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Brain abscess due to *Candida glabrata* in an immunocompetent patient. A case report with update and literature review

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ABSTRACT

Candida spp. brain abscess is scare. Clinical presentation is unspecific. Diagnosis requires mycological culture of a puncture or biopsy specimen. Therapeutic management is based on prolonged course of azole or liposomal amphotericin B. We reported the case of *Candida glabrata* brain abscess in a 27 year-old female patient, with no past history and not secondary to candidemia. The fungus was isolated from a puncture of abscess with complete resection. The outcome was favorable under antifungal treatment by voriconazole.

Introduction

Fungal central nervous system (CNS) infections are not common. They usually concern patients with compromised immune system, carrying an invasive medical device or presenting genetic immune disorder. The *Candida* genus is among the first pathogens to cause fungal CNS infections, however cerebral abscesses of *Candida* species remain a rarely encountered disease [1]. *Candida albicans* is by far the most encountered *Candida* specie, other species, notably *C. glabrata* are seldom identified in CNS infections.

We described a case of an immunocompetent female patient who presented with a fungal cerebral abscess due to *C. glabrata*. To our knowledge, this is the third described case of *C. glabrata* abscess; only two cases were reported in medical literature [2,3].

Case report

A 32 year-old-woman without past medical history, presented to emergency room for focal motor seizures of the right upper limb, happening thrice, with impaired awareness between the seizures. At admission, physical examination revealed a fever (39 °C) and regular heartbeat. Neurologic examination showed a Glasgow Coma Scale score of 15/15 (Eye opening = 4, Verbal response = 5, Motor response = 6). The patient did not complain about headache, vomiting or neck stiffness, she was only drowsy without focal abnormalities. Seizures were controlled with Intra-Venous (I.V) then oral antiepileptic treatment (clonazepam and levetiracetam). The initial anamnesis found no history of seizures, neither signs of high intracranial pressure.

Laboratory findings revealed high leukocytes count (15.5 Giga/mm^3) and elevated of C-reactive protein (70 mg/L). Brain Magnetic Resonance Imaging (MRI) showed a single round well circumcised lesion in the left frontal lobe, measuring 22*19 mm with low T1 and high T2 signal, heterogeneous with peripheral enhancement, with a distinctive high signal in Diffusion sequences, and ADC restriction in some areas (Fig. 1). These results were in favor of a brain abscess.

Extensive investigation found no history of immunologic deficiency, no susceptibility to infections, no diabetes, no intrauterine device, no injectable drugs use. However, the patient revealed that she was self-treating some “tooth pain” with only high doses of non-steroid anti-inflammatory three weeks before. Blood and urine culture were negative. A lumbar puncture (LP) was not performed, because of the raised intracranial pressure and the risk of cerebral herniation. Computed Tomography (CT) scan of chest, abdomen and pelvis showed no associated locations. Transthoracic and transesophageal cardiac sonography were normal. Serology for HIV, hepatitis B and C hepatitis and toxoplasmosis were negatives. Aspergillus antigenemia was also negative.

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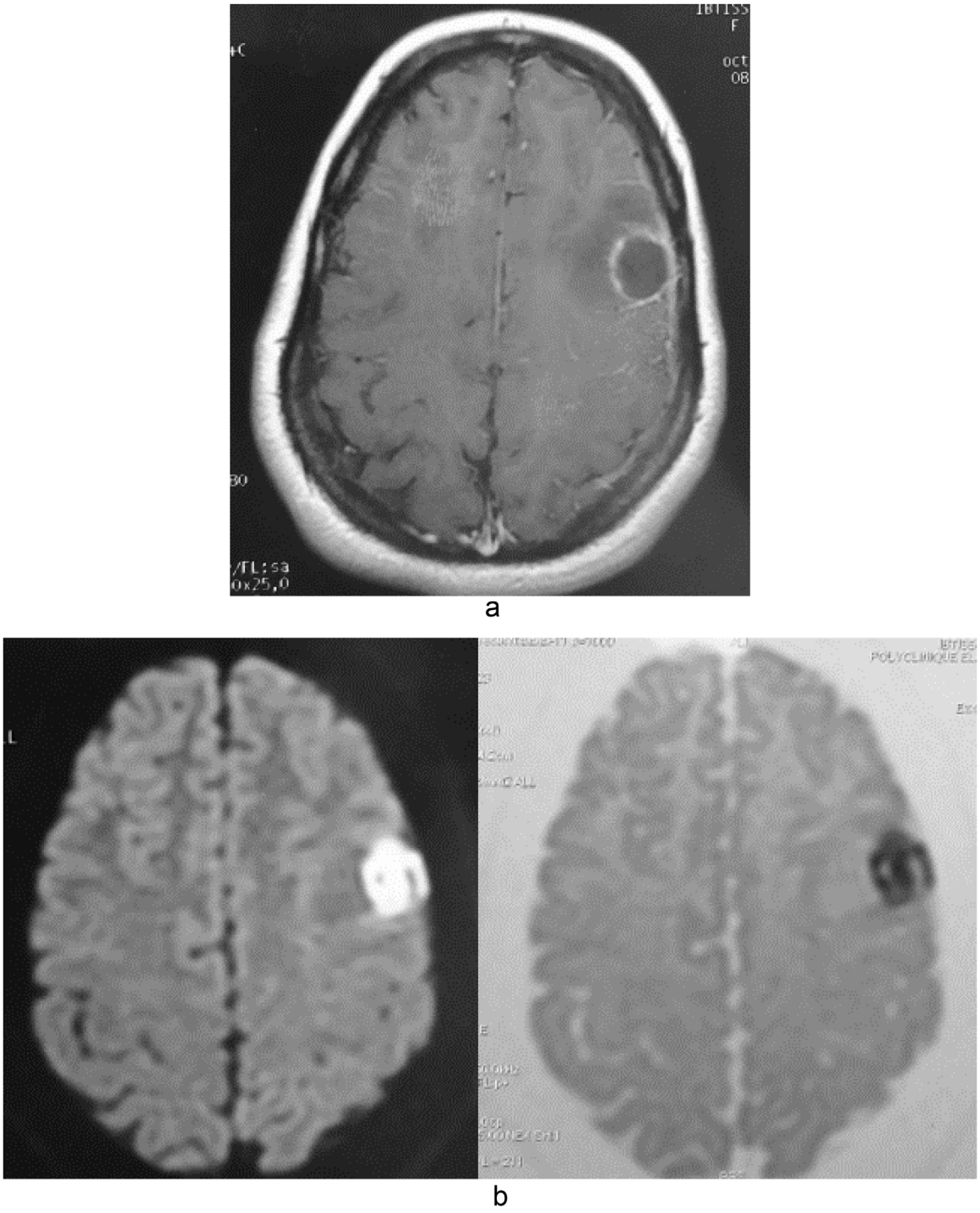

Fig. 1. a: Brain MRI. Axial T1 weighted image with gadolinium injection showing a left frontal round well circumcised lesion with peripheral enhancement. b: Trace DWI (left) showing a hyperintense lesion and a low ADC (right) indicating restricted diffusion.

The patient was operated: a puncture of the abscess and a removal of the shell (complete resection) were performed through a small frontal craniotomy, with no postoperative complications.

Treatment began with antimicrobial drugs empirically (cefotaxime 18 g IV infusion/d), levofloxacin (500 mg IV 2x/d) and metronidazole (500 mg IV 3x/d).

Direct bacteriological and mycological exams were negative. PCR-Based Rapid Detection of *Mycobacterium tuberculosis* was also negative. After 24 h of culture on Chloramphenicol Sabouraud agar medium with and without Actidione at 37 °C, white, creamy, flat, and shiny colonies appeared. *C. glabrata* was identified by VITEK® 2 (Fig. 2). To test the sensitivity to antifungals, we used the automated VITEK® 2 using the antibiotic susceptibility testing (AST) card. The antifungal susceptibility testing showed resistance to fluconazole and sensitivity to voriconazole, caspofungin, micafungin, amphotericin B and flucytosine. The Minimum Inhibitory Concentration (MIC) of voriconazole was 1 mg/L. Bacterial culture was negative.

Brain abscess due to *C. glabrata* without candidemia was diagnosed. Antifungal treatment began with voriconazole (400 mg

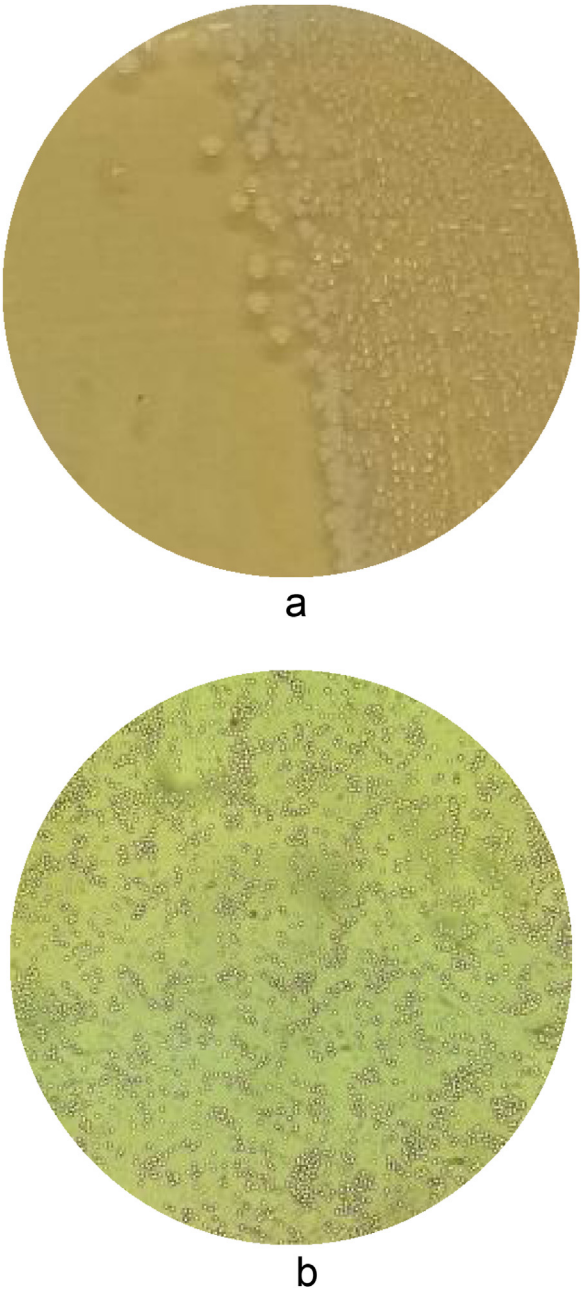

Fig. 2. a. *Candida glabrata* macroscopic colonies b. Microscopic structure on Chloramphenicol Sabouraud agar medium.

[6 mg/kg] twice first day orally then 200 mg [3 mg/kg] twice daily). The clinical course was rapidly favorable with resolution of neurological symptoms. The patient had undergone subsequent MRI brain (on day 21) showing complete resolution of the rim-enhancing lesion, without evidence of residual or recurrent abscess. Antifungal treatment was stopped on the day 24 and the patient was discharged.

Discussion

This case had essentially two particularities: first one is the occurrence of a fungal abscess in an immunocompetent and young person and second one is the isolation of the *glabrata* specie in a brain abscess without candidemia.

The Candida glabrata *(*Torulopsis glabrata*)*

The genus *Candida* includes commensal fungi. Some species live in human genito-urinary and gastro-intestinal tract and oral cavity. Local and systemic fungi infections may be the consequences of certain factors like the change of microbiota, the loss of the epithelial barriers, excessive growth or translocation of the fungi or immune deficiency [4,5].

For many years *C. glabrata* was considered as a relatively non-pathogenic saprophyte of the normal flora of healthy individuals and certainly not readily associated with serious infection in humans. However, following the widespread and the increased use of immunosuppressive therapies together with broad-spectrum antibiotic treatment, the frequency of mucosal and systemic infections caused by *C. glabrata* has increased significantly [5,6].

Epidemiology

The Incidence of Non Candida albicans Candida (NCAC), particularly *C.glabrata*, increased in the recent decades. That's mainly explained by the improvement of diagnostic methods, like for example the uses of chromogenic media [7]. It may also be due to the higher level of resistance of NCAC to antifungal drugs.

According to many studies, *C.glabrata* is among the four more prevalent species of *Candida*. The prevalence differs geographically. According to Pfaller et al., *C. glabrata* prevalence increases in USA and Europe with the age of patient : 2% of Candida infections for patients aged less than 20, and more than 20 % for patients older than 40, making it the second more encountered Candida in the latter group of patients [5,8]. However studies in Asia showed that *C.glabrata* comes third with 13.9 % of 1910 blood isolates, after *C. albicans* and *C.tropicalis* [9].

Tunisian studies found that 19.2 % of Candida isolated in blood culture of 130 case of invasive candidiasis [10] and 17.24 % of 406 yeast isolates (from different sites) [11] are *C. glabrata*, making it also the second more encountered Candida.

Microbiology

Unlike *C. albicans*, which is considered as polymorphic specie for its ability to form hyphae and/or pseudohyphae, *C.glabrata* is not polymorphic, as it grows only as a blastoconidia (yeast). This particularity is the reason why *C. glabrata* was not classified as a Candida before 1978 [12].

Another feature is the size of *C. glabrata* cells (1–4 mm) which is smaller than other species: *C. albicans* (4–6 mm) *C. tropicalis* (4–8 mm) and *C. parapilosis* (2.5–4 mm) [5].

On Sabouraud dextrose agar (SDA) *C. glabrata* appears as a glistening, smoot, and cream-colored colonies, which is not undistinguishable from other species. However on CHROM agar, colony color is white to pink purple, which make it quite distinguishable [5]. Another important distinguishing genetic feature of *C. glabrata* is the haploid genome it has, unlike the diploid genome of other Candida species [12]. On a metabolic level, *C. glabrata* ferments and assimilates only glucose and trehalose, unlike *C. albicans* which ferments and assimilates a larger number of sugars with the notable exception of sucrose [5].

Pathogenicity

Pathogenicity mechanisms include adhesions, biofilm formation and hydrolytic enzymes (Proteinase). *C. glabrata* is considered noticeably less pathogenic than *C. albicans* for the absence of invasive hyphal forms, secreted proteolytic activity and invasins, and the limited nutrient plasticity such as the non-utilization of hemoglobin as an iron source. Phenotypic switching is also

considered a pathogenic factor [12,13]. Nonetheless, *C. glabrata* infections remains dangerous for its low susceptibility to azole antifungals and emerging resistance to echinocandins [13].

C. glabrata isolates can be intermediately resistant to all azoles (especially to fluconazole) and a fifth of strains develop resistance during therapy or prophylaxis with fluconazole [5].

Concerning voriconazole, the antifungal agent used in our case, it is proven that it has fungicidal activity against most yeasts and opportunistic fungi, particularly against some NCAC including *C. glabrata* [14], and that is usually efficient against fluconazole-resistant *C. albicans* and *C. glabrata* [5].

Concerning its pharmacological characteristics, voriconazole has a lipophilicity that allows it to penetrate human brain tissue and abscess material, achieving peak concentrations similar or exceeding those found in plasma. However, its concentration in CSF tends to be lower, with CSF/plasma concentration ratios of <0.009 [15]. This makes it a good choice for Candida cerebral abscesses.

Generalities about cerebral abscesses

The histo-pathological genesis of cerebral abscesses begins with a local inflammation (cerebritis). This leads to a perivascular inflammatory response surrounding the necrotic center with increased surrounding edema. Subsequently the necrotic center reaches its maximum size, and with accumulation of fibroblasts and neovascularization a capsule is formed. This capsule will thicken through reactive collagen accumulation, but inflammation and edema will persist even beyond the capsule [16].

Clinical features are not specific. They consist mainly in fever, intracranial hypertension syndrome and focal neurological sign. Differential diagnosis includes a large specter of neurological diseases such as brain tumors, stroke, epidural abscess, subdural empyema and acute bacterial meningitis [17]. CT scan is a valuable tool for diagnostic, but MRI, combined with diffusion weighted and apparent diffusion coefficient images is more suited for differentiating brain abscess from primary, cystic or necrotic tumors [17].

Prognosis of brain abscesses has clearly improved in the last decades, due to improvement in cranial imaging techniques, the use of antifungal treatment regimens, and the introduction of minimally invasive neurosurgical procedures. Currently, 70 % of patients with brain abscess have a good outcome, with no or minimal neurologic sequelae, such as our patient [18].

Neurosurgical point of view

Neurosurgery has essentially two main goals. The first one is the identification of the causative agent, if it has not been determined otherwise (in the case of negative blood culture), and the second one is reducing the size of the abscess, and subsequently its mass effect, when needed.

Stereotactic aspiration is the more suited technique, allowing aspiration of the purulent center for diagnosis and decompression. Any abscess that measures more than 1 cm in diameter is candidate to stereotactic aspiration regardless of location [17]. Other techniques, for superficial and reachable abscesses, especially if stereotactic aspiration in not available, is abscess aspiration through a burr hole or through a small craniotomy [17].

Total resection of brain abscesses (aspiration plus shell removal) used to be recommended, but it has a limited role now, because of the improvement in medical and minimally invasive neurosurgical management. However for superficial abscesses that are not located in eloquent area, resection rather than drainage should be considered, especially when fungal, tuberculous or a branching bacterial infection (e.g., actinomyces or nocardia species) is suspected [17]. In our cases, the abscess was frontal, in a non-eloquent area, so a complete resection was performed.

Cerebral abscesses of Candida *species*

A literature review about cerebral abscesses du to *Candida* species (n = 148) and published by Fennelly et al. concluded that the majority of the cases were diagnosed after autopsy [19].

Main comorbidities included the use of antibiotics (52 %), prior surgery (28 %), malignancy (28 %), transplantation and inserted central venous.

Clinical features were not specific. It consisted of fever (76 %), altered neurological state (55 %), focal signs (52 %) followed by seizures, headache, and meningeal signs. However non autopsy cases consist only of 28 % of cases in this study (42/148).

Lumbar puncture was performed in 15 % of cases with 77 % of cultures being nondiagnostic for *Candida* cerebral abscess. Blood cultures were performed in 38 % of cases with only 55 % being positive for *Candida*, although the hematogenous spread is the most frequent source of brain abscesses. On the other hand, in 73 % of cases the diagnosis was established through tissue biopsy. Thus, candidemia and abnormal CSF studies may be a clue to the diagnosis, candida cerebral abscesses cannot be ruled out in the absence of such results.

Radiological study showed that in most cases (77 %) abscesses are multiple rather than unique. However, their appearance is non-specific.

C. albicans was the encountered specie, being identified in 56 % of cases. In 40 % of cases *Candida* specie was not identified. C. tropicalis was identified in 2 cases, while *C. parapilosis* and *C. guilliermondi* were identified in one case for each one. *C. glabrata* was not mentioned in this study.

The most common antifungal treatment was amphotericin B alone (40 %), followed by amphotericin B associated to fluconazole (20 %). According to this study, successful treatment requires early diagnosis and long-term antibiotic treatment, with endpoint determined by radiographic and clinical resolution of the abscess and symptoms [19].

Cerebral abscesses of Candida glabrata

So far, only two cases of *C. glabrata* brain abscess have been reported in medical literature, to our knowledge (Table 1). The first case was published by Strickland and al. [3] reporting (in 2017) a 33 year-old-woman, with a past history of diabetes mellitus and a presentation of a diabetic ketoacidosis and an acute encephalopathy with right oculomotor nerve palsy. Invasive disseminated *C. glabrata* candidiasis was diagnosed from results of mycological testing (isolanting of *C. glabrata* on blood culture) and computed tomographic imaging (showing multiple abscesses in liver, lungs, uterus, kidneys, and the pituitary gland). The abscess was evacuated via an endoscopic endonasal transsphenoidal approach. She was treated with received a voriconazole with a favorable outcome.

The second case, published by Zhu and al. [2] is about a 25 year-old-women with a past history of recent anal polypectomy admitted (in 2018) for an altered consciousness with fever. Blood and CSF culture were negative. Brain MRI showed multiple brain abscesses. A bilateral pneumonia was also diagnosed. The patient was treated empirically with antibiotics with no regression of fever and neurologic manifestations. Therefore, a stereotactic biopsy was performed; allowing a puncture of one of the abscesses, and antifungal treatment was introduced (itraconazole). Culture of the pus isolated a *C. glabrata*. After surgery and antifungal treatment, altered consciousness regressed and clinical outcome was favorable.

In the first case the main risk factor is diabetes mellitus, while in the second case, no immunological impairment was found.

Table 1
A summary of previously reported cases of C. Glabrata brain abscess including our case.

Case (Year)	Age(y) /Sex	Comorbid Conditions	Clinical presentation	Supposed Origin	Postive Exams	Candidemia	Location of abscesses	Antifungal treatment	Surgery	Clinical outcome
Strickland & al. (2017)	33/F	Type 2 diabetes	Encephalopathy, rightuculomotor palsy, panhypopituitarism, diabetes insipidus	Not precised	Blood culture	Yes	Pituitary abscess/ liver, lungs, uterus, kidneys	Voriconazole	Evacuation via an endoscopic endonasal transsphenoidal approach	Good outcome
Zhu & al. (2018)	25/F	Anal polypectomy	Meningeal syndrome, fever, poor neurological state	Digestive	Stereotactic biopsy and puncture of a brain abscess	No	Multiple brain abscesses	Itraconazole	Puncture via stereotactic method	Progressive clinical improvement
Current case (2020)	32/F	Ectopic pregnancy, miscarriage	Epilepsy, fever	Dented abscesses	Pus culture after surgery	No	Left frontal brain abscess	Voriconazole	Surgical resection	Good outcome

However, a clear entry point is objectified (anal polypectomy). Habitually, the gastrointestinal tract is a more likely source. In our case, no immunodepression status was found. However, our patient may have an unidentified genetic immune disorder predisposing to invasive fungal CNS infection. Corvilain et al. suggested that previously healthy patients with unexplained invasive fungal infection, at any age, should be tested for inherited CARD9 deficiency. Autosomal recessive CARD9 deficiency underlies life-threatening, invasive fungal infections. Fifty-eight patients have been reported in 14 countries and three of these patients had CNS *Candida* infection. CARD9 is expressed principally in myeloid cells, downstream from C-type lectin receptors that can recognize fungal components. Patients with CARD9 deficiency present impaired cytokine and chemokine production and defective killing of some fungi by neutrophils in vitro [20].

Even though most of the studies report a reduced sensitivity of *C. glabrata* to azoles, all three patients were treated with azoles (voriconazole in two cases and itriconazole one case), such as IDSA recommendations [21] with favorable evolution. Voriconazole, a moderately lipophilic molecule with good CNS penetration, is recommended in the first-line therapy of CNS aspergillosis [22,23]. Voriconazole has also demonstrated effectiveness in CNS and invasive candidasis [20]. CSF and vitreous concentrations are > 50 % of serum concentration, and voriconazole has been shown to be efficacious in case series for these infection sites [22]. Other triazoles, such as posaconazole and itraconazole, with negligible concentrations in the CSF are not considered effective drugs for therapy of CNS fungal neuroinfections [23]. Among antifungal drugs, voriconazole, fluconazole readily penetrate into the CNS, but itraconazole and posaconazole only penetrate to a minor degree [24]. In contrast, clinical data have shown that a novel triazole, isavuconazole, achieved considerable efficacy for the treatment of some fungal neuroinfections [23].

It is worth noticing that in all the cases, antibiotics were associated. Surgical treatment is also essential. It allows the removal of the abscess and its mass effect and helps with the mycological diagnosis through identification of the fungus and study of its antifungal sensitivity.

Conflicts of interest

No conflict of interest.

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Consent

No written informed consent was requested in this case report, as there are no identifying marks or features and no patient identifiers in the images or accompanying text.

Author contribution

All listed authors have made substantial contribution to the following aspects of the manuscript: Khaled Radhouane, Ridha Chkili and Maroua Jebari participated in diagnosing and treating the patient. Mohamed Dehmani Yedeas participated in acquisition of data. Aziz Bedioui collected the findings and drafted the manuscript. Khaled Radhouane and Souheil Zayet revised the manuscript. Ahmed Harbaoui and Mondher Yedeas Supervised the study.

CRediT authorship contribution statement

Khaled Radhouane: Conceptualization, Methodology. **Aziz Bedioui:** Writing - original draft. **Mohamed Dehmani Yedeas:** Visualization, Investigation. **Souheil Zayet:** Writing - review & editing. **Maroua Jebari:** Ressources. **Mondher Yedeas:** Project administration. **Ahmed Harbaoui:** Validation. **Ridha Chkili:** Supervision.

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