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Case Report

MRI changes in cryptococcal meningoencephalitis exacerbated by antifungal treatment due to post-infectious inflammatory syndrome: A case report ☆

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ABSTRACT

Cryptococcal meningitis is one of the most common fungal meningitis in adults and causes disabling morbidity and mortality worldwide. The occurrence of postinfectious inflammatory response syndrome during cryptococcal meningitis treatment presents a diagnostic challenge. This time course seems paradoxical because patients show worsening symptoms and imaging findings. However, laboratory data improve with antifungal treatments. Herein, we present a case of an older woman diagnosed with cryptococcal meningitis who later developed postinfectious inflammatory response syndrome. Despite the initial antifungal treatment and improvements in cerebrospinal fluid analysis results, the patient's neurological condition deteriorated; imaging findings worsened. Magnetic resonance imaging at the time of postinfectious inflammatory response syndrome showed more prominent meningeal enhancement and brain edema, consistent with postinfectious inflammatory response syndrome, combined with negative repeat cerebrospinal fluid cultures for cryptococcal species. This case highlights the importance of considering postinfectious inflammatory response syndrome when patients with cryptococcal meningitis show clinical worsening during treatment. Prompt corticosteroid therapy significantly improves patient outcomes. Radiologists and clinicians should be aware of postinfectious inflammatory response syndrome to provide appropriate therapeutic options and improve prognosis in patients with cryptococcal meningitis.

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Introduction

Cryptococcal meningitis (CM) is the most common cause of fungal meningitis in adults worldwide and results in significant morbidity and mortality [1–3]. Immune reconstitution inflammatory syndrome (IRIS)-related CM was first described in a report [4] in which the initiation of antiretroviral therapy (ART) in human immunodeficiency virus (HIV)-infected patients with CM caused a severe immune response. Diagnosing central nervous system (CNS) IRIS may be challenging because patients show new or worsening symptoms despite receiving appropriate treatment and improved laboratory data. Although CNS IRIS is confirmed by the exclusion of other disease conditions, neuroimaging plays an important role in diagnosing this syndrome. Radiological findings of IRIS-CM include contrast enhancement, interstitial edema, mass effects, and restricted diffusion on magnetic resonance imaging (MRI), which indicate the presence of IRIS [5].

However, in HIV-negative patients with CM, neurological decline is often observed not due to a failure of antifungal treatment, but rather an intensified immune reaction referred to as postinfectious inflammatory response syndrome (PIIRS) [6,7].

Differentiating PIRS from therapeutic failure in cryptococcal meningitis is crucial, as the administration of immunosuppressive treatments, such as corticosteroid therapy, is required for PIRS [8]. PIRS should be considered in the differential diagnosis when patients with CM demonstrate clinical exacerbation of meningitis during antifungal treatments and show contrast enhancement lesions on the meninges, interstitial edema, and mass effect on MRI, despite improvements in cerebrospinal fluid (CSF) and negative cryptococcal cultures.

Herein, we present the case of a previously healthy woman in her seventies who developed dysarthria and severe limb weakness. She had elevated CSF cell counts and protein levels, with positive results for cryptococci via India ink staining and CSF culture, confirming the diagnosis of CM. Despite antifungal treatment and improvement in CSF profiles, the patient exhibited worsening symptoms. MRI revealed worsening meningeal enhancement and brain edema that were not observed on the initial MRI, despite the absence of cryptococci in repeat CSF cultures, which was consistent with PIRS. This case represents an MRI manifestation of CM-PIRS. Radiologists should be aware that treatment of CM has the possibility of worsening symptoms and imaging findings to provide appropriate therapeutic options for clinicians.

Case presentation

A 72-year-old woman, developed dysarthria and experienced severe limb weakness, rendering her unable to walk independently. Due to worsening symptoms and increased fatigue, she was transported to the emergency room and hospitalized on the same day. The patient exhibited: temperature, 38.3°C; blood pressure (BP), 125/73 mmHg; and heart rate (HR), 93 beats per minute. Cardiovascular examinations did not reveal any murmurs; pulmonary sounds were clear. The abdomen was flat and soft during the examination. Neurologically, the patient showed moderate dysarthria and signs of meningeal irritation, such as a stiff neck and Kernig's sign. Other neurological assessments did not reveal any abnormalities in motor or sensory functions.

Laboratory test results showed white blood cell count (WBC) of 8.50 × 10^3 /μl and slightly elevated C-reactive protein (CRP) (0.14 mg/dL). Serological tests for infections, including syphilis, HIV, hepatitis B virus (HBV), hepatitis C virus (HCV), human T-cell leukemia virus type 1 (HTLV-1), Epstein-Barr virus (EBV), cytomegalovirus (CMV), and herpes simplex virus (HSV), were performed.

Testing for tumor markers such as squamous cell carcinoma (SCC) antigen, neuron-specific enolase (NSE), Carbohydrate Antigen 19-9 (CA19-9), and carcinoembryonic antigen (CEA) revealed results within normal limits. The soluble interleukin-2 receptor (sIL-2R) levels did not increase. Although T2-weighted imaging (T2WI) (not shown), fluid-attenuated inversion recovery (FLAIR) (Fig. 1a, c and e), and diffusion-weighted imaging (DWI) (not shown) performed on admission did not show any abnormalities, postcontrast T1-weighted images revealed subtle enhancement in the sulci of the cerebellum and left parietal lobe (Fig. 2a, c and e), indicative of meningitis. The cerebrospinal fluid (CSF) analysis revealed an elevated cell count (254 cells/μL), elevated total protein (51 mg/dL), and hypoglycorrhachia (43 mg/dL).

Blood cultures revealed no bacterial growth. Tuberculosis, herpes simplex virus, varicella-zoster virus, and cytomegalovirus were not detected in the blood or CSF. β-D-glucan (113 pg/mL) was high in the CSF, and an Indian ink stain test revealed a yeast-type fungus with a capsular membrane. Cryptococcal meningoencephalitis (CM), including *Cryptococcus neoformans* or *Cryptococcus gattii*, was suspected, and *Cryptococcus neoformans* was later found positive in the blood cultures. The final diagnosis was meningoencephalitis caused by *C. neoformans*. Combined Liposomal Amphotericin B and Flucytosine were administered for the treatment of CM, resulting in gradual improvement in her clinical symptoms and CSF findings; she was discharged.

However, she experienced a resurgence of headache and fever on the 52nd day of treatment. She also had an altered mental status. MRI revealed hyperintense lesions in the cerebellum and middle cerebellar peduncles (Fig. 1b and d) on T2WI (not shown). Cerebral edema was observed in the cortex and subcortical white matter of the left parietal lobe, combined with high FLAIR (Fig. 1f) and T2WI (not shown) intensities. The inferior horn of the lateral ventricle was enlarged compared with previous images, suggestive of hydrocephalus (Fig. 1d). There was more conspicuous enhancement of the meninges on postcontrast T1-Weighted than on previous images (Fig.2 b, d and f). These results led the clinician to suspect an exacerbation of CM; therefore, the patient was rehospitalized.

CSF findings showed that the titers of cryptococcal antigen and CSF cell counts were reduced, indicating that the patient was responsive to antifungal therapy. The symptoms and imaging exacerbations, despite improvement in laboratory data, were considered immune-mediated delayed exacerbations, known as postinfectious inflammatory response

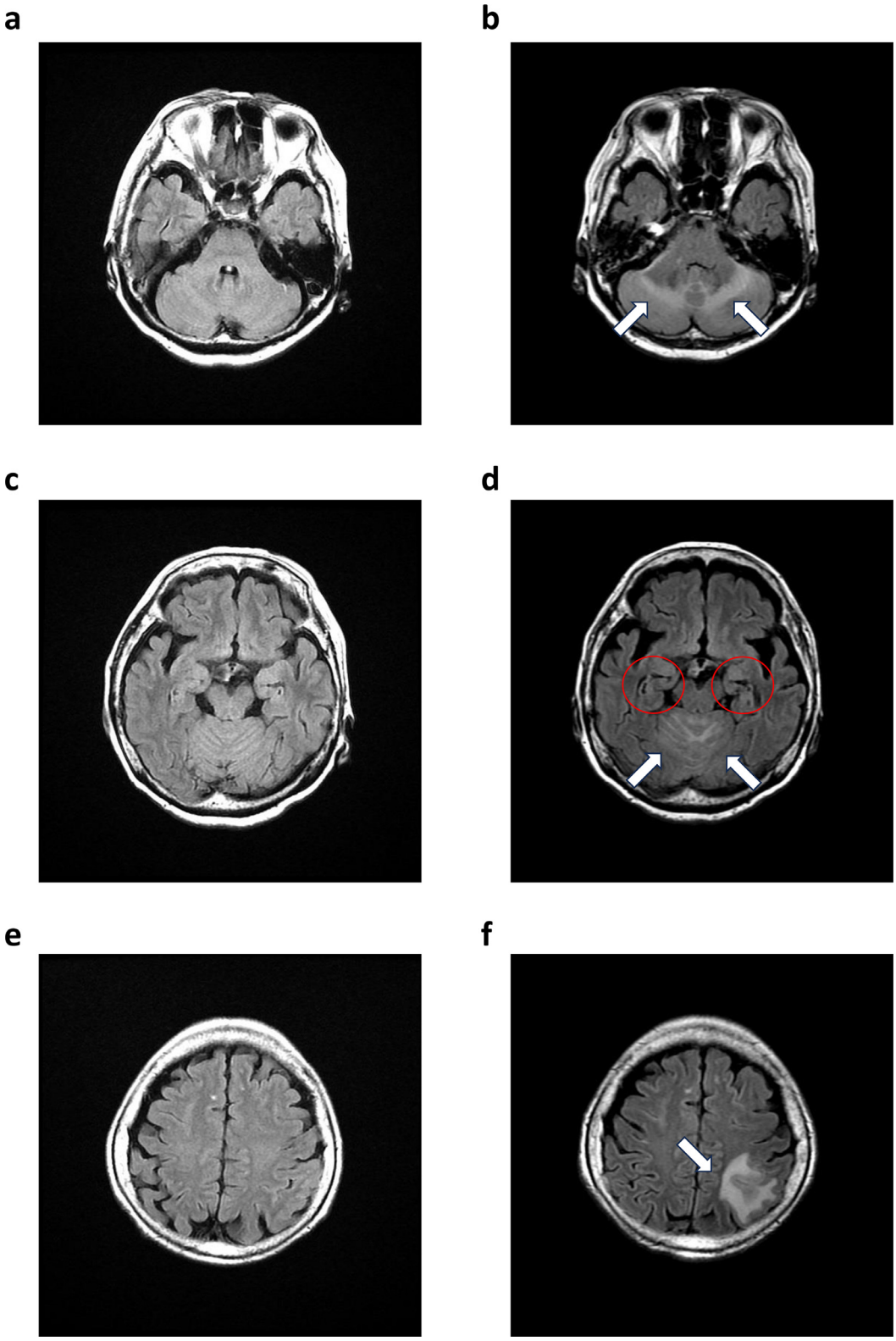

Fig. 1 – FLAIR (a, c, e) MRI performed on the day of admission does not reveal any abnormalities. At the onset of PIRS on the 52nd day of treatment (b, d, f) hyperintense lesions are observed in the cerebellum (arrows) (b) and middle cerebellar peduncles (arrows) (d) on FLAIR. The inferior horn of the lateral ventricle (red circles) is enlarged compared with previous images, suggestive of hydrocephalus (d). Cerebral edema is observed in the cortex and subcortical white matter of the left parietal lobe (arrows) (f), combined with high FLAIR intensities.

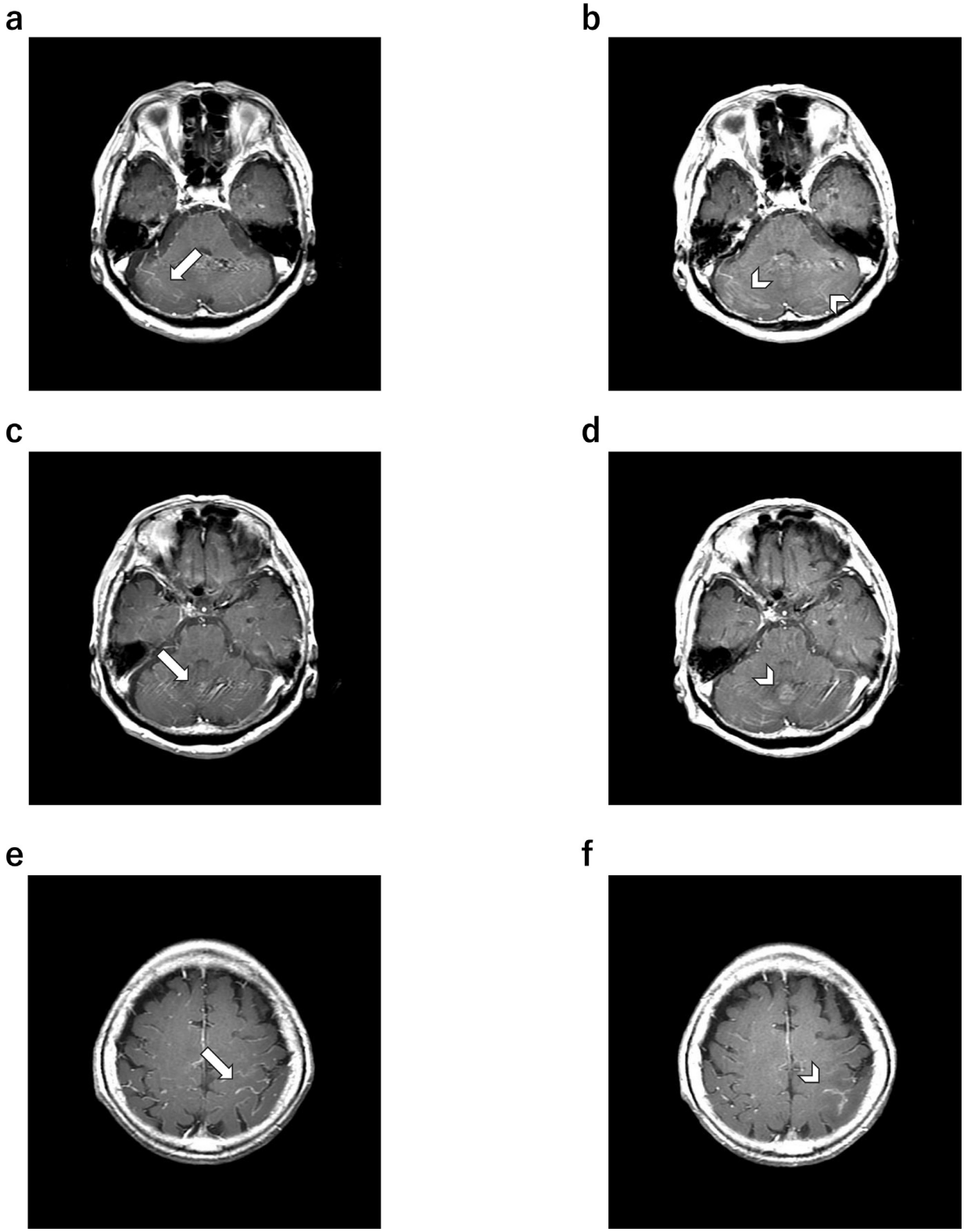

Fig. 2 – Postcontrast T1-weighted images on the day of admission (a, c, e) reveal subtle enhancement in the sulci of the cerebellum and left parietal lobe on the initial MRI (arrows). At the onset of PIRS on the 52nd day of treatment (b, d, f) there is a more conspicuous enhancement of the meninges on postcontrast T1-Weighted (arrowhead) compared with the previous images.

syndrome (PIIRS), rather than a recurrence. Steroid pulse therapy was initiated in accordance with PIRS treatment. As a result, her symptoms improved without any significant disabilities. MRI findings (not shown) also revealed that the high signal intensities of the lesions on FLAIR and T2WI improved. Furthermore, contrast enhancement was attenuated. The patient was discharged with a voriconazole regimen and experienced no recurrence.

Discussion

We present the case of an immunocompetent patient with *Cryptococcus neoformans* meningitis whose neurological worsening due to antifungal treatment, known as PIRS, was successfully treated with corticosteroid therapy. This case highlights the significant challenges in diagnosing PIRS and provides important information that clinical symptoms and MRI findings could worsen during CM treatment even though with improvements in laboratory data.

C. gattii and *Cryptococcus neoformans* are more commonly associated with infections in less immunocompetent individuals [9]. However, keeping in mind that Cryptococcus neoformans could infect healthy people without any immunocompromised conditions or significant previous medical history is important [10]. Therefore, CM should be considered in the differential diagnoses of both immunocompromised and immunocompetent patients. CM is difficult to treat, particularly in immunocompetent patients. A previous study reported mortality rates as high as 44%, exceeding those observed in HIV-infected hosts [11]. This underscores the need for thorough evaluation and appropriate management strategies tailored to patient's immune status for improving outcomes [11]. These results are attributed to delayed diagnosis, inadequate antifungal therapy, and host immune responses, which are typically better preserved than those in patients with HIV infection [11].

A previous study reported that [12] PIIRS in HIV-negative CM patients developed approximately 50 days after the start of antifungal treatment, which is consistent with our case (52 days from the start of treatment). Almost all patients experienced severe headaches, nausea, visual impairment, and auditory dysfunction; all showed negative CSF fungal cultures upon PIIRS diagnosis [12]. Additionally, according to another study, the most common clinical symptom of PIIRS is altered mental status, similar to that in our case [7].

In the present case, the patient tested negative for HIV, and other test results indicated that she was immunocompetent. It has been hypothesized that meningeal lesions could be caused by *Cryptococcus neoformans*, which invades the Virchow-Robin spaces in the cerebral cortex and deep white matter [13].

The initial brain MRI performed on the day of admission revealed no abnormalities on T2WI and FLAIR, with only slight contrast enhancement in the sulci of the cerebellum and left parietal lobe observed on CE-T1WI. The patient initially responded well to antifungal therapy for CM. However, she later experienced symptoms such as fever and headache. T2WI and FLAIR images revealed high signal intensities in the cerebellum, middle cerebellar peduncle, and left parietal lobe with edema, which were not observed in the initial study. Hydrocephalus was indicated by an enlarged inferior horn of the lateral ventricle compared with previous images. Additionally, there were more prominent meningeal contrast-enhanced lesions on contrast enhanced (CE)-T1WI than that in the initial MRI study. Considering the course of the disease, CM recurrence was suspected. However, the decrease in cryptococcal antigen titers and CSF cell counts compared with the initial data, along with negative blood and CSF cultures, suggests that the second event was not caused by cryptococcal infection, but by immune-mediated mechanisms, specifically PIRS.

Mild ventricular enlargement and meningeal enhancement are observed in approximately 10% of CM cases as MRI findings [14]. CE-T1WI also reveals solid or ring-shaped enhancement, commonly observed in the choroid plexus, which was not detected in this case [15]. There have been reports on cerebellar lesions in patients with CM, which showed T2WI and FLAIR hyperintense signal lesions, as shown in our case [16,17]. A systematic review [7] reported that among 15 patients, meningeal enhancement was the most common radiological finding at the time of PIRS, observed in 13 patients, hydrocephalus in 10 patients, and parenchymal enhancement in 9 patients. Determining whether condition could be PIRS or CM based on MRI findings alone is difficult. Therefore using other test results such as CSF findings is necessary. In the present case, meningeal enhancement and hydrocephalus were observed, consistent with previous reports, although enhancement of the brain parenchyma was not obvious. There are a few reports comparing MRI findings of PIRS with those after treatment. However, to our best knowledge, there have been no reports comparing MRI findings of CM at the time of diagnosis with those of PIRS.

Previous studies [18,19] reported that increased intracranial pressure and a disrupted blood-brain barrier may be induced by cytokines released in response to antifungal medications, which could exacerbate symptoms. This pathological condition was explained in a previous study that reported glucuronoxylomannan (GXM), a capsular polysaccharide of Cryptococcus, suppresses immune responses [20]. Since GXM decreases in response to antifungal treatment, leading to a release from immune response suppression, the Th1 system becomes more dominant than does the Th2 system, while the Th2 immune response diminishes because IL-10 activation is reduced [18].

In this case, the differential diagnoses included primary brain tumor and brain metastasis in addition to CM exacerbation. MR spectroscopy (MRS) is a newly developed technique that could be applied for evaluating cryptococcal infection. Neuronal injury and gliosis caused by cryptococcal infection was described as increased lactate and decreased N-acetyl aspartate, choline, and creatine [21–23]. Ex vivo MRS study using infected rats indicated that trehalose, which is a marker metabolite, can differentiate cryptococcal infection from normal tissue and gliomas [24,25]. A recent study also has suggested that trehalose detected on MRS is specific for diagnosis of cryptococcal lesions in the CNS [24]. Therefore, trehalose might be a useful quantitative biomarker for identifying failure of CM treatment and PIRS [26]. Furthermore, due to the high concentration of the fungal biomarker trehalose in cryptococcal cells, the CryptoCEST contrast allowed for

high-resolution identification of cryptococcomas and can be used to monitor the effect of antifungal treatment [27].

Consequently, cytokine secretion, such as vascular endothelial growth factor, increases vascular permeability, leading to higher intracranial pressure and disruption in the blood-brain barrier, contributing to delayed symptom exacerbation, as in the present case [18,19]. Steroids have been reported to be effective in reducing intracranial pressure and decreasing cytokine secretion in the early stages of this condition [28]. By mitigating the excessive immune response, steroids can help alleviate symptoms and improve outcomes in patients with severe PIRS [10]. This raises the likelihood that the worsening condition could be attributed to immune-mediated mechanisms rather than the resurgence of the infection.

Conclusion

We reported a case of PIRS in an immunocompetent woman. Diagnosing and treating PIRS as early as possible because delayed treatment can result in severe complications and poor prognosis in patients with CM are important. Immunosuppressants, such as corticosteroids, are key drugs for moderating inflammatory symptoms and improving outcomes, as demonstrated in our case. Clinicians, including radiologists, should consider the possibility of PIRS in immunocompetent patients with CM if imaging findings and clinical symptoms worsen despite improvements in CSF and blood test results during treatment.

Ethics approval

All procedures involving human participants in this study were performed in accordance with the ethical standards of the institutional and national research committees and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Patient consent

Informed consent was obtained from the patient.

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