

Surgical Treatment Alone of Cerebral Aspergillosis in Immunocompetent Patient

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Abstract

Aspergillosis is a disease that predominantly affects immunocompromised patients. The incidence in immunocompetents is rare, and manifestation is generally pulmonary. Few reports in the literature refer to isolated cerebral aspergillosis in individuals with no chronic comorbidities. We describe a case of a 59-year-old rural worker without previous pathologies who had a partial convulsive crisis in a subtle form, with self-limiting and nonrecurrent secondary generalization. Diagnostic investigation demonstrated a subcortical tumorlike lesion in the right precentral gyrus by nuclear magnetic resonance that allowed en bloc microsurgical resection, with histopathologic findings indicating cerebral aspergillosis. Because of the delay in obtaining the result of the biopsy due to technical difficulties with analysis, the diagnosis was delayed. The patient was clinically stable, with imaging without modifications and with negative serologic tests, so it was decided to follow the patient without antifungal therapy, which was successful. This was a case of isolated cerebral aspergillosis in an immunocompetent individual who was successfully treated by complete resection of the lesion alone, without combined antifungal therapy.

Keywords

- ▶ aspergillosis
- ▶ central nervous system
- ▶ seizures

Introduction

Aspergillosis is a disease caused by species of the genus *Aspergillus* (*fumigatus*, *flavus*, *niger*, *terreus*, *sudowii*, *ustus*, *versicolor*, *amstelodami*, *oryzae*, *candidus*, *restrictus*, or *nidulans*) that affects mainly the respiratory system of patients with immunosuppressive pathologies. The involvement of the central nervous system (CNS) is infrequent, especially in immunocompetent individuals, and it has high mortality rates despite adequate treatment with surgery and antifungals.¹

We describe a case of a 59-year-old rural worker without comorbidities who developed isolated aspergillosis of the CNS and was treated exclusively with complete microsurgical resection of the lesion, without combined antifungal therapy, showing cure.

Case Report

A 59-year-old man developed a subtle and single episode of a simple partial convulsive crisis in the left arm and left hemiface, with self-limiting secondary generalization. He was a farm worker who lived in a rural area. He had no comorbidities or previous surgeries, did not take regular medications, and did not abuse alcohol, cigarettes, or use illegal drugs. There was no report of signs/symptoms prior to the event, and afterward the patient showed no alterations on general physical and neurologic examination. Complementary blood tests on admission showed leukocytes 8,300 cells/mm³ (normal differential); creatinine, 0.9 mg/dL; urea, 25 mg/dL; glucose oxidase test, 24 IU/L; glutamic-pyruvic transaminase, 23 IU/L; alkaline phosphatase, 116 IU/L; γ -glutamyltransferase, 35 IU/L; albumin, 4.1 g/dL;

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Table 1 Complementary serum and cerebrospinal fluid (CSF) tests

Spinal CSF	Routine tests: normal	Culture for fungi: negative	Direct inspection for fungi: negative	<i>Aspergillus galactomannan</i> (enzymatic immunoassay): negative	Serology for <i>aspergillus</i> (double radial immunodiffusion): negative
Blood	Anti-HIV 1 and 2 (ELISA): negative	Peripheral blood culture (two samples): negative	<i>Aspergillus galactomannan</i> (enzymatic immunoassay): negative	Serology for <i>aspergillus</i> (double radial immunodiffusion): negative	

Abbreviations: HIV, human immunodeficiency virus; ELISA, enzyme-linked immunosorbent assay.

sodium, 139 mEq/L; potassium, 4.0 mEq/L; magnesium, 2.4 mg/dL; calcium, 1.23 mM; fasting glucose, 98 mg/dL; and normal blood gases. Imaging was performed using nuclear magnetic resonance (NMR) of the brain that demonstrated an expansive subcortical nodular formation in the right precentral gyrus, with perilesional edema, showing capsular loci with restriction of free water proton movement and nodular enhancement by contrast (→**Fig. 1**). Also performed were serum human immunodeficiency (HIV) 1 and 2 assays (enzyme-linked immunosorbent assay [ELISA]), one pair of blood cultures, and serum and cerebrospinal fluid (CSF) assays to test for aspergil-

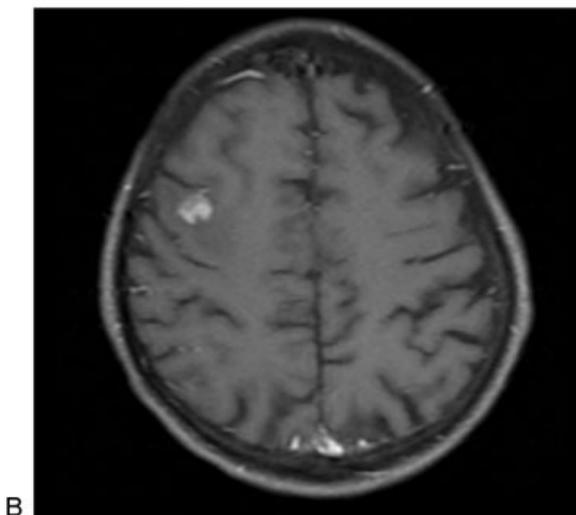
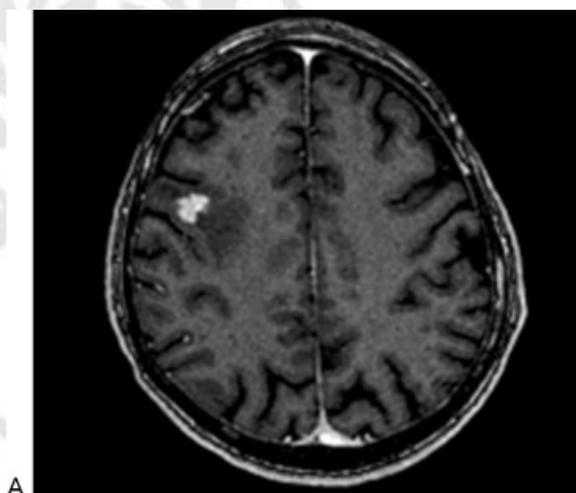


Fig. 1 Nuclear magnetic resonance (NMR). (A) T1-weighted NMR without contrast showing right frontal hyperintense expansive lesion. (B) T1-weighted NMR with gadolinium showing an expansive lesion with discrete contrast captation in right frontal region.

losis (→**Table 1**), along with radiography of the thorax and computed tomography (CT) of the thorax and sinuses of the face, which were all normal (→**Figs. 2, 3, and 4**).

As a result of the NMR findings of the cranium and no diagnostic confirmation by noninvasive methods, the patient was subjected to a neurosurgical procedure via right frontoparietal craniotomy, with later dissection of the precentral sulcus and en bloc microsurgical resection of the whole subcortical lesion. The procedure was completed without complications, with a good outcome in the immediate postoperative period, characterized by clinical stability and the absence of neurologic deficits. On the second postoperative day, however, the patient developed hemiplegia on the left side, combined with a decreased level of consciousness. An immediate CT of the cranium demonstrated an intraparenchymal hemorrhage in the surgical bed (→**Fig. 5**), requiring immediate drainage of the hematoma. The patient became stable, with partial improvement of his motor deficit, and he was discharged 5 days after the second surgical procedure, with a proposal of outpatient follow-up.

Macroscopic anatomopathologic evaluation demonstrated a lesion with indurated appearance, clear brown tone, irregular, measuring $2.7 \times 2.5 \times 1.0$ cm. Microscopy revealed chronic granulomatous cerebritis, and with Grocott staining, numerous structures consistent with hyphae and spores of *Aspergillus* (→**Fig. 6**). Culture of the lesion was negative.



Fig. 2 Radiography of thorax. Posteroanterior radiograph not indicating pleuropulmonary alterations.

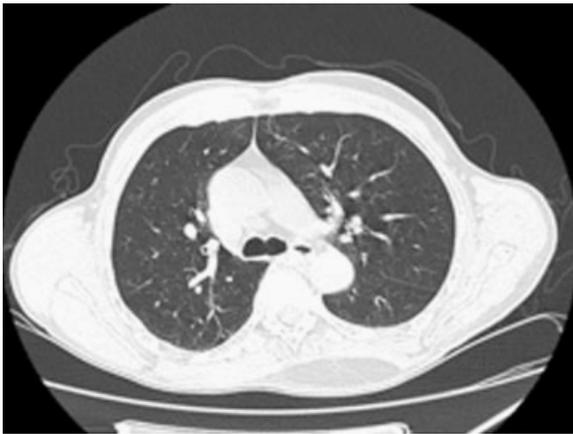


Fig. 3 Computed tomography (CT) of the thorax. Axial CT not indicating pleuropulmonary alterations.

Due to technical difficulties in the anatomopathologic evaluation, the diagnosis was established ~ 60 days after discharge. At this time, the patient had no systemic signs/symptoms, with progressive improvement of his left motor deficit resulting from the intraparenchymal hemorrhage, without other alterations on neurologic examination and imaging, and normal serum and spinal CSF tests. As a result, we decided on clinical follow-up without antifungal therapy. After 12 months of follow-up, the patient still showed no new clinical alterations suggestive of disease activity (► **Table 2**; ► **Figs. 7** and **8**) and he performed daily activities, with slight limitations, indicating a Modified Rankin Scale score of 2.²

Discussion

Aspergillosis of the CNS accounts for 5% of all intracranial fungal infections³ and shows a high mortality rate, as high as

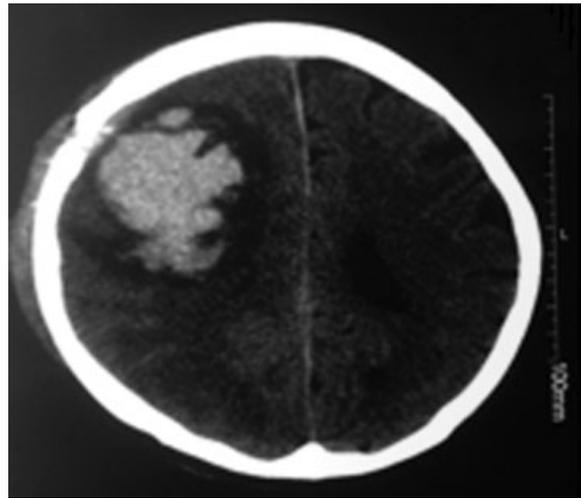


Fig. 5 Computed tomography (CT) of the cranium on postoperative day 2. Axial CT indicating right frontal intraparenchymal hemorrhage in the surgical bed.

80% in immunocompetents³ and ~ 100% in immunosuppressed patients,⁴ principal targets of the disease, particularly those with solid and hematologic tumors, transplanted individuals, and users of immunosuppressive drugs for autoimmune diseases and with other diseases causing immunodeficiency such as HIV/acquired immune deficiency syndrome (AIDS).⁵

Aspergillosis can occur in different forms, such as aseptic meningitis, meningoencephalitis, mycotic aneurysm causing ischemic or hemorrhagic cerebrovascular accidents, and tumor lesions and abscesses,⁶⁻⁸ with various possibilities of clinical manifestations, particularly focal neurologic deficits, convulsions, fever, alterations in the level and content of consciousness, and signs/symptoms related to involvement of the paranasal, orbital, and mastoid sinuses.⁵



Fig. 4 Computed tomography (CT) of the cranial sinuses. Coronal CT indicating deviation of nasal septum toward the left and absence of other alterations.

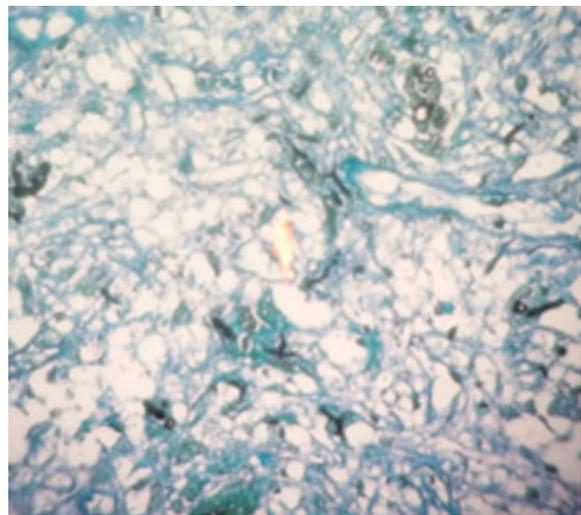


Fig. 6 Biopsy of the lesion. Slide with Grocott staining indicating numerous structures consistent with hyphae and spores of *Aspergillus* (original magnification $\times 200$).

Table 2 Complementary serum and cerebrospinal fluid (CSF) test after 12 months of follow-up

Spinal CSF	Routine tests: normal	Culture for fungi: negative	Direct inspection for fungi: negative	Aspergillus galactomannan (enzymatic immunoassay): negative	Serology for aspergillus (double radial immunodiffusion): negative
Blood	Peripheral blood culture (two samples): negative	Aspergillus galactomannan (enzymatic Immunoassay): negative	Serology for Aspergillus (double radial immunodiffusion): negative		

The invasion of the CNS by aspergillus can occur by the hematogenous route, by contiguity, mainly through the paranasal sinuses and the mastoid, by repeated lumbar punctures, and even after craniocerebral trauma and neurosurgical manipulation.⁹⁻¹² The mechanism in presumed immunocompetent hosts is still uncertain, but it is possibly directly related to the unknown degree of dysfunction in cellular immunity.¹³ In this population, the isolated forms in the CNS normally develop through blood dissemination of the colonizing fungus in airways or by extension of the involvement of the mastoid bone and base of the cranium.¹² With respect to the mechanism of the cellular lesion, recent *in vitro* studies demonstrated that cerebral damage is related to the secretion of necrosis factors that have toxic and lytic activity in neuronal and glial cells.^{3,14}

Neuroaspergillosis, particularly in the form of an expansive lesion and in patients without chronic comorbidities, is difficult to diagnose, and it is established definitively by histopathologic analysis of the lesion.⁵ Clinical, laboratory, and radiologic findings are not specific and, together with the rarity of the disease in immunocompetents, usually cause delays in the etiologic definition of the pathology.¹⁵ The signs and symptoms are diverse, as noted, and belong to a gamut of other neurologic diseases, such as the findings of CT and NMR. In relation to serum and/or spinal CSF microbiological assessment, cultures show low sensitivity and provide delayed

results.¹⁶ Serologic tests do not show acceptable positive and negative predictive values and should not be utilized for the diagnosis and follow-up of the disease.¹⁷ Serum tests for the polysaccharide antigen galactomannan by “double-sandwich” ELISA (Plateia-Bio/Rad), in turn, show moderate diagnostic accuracy (71% sensitivity and 89% specificity) in patients at high risk for invasive aspergillosis.¹⁸ Its detection in spinal CSF is also valuable in diagnosis^{17,19,20} and in follow-up of treatment, with reduction of titers corresponding to clinical improvement,¹⁷ which encourages the use of galactomannan antigenemia, making it and spinal CSF studies part of the arsenal of the investigation and follow-up of the disease. Polymerase chain reaction studies in spinal CSF have high sensitivity, but due to the small quantity of Aspergillus cells in spinal CSF for analysis, their diagnostic value is low.⁵

Surgical intervention combined with antifungal therapy is currently the treatment of choice in immunosuppressed individuals as well as immunocompetents.^{5,21-23} In relation to surgical technique, despite the lack of well-established evidence based on randomized prospective studies, total resection of the lesion is always sought, except in cases of difficult access, with a high risk of postoperative neurologic sequelae.²² With regard to pharmacologic treatment, the tendency is the early introduction and utilization of the triazole voriconazole, a drug that shows better penetration of the CNS and better therapeutic results.^{23,24} However, due to the high morbidity and mortality of the disease and to its rarity, there are no studies of surgical therapy alone in cases of

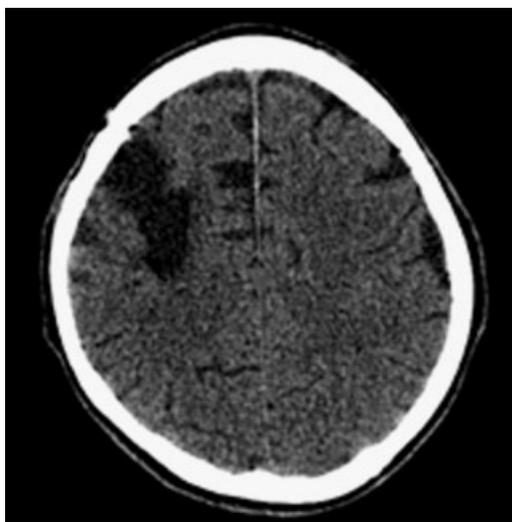


Fig. 7 Computed tomography (CT) of brain after 12 months of follow-up. Axial CT indicating right frontal hypodensity compatible with gliosis, without signs of relapse of aspergillosis.

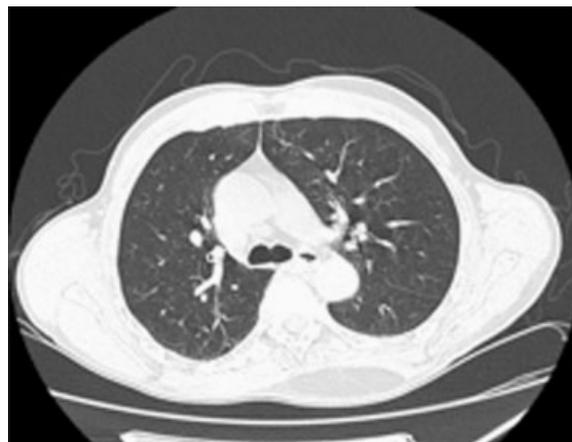


Fig. 8 Computed tomography (CT) of thorax after 12 months of follow-up. Axial CT not indicating pleuropulmonary alterations.

isolated involvement of the CNS in oligosymptomatic patients without comorbidities, with nonextensive lesions completely resected and with good initial results after surgery.

In our report, we describe a case of an older individual, without comorbidities, who showed as the only risk factor for aspergillosis living in a rural area and working on a farm. He developed primary aspergillosis of the CNS, without any clinico-radiologic sign of involvement of the respiratory system that characterizes primary neuroaspergillosis in an immunocompetent patient, which is extremely rare and with few reports in the literature. The form of the clinical presentation of the disease was a convulsive crisis, which prompted classic initial assessment by imaging, with detection of an expansive lesion, one of the possible forms of development of the disease. Laboratory serum and CSF tests were performed for diagnosis and later follow-up of the treatment, all showing negative results. Tests for galactomannan pre- and posttreatment were negative, which is explained by the form of the neurologic lesion and the patient having a low preclinical probability of aspergillosis of the CNS, as mentioned earlier. As to the specific serum and spinal CSF complementary examinations, we chose to perform the main tests used for the neuroaspergillosis diagnosis as serologic and microbiological examinations, including galactomannan, which facilitates follow-up as well. Other examinations, as noted previously, are not highly accurate in regard to the aspergillosis diagnosis.

A total resection of the lesion was performed, with the aim of a histopathologic analysis of the material and an elucidation of the case. However, there was technical difficulty with the evaluation by the laboratory and consequently delayed the diagnosis. Because of the good clinical outcome, we decided to maintain the patient on regular observation until the definitive result that took ~ 60 days. At that time, the patient continued to be without new neurologic or systemic changes, prompting us to forgo antifungal therapy, which resulted in a favorable outcome after 12 months. Because this is something that has not been previously described in the literature, it is not yet possible to compare the outcome with others.

Conclusion

We have demonstrated a successful surgical therapy alone, without additional antifungal therapy, in a particular case of cerebral aspergillosis in an immunocompetent patient, characterized by a not extensive expansive lesion, the absence of severe symptomatic repercussions, clinical stability, and negative tests for serum and CSF infection in the first 60 days after surgical treatment.

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