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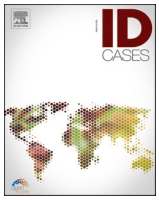

Case report

Survival in a pediatric patient with cerebral aspergillosis: A case report

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ABSTRACT

Aspergillosis is an infrequent infection in the Central Nervous System with a mortality rate higher than 95 %. Early diagnosis is challenging and crucial. In this report, we present the case of a six-year-old female with an intense headache accompanied by left hemiparesis, gaze deviation, horizontal nystagmus, and vomiting of mucous content on five occasions. After several approaches, a cerebrospinal fluid PCR resulted positive for *Aspergillus* spp., and then management started with amphotericin B at 2.6 mg/kg/day and was managed to have voriconazole. She survived, and two years after her first hospital admission, she suffered from cerebral aspergillosis sequelae. An area of improvement is the coordination between the request and delivery of studies outside the institution. In this case, the patient's mother did not report the analysis results on time, delaying the diagnosis.

Introduction

Aspergillosis is an infrequent infection in the central nervous system, constituting 4 % of invasive diseases, being a severe one, with a poor prognosis since it presents a mortality rate higher than 95 % [1,2].

Generally, invasive aspergillosis comes after malignant blood diseases, organ transplant recipients, congenital or acquired immunodeficiencies, and corticosteroids or immunosuppressive drugs use [3]. It has been associated with intravenous catheters, preterm birth, severe burns, abdominal surgery, and intravenous (IV) drug addiction [4,5].

Cerebral aspergillosis is present in 4 % to 20 % of the invasive forms. Early diagnosis of Central Nervous System (CNS) infection by *Aspergillus* spp. is a great challenge, where well-founded clinical suspicion is crucial in patient management since it presents high lethality, even with timely treatment [6]. The invasion of the CNS by *Aspergillus* spp. is the second most frequent after the lungs (respiratory system) [7].

Cerebral aspergillosis is a rare condition in the world. The relevance of this case is that the girl survived the infection.

Clinical case

The patient was a six-year-old female patient. Her delivery was eutocia, weighing 3100 kg at birth. She did not have any history of surgery, allergies, or hospitalizations. She reported previous febrile seizures at five years of age. The condition began on March 15, 2020, with an intense headache accompanied by left hemiparesis, gaze deviation, horizontal nystagmus, and vomiting of mucous content on five occasions. For this reason, she was admitted to the hospital, obtaining a simple tomography of the brain (Fig. 1), where was found frontal vasogenic edema, right temporoparietal and multiple areas of ipsilateral calcification.

On physical examination, superior mental functions were intact: bradylalia, bradypsychia, central facial palsy, left hemiparesis, and preserved sensitivity. Regarding weight and height, they were 20 kg. and 1.20 m., respectively. Due to suspicion of intracranial tumor and seizures, management started with ketorolac 10 mg IV every 8 h, diphenylhydantoin 7.5 mg/kg/day, ondansetron 2 mg IV every 8 h, omeprazole 20 mg IV every 24 h.

The laboratory parameters of the patient were: increased leukocytes (24,000/uL), leukocytosis with neutrophilia, prothrombin time equal to

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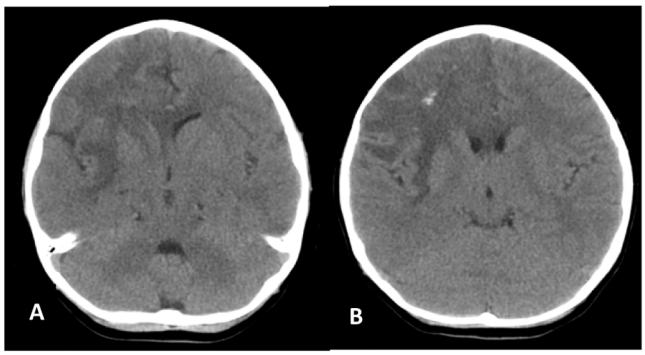

Fig. 1. Simple tomography of the brain showing hypodensity in the right frontal region with calcification areas and perilesional edema, without midline deviation and with compression of the right ventricle.
Source: Medical records.

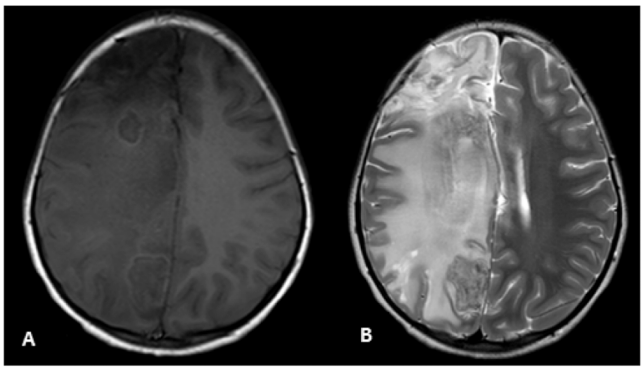

Fig. 2. Magnetic Resonance Image. A. T1 axial. Right hemispheric cerebral edema, right parietal annular lesions. B.T2. Axial. Right hemispheric edema with midline deviation, right parietal brain abscess.
Source: Medical records.

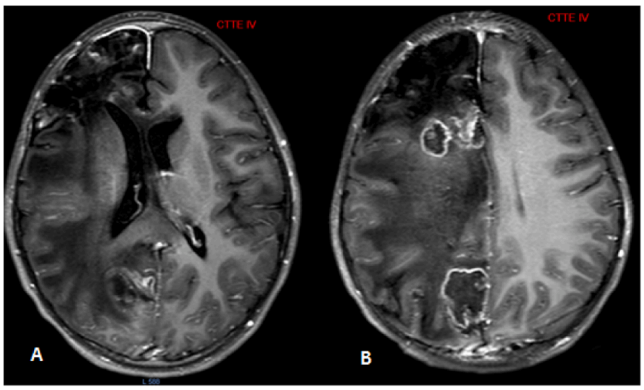

Fig. 3. Magnetic Resonance Image. T1 with gadolinium. A. Right hemispheric cerebral edema with right frontal encephalomalasia. B. Hemispheric cerebral edema with midline deviation, right brain abscesses with capsular enhancement.
Source: Medical records.

14.3 s, and partial thromboplastin time equal to 28.2 s.

Due to a possible intracranial tumor, a craniotomy and a frontal leptomeningeal biopsy were performed on March 18, 2020, with test results showing GRAM, KOH, BAAR stain negative, and *Mycobacterium tuberculosis* Polymerase Chain Reaction (PCR) negative. The biopsy slides were sent to neuropathology on March 31, 2020. Also, antibiotic treatment with vancomycin 60 mg/kg/day and dexamethasone 0.6 mg/kg/day stopped when bacterial infection was discarded by staining. From April 1 to July 7, 2020, the girl did not attend any health service The girl's mother reported the histopathological results to the treating doctor on July 8, 2020. On the same day, she presented to the Irapuato General Hospital with the girl showing seizures focused on the left hemi body accompanied by vomiting of food content, nystagmus, rash, and cognitive arrest.

The histopathological report described elements of the leptomeninges and cerebral cortex, presenting areas of coagulative necrosis with acute and chronic inflammation -associated with meningeal fibrosis and cerebral gliosis-. The inflammatory infiltrate showed a mixture of lymphocytes, macrophages, plasma cells, and some polymorphonuclear cells. Activation of microglia was also identified. In both components, the vessels showed obliteration and fibrosis with changes in the subintima and vessel wall, with subsequent thrombosis. These changes yielded thrombosis and the presence of ischemic lesions of different chronologies, but predominantly chronic. At diagnosis, alterations of leptomeningitis and cerebritis were found partially organized, with obliterative vascular changes, probably associated with yeast-like microorganisms.

Because of the biopsy result, on July 9, 2020, Cerebrospinal Fluid (CSF) was sent for a PCR test. It was negative for *Coccidioides immitis/Posadasii* and positive for *Aspergillus* spp. Hence, fluconazole was suspended. Management started with amphotericin B deoxycholate at 2.6 mg/kg/day, and voriconazole was prescribed. Nevertheless, the hospital was out of stock of the latter.

The search for anti-Rubella antibodies (IgG) and anti-Citomegalovirus (IgM) were positive. Meanwhile, antibodies anti-HIV-1 and 2, anti-*Toxoplasma* (IgM and IgG), and anti-Citomegalovirus (IgG) were negatives. Immunodeficiency was discarded because of the HIV test results and the levels of immunoglobins after being evaluated in the hospital immunology service.

The study approach continued, performing brain Magnetic Resonance Images (MRI) (Figs. 2 and 3). The results showed hemispheric vasogenic edema, multiple brain abscesses, and areas of calcification.

The CSF study results indicated rock water, cytological and cytochemical with 0 cells, glucose 36 mg/dl, protein 424.3 mg/dl, BAAR, ink Chinese, and GRAM-negatives. Due to negative TORCH and the suspicion of yeast-like microorganisms, treatment with amphotericin B deoxycholate 6.5 mg/kg/day, dexamethasone 0.8 mg/kg/day, levetiracetam 30 mg/kg/day started.

During the hospitalization and treatment, on July 22, 2020, she presented acute renal failure secondary to the use of amphotericin deoxycholate, with urea at 131 mg/dl, creatinine at 1.23 mg/dl, and Urea Nitrogen (BUN) at 61.4 mg/dl. For this reason, the amphotericin B deoxycholate dose was changed to 4 mg/kg/day. Nevertheless, elevated nitrogen levels (Schwartz of 58) and rash persisted. On July 26, 2020, it was decided to suspend amphotericin B deoxycholate, and management started with the impregnation of fluconazole at 15 mg/kg/dose and maintenance at 7.5 mg/kg/day.

She also presented a systemic inflammatory response with a positive urine culture for *E. coli* on August 5, 2020. Hence, meropenem 60 mg/kg/day was added to the prescription. Due to clinical improvement and lack of voriconazole, hospital discharge was decided after management with meropenem and 20 days with amphotericin B deoxycholate.

Afterward, intravenous voriconazole was available, and she was readmitted for treatment. It was administered at 8.9 mg/kg/day for 14 days. The management continued on an outpatient basis, with oral voriconazole at the same dose until completing six months. Therapeutic drug monitoring was not performed.

In 2021, a year after the CSF PCR test, *Aspergillus* negative and neuroimaging (Fig. 4) were reported in the control treatment. It showed cerebral edema decreasing compared to previous studies, resolution of brain abscesses, and right fronto-temporo-parietal areas of encephalomalacia.

In 2022, after two years of treatment, a neuroimaging control study

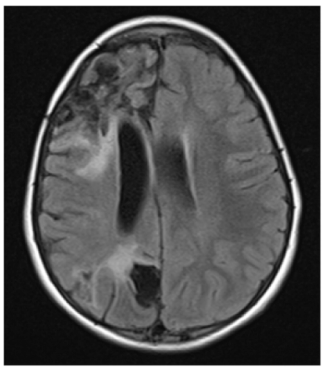

Fig. 4. Magnetic Resonance Image. T2 Axial cut. Right parietal encephalomalasia and leukomalacia.
Source: Medical records.

was performed (Fig. 5), finding complete resolution of brain abscesses, areas of encephalomalacia, and isolated calcifications.

At the same time, in 2022, the physical examination found left ophthalmoparesis, left central facial palsy, left upper extremity monoparesis, stretch reflexes +++, no clonus, no extensor plantar, and normal gait. She did not have clinical seizures under management with levetiracetam 60 mg/kg/day. The Electroencephalogram (EEG) control (Fig. 6) showed focal epilepsy -due to isolated spike outbreaks in the right frontotemporal region that sometimes become generalized-. The IQ assessment result using the Wechsler Intelligence Scale Test for Children (WISC) had borderline results (Total IQ 79), verbal comprehension was 98, perceptual reasoning 75, working memory 86, and processing speed 73.

After three years of evolution, in 2023, an MRI was performed (Fig. 7). It showed a right cerebral hemi atrophy with areas of encephalomalacia and ipsilateral leukomalacia.

Discussion

Invasive aspergillosis in children generally has difficulties in early diagnosis and timely treatment [9].

In the Dotis et al. [8] review, 74 cases were reported and located in PubMed; the first reported case was in 1955, but it was published in 1986 [10].

Generally, cerebral aspergillosis occurs in children under one year, with prematurity, Staphylococcus pneumonia, and liver failure. The most frequent underlying diseases for those older than one year were leukemia, solid tumors, liver transplantation, and chronic granulomatous disease [8].

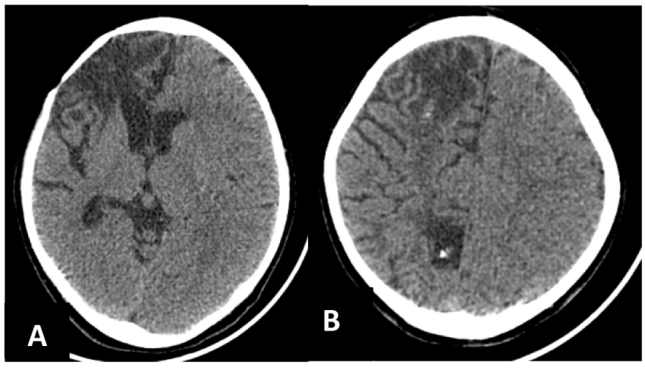

Fig. 5. Computed tomography axial section. A. Right frontotemporal encephalomalasia with retraction of the anterior horn of the right ventricle. B. Right parietal encephalomalasia with calcification.
Source: Medical records.

In this case report, the patient did not have previous underlying diseases, with no history of those reported as a history of cerebral aspergillosis.

In the report by Dotis et al. [8], the median age was nine years, ranging from 18 days to 18 years. The case of Guanajuato was six years old.

Dotis et al. [8] report that diagnosis of CNS aspergillosis was made post-mortem in 56.4 % of the cases, and the overall mortality was 65.4 % and 39.5 % in those treated after 1990.

In the case of Guanajuato, the etiological diagnosis was made by CSF PCR one month after the initial hospitalization, during the second hospitalization that caused the seizure.

In the reported case, she managed to survive, and two years after her first hospital admission, she suffered from cerebral aspergillosis sequelae.

The most common pathological types in CNS aspergillosis are abscesses in the brain, cerebellum, and basal ganglia; vasculitis and meningoencephalitis; the lesions are parenchymal necrosis with vascular invasion and secondary hemorrhages [8].

The girl from Guanajuato presented brain abscesses that were visualized in the magnetic resonance images (Figs. 2 and 3); In the magnetic resonance of the brain performed one year after diagnosis, the abscesses were resolved (Fig. 4).

The most common treatment for reported cases was amphotericin B, followed by azoles [8]. It was the treatment used in this case.

Surgery was used in 36.2 % of the reported cases [8]. In the case of Guanajuato, neurosurgery was performed due to suspicion of an intracranial tumor and for biopsy.

In a case of cerebral aspergillosis reported in 2021 by Frascheri et al. [11], presented in an immunocompromised patient, the brain abscesses resolved almost completely in 12 weeks. The correct identification of the causative agent and starting the treatment as soon as possible is crucial. The MRI allows us to distinguish between pyogenic and fungal brain abscesses.

Conclusions

This report presented an immunocompetent patient with a good response and evolution after developing an invasive form of aspergillosis despite the high mortality rate reported in these cases.

Despite the one-month delay in diagnosis, the patient survived in the long term.

Observational studies are required to establish, with greater certainty, risk factors for invasive aspergillosis since this case was in an immunocompetent child.

Key clinical message

Invasive aspergillosis is a rare form of infection. Between 39–65 % of the cases reported in the literature had a fatal outcome [8]. Despite the delay in the diagnosis of this case, the patient managed to survive, despite the kidney damage caused by the initial dosage of amphotericin B, with subsequent adjustment.

Ethical approval

The authors obtained the informed consent form signed by parents from the patient, to publish clinical and medical images from the patient.

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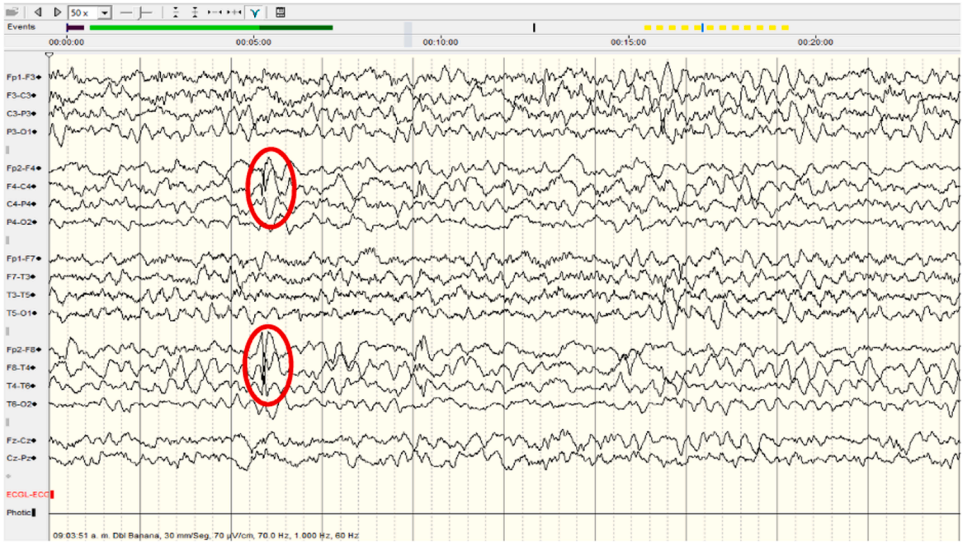

Fig. 6. Electroencephalogram showing focal epilepsy due to isolated outbreaks of spikes in the right frontotemporal region.
Source: Medical records.

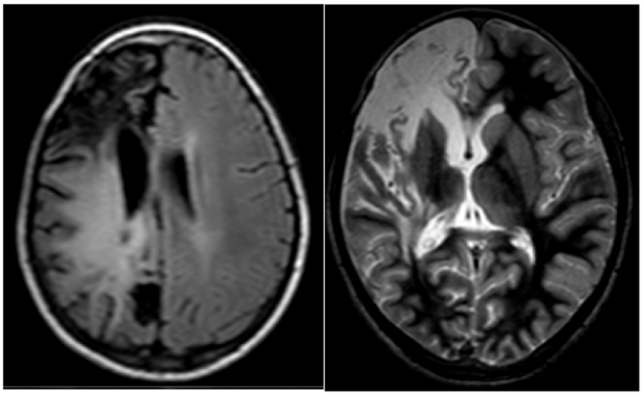

Fig. 7. Magnetic resonance image. A. T2 axial slice B. T1 axial slice. Right brain atrophy with ipsilateral encephalomalacia and leukomalacia.

Consent

We have the consent from the mother of patient to publish her clinical data and results of laboratory analysis and images test.

CRediT authorship contribution statement

Gilberto Flores-Vargas: Writing – review & editing. **Mariela Guadalupe Macedo-Montero:** Methodology. **Lilian Danae Acosta-Yebra:** Conceptualization, Supervision, Writing – original draft. **Ana Paula Ramírez-Acosta:** Data curation. **Nicolás Padilla-Raygoza:** Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Author contributions

Ana Paula Ramírez-Acosta. She gathered the information on the case from the medical file. Lilian Danae Acosta-Yebra. She wrote the first draft of the case report and collected information from the doctors responsible for treating the patient in different services. Mariela Guadalupe Macedo-Montero. She was responsible for the patient's hospital care and complemented the information of the patient's care. Jorge Antonio Marinez-Garcia. He performed pathological and laboratory studies of the patient.Gilberto Flores-Vargas. He reviewed and corrected the first draft. He edited the manuscript. Nicolas Padilla Raygoza. He reviewed the first draft, made the English translation, and finalized the manuscript.

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