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Case Report

Seizure in isolated brain cryptococcoma: Case report and review of the literature

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ABSTRACT

Background: Central nervous system (CNS) cryptococcosis is an invasive fungal infection predominantly seen among immunosuppressed patients causing meningitis or meningoencephalitis. Rarely, cryptococcosis can affect immunologically competent hosts with the formation of localized CNS granulomatous reaction, known as cryptococcoma. Common symptoms of CNS cryptococcoma are headaches, consciousness or mental changes, focal deficits, and cranial nerve dysfunction. Rarely, seizures are the only presenting symptom.

Case Description: We report the case of an immunocompetent patient with a solitary CNS cryptococcoma presenting with a long history of non-responsive generalized seizure who has been successfully operated.

Conclusion: CNS cryptococcoma is a rare entity, and in immunocompetent patients, its diagnosis can be challenging. The pathophysiology of lesion-related seizure is discussed along with a review of the pertinent literature.

Keywords: Central nervous system, Cryptococcoma, Seizure

INTRODUCTION

Cryptococcosis is an invasive fungal infection caused by two species of *Cryptococcus* spp. *Cryptococcus neoformans* is commonly related to immunocompromised patients mainly causing meningitis. *Cryptococcus gattii* is encountered in immunocompetent population and it is associated with cryptococcoma formation in the brain and lungs.[18] Accordingly, this infection is predominantly seen among immunosuppressed patients, typically those with HIV infection and from less-developed countries with significant morbidity and mortality.[13] Cryptococcosis can also occur in immunologically competent host providing localized reactions.[3] Hence, central nervous system (CNS) cryptococcosis could be meningeal (the most frequent) and/or parenchymal.[18] Cryptococcoma is a chronic granulomatous reaction due to a local inflammatory response in the immunocompetent host. Frequently, it may be misdiagnosed as a malignant lesion, and an accurate diagnosis can be achieved by histology following surgical resection.[19]

Here, we present the case of an intracranial cryptococcoma in a 32-year-old woman with normal immunity. The main mechanisms underlying seizure manifestation along with a review of the pertinent literature are reported.

CASE DESCRIPTION

A 32-year-old Indian woman presented with a history of tonic-clonic seizures since 2013, started during her first pregnancy. In 2016, she underwent electroencephalogram which confirmed the diagnosis of epilepsy. Accordingly, she started antiepileptic treatment with levetiracetam at initial daily dose of 1 g. Due to the recurrence of seizures, the drug was increased till a daily dose of 1.5 g with a poor seizure control. In 2019, a brain magnetic resonance (MR) examination revealed a right temporo-mesial lesion with an irregular peripheral contrast enhancement. The lesion appeared to protrude toward the right cerebral peduncle with brainstem compression, highly suggestive of low-grade glioma. MR spectroscopy supported the suspicion of glioma. The patient underwent functional MR showing anterior dislocation of the inferior longitudinal fasciculus. [Figures 1 and 2] show the main neuroradiological features. At admission, the neurological examination was negative. Her medical history did not reveal significant features, such as recurrent respiratory infection, and contact with pet animals. HIV serology was negative.

Surgical procedure

The procedure was performed by the use of neuronavigation. A right temporal craniotomy was performed. Through a transulcal approach, the lesion was reached. The lesion appeared as a calcified mass tenaciously attached to the contiguous structures. The lesion was entered, and a yellow-like material was found densely packing the mass. After a careful debulking, the capsule was removed in fragments except for its medial part being strictly adherent to the brainstem [Video 1].

Histopathology

Histopathology showed multiple yeasts consistent with *Cryptococcus* spp. strongly embedded into an amorphous eosinophilic fibrillar material. Period Acid–Schiff and mucicarmine stain revealed purple organisms and numerous budding yeasts consistent with *Cryptococcus* spp. [Figures 3 and 4].

Post-operative course

After surgery, the patient presented with a mild left leg coordination impairment which disappeared in a few days. Forty-four hours post-operative MRI showed a residual capsule fragment adherent to the midbrain [Figure 3]. A total body computed tomography (CT) scan and a lumbar puncture were performed without evidence of cryptococcal infection. Accordingly, no antifungal regimen was introduced. The

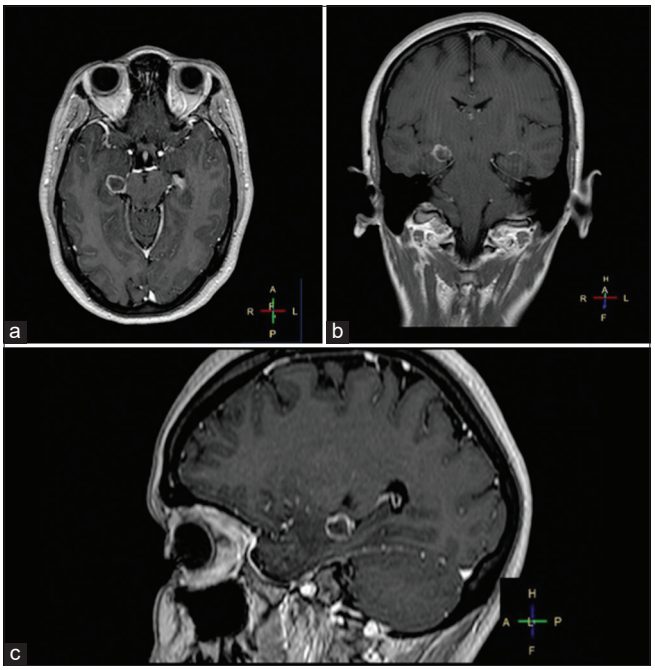

Figure 1: Pre-operative axial (a), coronal (b), and sagittal (c) post-contrast T1-weighted MR showing a right temporo-mesial lesion with an irregular peripheral enhancement.

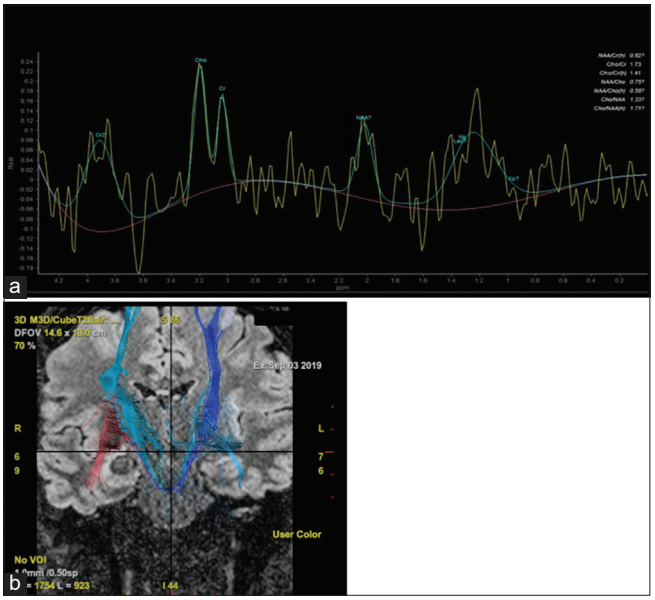

Figure 2: Pre-operative magnetic resonance (MR) spectroscopy (a) depicts a low N-acetylaspartate (NAA) with choline (Cho)/NAA of 1.33 compared to normal brain parenchyma, suggestive for low-grade glioma; functional MR (b) showing the anterior dislocation of the inferior longitudinal fasciculus (ILF) (red tract) and a unaffected corticospinal tracts (blue tracts).

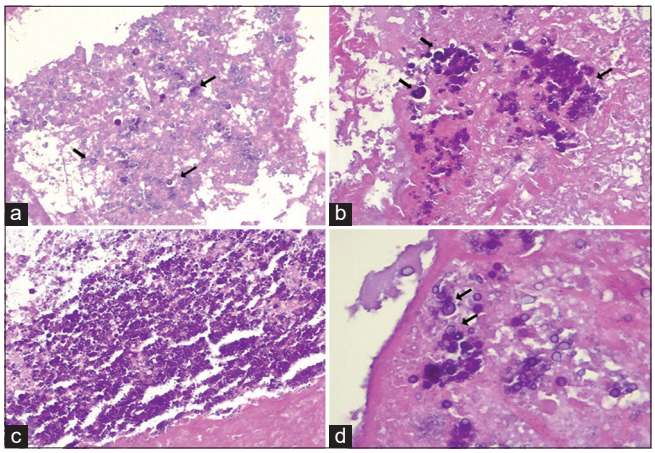

Figure 3: The histopathological findings. (a-c) *Cryptococcus* embedded in an amorphous eosinophilic fibrillary background. *Cryptococcus* is a round budding yeast (arrows) that varies in size enveloped by a mucoid capsule (E and E ×20); (d) focus on a cluster of *Cryptococcus* (arrows) (E and E ×40).

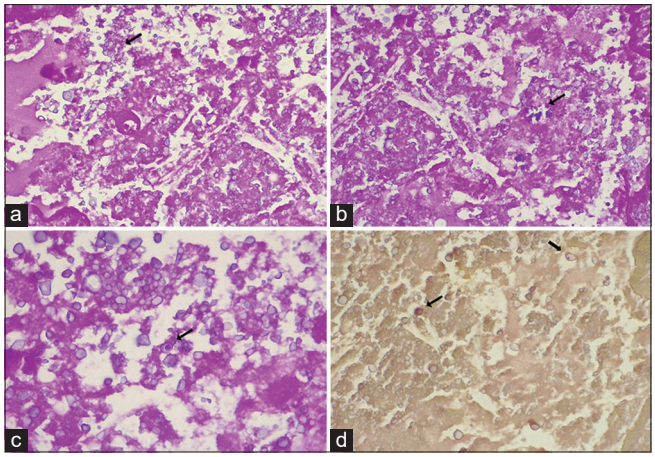

Figure 4: (a-c) Period Acid–Schiff staining the amorphous eosinophilic background and, weakly, the yeasts of *Cryptococcus* (arrows) (E, F ×20; G ×40); (d) Mucicarmine staining, patchy and weakly, in red the polysaccharide capsule of the yeasts (arrows) (×20).

patient was discharged on the 7th post-operative day without post-operative seizures and neurological deficits. At 6-month follow-up, no further seizures were reported.

DISCUSSION

Cryptococcal infection occurs by inhalation of infectious propagules from environmental reservoirs and pulmonary impairment constitutes the first manifestation.[13] Inhaled spores can colonize the host respiratory tract without symptoms leading the infection in a latent form for many times.[7] When local host immunity is suppressed, the fungus can reactivate and widely disseminate to several organs.[13] In immunosuppressed patients, *Cryptococcus* spp. can cross the blood–brain barrier (BBB) causing meningitis, encephalitis, meningoencephalitis, or ventriculitis. In immunocompetent patient, brain cryptococcal infection can present as single or multifocal granulomatous reaction known as cryptococcoma.[6,7,10,12] To date, only four cases of isolated brain cryptococcoma presenting with seizure have been reported [Table 1].[2,14,17,22] In two cases, seizure was associated with other presenting symptoms.[2] Three cases presented with generalized epilepsy,[2,17,22] as in our report, while one with focal epilepsy.[14] The working diagnosis was mostly brain tumor,[2,17] tuberculoma,[14] or vascular malformation.[22] Complete surgical excision was performed in 1 case,[17] subtotal in 1 case,[22] and stereotactic biopsy in 2 cases.[2,14] Post-operative antifungal drugs (i.e., fluconazole and amphotericin) were administered for the prevention of fulminant cryptococcal meningitis in three cases.[2,14,22] In our case, surgical treatment allowed cryptococcoma resection leaving a small capsule fragment adherent to the midbrain. Furthermore, considering the absence of active infection signs, no therapy was introduced.

It has been reported that *Cryptococcus* spp. enters the Virchow–Robin spaces and gives rise to small cysts in the brain parenchyma, inducing a chronic granulomatous reaction composed by macrophages, lymphocytes, and foreign body-type giant cells.[5] *Cryptococcus* spp. is a facultative intracellular pathogen, and macrophages can act as both a niche for fungal replication and a safe vehicle for spreading into the brain.[12,20] Studies on the pathogenesis of epilepsy due to brain infection distinguish between early and late seizures.[8] Early seizure occurs within the 1st 1–2 weeks after infection and it is considered to be insult related. Late seizure is seen months to years after infections and it occurs following resolution of the active phase.[20] During the phase between the infection and onset of seizures, *Cryptococcus* spp. induces brain damage and BBB impairment through the release of pro-inflammatory cytokines and activation of downstream signaling promoting the innate immunity reaction and later the adaptive immune response.[12,20,21] The risk for developing epilepsy after infections depends on the severity of brain injury, age, genetic factors, and many other unknown variables.[12,20]

Solitary cryptococcoma is a rare lesion,[7] and the absence of an immunosuppressed history or significant predisposing factors in immunocompetent patients makes the diagnosis challenging. In our case, cryptococcoma presented as a localized tumor-like mass with a 7-year seizures history without other symptoms. Indeed, without a clear clinical history, cryptococcoma can appear radiologically indistinguishable from other CNS lesions.[7,9,11,15,19] Differential diagnosis needs to include other neuroinfectious diseases, such as toxoplasmosis, lymphoma, tuberculoma, and primary or metastatic tumors.[1,4,15] These pathologies can produce similar clinical syndromes and MRI or CT findings to cryptococcoma.

Table 1: Cases of isolated brain cryptococcoma presenting with seizure.

Author, year	Patient's age, sex	Clinical presentation	Lesion site	MRI T1/T2-WI	Additional findings	Initial diagnosis	Treatment	Follow-up
Presenting Case	32 yr., F	7-yrs history of generalized seizures	Right temporo-mesial lesion	Heterogeneous hypointensity on T1 and FLAIR, with numerous areas of calcification hypointense on T2 and irregular contrast enhancement on lesion's marginal side	Spectroscopy showing low NAA with choline/ NAA of 1.33 compared to normal brain parenchyma	Tumor	Complete resection	4 months
Salvador *et al*., 2019[15]	26 yr., F	6-months history of seizures, diplopia and headache	Left parietal lesion	Predominantly hyperintense in T2, heterogenous enhancement in T1	Reduced relative cerebral blood volume in perfusion study	Tumor	Complete resection	Not reported
Zhu *et al*., 2013,[20]	1 yr., F	6-months history of seizures	Right parieto-occipital lesion	Mixed hypo- and hyper-intense on both T1 and T2		Vascular malformation	Partial resection+ Fluconazole	18y
Batista *et al*., 2012,[1]	37 yr., M	2-months history of headache and 1 episode of seizures	Right fronto-parietal lesion	Hypointense on T1, heterogeneously hyperintense on FLAIR/T2, with surrounding vasogenic edema and heterogeneous enhancement	No high perfusion or restricted diffusion was noted. MR spectroscopy demonstrated high choline peak, low NAA, and a peak of lipids/ lactate	Tumor	Stereotactic biopsy+ amphotericin B, intravenous steroids	Not reported
Nadkarni *et al*., 2005,[13]	22 yr., M	3-years history of left focal motor seizures with secondary generalizations	Right parietal lesion		CT scan revealed isodense lesion with peripheral enhancement	Tuberculoma	Stereotactic biopsy followed by surgical excision+ amphotericin	Not reported

In CNS cryptococcal infection, a combined medical and surgical approach is considered the optimal treatment.[18] Systemic antifungal treatment consists of amphotericin B as first-line drug, and flucytosine or fluconazole as second-class agents.[16,18]

According to our experience and based on the few reports available, we speculate that surgical resection should be always attempted to reach a firm diagnosis and brain decompression.[19]

CONCLUSION

CNS cryptococcoma is a rare entity and could affect immunocompetent individuals. It has no specific radiologic findings and can mimic CNS tumors. Our experience suggests that in immunocompetent patients, an isolated intracerebral cryptococcal granuloma can be challenging to diagnose where seizure is the only presenting symptom. In these cases, surgical treatment is mandatory for the diagnosis and seizure resolution.

Declaration of patient consent

Patient's consent not required as patients identity is not disclosed or compromised.

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Conflicts of interest

There are no conflicts of interest.

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