

FAILURE OF TREATMENT OF CRYPTOCOCCOSIS IN A NON-HIV INFECTED PATIENT

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Background: Most of the studies investigating the treatment of cryptococcosis in non-human immunodeficiency virus (HIV) infected patients have been with Amphotericin B (AmB) and 5-flucytosine (5FC). Retrospective studies indicate that treatment of this patient population with fluconazole (FCZ) is successful for most cryptococcal infections (88%). We report a case of cryptococcal cellulitis in a non-HIV patient who failed FCZ therapy.

Case: A 72 year-old man with a history of cirrhosis developed erythema around his left ankle. Medical history was significant for compensated cirrhosis with splenomegaly and pancytopenia. He was treated with different antibiotics for bacterial cellulitis without improvement for approximately one month. The lesion progressed over the entire left leg, leading to blisters and deep ulcers. He was admitted to the hospital with fever and hypotension, and cultures of the blood and wound grew *Cryptococcus neoformans*. His serum cryptococcal antigen (CrAg) was 1:512. He was started on FCZ 400mg/day with improvement. However, his leg infection required further surgical debridement and after 6 weeks of FCZ therapy he was transferred to our hospital for further care.

Cultures from his left lower extremity continued to show *C. neoformans*. Repeat serum CrAg was 1:256. HIV ELISA was negative. Susceptibility testing using standard microdilution methodology revealed a susceptible isolate (MIC to AmB and FCZ was 0.125 and 2, respectively). Additional nodular lesions were found on his right leg. Therapy was changed to liposomal-AmB and 5-FC. After 1 week, his repeat CrAg was 1:32. Despite aggressive care, his infection progressed and an amputation was performed. His status worsened and after discussions with the family, care was withdrawn.

Conclusion: We report a case of cryptococcosis in a non-HIV patient that failed FCZ therapy. Despite 6 weeks of FCZ, his serum CrAg was essentially unchanged, the patient's skin lesions did not improve, and new lesions developed on the other leg. We hypothesize FCZ failure despite susceptibility data for a number of reasons. First, he had multiple poor prognostic factors including age >60 and organ dysfunction. In addition, mortality is increased with delays in diagnosis due to atypical presentations, like cellulitis. Second, susceptibility testing is routinely performed at 35°C, however heteroresistance to azoles has been described at lower temperatures. The patient's core body temperature was lower due to his cirrhosis, and the location of the ulcerations around his ankles provided an even lower temperature. *Cryptococcus* may have been resistant to FCZ in this area despite *in vitro* data. Third, devitalized tissue in his wound provided a reservoir of infection due to poor penetration of FCZ. FCZ therapy for *C. neoformans* in HIV negative patients may be adequate for most infections. We caution its use in severe cellulitis with a high CrAg. Serum CrAg can be used to monitor response to therapy. In addition, adequate surgical debridement is necessary.