofungin Therapy in a Patient with a Liver Transplant: Documentation of Biliary Excretion of Caspofungin

Str—Cholangitis due to candidiasis is a rare infection in patients without predisposing factors, but it has become an increasingly recognized complication in patients who have received a liver transplant [1]. After liver transplantation is performed, strictures may develop in the extrahepatic biliary tract and lead to secondary sludge formation, which can predispose a patient to recurrent cholangitis. Cases of biliary candidiasis in patients with liver transplants are further complicated by the potential for infection with azole-resistant isolates [2] and the potential for pharmacologic interactions between immunosuppressants and other drugs [3]. Here, we present a case of recurrent polymicrobial cholangitis due to infection with *Candida albicans* in a patient with a liver transplant whose case was conservatively managed with percutaneous drainage and systemic antimicrobial therapy.

A 54-year-old man who had received a liver transplant 4 years earlier presented with fever and chills. The patient had been diagnosed 6 months earlier with recurrent cholangitis after imaging studies demonstrated markedly dilated hepatic ducts with numerous filling defects. Alkaline phosphatase levels were 5–10 times the normal level, and cultures of bile samples obtained from the patient were positive for *Enterococcus* species, *Streptococci milleri*, anaerobes, and *C. albicans*. Prior to admission, the patient had undergone multiple failed endoscopic procedures to relieve the biliary obstruction, and his case had been managed with external biliary drainage and chronic suppressive antimicrobial therapy with levofloxacin, metronidazole, and intrabiliary infusions of amphotericin and fluconazole. Microbiological testing of bile samples obtained from the patient at admission again yielded multiple organisms, including yeasts. Management of the patient's case was further complicated by elevated tacrolimus levels (which were 5 times greater than the target concentration) and chronic renal insufficiency.

The principal pathogen involved in the patient's infection was considered to be *Candida* species on the basis of a chronic candidal cast along the biliary tree. The patient was administered parenteral caspofungin therapy. The patient’s condition improved, and cultures of additional bile samples again showed the presence of fluconazole-susceptible *C. albicans*. Tacrolimus levels were adjusted, and the patient was discharged from the hospital and given a regimen of fluconazole in addition to combination amoxicillin-clavulanate for chronic suppressive antimicrobial therapy of polymicrobial cholangitis. Cultures of bile samples obtained from the patient 3 months after hospital discharge showed no growth of *C. albicans*.

After allowing all antifungal agents to washout, biliary excretion of caspofungin was measured by determining caspofungin levels in both serum and bile samples. Serum and bile samples were obtained 1 h after a 70-mg infusion of caspofungin, and additional bile samples were obtained at 2 h and 3 h after the infusion. An agar well diffusion bioassay with *C. albicans* ATCC 24933 as the assay organism was used to quantify levels of caspofungin in bile and serum samples. Levels of caspofungin in bile samples were as follows: 0.8 µg/mL at 1 h, 1.0 µg/mL at 2 h, and 0.6 µg/mL at 3 h after the infusion. In the serum sample, obtained 1 h after the infusion, the caspofungin level was 3.1 µg/mL. Bioassays have been successfully used to quantify antifungal agents and are comparable with high-performance liquid chromatography [4, 5].

The decision to use caspofungin therapy in treating our patient was influenced by several factors, including initial concerns over the recent emergence of azole resistance and possible drug interactions with fluconazole and tacrolimus. Finally, the presence of chronic renal insufficiency made treatment with systemic amphotericin a less attractive alternative. To our knowledge, this is the first report to document biliary caspofungin levels in samples obtained from a patient with a liver transplant. The level of caspofungin in the bile sample obtained 2 h after the infusion was ~30% of the level of caspofungin in the serum sample. This is greater than the in vitro MIC₅₀ of caspofungin for *C. albicans* (0.12 µg/mL) [6]. Whether this is clinically significant remains to be validated in clinical studies. However, caspofungin therapy may be considered for use in treating candidal biliary infection.

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References

Haemophilus influenzae Serotype e Meningitis in an Infant

Str—We read with great interest the article by Campos et al. [1], which described 26 cases of infection due to Haemophilus influenzae serotype e (Hie) that occurred in Spain after the introduction of widespread vaccination against H. influenzae type b (Hib). The clinical presentations of these patients included cases of both invasive and noninvasive disease. The median age of the patients was 35.5 years, and approximately one-half of the patients had previous underlying conditions. Of the 26 cases of Hie infection, only 5 occurred in children aged ≤5 years, and, of these, only 1 occurred in an infant who actually had a case of invasive disease (meningitis). On the basis of their data, Campos et al. [1] state that the clinical presentation of Hie disease does not resemble that of Hib disease and that Hie is quite an opportunistic pathogen (one more able to cause infection in patients with serious underlying disease than in healthy individuals, although severe infection in healthy children may sporadically occur).

In a previous study, we described the first reported cases of invasive Hie disease in Italy. These cases were recently detected through the active surveillance of invasive H. influenzae disease [3]. All cases occurred in adults, the majority of whom (4 of 5 patients) presented with severe underlying conditions. Molecular analysis of the isolates obtained from these patients demonstrated that all of the isolates contained a single copy of the capsulation locus, suggesting that the isolates did not possess unusual virulent traits related to the capsule.

However, we recently identified a case of meningitis due to Hie in a previously healthy 5-month-old female infant. In February 2003, the infant was hospitalized with fever and lethargy. Cultures of CSF and blood samples obtained from the infant grew mucoid colonies of H. influenzae. The infant had not previously received any dose of Hib-conjugate vaccine and had no obvious risk factors. No presence of underlying disorders was demonstrated. She was treated in the intensive care unit and received antimicrobial therapy with ceftriaxone and chloramphenicol for 8 days. An additional lumbar puncture was then performed, and culture of the CSF sample showed no growth. At the follow-up visit 3 months later, the child showed no neurological deficits. The H. influenzae isolate was sent to the national reference laboratory at the Istituto Superiore di Sanità (Rome), where serotyping by slide agglutination and capsular genotyping by PCR were performed [2]. The isolate was identified as Hie by both methods. Contrary to what Campos et al. [1] reported for the Spanish Hie isolates, no resistance to ampicillin, cefotaxime, ciprofloxacin, chloramphenicol, or azitromycin was detected. Like the previously identified Hie strains that were isolated from adults, this isolate contained a single copy of the cap e locus.

In conclusion, we describe a patient with a case of Hie infection whose clinical and epidemiological features strikingly resemble those associated with invasive Hib disease. Of note, both cases of Hie meningitis (the case we observed and the case reported by Campos et al. [1]) occurred in infants in the first months of life, when children are more prone to invasive disease. Few such cases have so far been described [4, 5]. Although we agree with the statement by Campos et al. [1] that Hie may, in many respects, be regarded as an opportunistic pathogen, we would like to emphasize the importance of reporting primary invasive infection caused by non-Hib strains in children, especially in countries where Hib vaccine coverage has reached high levels.

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