Cerebral Aspergillosis in an Immunocompetent Patient after COVID-19 Infection

Aspergilose cerebral em paciente imunocompetente após infecção por COVID-19

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Abstract Fungal brain abscesses are an uncommon condition in the immunocompetent population, especially due to the etiologic agent Aspergillus sp. The emerging coronavirus disease 2019 (COVID-19) pandemic brought about neurological manifestations that were previously little known, caused by the direct manifestations of the virus, as well as by the therapy itself, with hospitalization and use of corticosteroids. This highlights the need for attention in the management of patients with neurological disorders and history of virus infection. In the current paper, we report the case of a patient without comorbidities who presented multiple brain abscesses caused by Aspergillus fumigatus, after infection by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

Keywords ► neuroaspergillosis ► brain abscess ► COVID-19 ► aspergillosis

Resumo Abscessos cerebrais fúngicos são uma condição incomum na população imunocompetente, especialmente quando provocada pelo agente etiológico Aspergillus sp. A epidemia emergente do novo coronavírus (COVID-19) trouxe acometimentos neurológicos até então pouco conhecidos, ocasionados pelas manifestações diretas do vírus, como também pela própria terapia, com internação e uso de corticoesteróides. Este manuscrito destaca a necessidade de atenção no manejo de pacientes com alterações neurológicas e história de infecção pelo vírus. No presente trabalho, relatamos o caso de um paciente sem comorbidades que apresentava múltiplos abscessos cerebrais causados por Aspergillus fumigatus, após infecção pelo SARS-CoV-2.

Palavras-chave ► neuroaspergilose ► abscesso Encefálico ► COVID-19 ► aspergilose

Introduction Cerebral aspergillosis is a rare infectious condition that accounts for ~5% to 10% of all fungal infections of the central nervous system (CNS).

The incidence of patients diagnosed with this pathology has increased in recent years due to the rise in the number of solid organ and bone marrow transplants, consequently increasing the immunosuppressed population. Other immunosuppressive states that present the risk of developing
the disease are AIDS, alcohol abuse, diabetes, and hematologic diseases with neutropenia.\textsuperscript{3,4}

The reports of patients with an intact immune system who manifest this infection in the brain are rare. However, when reviewing in detail the history of these patients, it is possible to identify that there was some factor promoting transient immunosuppression, such as the use of chemotherapy, high doses of corticosteroids or poor glycemic control.\textsuperscript{5}

In the present paper, we report the case of a man with no previous comorbidities whose only immunosuppression factor in his history was the use of corticosteroids for the treatment of coronavirus disease 2019 (COVID-19).

Case Report

A 64-year-old male rural worker, previously healthy, started to experience changes in his mental state with bradypsychism and ideomotor apraxia. He had a history of infection by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) for \(\sim\) 2 months, with hospitalization in another service. According to the discharge report, he did not need ventilatory support but received a course of corticosteroid therapy with dexamethasone during the 7-day period he was hospitalized and for another 12 days after discharge. Since then, he started to have a lack of glycemic control, and treatment with metformin was started.

Due to the progression of the neurological condition, he was admitted to a local hospital, and underwent an investigation with brain magnetic resonance imaging (MRI) scans that showed multiple lesions in both cerebral hemispheres, characterized by annular contrast enhancement and diffusion restriction, suggesting brain abscesses (\textsuperscript{\texttt{Fig. 1}}). Empirical treatment was started with vancomycin, ceftriaxone, metronidazole, and dexamethasone 4 mg 4 times a day for the vasogenic edema caused by the lesions.

He was transferred to the neurosurgery service of our hospital with a proposal for a surgical approach to the brain injuries. The antibiotic therapy regimen was expanded to meropenem and vancomycin. We performed a complementary investigation with serology for HIV, hepatitis B, and C, all of which were negative. Chest X-ray (\textsuperscript{\texttt{Fig. 2}}) and transthoracic echocardiography did not identify abnormalities. A stereotaxic biopsy of one of the lesions was then performed with the aspiration of purulent content (\textsuperscript{\texttt{Fig. 3}}).

He remained hospitalized in the Intensive Care Unit (ICU) postoperatively, receiving empirical antibiotic therapy until we received the results of the cultures. He was discharged to the ward on the second postoperative day, in good clinical condition. The results of the pathological examination and

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{Fig_1.png}
\caption{Brain magnetic resonance imaging (MRI) scan showing multiple hypointense brain lesions with a halo of enhancement and surrounding edema on a T1-weighted image (above). Diffusion-weighted imaging (DWI) (below) showing hyperintense lesions.}
\end{figure}
cultures were available on the fifth day after surgery, and were compatible with a fungal infection, and Aspergillus fumigatus was identified as the etiological agent (Fig. 4). Endovenous voriconazole was indicated.

On the seventh day after surgery, his neurological condition worsened, and he experienced sudden sensorium alteration. An emergency cranial computed tomography (CT) scan was performed, which showed recurrence of the lesion that had been surgically aspirated and important cerebral edema with midline deviation (Fig. 5). As the patient’s score on the Glasgow Coma Scale (GCS) was of 3 and bilateral mydriasis had no reactivity, we did not indicate a new surgical approach. After two days of hospitalization in the ICU, the criteria to determine brain death were met.

Discussion

After the respiratory tract, the brain is the site most affected by invasive aspergillosis. The main etiological agent is A. fumigatus, with cases of infection by A. nidulans, A. terreus, or A. flavus.

Presentations in the CNS can be due to meningitis, granulomatous reaction with abscess, or vasculopathy. Aspergillus hyphae have tropism for vessels and can produce thrombosis, infarction, hemorrhagic changes, or mycotic aneurysms. Meningeal lesions usually represent contiguity after infection of the paranasal sinuses, mastoiditis, trauma, or neurosurgery. Parenchymal abscesses are most commonly located in the cerebral hemispheres; however, they may also present in the basal ganglia, corpus callosum, thalamus, or perforating artery territory, suggesting hematogenous dissemination.

The clinical presentation is variable, and localized neurological manifestations may be observed. Ruhnke et al. reviewed the results of 4 studies on clinical manifestations of cerebral aspergillosis totaling 90 patients. The most common symptoms were persistent fever, changes in mental status, and seizures. Headache, vomiting, and papilledema with signs of intracranial hypertension may also be observed.

The MRI findings are similar to a common pyogenic abscess, with a hypodense lesion on T1, hyperdense on T2, ring contrast-enhancing, surrounding cerebral edema, and with diffusion restriction. The analysis of the cerebrospinal fluid (CSF) usually shows pleocytosis with a slight increase in protein, and the aspergillus antigen, galactomannan, can be found.

The definitive diagnosis is histopathological; however, it is usually not possible to perform a surgical approach to obtain material for analysis, given the severity that many patients present.

The treatment commonly employed involves a combined approach of surgical evacuation and prolonged antifungal administration. There is no consensus regarding the best surgical strategy, since most studies are small retrospective series. However, the most adopted approach in cases of location in an eloquent area is minimally-invasive aspiration by the stereotaxic method or by neuronavigation. In cases in which resection is feasible, a more extensive surgery should be performed.

The first-line antifungal therapy consists of voriconazole; however, there are reports of successful treatments with new-generation azole agents, liposomal amphotericin B, caspofungin, or micafungin. The proposed duration of the...
treatment varies in the literature and can be influenced by the type of surgery performed. Shorter treatment regimens are employed in cases in which total lesion resection has been performed, with some institutions describing 6 months of therapy with satisfactory results. In cases of subtotal resection, a regimen of 12 to 18 months is advocated.\textsuperscript{1}

Despite the appropriate therapy, the disease has an unfavorable prognosis, with reported mortality rates of 10\% to 20\% in immunocompetent patients, and of 85\% to 100\% in immunosuppressed patients.\textsuperscript{2}

**Conclusion**

In the case herein reported, an important factor in the previous pathological history was the recent infection by COVID-19. Despite being a disease that has emerged recently, there are already several studies on the manifestations of the virus in the CNS. Neurological involvement may be secondary to the systemic proinflammatory state that may develop in some infected patients, with a predisposition to endothelial dysfunction and prothrombotic events.\textsuperscript{16}

There are also changes directly caused by the presence of the virus in the nervous system, explained by the binding of viral proteins to neuronal and glial receptors, leading to viral encephalitis, meningoencephalitis, Guillain-Barré syndrome, and seizures.\textsuperscript{17}

Fungal brain abscess in an immunocompetent patient was probably a consequence of a combination of factors such as
hospitalization, microvascular alterations caused by the virus, and prolonged use of corticosteroids. We found sparse similar reports in our research, 18,19 which enabled us to raise the hypothesis that despite being a rare condition, it can also be a poorly-recognized change, due to the severity that many patients evolve with the need for ventilatory support and high doses of sedatives, making it difficult to diagnose neurological changes.

A postmortem study would enable a better understanding of the pathophysiological mechanisms responsible for brain involvement; however, this was not an option accepted by the patient’s family.

Informed Consent
The patient’s family consented to the presentation of the case for submission to the journal.

Conflict of Interests
The authors have no conflict of interest to declare.

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