Successful treatment with isavuconazole and liposomal amphotericin B for relapsed HIV-associated cryptococcosis: A case report

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Introduction

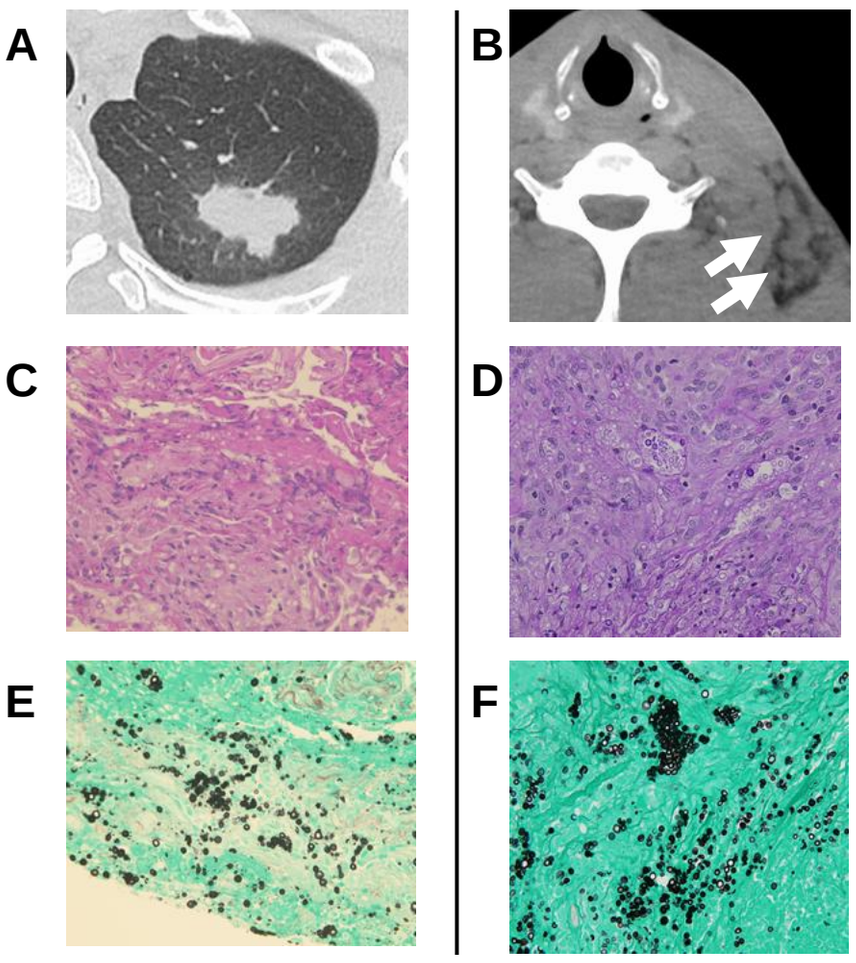
Disseminated cryptococcosis is a severe fungal infection. Standard treatment includes liposomal amphotericin B and flucytosine, followed by fluconazole. However, resistance to fluconazole is an increasing concern. Isavuconazole, a broad-spectrum triazole, has shown promise in clinical trials but remains off-label for cryptococcosis in the United States and Europe. We report a case of HIV-associated cryptococcal meningitis that relapsed as disseminated disease and was successfully treated with liposomal amphotericin B and isavuconazole.

Case Presentation

A Japanese man in his 20s was diagnosed with HIV-1 infection and cryptococcal meningitis. Due to intolerance to flucytosine, induction therapy with liposomal amphotericin B monotherapy was administered, followed by fluconazole (400 mg/day) for consolidation and 200 mg/day for maintenance **(first hospitalization).**

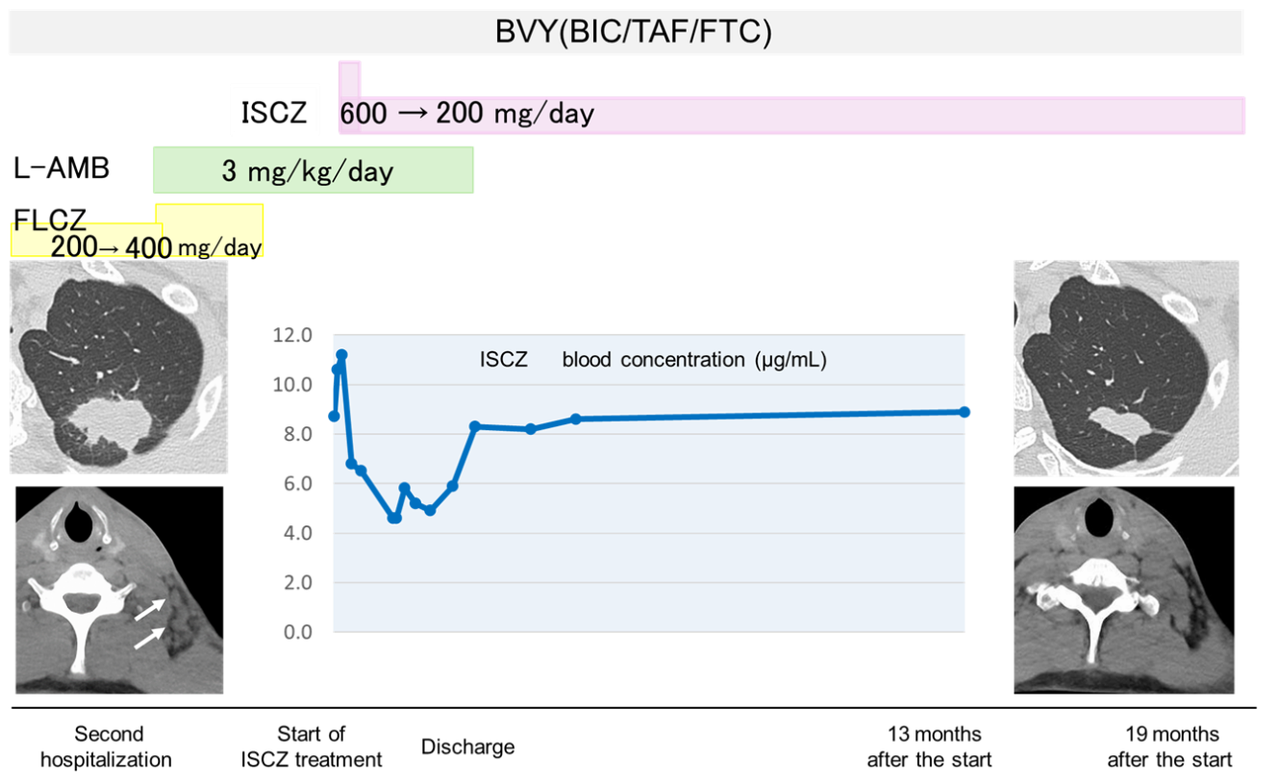
Four months into maintenance therapy, the patient developed fever and cough. Imaging and biopsies revealed disseminated cryptococcosis involving the lungs and cervical lymph nodes **(second hospitalization).**

Figure 1: CT images and pathological findings at second hospitalization



Chest CT revealed (A) a large nodule in the left upper lobe, (B) cervical lymphadenopathy. Histology showed round microorganisms in both lung and lymph node specimens, positive with (C,D) PAS and (E,F) Grocott's stains, consistent with *Cryptococcus spp.* (×40).

Figure 2: The clinical course during the second hospitalization



Although re-induction with fluconazole and liposomal amphotericin B was ineffective, a combination of isavuconazole and liposomal amphotericin B led to clinical improvement, and maintenance with oral isavuconazole achieved sustained disease control. Blood levels of isavuconazole was monitored for adequacy while treatment continued. The CD4-positive T lymphocyte count increased from 11 to 139/μL, and the cryptococcal antigen titer decreased from 1:2048 to 1:256.

Discussion

① Relapse of HIV-associated cryptococcosis

Relapse of cryptococcal meningitis is rare after ≥1 year of antifungal therapy in people living with HIV on antiretroviral therapy who are virologically suppressed or have CD4 counts ≥100 cells/mm³ [1].

In our case, inadequate induction therapy without flucytosine and profound CD4 lymphopenia (11/μL) likely contributed to relapse. Low fluconazole concentrations were unlikely, as standard doses were administered and no interacting drugs were used.

② Fluconazole resistance in *Cryptococcus*

Fluconazole resistance has been reported in 24.1% of relapse isolates [2].

In our case, the MIC for fluconazole at the initial episode was 4 μg/mL. However, *Cryptococcus* spp. was not isolated at relapse, so resistance could not be evaluated.

③ Treatment options for relapsed disseminated cryptococcosis

For patients intolerant to flucytosine, liposomal amphotericin B (3–4 mg/kg) plus high-dose fluconazole (800–1,200 mg/day) is recommended [3].

In our case, liposomal amphotericin B (3 mg/kg) plus fluconazole (400 mg/day) was ineffective. Higher fluconazole doses (800–1,200 mg) are not approved in Japan, and the patient relapsed while on standard-dose fluconazole.

④ Characteristics of isavuconazole

- Rapidly penetrates most tissues, including the brain, achieving potentially therapeutic concentrations in animal models [4]
- Low MIC against many fungi, including *Cryptococcus* spp. [5]
- Minimal CYP2C9 and CYP2C19 inhibition, fewer drug–drug interactions than voriconazole or posaconazole
- Fewer adverse effects such as visual disturbances, hallucinations, and photosensitivity compared with voriconazole [6]

In our case, isavuconazole appeared effective, as evidenced by clinical improvement after switching from fluconazole.

Conclusion

We report a relapsed case of HIV-associated disseminated cryptococcosis successfully treated with liposomal amphotericin B and isavuconazole. In general, MICs of isavuconazole against *Cryptococcus neoformans* are much lower than those of fluconazole. In addition, isavuconazole has excellent drug transferability to the central nervous system (CNS), representing a promising therapeutic option for cryptococcosis, including CNS infections.

References

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