Antifungals/immunosuppressants

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Cryptococcus gattii Meningoencephalitis, immune reconstitution syndrome and prolonged QTc: case report

A 55-year-old man developed *Cryptococcus gattii* meningoencephalitis leading to immune reconstitution syndrome during immunosuppressive therapy with mycophenolate, prednisone and tacrolimus. The antifungals therapy with amphotericin-b-liposomal, fluconazole and flucytosine contributed to the development of immune reconstitution syndrome and he also experienced prolonged QTc secondary to fluconazole [*routes and durations of treatments to reactions onsets not stated; not all dosages stated*].

The man presented to the hospital with cough, nausea, vomiting, neck pain, confusion and headaches. He had a significant history of renal transplantation (9 years prior) and immunosuppressive regimen included tacrolimus 1mg in the morning and 2mg in the evening, prednisone 5mg/day and mycophenolate 1000mg twice daily. Currently, he was disabled, but prior was an airline mechanic and a travel history to Philippines, Hong Kong, China and Surinam. No significant changes to his immunosuppressive regimen were noted in the months prior to hospitalisation. At current admission, his WBC count was 7.2×10^6/mL, creatinine was slightly elevated and non-reactive fourth-generation HIV antigen/antibody test. He underwent lumbar puncture and cerebrospinal fluid (CSF) opening pressure was above normal, WBC was 70 cell/µL (62% lymphocytes), glucose was 25 mg/dL and protein was 115 mg/dL. His CSF India ink stain was positive for meningoencephalitis and CSF polymerase chain reaction positive for *Cryptococcus neoformans/gattii*, but the culture yielded *Cryptococcus gattii*. Additionally, a cryptococcal antigen was reactive at a titer of 1:2560 in serum and CSF. However, dilated fundoscopic examination was negative for signs of cryptococcal intraocular invasion. His chest CT scan demonstrated 2 solid nodules in the right lung and biopsy of the nodule showed encapsulated yeast forms consistent with Cryptococcus.

Induction therapy with amphotericin-b-liposomal [liposomal amphotericin B] and flucytosine [5-flucytosine] was initiated and he was restarted on tacrolimus. On day 5 of hospitalisation, due to persistent confusion, an MRI of brain was performed and it showed multiple acute ischemic infarcts in the bilateral cerebellar hemispheres. Also, transthoracic echocardiogram with contrast showed a thrombus within the apex of the left ventricle. On day 9 of hospitalisation, his mental status improved to baseline. His culture test was negative and the CSF opening pressure normalised with persistent CSF pleocytosis. His antifungal therapy was switched to fluconazole in accordance with the guidelines. Although initial improvement was noted, but his mental status deteriorated along with recurrence of nausea and vomiting. Repeat lumbar puncture showed negative CSF culture with WBC of 205 cell/µL (95% lymphocytes) and CSF opening pressure was 15 cmH_2O. His serum absolute lymphocyte count had increased 2.5 fold times form the admission. Non-contrast brain CT was non-significant for new hemorrhagic or ischemic stroke. Treatment with dexamethasone was initiated due to immune reconstitution syndrome and tacrolimus was continued. However, he experienced prolonged QTc secondary to fluconazole and treatment was switched to isavuconazole. Thereafter, transition from dexamethasone to methylprednisone was carried out. Three days following isavuconazole and corticosteroids therapy, his QTc and metal status improved. A week after the corticosteroids therapy, he experienced nausea and vomiting. An MRI of brain showed new lacunar infarct of the left internal capsule and new enhancement of bilateral basal ganglia encompassing dilated perivascular spaces along with previously demonstrated changes. Following treatment with antiemetics and repeat corticosteroid, his symptoms improved. He was discharged on ciclosporin, isavuconazole and low dose of prednisone. It was concluded that immunosuppression lead to *Cryptococcus gattii* meningoencephalitis and immune reconstitution syndrome was secondary to reduction of immunosuppression, administration of antifungal therapy and *Cryptococcus gattii* meningoencephalitis.

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