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Case Report

A case of immunocompetent intracranial cryptococcoma in which intraoperative rapid pathological diagnosis and polymerase chain reaction led to early treatment: What to know to avoid misdiagnosis as brain tumor

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ABSTRACT

Background: Cryptococcal infections of the central nervous system are infrequent in immunocompetent hosts and usually present as meningitis. However, a fungal mass called a cryptococcoma may form, requiring caution in therapeutic intervention. Here, we report a rare case in which treatment of intraventricular cryptococcoma in an immunocompetent patient was facilitated by rapid pathological diagnosis.

Case Description: A 58-year-old previously healthy man was admitted to our hospital with fever, headache, and gradually worsening hearing loss over 1 month. Cerebrospinal fluid analysis showed moderately elevated levels of protein and lymphocytic cells and decreased glucose. In addition, β2-microglobulin was highly elevated. Magnetic resonance imaging showed homogeneously enhanced lesions in lateral ventricles of the left and right hemispheres and the subarachnoid space, and ^{18}F-fluorodeoxyglucose positron emission tomography revealed abnormal uptake corresponding to the lesion. A surgical excision was performed to achieve a definitive diagnosis. Intraoperative rapid pathology, including immunohistochemistry (IHC), yielded negative results for malignant tumor, suggesting the possibility of inflammatory granuloma. Additional targeted pathological diagnosis was immediately performed. Paraffin-embedded histopathological examination showed fibrocaseous granuloma and numerous fungal spores. *Cryptococcus neoformans* within the granuloma were suggested by Fontana–Masson and Grocott staining and confirmed by polymerase chain reaction (PCR), leading to a diagnosis of cryptococcoma. Antifungal agents were started 3 days postoperatively. The patient has since been doing well, with no recurrence.

Conclusion: This pathology can be difficult to distinguish from a brain tumor, so early pathological diagnosis, including rapid pathology with IHC and PCR, may be crucial.

Keywords: Cryptococcoma, *Cryptococcus neoformans*, Fontana-Masson staining, Polymerase chain reaction, Rapid pathology

INTRODUCTION

Fungal infection of the central nervous system (CNS) is termed "neurocryptococcosis." This pathology is well known as an opportunistic infection of immunocompromised patients but is also occasionally encountered in healthy individuals. The disease can progress to granuloma in the brain parenchyma, as cryptococcoma, which is often fatal if not adequately treated.[1,3,8,10]

Neurocryptococcosis is usually diagnosed on the basis of the clinical picture and a typical association with the human immunodeficiency virus.[7] Infection usually begins with meningitis, but the cerebral parenchyma may also be involved with cryptococcoma, widening of the Virchow–Robin spaces, or gelatinous cortical nodules. Cryptococcoma is more common among immunocompetent patients and generally presents with intense contrast enhancement associated with greater immune response.[7,10] Once the diagnosis is made, treatment with antifungal therapy is usually successful, but neuroimaging can be challenging due to the nonspecific features of the pathology, particularly in immunocompetent individuals.[1,3] Here, we report a case of cryptococcoma in the lateral ventricles of an immunocompetent patient in whom rapid diagnostic techniques, including immunohistochemistry (IHC) and polymerase chain reaction (PCR), led to early therapeutic intervention and good treatment outcomes. We also present the usefulness of rapid pathological analysis, including IHC and the detection of *Cryptococcus neoformans* using PCR techniques.

CASE DESCRIPTION

A 58-year-old man with no relevant medical history was admitted to our hospital with fever, headache, and gradually worsening hearing loss over 1 month. The patient had been involved in the production of fertilizer with the use of pigeon droppings for the past 20 years. First, a neurologist (S.F.) had performed an outpatient examination. Magnetic resonance imaging (MRI) showed homogeneously enhanced lesions in lateral ventricles of the left and right hemispheres and the subarachnoid space [Figures 1a-c]. Markedly high ^{18}F-fluorodeoxyglucose (FDG) uptake was seen on positron emission tomography (PET) within the enhanced region (tumour-to-contralateral normal brain tissue ratio [TNR]: 3.1) and subarachnoid space [Figure 1d]. Cerebrospinal fluid (CSF) analysis on admission showed meningitis with a white blood cell count of 302 cells/mm^3 (lymphocytes, 84%; polymorphonuclear leukocytes, 16%); proteins, 306 mg/dL; and glucose, 11 mg/dL. The level of β2-microglobulin (β2-MG) was highly elevated at 12.2 mg/L. No other laboratory findings were abnormal. On initial consideration, the history and results of laboratory examinations and radiological studies seemed most consistent with malignant lymphoma. To clarify the histological diagnosis and plan effective treatment for the primary disease, he was referred to the hospital neurosurgical department for a surgical biopsy of the left lateral ventricular lesion under image-guided navigation (A.I.). The lesion showed no fluorescence on photodynamic diagnosis using 5-aminolevulinic acid [Figure 2a]. Intraoperative rapid histopathology using frozen sections revealed granuloma with central necrosis against a background of tissue that appeared to be choroid plexus. Multinucleated giant cells appear in the surrounding area. No obvious atypical lymphocytes were present. In addition, intraoperative rapid IHC revealed that most giant cells showed positive staining for a cluster of differentiation (CD)68, while other small cells stained positively for CD3 or CD20 [Figures 2b-e]. This information suggested the possibility of inflammatory granuloma, so additional targeted pathological diagnosis was immediately performed using paraffin-embedded sections. MRI performed on postoperative day 3 confirmed that the target lesion was removed from the left lateral ventricle [Figures 3a and b]. Postoperative histopathology using hematoxylin and eosin (HE) staining demonstrated a fibrocaseous granuloma surrounded by histiocytes and multinucleated giant cells [Figure 3c]. On immunohistochemical investigation, Gomori–Grocott staining and Fontana–Masson staining revealed multiple encapsulated structures, round to oval, with thin cell walls that appeared to be capsular polysaccharides of variable size (diameter, 8.0–10.0 μm) [Figures 3d and e]. HE staining and immunohistochemical studies revealed morphological characteristics consistent with cryptococcoma. In addition, molecular analyses using DNA extracted from paraffin sections confirmed *C. neoformans* and a definitive diagnosis was made. On postoperative day 3, the patient started treatment with intravenous liposomal amphotericin B and flucytosine for 3 weeks and oral fluconazole as an outpatient maintenance treatment that has continued for 3 months, and no recurrences have been identified on MRI [Figure 4]. Informed consent was obtained from the patient.

DISCUSSION

Cryptococcosis is an invasive fungal infection that primarily affects the lungs and can spread to the CNS. This fungal infection can be misdiagnosed as other infectious diseases such as tuberculosis, granulomatous diseases such as sarcoidosis, and even neoplastic diseases.[1,3,8,10] Some reports have described cases of cryptococcoma mimicking brain tumors.[1,2,3,11] In fact, the features of cryptococcoma on MRI are extremely nonspecific. In general, cryptococcoma presents as hypo- or isointense lesions on T1-weighted imaging (WI) and hyperintense on T2-WI, with variable enhancement by gadolinium.[2,11] The clinical manifestations of cryptococcoma

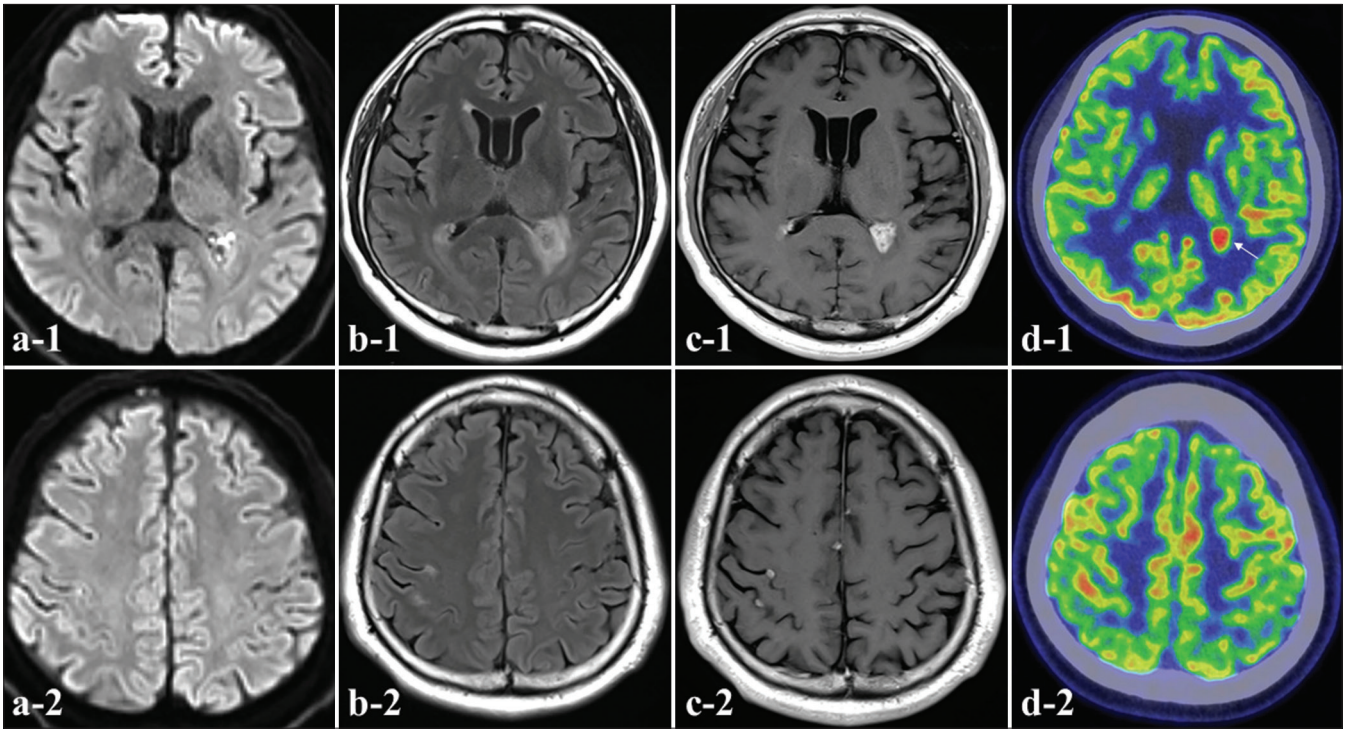

Figure 1: (a-c) Preoperative magnetic resonance imaging (MRI) on initial admission shows multiple lesions in bilateral ventricles and the subarachnoid space. Lesions are hypointense on (a-1, a-2) diffusion-weighted imaging (DWI) and hyperintense on (b-1, b-2) fluid-attenuated inversion recovery (FLAIR). (c-1, c-2) The lesion appears enhanced following administration of gadolinium (Gd). Imaging with (d-1, d-2) 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET) reveals abnormal uptake in the focal space-occupying lesion identified on MRI (white arrow) (tumor-to-contralateral normal brain tissue ratio: 3.1).

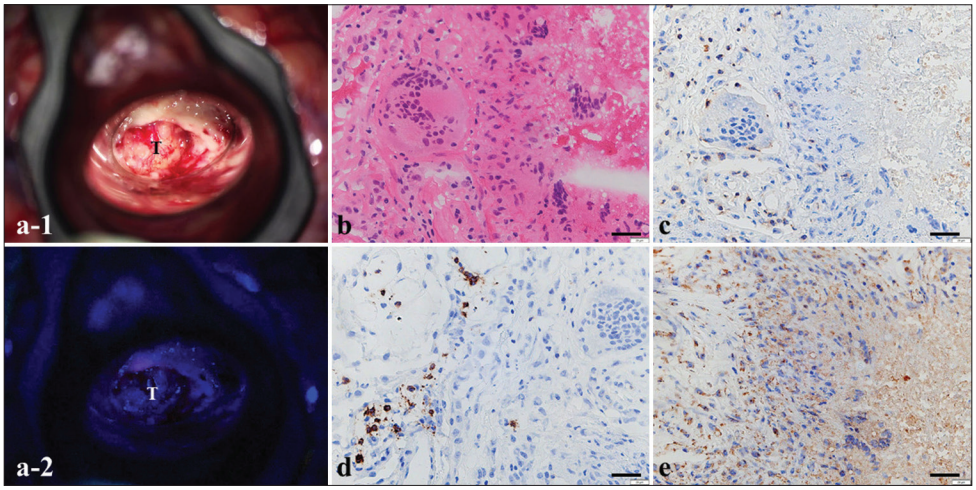

Figure 2: (a-1, a-2) Intraoperative findings show a solid tumor mass with no fluorescence at all on photodynamic diagnosis using 5-aminolevulinic acid. T: tumor. Photomicrographs reveal intraoperative rapid pathological analysis including immunostaining. (b) Hematoxylin and eosin (HE) staining.Immunohistochemically, cells are negative for (c) cluster of differentiation (CD) 3 and (d) CD20, but positive for (e) CD68, indicating histiocytes and multinucleated giant cells.

were reported by Li *et al.* as the onset of fever, headache, and vomiting in 64.7% of patients, mild disturbance of consciousness and personality change in 41.2%, focal neurological signs in 29.4%, and epileptic seizures in 11.8%, but symptoms were consistently very mild with slow progression over 2–4 weeks.[6] CSF evaluation and neuroimaging may

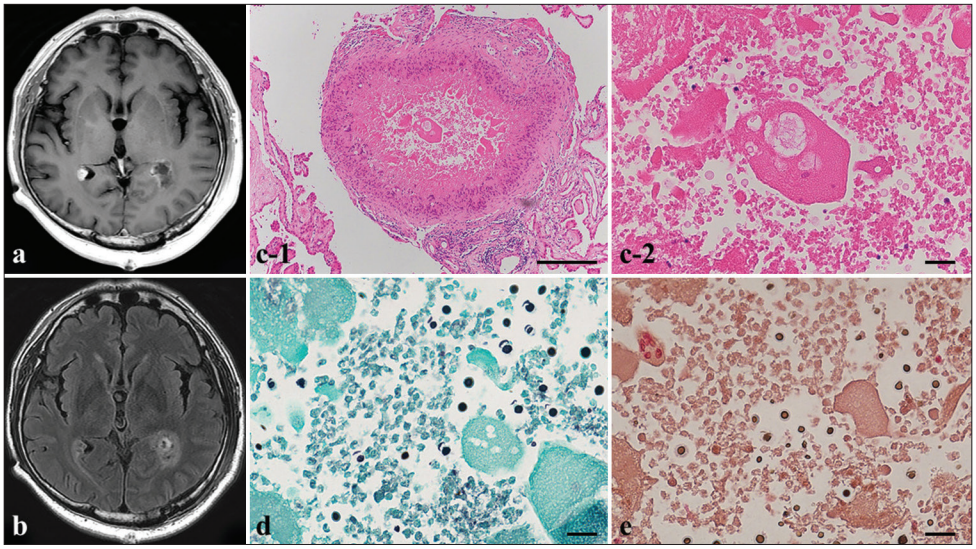

Figure 3: Postoperative (a) T1-Gd and (b) FLAIR MRI. Resection of the tumor within the left lateral ventricle has been successful. Histological examination of a paraffin-embedded specimen from surgical biopsy shows granulomatous nodule surrounded by histiocytes and multinucleated giant cells (c-1, c-2) (HE stain). (d) Grocott stain and (e) Fontana-Masson stain reveal cryptococcal organisms.HE: Hematoxylin and eosin. (c-1) Magnification, ×100; scale bar, 50 μm. (c-2) Magnification, ×400; scale bar, 100 μm. (d and e) Magnification, ×600; scale bar, 150 μm. FLAIR: Fluid-attenuated inversion recovery.

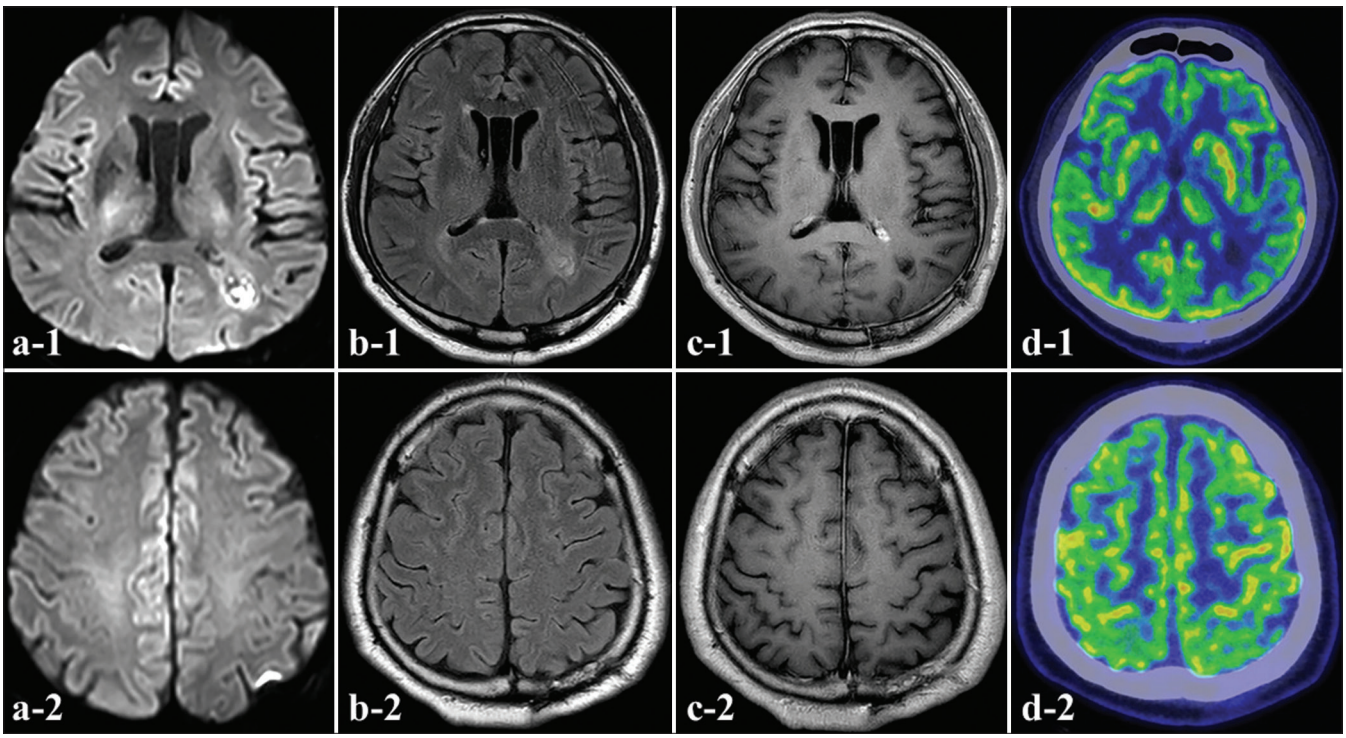

Figure 4: Three months after surgery, no recurrences are apparent on magnetic resonance imaging (MRI) and ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET). (a-1, a-2) Diffusion weighted imaging; (b-1, b-2) Fluid attenuated inversion recovery; (c-1, c-2) Gadolinium-MRI; (d-1, d-2) ^{18}F-FDG-PET.

also help. Once the diagnosis is established, treatment with antifungal agents is usually successful. *C. neoformans* antigen testing of CSF samples, India ink staining, and CSF culture are important for definitive diagnosis, but the positive rate from CSF testing is low, and blood β-D glucan is often not clearly elevated.[6] This is the largest problem for cryptococcoma

occurring in healthy subjects, and the causative *C. neoformans* in the present case could not be detected in CSF even in the pre and postoperative periods. In other words, definitive diagnosis by imaging and clinical examination is extremely difficult. In the majority of cases, definitive diagnosis is ultimately made from histopathological examination of biopsy specimens. The possibility of cryptococcoma should, therefore, always be considered for intracranial lesions in patients with fever of unknown origin.

In April 2020, we started intraoperative rapid IHC mainly for use in surgery to diagnose primary CNS lymphoma (PCNSL) in our institution. We found that this method is very useful for differentiating PCNSL from other brain tumors, particularly glioblastoma.[5] Intraoperative rapid immunodiagnosis is actively performed for early therapeutic intervention, especially when malignant lymphoma is suspected, and staining for CD20, CD3, glial fibrillary acidic protein, and leukocyte common antigen is routinely performed. In the present case, rapid intraoperative diagnosis using CD68 was extremely useful to determine a treatment plan at an early stage. Although a brain tumor was initially suspected, the addition of intraoperative rapid immunodiagnosis using CD68 completely ruled out the possibility of malignant lymphoma or glioma and allowed pathological diagnosis using paraffin-embedded sections targeted to inflammatory disease, leading to early diagnosis on postoperative day 3 and very early therapeutic intervention.

Another important factor relevant to the treatment of cryptococcoma is the type of *Cryptococcus* involved. *C. neoformans* is more common in immunocompromised individuals, usually presenting with meningitis, while *Cryptococcus gattii* has a higher incidence in immunocompetent individuals and is more closely related to cryptococcoma.[1,9] In the present case, a detailed examination using PCR of excised tissue revealed *C. neoformans*, contrary to previous reports. Verification of cryptococcal subtypes by PCR seems warranted for accurate diagnosis of cryptococcoma. In addition, in our previous report, we proposed that both β2-MG >2.0 mg/dL in CSF and TNR >2.4 from ^{18}F-FDG-PET allow quantitative differentiation of PCNSL from glioblastoma, potentially representing clinically useful indicators. In that report, the mean β2-MG level was significantly higher in the PCNSL group (3.60 ± 1.20 mg/L) than in the glioblastoma group (1.30 ± 0.60 mg/L; $P < 0.001$).[4] In the present case, because the β2-MG in CSF was as high as 12.2 mg/L and the TNR on ^{18}F-FDG-PET was high at 3.1, so we initially assumed that the patient most likely had lymphoma, but this was not the case. However, compared to our previous reports, the CSF β2-MG level in our present case was abnormally high [4], and whether the β2-MG level is a finding that can be used to differentiate malignant lymphoma from cryptococcoma should be further investigated.

CONCLUSION

The present report describes a rare case of CNS cryptococcoma in an immunocompetent adult. Given the rarity of this pathology, a multidisciplinary approach is indispensable. Because the characteristics of cryptococcoma on MRI are extremely nonspecific, cryptococcoma should always be included among the differential diagnoses of brain lesions, whether malignant or benign. Surgical biopsy should always be performed in cases of possible cryptococcoma to clarify the diagnosis and avoid inappropriate treatment and prognostic decisions based solely on radiological patterns. In addition, rapid immunodiagnosis and PCR techniques should also be performed when necessary for early diagnosis and therapeutic intervention. Further research and accumulation of more cases are needed to understand the behavior of this pathology better, to identify optimal treatment plans, and to standardize immunohistochemical and genetic analyses for diagnosis.

Ethical approval

Institutional Review Board approval is not required.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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