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Case Report

Cerebral cryptococcoma successfully treated by isavuconazole in an immunocompetent patient: A case report [☆]

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ABSTRACT

Cryptococcosis has been recognized as an increasing cause of severe systemic mycosis in immunocompetent patients in the last few years. Cerebral cryptococcomas are a more uncommon manifestation of cryptococcal meningitis, which are not usually included in the differential of brain masses. We report a case of a young, immunocompetent woman that rapidly developed severe neurological deficits. She was ultimately diagnosed with cerebral cryptococcoma caused by both *Cryptococcus neoformans* and *Cryptococcus gattii*, and was treated with amphotericin B and isavuconazole. After several complications during hospitalization, including hydrocephalus and cerebellitis, she was discharged home on isavuconazole. On follow-up, she only complained of anosmia. We review the clinical and radiological findings of similar cases. It is the first time that this form of cryptococcal meningitis is favorably treated with isavuconazole and is caused by 2 species of *Cryptococcus*. We emphasize that cerebral cryptococcomas should be suspected in immunocompetent patients that present with brain masses.

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Introduction

Cryptococcosis is a systemic and invasive mycosis caused by fungi of the genus *Cryptococcus* sp., mainly *C. neoformans* and *C. gattii*. The latter is more globally distributed, but the former is responsible for approximately 95% of cases. Cryptococcal meningitis is the most common and severe presentation in immunosuppressed subjects, such as in late HIV infection and transplant patients, with an annual incidence of 223,000 cases and 180,000 deaths [1,2]. However, cryptococcosis may also occur in immunocompetent hosts, though in only 5% of cases. Its incidence has increased in the last few years in this population, due to still unknown reasons [2].

The disease transmission occurs by inhalation of *Cryptococcus* spores, initially infecting the lungs. The infectious propagules may also spread to the central nervous system (CNS), causing cryptococcal meningitis, meningoencephalitis, and cerebral cryptococcomas [1]. The main manifestations are meningism (a triad of nuchal rigidity, photophobia, and headache), fever, and intracranial hypertension [3]. Altered mental status, seizures, visual changes, and focal neurological deficits may occur as well [4].

Diagnosis is made by visualization of encapsulated yeasts in the cerebrospinal fluid (CSF) by staining with India Ink, with a sensitivity of 50% in immunocompetent individuals. Biopsy of lungs, skin, bone marrow, brain, and other organs may be performed as well, with a greater sensitivity than the first method. Other tests include CSF, sputum, and skin cultures [2].

The gold standard treatment is a combination of amphotericin B and 5-flucytosine during the induction phase, which aims to reduce fungal load, followed by oral fluconazole, in the maintenance phase. Cerebral cryptococcomas, on the other hand, require longer treatment duration associated with more antifungals [5].

We present a case of an immunocompetent woman with a cerebral cryptococcoma that was successfully treated with isavuconazole after a series of complications during her hospitalization.

Case report

A 20 year-old woman presented to the emergency department with right hemiparesis, nausea, vomiting, and vertigo. Physical examination showed bilateral abducens nerve palsy, right central facial palsy, left uvula and right tongue deviation, dysarthria, and 4-/5 muscle strength in right upper and lower limbs. She had a 1-week history of progressively severe frontal headaches, and 2 days before admission she developed slowness of speech, left deviation of angle of mouth, and diplopia. There was no history of smoking, substance abuse, or sexual intercourse. She lived in an area surrounded by eucalypti and her sister was a bird breeder.

On the same day of admission, she developed bilateral papilledema, hemorrhage and hard exudates on fundoscopy, peripheral facial palsy, hemiplegia, and right Babinski sign. A brain computed tomography (CT) scan showed a hypo-

dense lesion in the left internal capsule (Fig. 1). Analysis of CSF revealed an opening pressure of 100 mmH₂O, encapsulated yeast cells, and a positive culture for *Cryptococcus neoformans* and *Cryptococcus gattii*. Treatment with amphotericin B, fluconazole, and serial lumbar punctures was started. A brain magnetic resonance imaging (MRI) scan exhibited a non-enhancing cystic lesion in the left gangliocapsular region with adjacent edema, suggesting a cryptococcoma (Fig. 1).

The patient developed left hemiparesis and acute kidney injury after a 750 mg cumulative dose of amphotericin B. Treatment was then switched to isavuconazole. However, CSF opening pressure was greater than 400 mmH₂O and cultures were positive for *Cryptococcus* sp., requiring implantation of an external lumbar drain. Some days later she developed a persistent fever around 38°C. After excluding other infectious foci, another brain MRI scan showed a new lesion in the left cerebellar hemisphere (image not available), which was due to the brain inflammatory reaction to the fungi.

After 40 days of treatment the lumbar drain obstructed, resulting in delirium, psychomotor agitation, and transcortical motor aphasia. The drain was removed and serial lumbar punctures were resumed, with a gradual improvement of aphasia. After 7 days of negative CSF cultures, the patient underwent ventriculoperitoneal shunt placement.

Our patient was discharged with oral isavuconazole and with a referral to physical rehabilitation. Sixty days later, she was still on isavuconazole, was walking independently, and communicating well, but complained about anosmia. The case timeline is summarized in Fig. 2.

Discussion

Cerebral cryptococcomas are rare in immunocompetent hosts. To our knowledge, it is the first time that a cryptococcoma is successfully treated with isavuconazole and is mutually caused by *Cryptococcus neoformans* and *Cryptococcus gattii*. It is also the first time it leads to cerebellitis; however, recurrent cerebellitis was once seen after cryptococcal meningitis [6]. Anosmia has never been reported as a long-term complication as well.

Following the model of Li et al. [7], we performed a systematic review on case reports of CNS cryptococcoma since 2009 on PubMed. Twenty-eight reports on 29 cases were found [8–35]. The mean age of diagnosis was 43.62 years, with 19 males and 10 females. Headache (especially of progressive nature) was the most common presenting symptom, followed by vomiting, fever, change in mental status, hemiparesis, generalized tonic-clonic seizures, and visual changes. The basal ganglia and the frontal, parietal, and temporal lobes were the most frequent lesion sites. Regarding MRI findings, most lesions were either hyperintense or hypointense at T1 and hyperintense at T2, and edema and ring enhancement were usually found. However, cystic changes were not as common. Most cases were treated with amphotericin-B, 5-fluorocytosine, fluconazole, and corticosteroids, but surgical resection was performed in more than half of cases. The initial diagnoses were often mistaken for metastases and gliomas. Finally, follow-up of cases ranged from 83 days to 4 years, and death occurred in

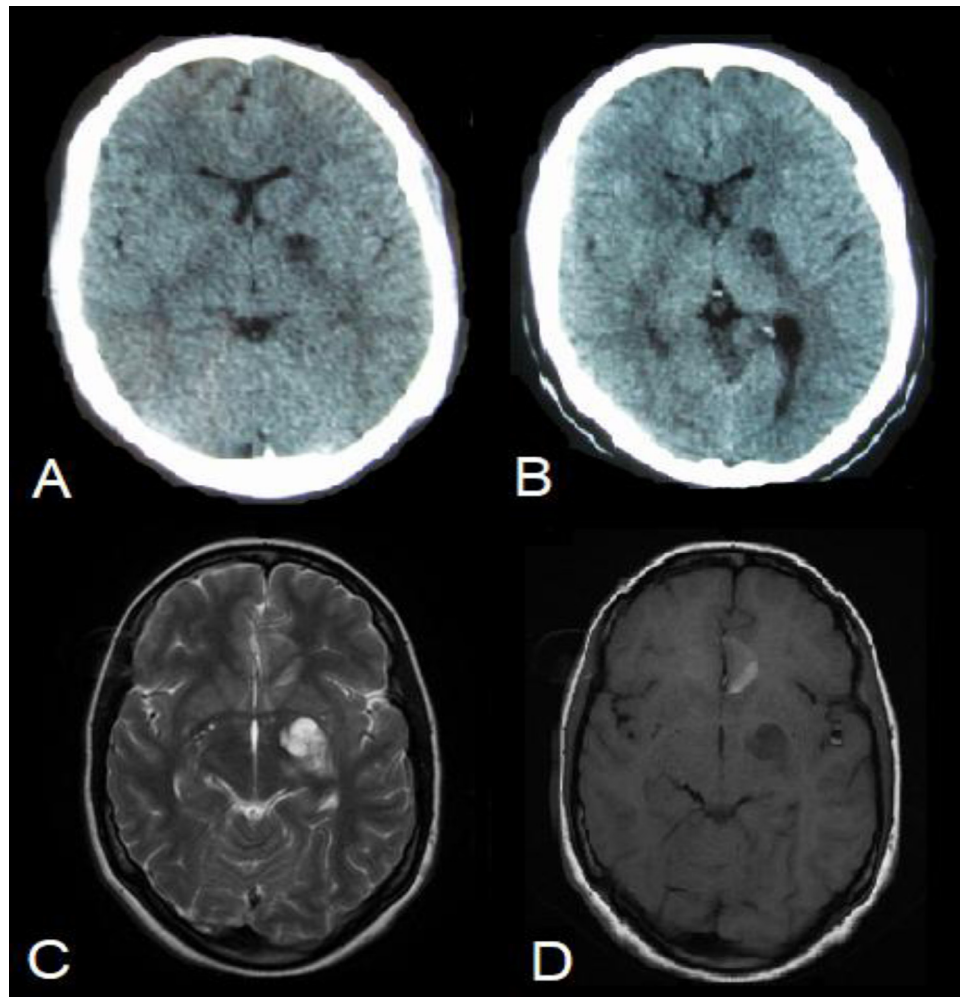


Fig. 1 – Brain computed tomography (CT) and magnetic resonance imaging (MRI) axial scans. (A) CT scan at arrival with a hypodense lesion in the left internal capsule. (B) Persistence of lesion on day 11. (C) T2-weighted and (D) T1-weighted MRI scans at day 12 with a non-enhancing cystic lesion in the left gangliocapsular region with adjacent edema, suggestive of cryptococcoma.

9 reports, mainly due to secondary infection. Nine cases had a complete resolution of symptoms, 4 had residual neurological symptoms, and recurrence was seen in 2 cases [8–35].

Gadolinium-enhanced MRI imaging is preferred for detecting cryptococcomas, yielding higher sensitivity and specificity than standard MRI and CT. Findings are variable, including both hyperintensity and hypointensity on T1- and T2-weighted images, enhancing and nonenhancing on post-contrast T1-weighted images, ring-enhancing lesions, single and multiple lesions, perilesional vasogenic edema, and hydrocephalus. The most commonly affected regions are the frontal lobes and basal ganglia [36]. In cryptococcal meningitis, meningeal enhancement [37,38] and non-granuloma intraparenchymal lesions [39] are the most common imaging findings in immunocompetent hosts.

According to a systematic scoping review of cerebral cryptococcomas, the mean age of presentation is 48.5 years and 75% of cases are males. Few reports have a description of a

known exposure to *Cryptococcus sp.* vectors; only 2 cases in the review had close contact with pigeons. Our patient lived in an area surrounded by eucalypti and her sister was a bird breeder. Headache is the most common presenting symptom (58%), followed by altered mental status (38%) and vomiting (31%). Papilledema (18%) and upper (16%) and lower (11%) extremity weakness are the most frequent findings on physical examination. Time to admission from the first symptom varied from 1 to 365 days [36]. Our patient presented with a wide diversity of symptoms and findings, and presented to the emergency department after 7 days of headache onset. The initial diagnosis is usually a brain malignancy, mainly high-grade gliomas, and cerebral abscesses and tuberculomas are considered in the differential as well [36].

Data on outcomes of cerebral cryptococcomas are scarce, and most studies are about cryptococcal meningitis. Mortality of immunocompetent patients was shown to be greater than in immunosuppressed patients, as well as disease burden.

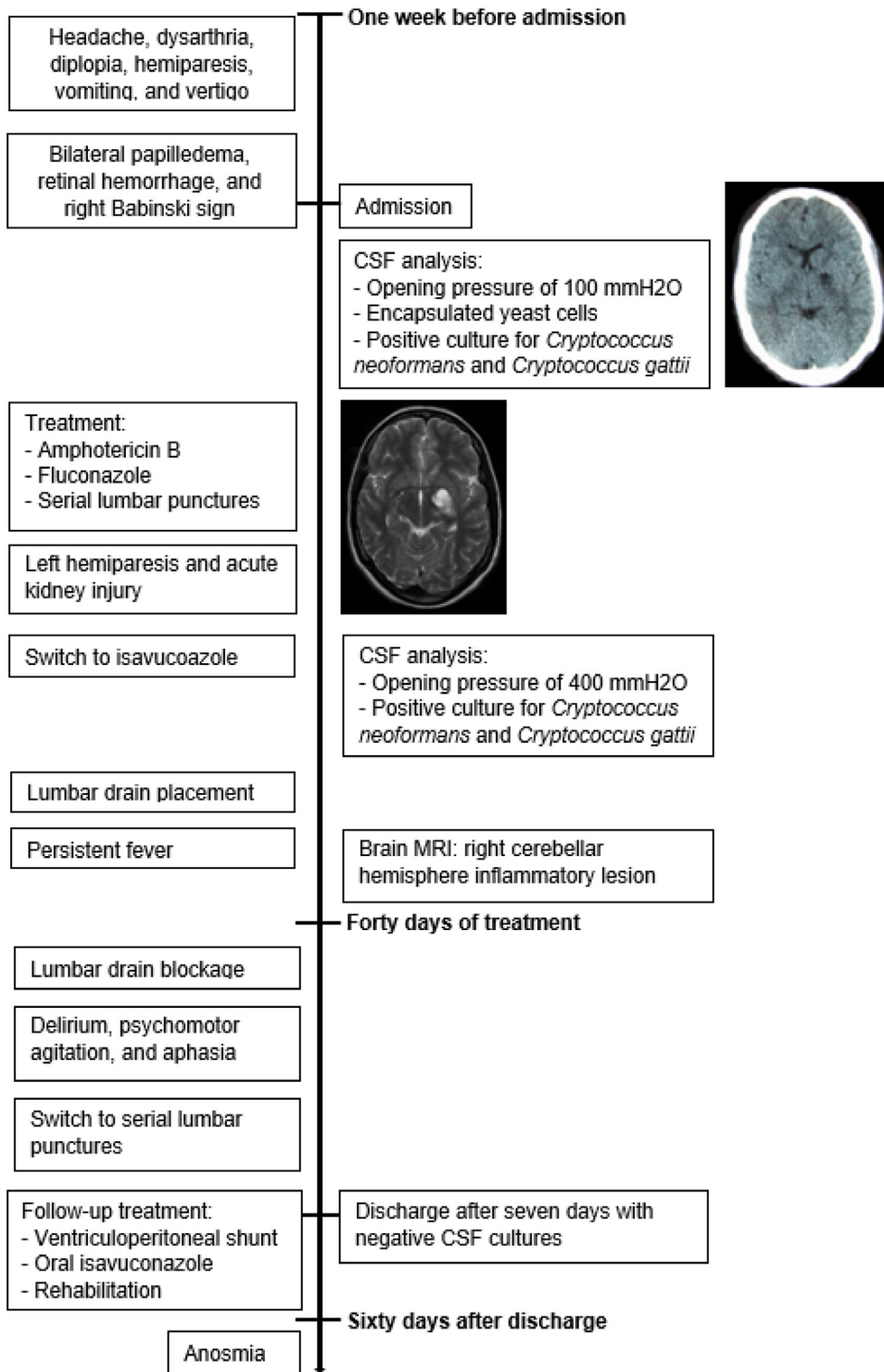


Fig. 2 – Timeline of symptoms, treatments, and follow-up of our patient.

There is still no solid explanation for this, but it may be related to delayed diagnosis in immunocompetent patients [40–42]. The pooled mortality of cerebral cryptococcosis, however, reaches 31%, with the main causes of death being refractory hydrocephalus, sepsis or septic shock, and postoperative cardiovascular complications [36].

Conclusion

Cerebral cryptococcomas should be considered in the differential when an immunocompetent patient presents with multiple neurological symptoms and a brain mass. Symptom

progression may be rapid, sometimes with a lethal outcome. Isavuconazole appears to be an effective antifungal medication for cryptococcomas, but this should be tested in larger studies.

Patient consent

A written informed consent term was obtained from the patient prior to publication.

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