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Research Article

Pulmonary Aspergillosis in Pediatric Patient

Coral-García Miguel Ángel[1], Serrano-Guevara Christian Mauricio[2], León-López Magdalena[2], López-Santos Héctor Alfonso[3], Barbosa-Contreras Meylin[3], Maldonado-Castañeda Sandra[2], Rubio-Nava Karla María[1], Guevara-Navarrete César Martín[3], Silva-Campos Irlanda Mariel[3] and Yaneth Martínez Tovilla[3]*

[1]*International Laboratory EPIGEN- CONCYTEP- BUAP, Mexico*

[2]*General Hospital "Dr. Eduardo Vázquez Navarro", México*

[3]*Facultad de Medicina, Benémerita Universidad Autónoma de Puebla, México*

***Corresponding Author:** Yaneth Martínez Tovilla, Facultad de Medicina, Benémerita Universidad Autónoma de Puebla, Puebla, Mexico.

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Abstract

Introduction: *Aspergillus* is a branched septate filamentous fungus that can induce lethal and invasive infections in patients suffering from autoimmune or inflammatory diseases, as well as patients undergoing organ transplantation and/or treatment for malignant neoplasms [5]. Since aspergillosis is not a reportable infection in many countries, it is difficult to have an accurate estimate of the number of cases worldwide. Even so, most cases of this disease are sporadic and occasionally in hospitalized patients, with a reported mortality of 30% to 85% [6].

Voriconazole is the recommended drug in invasive aspergillosis, which is an azole agent that inhibits cytochrome P450 (CYP 450)-dependent demethylation of 14α-lanosterol in the synthesis of ergosterol in the fungal cell membrane [7].

The importance of this work lies in the need to recognize in early stages this pathology, often diagnosed in autopsies. Therefore, we offer a clinical perspective on the comprehensive approach to invasive pulmonary aspergillosis in a pediatric patient.

Case: 15-year-old male with no relevant history. He was admitted to the General Hospital of Puebla "Dr. Eduardo Vazquez Navarro" after suffering trauma to the frontal bone of the skull (kicked by an equine). After his recovery, he presented fever despite administration of ceftriaxone and vancomycin, for which reason meropenem was added and a bronchial aspirate culture was obtained with a report of *Aspergillus fumigatus*; a positive determination of galactomannan in bronchial aspirate; a chest CT scan with ground glass image in the right upper lobe, consolidation at the level of segments 6 - 10 right and right basal laminar atelectasis. Overall, a diagnosis of pulmonary aspergillosis was made and treatment with voriconazole was started. Once stable, the patient was discharged with the following drugs: voriconazole, levetiracetam, carbamazepine, captopril, omeprazole, beclomethasone and prednisone, as well as follow-up and outpatient appointment by the pediatrics, neurology, pneumology and cardiology specialties.

Pulmonary aspergillosis is a disease that induces high mortality due to its late diagnosis. Early diagnosis and efficient targeted therapy had a positive impact on the prognosis of this patient. *Aspergillus* infections can be catastrophic in different situations. Clinical suspicion and efficient use of different healthcare resources (e.g. laboratory and imaging studies) can improve the prognosis of these patients.

Keywords: *Aspergillosis; Pulmonary; Pediatric; Report Case*

Abbreviations

ABPA: Allergic Bronchopulmonary Aspergillosis; CYP 450: Cytochrome P450; CT: Computed Axial Tomography

Introduction

Aspergillosis is a concept that refers to all diseases caused by *Aspergillus* [1], which is a branched septate filamentous fungus that can induce lethal and invasive infections in immunodeficient patients; *Aspergillus fumigatus* is the most common species [2]. It has a worldwide distribution and can be found in the air, indoor and outdoor surfaces and even in surface water reservoirs, often growing on decaying vegetables and bedding [1].

There are different clinical presentations of aspergillosis: cutaneous, airway, pulmonary, extrapulmonary and disseminated [3]. Clinically, pulmonary aspergillosis be present in four forms: 1) allergic bronchopulmonary aspergillosis (ABPA), 2) saprophytic infection (aspergilloma), 3) chronic necrotizing aspergillosis (semi-invasive form) and 4) invasive aspergillosis (angioinvasive or bronchoinvasive forms) [4].

Aspergillosis has been reported worldwide, however, it is difficult to have an estimate, as many cases go undiagnosed. However, the patients most prone to *Aspergillus* infection are those with autoimmune or inflammatory diseases, as well as patients with organ transplantation and/or treatment of malignant neoplasms [5]; the highest mortality (30% to 85%) is observed in invasive aspergillosis [6].

Clinically, pulmonary aspergillosis presents a challenge because the symptoms are nonspecific: fever that does not respond to antibiotics, cough, sputum production and dyspnea [5]. A positive culture or a positive histopathological test is required for definitive confirmation of the diagnosis [1].

Although different drugs are available for the treatment of invasive aspergillosis, voriconazole is the drug of first choice recommended by different working groups. Voriconazole is an azole agent that inhibits cytochrome P450 (CYP 450)-dependent demethylation of 14α-lanosterol, which is a vital step in cell membrane ergosterol synthesis by fungi [7].

The importance of this work lies in the need to know and recognize in time this pathology, which is often diagnosed in autopsies. The following work offers a clinical perspective on the comprehensive approach to pulmonary aspergillosis in a pediatric patient.

Materials and Methods

Basic patient information

For this retrospective study, the information contained in the clinical record was reviewed. The medical care of this patient was provided by the Pediatrics Service of the Hospital General de Puebla Dr. Eduardo Vazquez Navarro (Puebla, Mexico). In addition, the publication of this work was supervised by the Head of Teaching and Research of the same hospital, in charge of Dr. Sandra Maldonado Castaneda.

Bronchial aspirate culture

Growing the fungus by means of samples (blood, cerebrospinal fluid, pus, urine, tissue, respiratory samples, etc.) is the most direct way to establish the diagnosis of a fungal infection [17] and although molecular tests are currently available, culture is still recommended for the identification of *Aspergillus* [18].

Different conditions are required to achieve an adequate culture of *Aspergillus*. In this case, Sabouraud dextrose agar medium was used and Grocott staining was added. This staining uses periodic acid which, upon contact with the polysaccharides of the fungal cell wall, oxidizes the aldehydes generating reduction of the nitrate-silver methenamine complex. The deposit of reduced silver on the aldehydes produces a brown to black coloration [19]. For further specifications of this technique, the following literature can be consulted [17].

Determination of galactomannan in bronchial aspirate

The determination of galactomannan in bronchial aspirate is a recommended method for the diagnostic support of pulmonary aspergillosis [20]. Galactomannan is a component of the water-soluble polysaccharide cell wall of *Aspergillus* species and has the advantage that it can be detected early in bronchial aspirate, even before the onset of severe symptoms [21].

The tests used for the detection of *Aspergillus* sp wall antigens are performed by techniques such as enzyme-linked immunosorbent assay and lateral flow assay (immunochromatography). In our case, the enzyme-linked immunosorbent assay technique was used, which is based on a one-step ELISA (double sandwich) plate that detects galactomannan in human serum. EBA-2 monoclonal antibodies were used to coat the wells of the microplate directed against the 1-5 D-Galactofuranoside side chains of *Aspergillus* galactomannan, used as both the antigen acceptor and detector. 0.5 is the accepted cut-off point for serum samples from neutropenic patients, regardless of the patient's baseline condition. For further specifications of the technique the following literature can be reviewed [22].

Chest CT

Chest CT is fundamental in different types of pulmonary infections, especially in immunocompromised patients, due to its much higher sensitivity and specificity than chest radiography [23] and it is also an important resource in the evaluation of patients with pulmonary aspergillosis because it generates characteristic images that support early clinical diagnosis, so that this imaging study has been used in different investigations on pulmonary aspergillosis [24].

Results and Discussion

Case report

15-year-old male with no relevant history. He was admitted to the General Hospital of Puebla "Dr. Eduardo Vazquez Navarro" (April 4, 2022) after suffering trauma to the frontal bone of the skull (kick by equine). On admission the patient showed neurological and hemodynamic deterioration, for which reason he was kept under sedation, analgesia, ventilatory support, amines and antibiotic therapy. Computed axial tomography (CT) of the skull showed soft tissue edema with subcutaneous emphysema in the orbit and right frontal region, multifragmented fracture with frontal bone and sphenoid bone collapse, in addition to hemorrhagic contusions, edema and pneumocephalus (Figure 1A). For this reason, craniotomy was performed with fixation of the fractures using titanium microplates (Figure 1B).

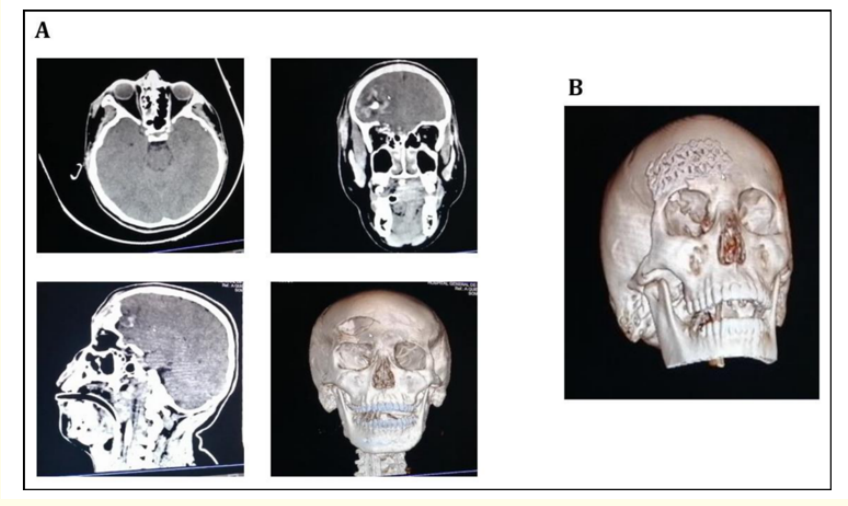

Figure 1: *CT scan of the skull on admission (A) and after craniotomy (B). A. Initial CT scan of the skull showing different types of lesions secondary to trauma (equine kick). B. CT scan of the skull after surgical treatment (craniotomy with fixation of the fractures using titanium microplates).*

Subsequently, sedation, analgesia, ventilatory support and amines were gradually withdrawn. However, he presented fever despite antibiotic therapy with ceftriaxone and vancomycin, for which reason meropenem was added and the following studies were requested:

- Bronchial aspirate culture (Table 1).
- Determination of galactomannan in bronchial aspirate (Table 2).
- Chest CT scan (Table 3 and figure 2).

Medium	Sabouraud dextrose agar
Stain	Grocott
Outcome	At 72 hours: brown colouring
Interpretation	Presence of fungus

Table 1: *Bronchial aspirate culture.*

Company	Pfizer
Technique	Enzyme-Linked Immunoadsorption Assay (ELISA)
Reference values	Negative = <0.50 Positive = >0.50
Outcome	1.14
Interpretation	Positive

Table 2: *Determination of galactomannan in bronchial aspirate.*

Company	Siemens
Courts	64
Protocol	Lung and mediastinum with 3 mm cephalocaudal slices
Ppch	1.5 de 16 seconds
Outcome	Ground-glass image in right upper lobe, consolidation at level of right 6 - 10 segments and right basal laminar right atelectasis.

Table 3: *Chest CT.*

With all this, the diagnosis of pulmonary aspergillosis was made (April 20, 2022), and treatment with voriconazole at 4 mg/kg/dose was started.

On May 4, 2022, the patient was stable, active, reactive to external stimuli, afebrile, with adequate oxygenation without requiring supplemental oxygen, hemodynamically stable with arterial pressures and heart rate within normal parameters for his age, with adequate uresis and bowel movements maintaining adequate water balance. Also, there was difficulty in ambulation and decreased muscle

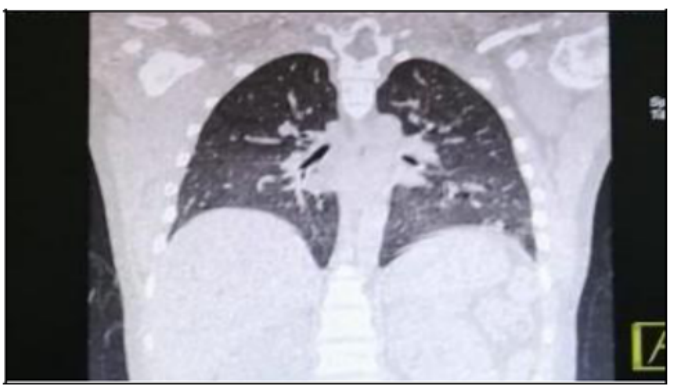

Figure 2: *Chest CT scan. Chest CT scan after the onset of febrile illness, showing various pulmonary alterations.*

strength in the 4 extremities, due to prolonged immobilization for his condition. For this reason, it was decided to discharge her from the hospital with the following indications: treatment with voriconazole for 1 month; levetiracetam and carbamazepine until evaluation by the Neurology specialty; captopril, omeprazole, beclomethasone and prednisone in weaning doses until evaluation by the Pneumology and Cardiology specialties.

Discussion

Aspergillus fumigatus can cause respiratory infections when conidia is present in the air and it is inhaled, being sufficient between 1 and 100 conidia per m^3 [8]; it is usually found in soil, dust and decomposing vegetation [9], environmental conditions that were present from the beginning of the condition (kicked by equine) of our case Although, in healthy patients the inhalation of *Aspergillus* could not generate pathology, immunocompromised patients can have different consequences [10]. The patient presented here had no history of other pathologies, but the facial lesion that affected part of the airway together with the metabolic response to trauma (characterized by endocrine, metabolic and immunologic changes) [11] are factors that contributed to the development of pulmonary aspergillosis.

During the patient's recovery, fever was observed that did not subside with initial antibiotic therapy (ceftriaxone and vancomycin). This led the health personnel to two objectives: to find the origin of the fever and to progress the antibiotic (meropenem). Bronchial aspirate culture was used for diagnosis, which was positive for *Aspergillus* and was complemented with galactomannan detection, which was also positive. Culture is an essential but limited method, so it is recommended to increase its performance with detection of the fungal cell wall component galactomannan [12]. Imaging studies are essential in the diagnosis of respiratory diseases that cause high morbidity and mortality [13], because of this, a chest CT scan was requested, which showed different lesions, one of them common in pulmonary aspergillosis: localized image in ground-glass appearance, also known as halo sign [1].

There are three main groups of antifungal drugs: polyenes, echinocandins and azoles [14]. The latter group includes voriconazole, a broad-spectrum triazole drug that inhibits ergosterol synthesis [15], which has been recommended in guidelines for the treatment of invasive fungal infections [16]. In our case, voriconazole was administered at 4 mg/kg/12 hrs intravenously in-hospital. It is important to note that in pediatric patients aged 15 to 17 years, intravenous voriconazole is administered as follows: loading dose for 24 hrs (6 mg/

kg/12 hrs), followed by maintenance dose (4 mg/kg/12 hrs) [15]. For hospital discharge, oral voriconazole (200 mg every 12 hours for 1 month) was indicated at home.

Conclusion

Pulmonary aspergillosis is a disease prevalent in immunocompromised patients with high mortality. Early diagnosis (clinical, laboratory and imaging) and efficiently targeted therapy (voriconazole) were outstanding aspects that positively impacted the prognosis of our case. The timely interdisciplinary approach led to the successful treatment of the patient in our case.

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Conflict of Interest

We declare don´t have any financial interest or any conflict of interest exists.

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