CASE REPORT

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Fungal brain abscess caused by azole-resistant cellulolytic yeast in an immunocompetent patient: case report and literature review

LEDIANY SCHUNCK FERRARINI[1], GIOVANNA LOPES CONSTANT[1], VICTOR HENRIQUE PEREIRA CINTRA[2], ISABELLY SILVA DE OLIVEIRA[1], CÍNTIA HORTA REZENDE[3]

[1] FACULDADE DE CIÊNCIAS MÉDICAS DE MINAS GERAIS – BELO HORIZONTE, MG-BRASIL
[2] UNIVERSIDADE FEDERAL DE MINAS GERAIS – BELO HORIZONTE, MG-BRASIL
[3] FUNDAÇÃO HOSPITALAR DO ESTADO DE MINAS GERAIS – BELO HORIZONTE, MG-BRASIL

ABSTRACT

Introduction: Brain abscess is a rare infection, which in healthy patients is usually caused by bacteria, and in immunocompromised individuals, by fungi and protozoa. The latter group is often treated with azoles. Abscesses caused by azole-resistant yeast in immunocompetent patients are particularly uncommon and challenging. **Objective:** To describe a rare case of brain abscess caused by fluconazole-resistant yeast in an immunocompetent patient and to discuss pathogenesis, diagnosis, and treatment based on a literature review. **Methods:** Clinical and laboratory data were collected through medical reports, copies of medical records, and interviews provided by the patient. **Results:** A young patient, previously healthy and immunocompetent, initially presented with a headache and subsequently deteriorated clinically. Magnetic resonance imaging revealed an encapsulated nodular image with homogeneous enhancement limited to the capsule, regular contours, thick content, and voluminous surrounding edema. After neurosurgical intervention to resect the lesion, a brain abscess caused by cellulolytic yeast resistant to fluconazole and sensitive to amphotericin B was diagnosed. Unusual differential diagnosis of brain tumors and uncommon pathogenesis and resistance hindered early and assertive treatment. **Conclusion:** It's essential to make an early diagnosis of brain abscesses in patients with acute neurological symptoms and focal lesions on cranial imaging exams. Additionally, early antimicrobial treatment is crucial, even when facing other differential diagnoses, and consideration should be given to the possibility of unusual etiological agents, such as resistant fungi.

Keywords: Drug Resistance; Differential Diagnosis; Fungi; Fluconazole; Brain Abscess.

Abbreviations:
Central nervous system: CNS
Computerized tomography scan: CT scan
Glasgow Coma Scale: GCS
Intracranial hypertension: ICH
Magnetic resonance imaging: MRI

INTRODUCTION

Brain abscesses are rare neuroinfectious diseases that present as encapsulated focal areas of purulent secretion within the brain parenchyma. There can be cerebellar abscesses within the cerebellar parenchyma or even within the brainstem, though these are rarer. They are usually secondary to infections disseminated hematogenously or by contiguity from an adjacent infectious condition to the brain parenchyma. They can also occur after cranial trauma, with disruption of the protective skin and bone barriers, dural injuries, and consequent contamination and infection of the brain by pathogenic etiological agents.[1-8]

The pathogens most frequently isolated from brain abscesses are bacteria from the oral cavity and ear, such as *Streptococcus anginosus* and *Fusobacterium spp*, which cause dental infections, otitis, and mastoiditis. Etiological agents like *Staphylococcus aureus*, *Mycobacterium tuberculosis*, *Nocardia spp.*, gram-negative bacilli, fungi, and parasites are less common and usually affect immunocompromised individuals.[1,2]

The incidence of brain abscesses is estimated at 0.3 to 1.3 per 100,000 people per year, and the mortality rate is about 20%. However, a declining trend in this percentage has been reported in recent decades.[1,2,3]

Invasive fungal pathogens are increasingly being identified as causes of infections in the central nervous system (CNS). In the absence of antimicrobial therapy, these infections are inexorably fatal, especially in susceptible patients: immunocompromised individuals, those at extreme ages, or those in the postoperative neurosurgical period. The number of reported fungal infections in the CNS is increasing, with the discovery of new species of increasingly pathogenic infectious agents.[4-8]

The diagnosis of brain abscesses is challenging, as clinical symptoms can be nonspecific, with the presence of the triad: fever, headache, and focal neurological deficits, which vary according to the size and location of the brain parenchymal lesions. Complementary imaging tests are necessary to establish the diagnosis, which is generally made, on average, 8 days after the onset of symptoms.[3]

Fluconazole is a widely recognized triazole compound broadly indicated for treating specific systemic fungal infections. However, its frequent and indiscriminate use has led to the emergence of resistant fungal strains causing CNS infection. In the scientific literature, there are descriptive reports of yeasts resistant to fluconazole: *Candida auris*, cryptococcosis (*Cryptococcal spp*), and coccidioidomycosis (Coccidioides).[9,10]

Although clinically relevant, azole-resistant fungal brain abscesses are not very prevalent, with few documented reports in the scientific literature. Thus, this article aims to describe a clinical case involving an immunocompetent patient affected by a brain abscess caused by an azole-resistant yeast susceptible to amphotericin B. Additionally, it seeks to conduct a comprehensive review of the academic literature to provide a detailed analysis of the pathogenesis, diagnosis, and therapeutic strategies employed in treating these intracranial infections.

METHODS

Study Design

This is a case report study.

Participants

A 32-year-old patient with a rare diagnosis of brain abscess caused by fluconazole-resistant cytolytic yeast.

Instruments

Interviews were conducted with the patient, during which she provided the results of the diagnostic investigation, medical reports, and copies of medical records that she had at home.

Procedures

For the development of this study, an interview was conducted with the patient, who agreed to contribute to the report, signed the Informed Consent Form, and provided the results of the diagnostic investigation, medical reports, and copies of medical records.

This study received approval from the Research Ethics Committee under the Certificate of Ethical Appreciation Submission number 79874724.2.0000.5134, following the ethical and legal principles established by Resolution 466/12 of the National Health Council. There is no conflict of interest of any nature, nor any direct or indirect benefits that could influence the results of the discussion related to the research.

RESULTS

On January 8, 2020, a 32-year-old female patient sought medical care at an Urgent Care Unit presenting with a severe unilateral left-sided, pulsatile headache that had started a week earlier and had intensified in the past 24 hours. The headache was associated with photophobia, general malaise, vomiting, anorexia, and a recorded fever of 37.8°C. No other neurological complaints were reported, although the patient had a prior history of episodic chronic headaches previously diagnosed as migraine. There was no history of previous immunosuppressive pathologies.

On physical examination, the patient was conscious and scored 14 on the Glasgow Coma Scale (GCS): Eye Opening: 3; Verbal Response: 5; Motor Response: 6. However, she complained of severe headache, had minimal interaction with the examiner and no focal deficits or meningeal irritation signs were identified. She was prescribed an intravenous opioid analgesic (tramadol), but her encephalic pain persisted. During clinical observation, she had a seizure and posttally scored 13 on the GCS: Eye Opening: 3; Verbal Response: 4; Motor Response: 6.

The patient was then transferred to the hospital's inpatient unit for continued neurological investigation, with a suspicion of CNS infection. Upon admission, she was hospitalized, treated with phenytoin, and given analgesic/antipyretic medication (dipyrone). On the same day, a non-contrast cranial computerized tomography scan (CT scan) (Figure 1) revealed a nodular expansile formation in the left temporal parenchyma, approximately 1.8 cm in diameter, associated with extensive perilesional edema and obliteration of the corresponding cortical sulci. A complete blood count revealed leukocytosis (17,270/mm^3) with a predominance of segmented neutrophils.

On January 9, a contrast-enhanced cranial CT scan was performed (Figure 2), which revealed, according to the report, an "ovoid lesion with a ring-like appearance, with slight peripheral contrast enhancement and a hypodense center suggesting necrosis, associated with extensive edema in the left temporal lobe, suggestive of a brain abscess or CNS tumor." The patient remained hospitalized under observation, receiving tramadol, dipyrone, bromopride, and phenytoin. After 24 hours, another contrast-enhanced cranial CT scan was performed for imaging control. The examination revealed a worsening of the topographic condition of the left temporal lesion, still poorly defined, with capsular contrast enhancement, measuring approximately 2.1 x 1.7 x 1.6 cm, associated with extensive surrounding edema that obliterated the basal cisterns and adjacent cortical sulci, as well as a rightward midline shift. The result was suggestive of a CNS infectious process.

On January 13, the patient experienced a clinical worsening of the headache and the onset of psychomotor agitation. A cranial magnetic resonance imaging (MRI) was performed (Figures 3 and 4), which

showed an encapsulated nodular image, with homogeneous enhancement confined to a thin capsule, with regular contours and thick content, measuring 3.3 x 4.5 x 3.2 cm in the left temporal region, along with extensive surrounding edema causing obliteration of the basal cisterns, rightward midline shift, and pressure on the basal nuclei. Once again, the result was compatible with an inflammatory infectious process, a brain abscess.

On January 15, the patient experienced a worsening of the headache, which became holocranial, persistent, and excruciating, along with uncontrollable vomiting and drowsiness without apparent focal deficits. She was urgently taken to the surgical suite for a left frontotemporal craniotomy with only partial resection of the lesion due to intraoperative clinical instability and intracranial hypertension (ICH). The biopsy of the lesion revealed exclusively the presence of an acute suppurative inflammatory infiltrate. The patient was sedated and on mechanical ventilation and was transferred to the Intensive Care Unit, where broad-spectrum empirical antibiotic therapy was initiated for CNS infection coverage, using intravenous metronidazole and ceftriaxone for six weeks.

For follow-up, a contrast-enhanced cranial CT scan was performed on January 23, identifying a cystic image in the left temporal lobe with thick walls, peripheral contrast enhancement, perilesional edema, and mild midline shift. Subsequently, on January 29, a contrast-enhanced cranial MRI with diffusion (Figure 5) revealed a large expansile lesion with peripheral contrast enhancement and diffusion restriction, measuring 2.1 x 5.3 x 2.6 cm.

On February 6, the patient underwent a second neurosurgical intervention for the total excision of the brain abscess. Following the procedure, a sample was sent for anatomopathological laboratory examination, which revealed the presence of a non-human, cellulolytic yeast (i.e., capable of degrading cellulose) that was resistant to azoles but sensitive to amphotericin B. The results were negative for Candida and Cryptococcus. Consequently, the initially proposed intravenous antibiotic therapy was maintained, and the antimicrobial therapeutic coverage was expanded to include an antifungal: intravenous liposomal amphotericin B for four weeks. The patient remained sedated and intubated.

On March 11, imaging tests demonstrated the complete resolution of the brain lesion. With no clinical signs of ICH, the patient was extubated, discharged from the hospital, and referred for outpatient neurological follow-up.

It is noteworthy that the patient was young, previously healthy, immunocompetent, did not use continuous medications, and had no recent history of oral surgery, sinusitis, otitis, or any other infectious condition in the cranial or cervical region. Therefore, there was an absence of any identifiable risk factor for CNS infection.

Figure 1. Non-contrast computed tomography from January 8, 2020.

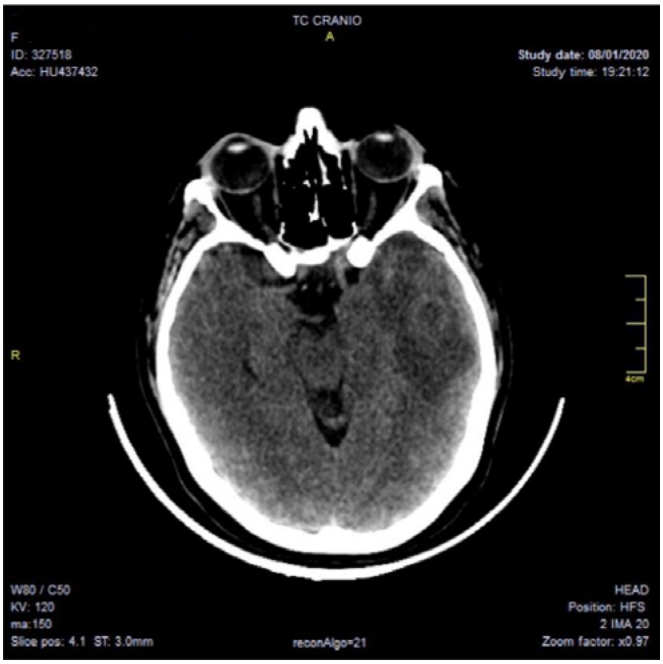


Figure 2. Contrast-enhanced computed tomography from January 9, 2020.

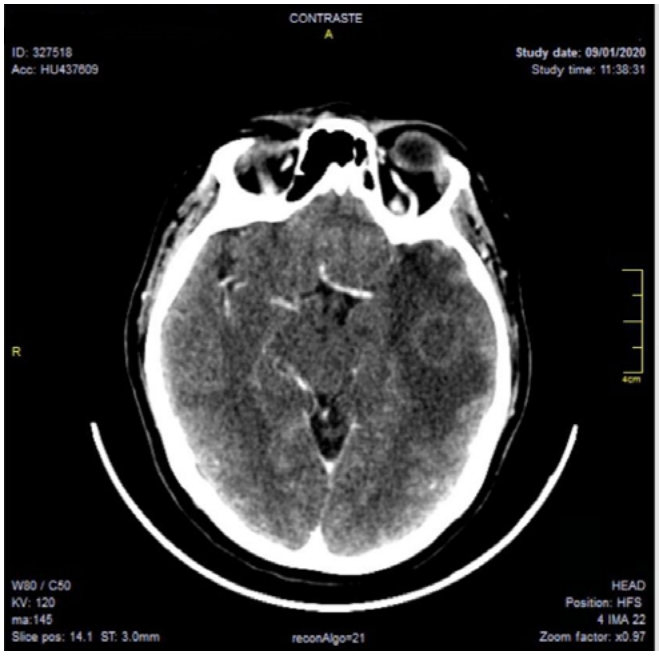


Figure 3. Contrast-enhanced and diffusion sequence cranial magnetic resonance imaging performed on January 13, 2020.

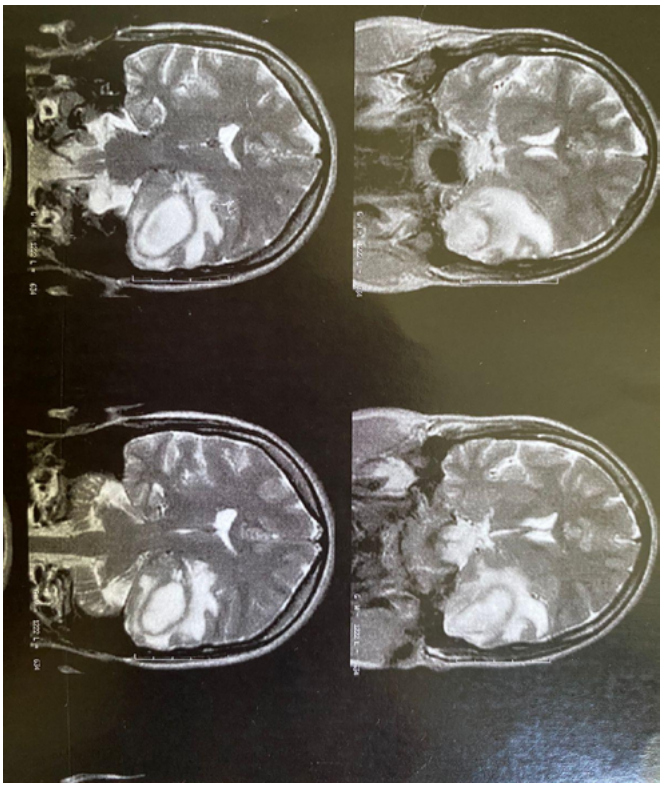


Figure 4. Contrast-enhanced cranial magnetic resonance imaging performed on January 13, 2020.

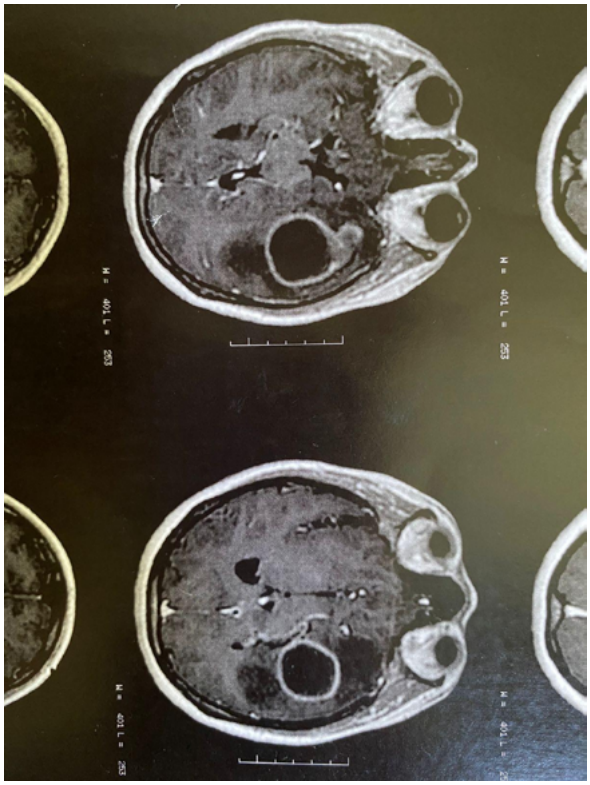
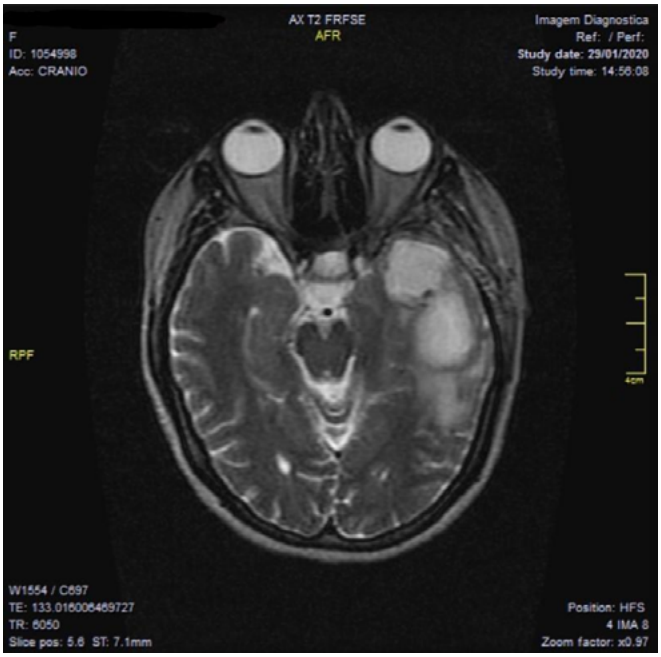


Figure 5. Contrast-enhanced cranial magnetic resonance imaging, axial, T2, performed on January 29, 2020.



DISCUSSION

Differential diagnosis between tumor and abscess

The classic triad of fever, headache, and focal neurological deficit is not specific for diagnosing brain abscesses, as only a minority of patients exhibit all these symptoms.[1,9] Therefore, it is crucial to perform complementary imaging tests. Clinical manifestations of a brain abscess tend to be nonspecific, leading to diagnostic delays of up to 8 days after symptom onset.[3] In the case described for this patient, there was a history of headache, fever, and seizures, although no focal neurological deficit was reported.

Typically, routine cranial MRI findings are not specific for diagnosing brain abscesses. Diffusion-weighted imaging is more sensitive but can also be found in other clinical conditions. Multimodal cranial MRI can assist in differentiating between abscesses and brain tumors.[1,11]

The most common locations for brain abscesses are the frontal and temporal lobes.[1] Blood cultures should be performed early, although the positivity rate with identification of etiological agents is not high. Analysis of cerebrospinal fluid (CSF) can suggest an infectious process and identify the etiological agent, but it can also be normal in a significant proportion of patients.[3]

Neurosurgical treatment varies depending on the location, size of the abscess, and the patient's clinical condition. Surgery should be considered if there is no improvement within 1 to 2 weeks of empirical antibiotic therapy, or in cases of specific clinical complications—such as intracranial hypertension due to the mass effect of the abscess and secondary hydrocephalus—or if it is a complication of bacterial or fungal meningitis.[3]

Early diagnosis and treatment of brain abscesses are crucial for favorable clinical outcomes.[1,9,10] Initial antimicrobial therapy is based on the patient's medical history, prior condition, and suspected previous infections. Typically, antibiotic therapy includes a third-generation cephalosporin combined with metronidazole and/or vancomycin for coverage of staphylococcal infections. If a specific pathogen is not isolated, broad-spectrum antibiotics are indicated. Antibiotic treatment may extend for 6 to 8 weeks for bacterial brain abscesses.[2,12]

The main differential diagnosis for brain abscesses is tumors. In these cases, the clinical picture does not suggest an infection but may be insidious or subacute, with nonspecific neurological signs and symptoms developing over weeks to months. Similarly, brain abscesses often have an insidious or subacute course, with nonspecific neurological symptoms developing over days to weeks.[2,3] Both conditions can also present as acute events, with seizures and sudden focal neurological deficits.

In this context, based on the patient's clinical picture and the non-contrast cranial CT findings, the initial diagnostic suspicion was a brain tumor. However, the cranial MRI, performed six days after the CT scan, revealed a nodular encapsulated image in the left temporal region, strongly suggestive of a brain abscess. This observation indicates that the initial differential diagnosis, which suggested the possibility of a tumor, delayed the immediate neurosurgical intervention for abscess treatment. Ideally, an early cranial MRI should be performed to confirm the diagnosis and plan appropriate treatment.

Resistance to Azoles in Immunocompetent Patients

Invasive fungal pathogens are etiological factors of central nervous system (CNS) infections, particularly in susceptible individuals such as those with compromised immunity, extreme ages, or after neurological surgery. Therefore, microbiologists need to remain vigilant regarding unusual isolates of brain abscesses and their complex nature.[9,10,13-15]

This group includes Aspergillus spp., Mucorales, *Cladophialophora bantiana*, *Candida spp.*, *Cryptococcal spp.*, *Blastomyces*, *Coccidioides,* and *Histoplasma*. Among these, Candida spp., Cryptococcus spp., Blastomyces, Coccidioides, and Histoplasma are described in their yeast forms. Fluconazole, a triazole compound widely recognized by the medical community, is a frequently used therapeutic option for these infections. However, its indiscriminate use has led to the emergence of resistance in some species. In the literature, yeasts and/or diseases affecting the CNS that exhibit resistance to fluconazole include candidiasis (*Candida auris*), cryptococcosis (*Cryptococcus spp.*), and coccidioidomycosis (Coccidioides).[9-11,16-19]

Candida auris has become one of the most frequently identified fungal pathogens, largely due to its high fluconazole resistance rate (approximately 90%), contributing to the increasing number of infections caused by this pathogen. In the adult population, invasive neurological procedures, particularly in immunocompromised patients, are risk factors for *C. auris* meningitis.[9,10,20]

In paracoccidioidomycosis, risk factors for the dissemination of the infection include immunosuppression, advanced age, diabetes mellitus, pregnancy, and African or Filipino descent. Fluconazole is the recommended initial treatment; however, therapeutic failure with disease relapse is common. In such cases, lifelong therapy with alternative azoles or, in refractory cases, intrathecal amphotericin B may be indicated.[9,10]

Cryptococcosis is the most common cause of fungal meningitis worldwide, including in the United States. Approximately 79% of patients with cryptococcal meningitis in the country are affected by Acquired ImmunoDeficiency Syndrome.[4] The recommended treatment for cryptococcal meningitis is induction therapy with liposomal amphotericin B combined with flucytosine for at least 2 weeks, followed by prolonged therapy with azoles.[9,10]

In this case, however, there were challenges in the diagnosis: the patient had no history of immunosuppression or previous infections. Additionally, fungal brain abscesses are rare, so the initial empirical treatment involved broad-spectrum antibiotics because the lesion biopsy was inconclusive after the first surgical intervention. In the case discussed, following the clinical progression of the disease and the enlargement of the brain abscess, the biopsy performed during the second surgery surprisingly revealed the absence of the more expected pathogens in brain abscesses (Candida and Cryptococcus) and the presence of cellulolytic yeasts, as well as unusual resistance to azoles, particularly fluconazole—a medication widely used in the treatment of fungal infections of the CNS. Based on this second laboratory report, effective treatment

was subsequently administered with liposomal amphotericin B.

Limitations

The main limitation is the restricted generalizability, as a single case cannot represent the general population. Additionally, case reports do not include control groups and are subject to recall bias, as much of the information is obtained through interviews with those involved. However, despite these limitations, case reports are valuable for identifying new diseases and adverse effects of treatments, and for generating hypotheses for more rigorous studies.

CONCLUSION

The clinical case underscores the importance of considering a brain abscess diagnosis in patients with acute neurological symptoms, fever, and cerebral lesions with peripheral contrast enhancement identified on cranial CT scans. Additionally, it is crucial to differentiate from brain tumors; however, this should not delay early antimicrobial treatment, which improves prognosis and accelerates clinical recovery in patients with brain abscesses.

Furthermore, it highlights the need to consider various etiological agents causing CNS infections, including both bacteria and fungi, as well as the potential for resistance to commonly used medications. Routine use of fluconazole may be effective in many cases but can also lead to the emergence of resistant fungal strains. If there is no effective response to treatment and clinical improvement in patients, a biopsy of the lesions may be necessary, followed by laboratory tests and cultures to identify the etiological agents and guide the selection of an effective, specific, and targeted antimicrobial treatment.

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21.
22. **Figure and table legends**
23. Figure 1: Non-contrast computed tomography of January 8, 2020. Source: patient's personal archive.
24. Figure 2: Contrast-enhanced computed tomography of January 9, 2020. Source: patient's personal archive.
25. Figure 3. Contrast-enhanced and diffusion sequence cranial magnetic resonance imaging performed on January 13, 2020. Source: patient's personal archive.
26. Figure 4. Contrast-enhanced cranial magnetic resonance imaging performed on January 13, 2020. Source: patient's personal archive.
27. Figure 5: Contrast-enhanced cranial magnetic resonance imaging, axial, T2 sequence, performed on January 29, 2020. Source: patient's personal archive.