Letter to the Editor

Intracranial granulomatous inflammation caused by cryptococcal infection: a case study and literature analysis

Xinru Deng^, Xinlan Xiao^

Department of Radiology, The Second Affiliated Hospital, Jiangxi Medical College, Nanchang University, Nanchang, China

Correspondence to: Xinlan Xiao, MS. Department of Radiology, The Second Affiliated Hospital, Jiangxi Medical College, Nanchang University, 1 Minde Road, Nanchang 330006, China. Email: jx_xiaoxinlan@sina.com.

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Introduction

Cryptococcal infection is a subacute or chronic infectious disease caused mainly by the inhalation of pathogens *Cryptococcus neoformans and Cryptococcus gattii* (1), which are found mainly in the natural environment, especially in soil contaminated with bird droppings and decaying wood. *Cryptococcus neoformans* primarily affects immunocompromised individuals, while *Cryptococcus gattii* generally affects immunocompetent individuals (1-3). The spore form of *Cryptococcus* is environmentally stable, and the rapid antigenic variation in its pod polysaccharide allows it to evade host defense (4). This gives it high virulence and the ability to penetrate the blood-brain barrier to cause central nervous system (CNS) infections (2,5).

Cryptococcosis has become a prominent infection in both immunocompromised and immunocompetent hosts. *Cryptococcus* can infect any tissue or organ in the human body, but the common infection site of serious consequence is the CNS, with cryptococcal meningoencephalitis being the most frequently encountered manifestation (1). Cryptococcal granulomatous inflammation is relatively less common compared to cryptococcal meningitis in cryptococcal infections, which can have dangerous and even fatal consequences. We report a case of a patient with intracranial granulomatous inflammation caused by cryptococcal infection at The Second Affiliated Hospital of Nanchang University, emphasizing the medical history, clinical symptoms, imaging manifestations, and setting of the reported case in relation to the literature data to draw attention to this clinical condition.

Case description

The patient, a 74-year-old woman, was admitted to hospital with a headache for more than a month, accompanied by personality changes, hearing impairment, and decreased retention. Physical examination was unremarkable, and she was conscious and negative for meningeal irritation signs. Five years prior, the patient experienced a traumatic left temporal lobe contusion with subdural hemorrhage and was treated conservatively. Occasional headaches continued for several years, mainly on the left side. She contracted the coronavirus disease 2019 (COVID-19) three months before admission, and then developed headaches, cognitive decline, olfactory and gustatory dysfunction, and muscle weakness, with the headaches worsening until she was admitted to hospital. The patient had no history of chronic diseases, such as hypertension, diabetes mellitus, hepatitis, pulmonary tuberculosis, or malignancies, and no history of administration of immunosuppressive agents or corticosteroids. She denied smoking or consuming alcohol. The routine preoperative blood examination revealed a white blood cell (WBC) count of 3.9×10^9/L, a red blood cell (RBC) count of 3.23×10^{12}/L, a platelet count of 90×10^9/L, a neutrophil percentage of 83.9%, a lymphocyte percentage

^ ORCID: Xinru Deng, 0009-0002-6692-1796; Xinlan Xiao, 0000-0001-9701-5062.

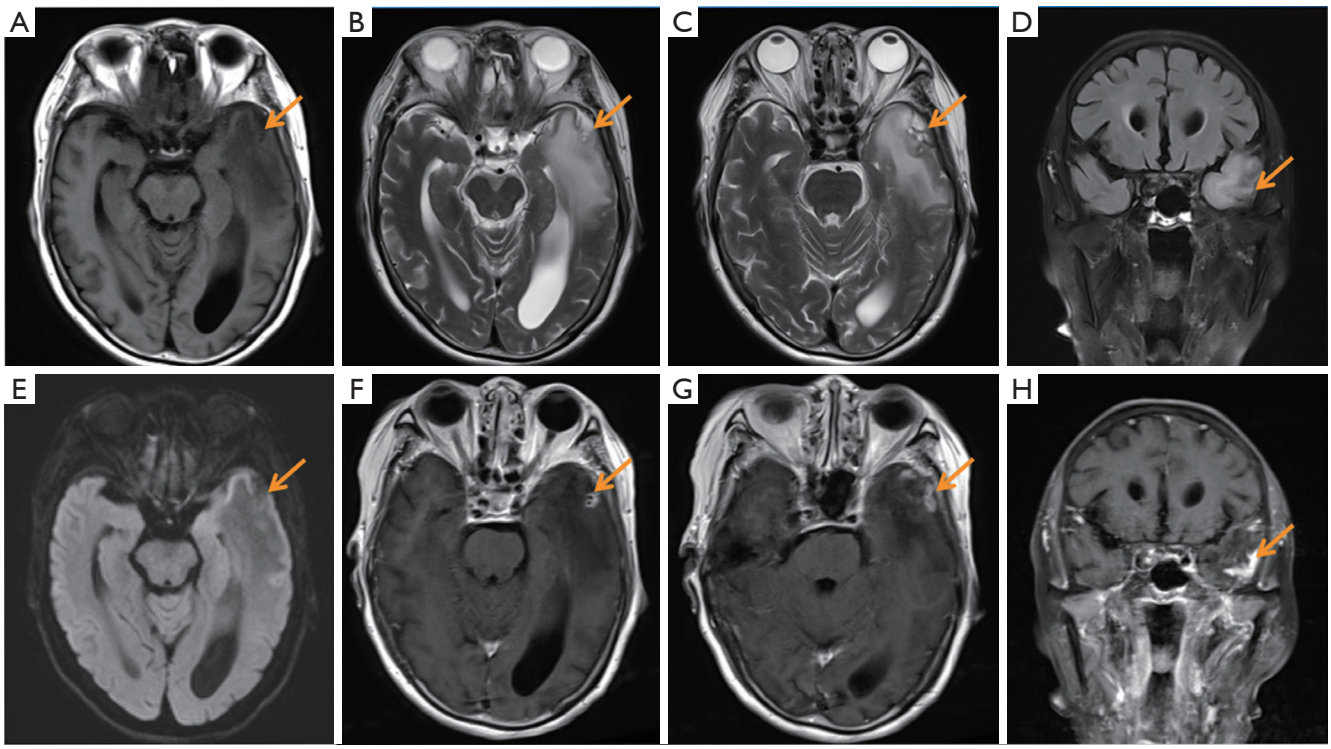

Figure 1 MRI findings of the lesion. (A) T1W images. (B,C) T2W imaging showed multiple small circumferential lesions in the left temporal lobe with hypointensity on T1W imaging and hyperintensity on T2W imaging (arrows). (D) FLAIR imaging showed an irregular strip-like area with hypointensity on the surface of the left temporal pole (arrow). (E) DWI showed the left temporal lobe lesion with hypointensity (arrow). (F,G) In enhanced scanning, there was a left temporal lobe lesion with multiple ring enhancement (arrows). (H) A strip-like marked enhancement corresponding with (D) (arrow). MRI, magnetic resonance imaging; T1W, T1-weighted; T2W, T2-weighted; FLAIR, fluid-attenuated inversion recovery; DWI, diffusion-weighted imaging.

of 6.3%, and a D-dimer level of 1.62 mg/L fibrinogen equivalent units (FEU). The biochemical, C-reactive protein, and coagulation indicators were all within normal range. Additionally, the patient tested negative for human immunodeficiency virus (HIV) antibodies, *Treponema pallidum* antibodies, hepatitis C antibodies, and hepatitis B surface antigen. The cerebrospinal fluid (CSF) parasite smear microscopy yielded negative results, but no other CSF examination was performed.

An unenhanced computed tomography (CT) scan showed edema in the left temporal and insular lobes, accompanied by paranasal sinusitis. The chest CT scan revealed a calcified nodule in the right middle lobe of the lung and coronary artery sclerosis, with no other pathological findings. Magnetic resonance imaging (MRI) showed multiple small lesions on the left lateral inferior temporal pole with a polycyclic morphology, and these circular lesions were hyperintense on T2-weighted (T2W) imaging and hypointense on T1-weighted (T1W) and diffusion-weighted (DW) imaging. Irregular large patchy areas of edema were discernible in the cerebral parenchyma surrounding the lesions (*Figure 1A-1E*). An axial enhancement scan showed small lesions in the left temporal pole with polycyclic enhancement (*Figure 1F,1G*). The coronal image revealed a streak-like area of significant enhancement on the surface of the left temporal pole (*Figure 1H*), which was isointense on T1W images and hypointense on fluid-attenuated inversion recovery (FLAIR) and DW imaging (*Figure 1A,1D,1E*). In addition, the ventricles system was dilated, the left fissure pool was narrowed, and the midline structure of the brain was slightly shifted to the right. We thus considered infectious lesions to be highly probable but did not exclude parasitic infections. However, given the patient's persistent headaches, the neurosurgeon opted for surgical excision to further characterize and treat the lesion.

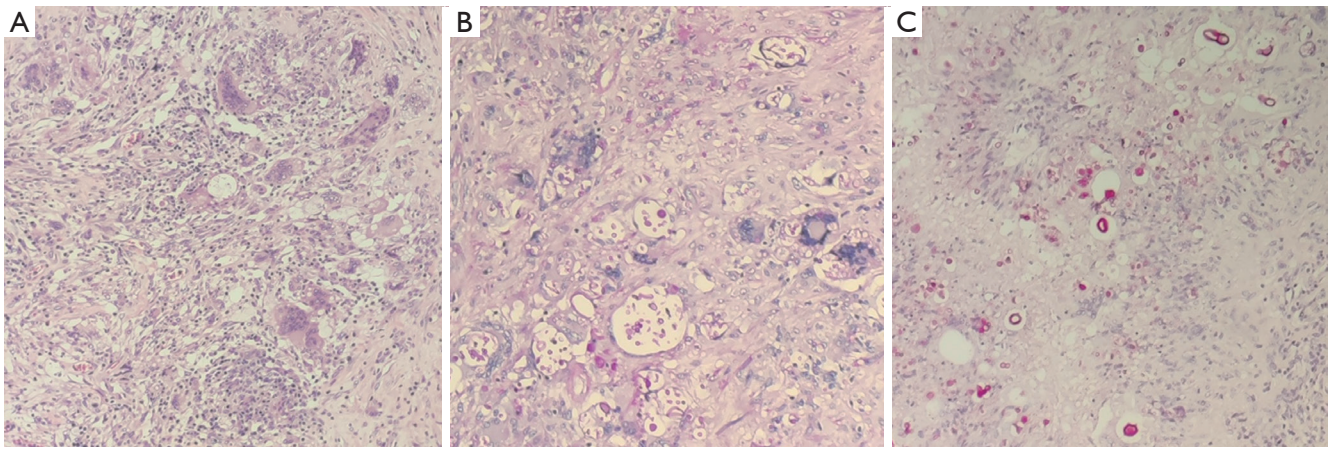

Figure 2 HE staining and special stains including PAS staining and mucicarmine staining were performed on the lesions of this patient. (A) HE staining: the fungi appeared thin-walled, round, and vacuolated, with a transparent halo visible, and was surrounded by epithelioid cells and multinucleated giant cells (200×). (B) PAS staining: the fungi appeared purplish red in color (400×). (C) Mucicarmine staining: the pods of *Cryptococcus* were stained red (200×). HE, hematoxylin and eosin; PAS, periodic acid-Schiff.

Under general anesthesia, the skull was opened, and a lesion was observed at the base of the temporal pole with yellow staining of the surrounding brain tissue and was accompanied by an indistinct cerebral sulcus and partial cystic degeneration of the cerebral cortex with thickening of the adjacent dura mater. The left temporal lobe lesion, which was approximately 4.0×2.8×1.2 cm in size with a slightly hard texture, was then removed. The incision was closed after hemostasis and irrigation.

Pathologic microscopy revealed variable-sized granulomas with central necrosis, surrounded by epithelioid cells and multinucleated giant cells, within which yeast-like fungi with capsules were observed. The immunohistochemical results were as follows: proliferating glial cells glial fibrillary acidic protein (GFAP) (+), cytokeratin (CK) (–), isocitrate dehydrogenase (IDH)-1 (–), alpha-thalassemia/mental retardation X-linked (ATRX) (–), Recombinant S100 Calcium Binding Protein (S100) (+), oligo-specific nuclear transcription factor (Olig-2) (–), tumor protein 53 (P53) about 5% (+), and proliferation index (Ki-67) about 3% (+). Meanwhile, the special staining results were as follows: periodic acid-Schiff (PAS) (+), Periodic Acid-Schiff-Methenamine Silver (PASM) (+), antacid (–), and mucus carboxin (+) (*Figure 2*). Subsequently, a cryptococcal capsular polysaccharide antigen test was performed on the CSF, yielding a positive result. The occupying lesion in the left temporal lobe was eventually diagnosed as granulomatous inflammation due to cryptococcal infection, with significant peripheral glial cell proliferation. Therefore, the patient began antifungal therapy for over six months, starting with intravenous fluconazole treatment for two days at our hospital, followed by amphotericin B intravenous treatment for 1.5 months at another hospital, and then oral fluconazole for 6 months (*Figure 3*). Nine months after surgery, the patient demonstrated remarkable improvement in cognitive function, with a return to normal sensation of smell and taste. Additionally, the individual has shown a significant reduction in headache and an overall increase in quality of life.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was provided by the patient for publication of this article and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

Cryptococcal intracranial infections have a diverse clinical presentation, with most patients having a subacute or chronic onset of disease and their clinical symptoms worsening over time (6). Its main manifestations include fever, headache, increased intracranial pressure, and symptoms related to the affected cranial nerves (7). CNS

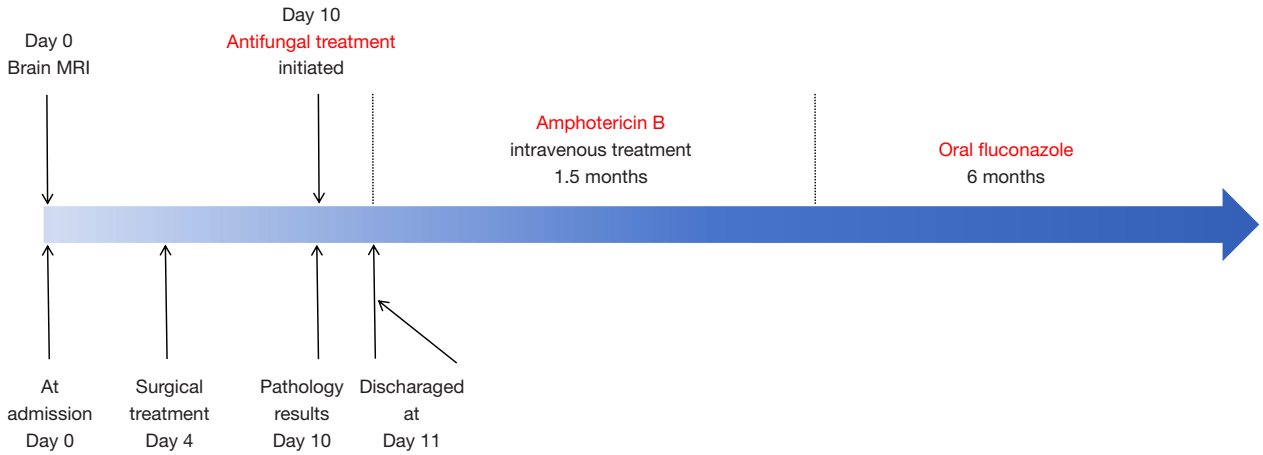

Figure 3 Timeline of disease course of the patient, with the therapeutic details according to days from hospital admission and discharge. MRI, magnetic resonance imaging.

infections may be accompanied by disseminated infections, such as isolated skin rashes and soft tissue infections, in the lungs or elsewhere (2,8,9). Untreated patients may progress to impaired consciousness or even coma and have a poor prognosis. In this case, the patient did not have an immunodeficiency disease such as acquired immunodeficiency syndrome (AIDS) or a wasting disease such as neoplastic disease or diabetes mellitus. However, the patient experienced COVID-19 three months prior to disease onset, with monocyte/macrophage, dendritic-cell, mast-cell, and T-cell activation during infection, potentially triggering a hyperinflammatory cytokine storm response. Specifically, the severe acute respiratory syndrome-related coronavirus (SARS-CoV-2) spike protein caused blood-brain barrier instability in the brain endothelium, promoting a proinflammatory state (10). Although her symptoms of headache, hearing loss, and memory impairment were consistent with the common clinical manifestations of cryptococcal intracranial infection, the absence of fever and meningeal irritation symptoms hindered CSF testing, leading to diagnostic delays.

When patients present with symptoms similar to those of cryptococcal intracranial infections, radiologic imaging should be performed to examine the intracranial situation, with MRI being more valuable than CT in this regard (11). The imaging manifestations of intracranial cryptococcal infection are diverse, including dilated Virchow-Robin (V-R) spaces and pseudocysts, cryptococcal granulomas (cryptococcomas), cornified nodules or patchy signals, meningitis with edema, and meningeal enhancement (12,13). The lesion in this patient was located in the left temporal pole, an atypical site (14). The patient had a history of left temporal cerebral contusion, which could have led to an increase in blood-brain barrier permeability (15). An important function of the blood-brain barrier is to maintain homeostasis in the CNS, and its disruption can make the brain more susceptible to injury (16,17). Similarly, a case has been reported in which a patient with traumatic intracerebral hemorrhage who did not undergo surgery developed a brain abscess at the same site (18). This may make the lesion more likely to be located in the left temporal lobe than in other locations. Multiple small foci in the left temporal pole subcortex are probably caused by *Cryptococcus* invading the deep white matter VR interstitial space and forming a small capsule or gelatinous pseudocyst in the brain parenchyma (12,13). This is followed by the formation of characteristic chronic granulomas in the brain of immunocompromised hosts in the presence of infiltration of macrophages, lymphocytes, and foreign body giant cells, accompanied by disruption of the blood-brain barrier (5,19,20). Involvement of the meninges results in meningeal granulomatous inflammation so that the thickening and hardening of the meninges are irregularly linear, with a tendency to burrow into the brain parenchyma.

Cryptococcal granulomatous inflammation is similar to other hematogenous granulomatous infections. The characteristic imaging findings include cryptococcal granulomas, also known as *cryptococcomas*, which are predominantly located in the brain parenchyma adjacent to the basal ganglia and lateral ventricles bilaterally and may

be miliary (<3 mm) or larger (19). Typical manifestations on MRI vary depending on the component, but mild hypointensity on T1W images, isointensity or hyperintensity on T2W and FLAIR images, and hypointensity on DW images are the most common. Enhancement scans show prominent nodular, circumferential, or bead-like enhancement, but some lesions show no enhancement (21). The MRI findings of the case discussed here differ from those typical of cryptococcal meningitis, particularly in terms of the thicker meningeal enhancement and atypical lesion location. However, the presence of the ring-enhancing lesion is consistent with the typical presentation, and this gelatinous pseudocystic lesion suggests the possibility of cryptococcal infection.

In addition to conventional MRI, there are now some more advanced MR approaches, such as quantitative MRI (qMRI) technology. For example, MR spectroscopy (MRS) enable the noninvasive detection of the disaccharide trehalose in cryptococcomas. Previous studies have shown that trehalose is an important virulence factor for *Cryptococcus* and may serve as a diagnostic marker for cryptococcosis-related lesions (22). The use of noninvasive MRS visualize the trehalose peak in cryptococcoma, where it appears as multiple signals ranging from 3.6 to 3.8 ppm. This peak is absent in a healthy brain or noninfectious lesions such as glioma (23). Additionally, a recent study found that cryptococcomas in the murine model exhibited a higher apparent diffusion coefficient (ADC) value and T1 and T2 relaxation times compared to the contralateral brain, and this has been confirmed in cryptococcomas caused by several of *Cryptococcus neoformans* varieties (24). High ADC values in human cerebral cryptococcomas have occasionally been reported (25). The MR characteristics of cryptococcomas correspond to their typical components: fluid-filled, pseudocystic lesions containing abundant cryptococci and highly hydrated capsular material. This demonstrates the potential of qMRI technology to assist in the noninvasive identification of different lesion types, such as tumors, bacterial abscesses, or different fungal lesions.

Confirmation of cryptococcal infection requires etiological tests, and HIV testing is also recommended (6). Etiological tests mainly include ink-stained smears and fungal cultures, and the CSF is commonly used as a specimen (6,26). Because of its low cost and simplicity, cryptococcal antigen testing of the CSF is recommended by the World Health Organization as the mainstay of diagnosis (12). One of them is lateral flow assay detection, which is inexpensive and rapid and can detect CSF, blood, or urine samples with high sensitivity and specificity for CSF detection (2). In the present case, the patient did not undergo lumbar puncture for routine CSF examination or further fungal culture and identification prior to the surgery. Therefore, pathogen detection with high specificity and sensitivity is important to improving diagnostic accuracy and avoiding missed diagnoses. Of course, histopathological examination is a gold standard for a final diagnosis (27).

One of the differential radiological features between cryptococcal granuloma and intracranial tuberculosis is the site of occurrence. Intracranial tuberculoma is more likely to occur at the base of the brain. In addition, MRS may have the potential for discrimination, as trehalose levels in *Cryptococcus* are significantly higher than are those in *Mycobacterium tuberculosis*, with trehalose resonance in MRS being absent in the tuberculomas of patients (22). CSF study can help the evaluation of CNS tuberculosis. It may reveal turbid color, increased pressure, increased cell count with lymphocyte predominance, increased protein, low sugar, and low CSF serum sugar ratio (<0.6) (28). In addition, this condition needs to be differentiated from brain parasitosis (especially cysticercosis), toxoplasmosis, lymphoma, sarcoidosis, abscess, primary CNS malignancy, and brain metastases. The localized thickening and enhancement of the meninges suggests a higher likelihood of infectious pathology and provides discriminative value from tumor. Hypointensity on DW images is inconsistent with the typical presentation of lymphoma and abscess. In addition, toxoplasmosis often occurs in the basal ganglia region and has negative findings for the CSF parasite test. Brain metastases tend to present as multiple occupying lesions at the gray-white matter junction, and radiographic examination should be used to determine the presence of primary tumor.

In conclusion, the differential diagnosis of cryptococcal granulomatous inflammation requires a comprehensive consideration of lesion characteristics, clinical manifestations, and laboratory examinations.

Based on our case and the literature review, cryptococcal granuloma with peripheral edema and leptomeningeal enhancement may be the more characteristic imaging manifestation of cryptococcal granulomatous inflammation, which commonly occurs in the basal ganglia and parietal ventricles. The definitive diagnosis still depends on the histopathology and detection of cryptococcal antigen in the serum or CSF. Heightened clinical suspicion and early

identification of this entity via imaging can allow clinicians to pursue more aggressive treatment options, thereby reducing fatal outcomes.

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Footnote

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-23-1860/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was provided by the patient for publication of this article and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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