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Case Report

Successful Treatment with Triple Therapy of Amphotericin B, Voriconazole and Flucytosine on an AIDS Patients with Severe Cryptococcal Meningitis

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A 35-year-old man (body weight = 63 kg) with AIDS complaining fever and headache after having commenced anti-retroviral therapy (ART) for a week was admitted to our hospital. Five lumbar punctures performed during 38 days could not confirm a cryptococcal meningitis (CM) based on staining or culture methods for cerebrospinal fluid (CSF). The disease quickly progressed with serious hearing/vision impairment and frequent onset of seizure and coma after being treated with corticosteroids for five days, and then CM was confirmed. Subsequent lumbar puncture showed elevated intracranial pressure as high as 870 mm H_2O, even though treated with standard anti-fungal regimens for CM. His disease was finally controlled by a new triple therapy with amphotericin B (0.7 mg•kg^{-1}•day^{-1}, intravenously), flucytosine (100 mg/kg perday, orally in four divided doses), and voriconazole (200 mg every 12 hours) and ART containing lamivudine (300 mg/day), stavuding (30 mg, twice a day) and efavirenz (300 mg, orally every night). Although it is rare, negative CSF stain or culture for cryptococci in AIDS patients with CM can persist for a long time. Corticosteroids should be used cautiously when an effective anti-fungal therapy is not administered. Triple therapy with amphotericin B, flucytosine and voriconazole may be selectively applied in severe CM. Voriconazole can be co-administered with efavirenz with modified dosing.

Key words: Cryptococcal meningitis; Anti-retroviral therapy; Corticosteroids; Voriconazole; Efavirenz

Cryptococcal meningitis (CM) is a common cause of mortality in advanced HIV infected patients. Recent data shows that approximately 1 million cases of cryptococcal meningitis occur each year, which may lead to more than 600,000 deaths.[1] Current clinical practice guidelines recommend amphotericin B deoxycholate [AmBd; 0.7 mg•kg^{-1}•day^{-1}, intravenously (IV)] plus flucytosine (100 mg•kg^{-1}•day^{-1}, orally in four divided doses) as the first line initial therapy for CM in AIDS, and high dose fluconazole (800 mg daily) in combination with AmBd can be chosen as an alternative therapy when flucytosine is unavailable. Despite access to advanced medical care, the 3-month mortality rate during management of acute CM approximates 20%.[2] New approaches to manage refractory or severe CM in AIDS still need to be developed. Although voriconazole showed excellent activity against cryptococci both in vitro and in animal model, it is not recommended for CM in AIDS due to its limited data in clinical practice, nor is it recommended for combination with efavirenz due to pharmacokinetic interactions leading to increased efavirenz and reduced voriconazole serum concentration.[2-5] The efficacy of voriconazole administered in combination with amphotericin B or flucytosine were also scarcely recognized in patients with CM. As far as we know, voriconazole-based triple therapy as a salvage therapy for severe CM in AIDS is not well reported.

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CASE PRESENTATION

A 35-year-old man with AIDS (HIV-1 antibody positive, $CD4^+$ lymphocytes = 32 cells/μl, body weight = 63 kg) complaining fever and headache after having commenced ART with lamivudine (300 mg once daily) and stavuding (30 mg, twice daily) and efavirenz (600 mg, once daily) for a week was admitted to our hospital. The physical examination was normal except for a stiff neck and oral thrush. Lumbar puncture showed normal cerebrospinal fluid (CSF): opening

pressure (120 mm H_2O), slightly elevated white blood cell count (WBC, 16×10^6/L) and relatively normal biochemical parameters. India ink prepatation, alcian blue staining and CSF culture showed a negative result for CM (Figure 1a). Plasma cytomegalovirus DNA was 3.46×10^3 copies/ml. The patient was firstly diagnosed as viral meningitis and treated with ganciclovir as well as adjunctive corticosteroids for relief of the fever. Fluconazole (400 mg/day) was also added for oral candidiasis. Symptoms were controlled and the patient felt well except for occasional dizziness. Headache reoccurred after 38 days during when five lumbar punctures were performed, which showed relatively normal CSF biochemistry and pressure findings. India ink preparation, alcian blue staining and CSF/blood culture couldn't confirm CM. Diagnostic anti-tuberculosis treatment with isoniazid (900 mg/day, IV), pyrazinamide (1,500 mg/day, orally), ethambutol (1,000 mg/day, orally) and amikacin (400 mg/day, IV) was initiated in combination with dexamethasone (10 mg/day). Fever reappeared 3 days later and the CD4 cell count increased to 101 cells/μl. Immune reconstitution inflammatory syndrome was suspected. Then the patient received meprednisone (160 mg/day) for two days. Fever and headache exacerbated and seizure occurred. Lumbar puncture showed elevated CSF opening pressure (620 mm H_2O) and WBC count (140×10^6/L), worsened biochemical parameters (glucose 0.2 mmol/L, protein 1086 mg/L), and positive culture and stain for cryptococcus neoformans (Figure 1b).

As flucytosine was unavailable in our hospital at that time, amphotericin B deoxycholate (AmBd, 0.7 $mg \cdot kg^{-1} \cdot day^{-1}$, IV) and fluconazole (800 mg/day, IV) were administered based on the established practice guidelines.[2] Five days later, as flucytosine was available and the patient's symptoms were still not under control, regimen was changed to AmBd plus flucytosine (100 $mg \cdot kg^{-1} \cdot day^{-1}$, orally in four divided doses). The patient's disease still progressed with serious hearing/vision impairment and frequent onset of seizure and coma. Lumbar puncture performed after two days showed a very high CSF opening pressure (870 mm H_2O) even though 20-40 ml CSF was removed daily by lumbar puncture and 250 ml of 20% mannitol was supplied every 40-60 minutes (IV). Voriconazole (200 mg every 12 hours, IV) was added and dosage of efavirenz was adjusted to 300 mg every night.

The CSF was sterile after 10 days triple anti-fungal therapy with amphotericin B, flucytosine and voriconazole. Voriconazole was then administered orally with the same dose. This triple therapy was continued up to 32 days and was well tolerated. Efavirenz 600 mg once daily was continued when the induction therapy finished. At the end of the induction therapy, the patient did not completely recovered with slight headache, moderate hearing/vision impairment, elevated intracranial pressure (ICP, 300 mm H_2O) and low glucose lever (1.9 mmol/L) in CSF. However, the patient was unwilling to extend the induction therapy due to inconvenience of infusion and then given consolidation therapy with fluconazole (800 mg/day, orally) for 18 weeks until the ICP and CSF biochemical parameters became relatively normal. Subsequently, fluconazole (200 mg/day, orally) was given as a maintenance therapy. CD4 cell count gradually increased to 140 cells/μl eight months after commencing ART. Plasma HIV-RNA was negative after commencing ART for five months.

DISCUSSION

CM is lethal in AIDS patients if left untreated. Diagnosis can be based on positive CSF India ink staining or culture. Some other staining methods (e.g. Alcian Blue and Nuclear Fast Red staining) for cryptococci have been evaluated which also showed effective to confirm CM.[6] Negative CSF staining or culture for crytococci is rare in CM with AIDS. Repetitive negativity for a period as so long is rarely reported before. Some researchers showed that cryptococcal antigen titer test had enhanced diagnostic sensitivity,[7,8] but it is still unavailable in some

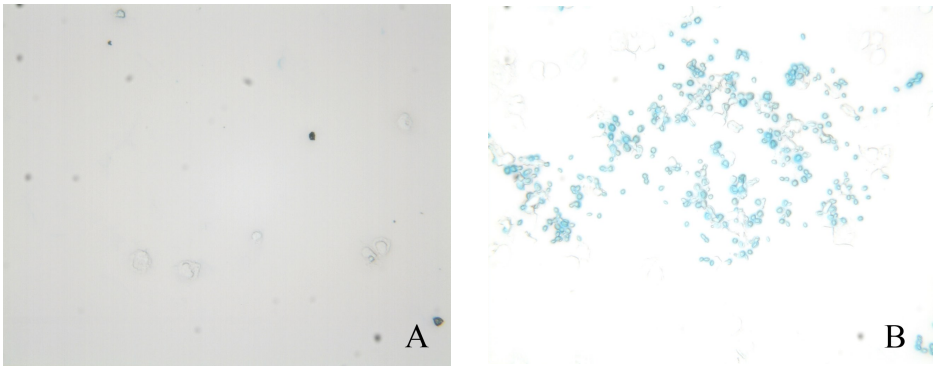

Figure 1. Alcian blue staining procedures for the presence of cryptococci in CSF (400 ×).
Notes: A: alcian blue staining showed a negative result for CM; B: yeast-like cryptococci were seen in CSF.

developing countries. Differential diagnosis between CM and tuberculous meningitis may be difficult when microbiologic evidence cannot be acquired. Corticosteroids should be used cautiously when CM couldn't be excluded because those drugs may quickly exacerbate CM without effective anti-fungal treatment, as shown in this case.

Both stringent control of elevated ICP and effective anti-fungal therapy are important for CM management. CSF drainage is recommended to relieve the increased ICP and mannitol is not prefered.[2] As for this patient, elevated ICP could not be controlled by frequently performed lumbar punctures. Recently, it is common that HIV infected patients are shut out on surgery in China, thus ventriculoperitoneal shunt cannot be performed for this patient in our hospital. Mannitol still required at his serious stage, otherwise he would have convulsion and then become unconscious.

Stepwise anti-fungal therapy containing induction therapy to sterilize the CSF which was followed by consolidation and maintenance therapy is generally accepted.[2] This patient's disease could not be controlled by gold standard induction therapy of AmBd plus flucytosine as well as AmBd plus fluconazole. Flucytosine and fluconazole are excreted through the kidney. Frequently administered mannitols, as shown in this case, may probably influence the metabolism of those drugs. Drug concentration in serum or CSF could not be measured due to limited resource, so it needs to be further evaluated. As the disease was still progressing, voriconazole was added with AmBd and flucytosine to form a triple therapy, which successfully sterilized the CSF. This triple therapy is promising and worth further studying.

Previous study alarmed that co-admistration of voriconazole with efavirenz was contradicted because of pharmacokinetic interactions between them.[5] Studies regarding the clinical outcome of voriconazole/efavirenz combination in patients with AIDS are scarce. To our knowledge, only one case report published recently can be referred that adequate concentrations of voriconazole in both plasma and cerebrospinal fluid were obtained and target plasma concentrations of efavirenz were achieved at final dose adjustment (voriconazole 200 mg, twice daily, plus efavirenz 300 mg, once daily, both administered orally).[9] This dose adjustment was further supported by this case.

This patient complained headache after commencing ART, which may be classified as unmasking cryptococcal IRIS (new presentation of cryptococcal disease after initiation of antiretroviral therapy) according to case definition proposed by Haddow.[10] The entity of unmasking cryptococcal is still controversial and need to be further modified. Long-time treatment is required for CM and it is hard to interpret whether a sterile CSF means permanently unviable cryptococci. Positive CSF staining for cryptoccocci may persist for a long time even though CSF is sterilized. During the treatment, static cryptococci may exist and it is hard to be completely eliminated by anti-fungal treatment without immune recognition. This may partially explain why elevated CD4 cell count is necessary for discontinuing maintenance therapy for CM patients.[2] As mentioned above, CM was quickly exacerbated by corticosteroid administration. This implies that immune defense may play a very important role in controlling this disease. However, inflammation may also be harmful, which is well recognized in septicemia.[11,12] Anti-inflammatory drugs may be helpful in this condition, and that is why corticosteroids are used to manage IRIS.[10] However, corticosteroids for cryptococcal IRIS without effective anti-fungal drugs are not preferred. Suppressed immune response may result in reactivation of the static cryptococci, which may lead to rapid deterioration of the patient's condition.

CONCLUSIONS

Although it is rare, negative CSF staining or culture for cryptococci in CM with AIDS can persist for a long time. Corticosteroid administration should be used cautiously in this condition when an effective anti-fungal therapy is not administered. Triple therapy with amphotericin B, flucytosine and voriconazole may be selectively used in severe CM, and co-administraion of voriconazole with efavirenz is safe and effective with modified dosing. More studies are needed for the nomenclature of cryptococcal IRIS.

Consent

Written informed consent was obtained from the patient for publication of this case report.

Conflict of interest

The authors declare that they have no competing interests.

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