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# *Aspergillus flavus* endocarditis in an immunocompetent child. Case report

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ABSTRACT

Fungal endocarditis (FE) is a rare infection in pediatrics which accounts for 5% of the cases of infective endocarditis. This pathology affects immunosuppressed patients in a greater proportion. We present an immunocompetent 7- year-old female with a history of multiple cardiac surgeries who developed fungal endocarditis due to *Aspergillus flavus*. The histology study showed liquefactive necrosis and septate hyphae of *Aspergillus sp* type. The clinical outcome was favorable and the ambulatory follow-up after 12 months showed no new complications.

## 1. Introduction

Fungal endocarditis (FE) due to *Aspergillus* is an uncommon infection in pediatrics which generally occurs in patients with various immunosuppression states [1,2]. The main risk factor for its development is the presence of congenital heart diseases [3]. Considering that blood cultures are reported as negative in up to 80% of cases [1], the diagnosis of FE due to *Aspergillus* requires a high index of suspicion and it is based mainly on microscopic direct examination and on histopathological and microbiological documentation of this fungus, in samples of cardiac origin (vegetation, valve prostheses, grafts and emboli) [4,5]. Regarding treatment, the recommendation is to perform a surgical debridement and apply antifungal therapy in the vast majority of patients, since better survival rates compared with unique antimycotic therapy have been documented. We report a rare case of endocarditis due to *Aspergillus flavus* in an immunocompetent 7-year old patient. The clinical outcome was favorable and the ambulatory follow-up after 12 months showed no new complications.

## 2. Case

A 7 year old female patient, with a history of congenital heart disease of pulmonary atresia type, corrected in the first week of life, with a pulmonary valve replacement at 6 years of age. Two months after the intervention, nonspecific and intermittent clinical manifestations began with sporadic fever, chest pain, respiratory distress, cough with occasional hemostatic expectoration and functional class deterioration. She was hospitalized on 6 occasions, in institutions of less complexity due to apparent bacterial pneumonia where multiple antibiotic therapy schemes were administered, resulting in partial improvement of the symptoms. She was then referred to a fourth complexity level Institution in the city of Bucaramanga, Santander – Colombia (day 0) presenting similar symptoms to the ones described above. Upon admission, she went through a physical examination and was found in poor general conditions. Weight: 19.9 kg; height: 114 cm, heart rate (HR): 116 beats/min; respiratory rate (RR): 20 breaths/min; blood pressure (BP): 99/69 mmHg; pulse oximetry (SPO2): 96%; temperature: 36.8 °C; cardiopulmonary auscultation with systolic murmur in *meso*-cardium and moderate hepatomegaly: blood count with leukocytosis (26,600/mm3) and deviation to the left (neutrophils 88%, lymphocytes 6%); moderate thrombocytopenia (platelets: 93,000 / mm3), high C reactive protein (68 mg/L). On day 1, an echocardiogram was performed for base pathology. There was evidence of a pulmonary valve with poor mobility and a thrombus which was almost completely obstructing pulmonary blood flow, dilatation and severe right ventricular dysfunction and tricuspid regurgitation (Fig. 1). At this point, It is

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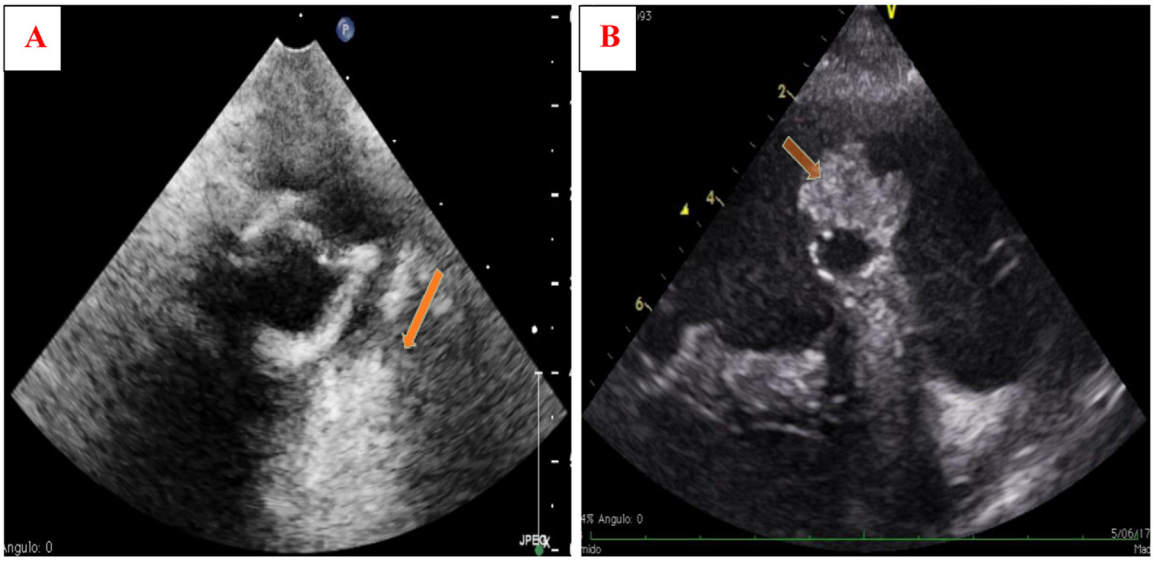


**Fig. 1. (A)**. Pulmonary valve with little mobility with a 3 × 1.5 cm thrombus that almost completely obstructs pulmonary blood flow, with dilatation and severe right ventricular dysfunction and tricuspid regurgitation. **(B).** Mobile thrombus (vegetation) of 30 × 10 mm at the homograft lung level on the right posterior leaflet and one of 12 × 10 mm on the left posterior leaflet.

highly suspected that the patient suffers from subacute infective endocarditis, which is why a broad-spectrum antibiotic treatment with cefepime, vancomycin and amphotericin B is started. The angiotomography performed shows thrombus on pulmonary prosthetic valve, with multiple pulmonary thromboembolism. On day 8, the patient is taken to surgery with multiple thrombi in bifurcation of pulmonary arteries. The biological pulmonary valve was replaced for a pulmonary homograft; the outflow tract of the right ventricle was reconstructed and the thrombi were removed through an endarterectomy. Crops for thrombus microorganisms were taken and the prosthetic valve was removed without growth of pathogens. Three sets of negative blood cultures were collected to discontinue amphotericin B. The patient was discharged from hospital after 4 weeks of antibiotic therapy with oral anticoagulation (day 28).

The patient re-enters 2 months later (day 90), with similar clinical symptoms of 2 days of evolution, in poor general conditions, with HR: 146 beats/min, FR: 28 breaths/min, BP: 100/59 mmHg; T: 38.6 °C, SPO2 88%; cardiopulmonary auscultation with persistent III/VI degree systolic murmur, at the *meso*cardium level; hepatomegaly of 6 cm below the costal margin and petechial lesions on the trunk and extremities. Lab tests taken on admission showed leukocytosis and neutrophilia (23,000/mm3, 79%, respectively); severe thrombocytopenia (25,000/mm3); elevated CRP (168 mg/L) and markedly elevated D-dimer (6970 mg/mL). A chest x-ray showed no pleuropulmonary lesions. On day 91, a new echocardiogram performed shows evidence of vegetation in pulmonary homograft on right and left posterior leaflet (Fig. 1). Due to the possibility of endocarditis recurrence, treatment with meropenem and vancomycin is initiated. The patient presents persistent fever for 4 days after starting antibiotic treatment. Fungal endocarditis is suspected and amphotericin B deoxycholate (1 mg/kg/day) is added (day 95). On day 96, a new angiotomography shows massive pulmonary thromboembolism (Fig. 2). On day 108, with the new pulmonary homograft change, histopathological findings evidenced the following: extensive endocarditis with positive removed homograft culture for *Aspergillus flavus* (microscopic identification for its typical characteristics), biopsy with liquefactive necrosis and septate hyphae of *Aspergillus sp* type (Fig. 2.). No susceptibility tests were carried out because these are not available at our institution; universal polymerase chain reaction and negative (panfungal) sequencing for fungi; four sets of blood cultures for aerobic, anaerobic and negative fungi. Galactomannan antigen was reported as negative and the Infectious and immunological profile showed no alterations; non-reactive for HIV; CD3 + lymphocyte count: 1519 (59%); CD4 + : 825 (32%), CD8 + : 705 (27%) to discard compromise in cellular immunity. Liposomal amphotericin B is initiated (5 mg/kg/day) (day 112). However, due to a torpid clinical course we changed to voriconazole (9 mg/kg/dose) (day 121). After 5 weeks of antifungal therapy with voriconazole, vegetation in the right ventricle outflow tract persists. Because of the recurrence of fungal endocarditis due to *Aspergillus*, rescue therapy is initiated combined with caspofungin in high doses (day 156). On day 177, echocardiographic control was carried out and vegetation resolved. Management with caspofungin continued for 6 weeks. The patient is discharged from hospital with treatment on voriconazole and after following up 12 months later, there were no complications.

## 3. Discussion

FE FE due to *Aspergillus* is an unusual entity in the pediatric population [1]. However, in the context of FE it is responsible for 20–30% of the cases, constituting the second most frequent etiology after *Candida sp*. The species of *Aspergillus* most frequently involved are: *A. fumigatus* (54%), *A. terreus* (18%), *A. niger* (7%) and *A. flavus* (7%) [3]. The incidence of this pathology is currently uncertain, but a growing increase has been observed mainly in preterm infants or children with cardiac defects [4]. Generally, fungal endocarditis due to *Aspergillus* occurs in patients with various immunosuppression states [3]. The main risk factor for its development is the presence of congenital heart diseases observed in up to 67% of cases [3]. Other risk factors include the use of valve prostheses, hematological neoplasms, chemotherapy and cytotoxic therapy, prolonged use of corticosteroids or antibiotics and solid organ or bone marrow transplants [3]. In our patient, we can observe several of these risk factors such as multiple heart-level interventions for basic pathology, prolonged use of antibiotics and the use of prosthetic valve. However, contrary to what's described in literature [3], our patient's cellular immunity was not compromised. Additionally, the precise etiology of our case was *Aspergillus flavus* (microscopic identification for its typical characteristics), which has previously been described only in 7% of patients with fungal endocarditis due to *Aspergillus* [3]. The initial clinical manifestations can be nonspecific and among the most frequently observed are the presence of abnormal heart sounds, fever, pleuritic pain, hemoptysis, cyanosis, dyspnea, anorexia and weight loss [3], most of which are evidenced in our case. Although

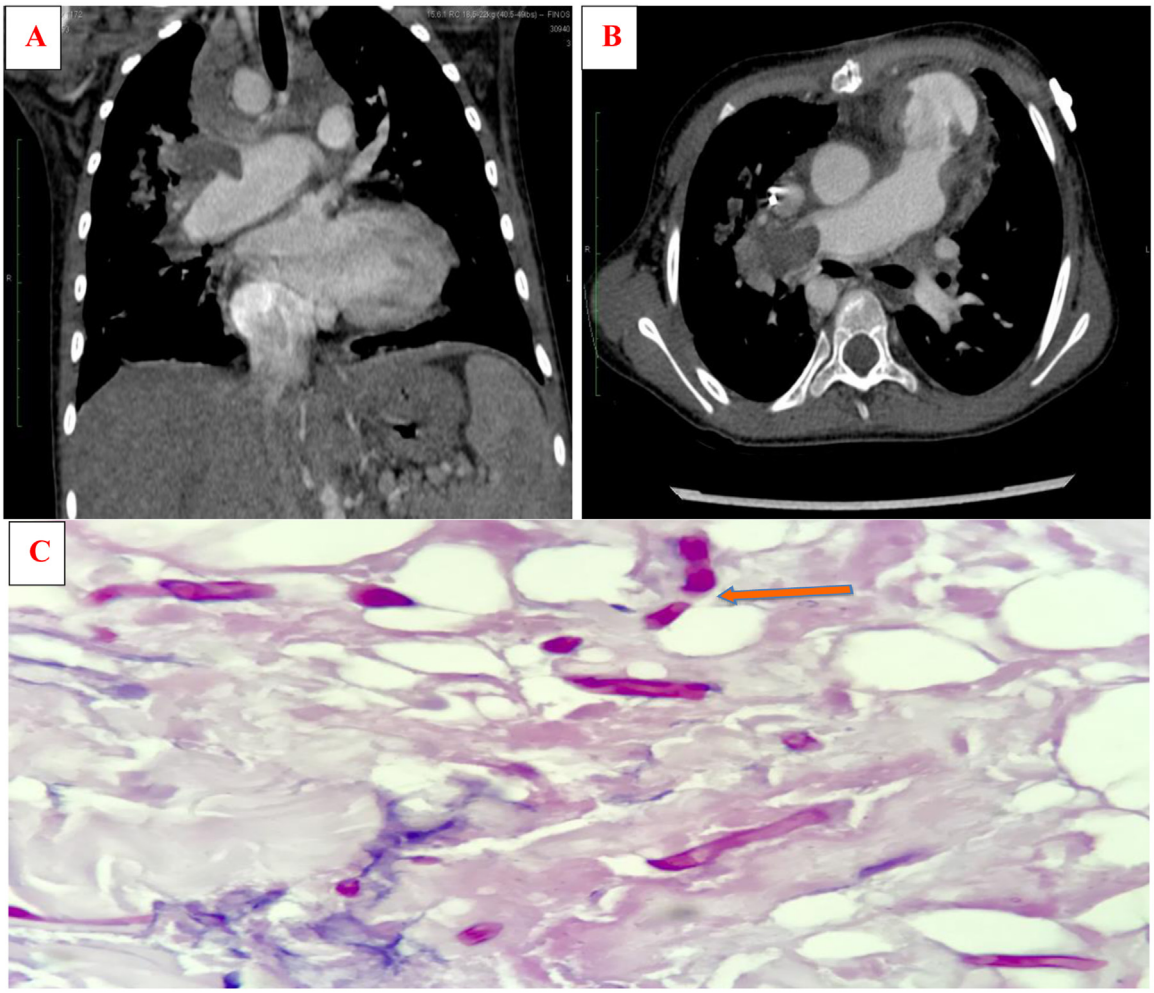


**Fig. 2. (A)**. Coronal section, **(B)**. Axial section: Pulmonary valve dilatation surgically manipulated with hypodense vegetations of valvular walls (axial section). In addition, a dilated aspect of the main pulmonary artery with a diameter greater than 25 mm and the right pulmonary artery with a diameter greater than 22 mm. There is also a large defect in right pulmonary artery filling in the saddle, a thrombus that extends to its segmentation and is accompanied by a right hilar alveolar opacity. **(C)**. PAS staining: Severed hyphae of *Aspergillus sp* type are observed on the pulmonary homograft.

in the patient's first hospitalization episode no microorganism isolation was achieved, we believe that the etiology was of fungal nature since then, specifically, *Aspergillus*. However, considering that the patient only received 12 days of amphotericin B (1 mg/kg) the treatment was incomplete and only 2 months after in the episode that followed with similar clinical manifestations to the ones in the first hospitalization episode, definite etiological isolation was achieved in the removed homograft. On the other hand, pulmonary thromboembolic disease, one of the main complications for fungal endocarditis reported in the literature was observed in our patient. This complication might also extend to the cerebral, hepatic, mesenteric, splenic or renal level [3]. Considering that blood cultures are reported as negative in up to 80% of cases [1], the diagnosis of FE due to *Aspergillus* requires a high index of suspicion and it is based mainly on microscopic direct examination and on histopathological and microbiological documentation of this fungus in samples of cardiac origin (vegetation, valve prostheses, grafts and emboli) [1,5]. Other studies such as galactomannan antigen detection or polymerase chain reaction do not show enough evidence in the diagnostic process of fungal endocarditis due to Aspergillus [1]. Our case further reaffirms this aspect, since, in spite of finding a positive culture for *Aspergillus flavus* and evidence of the presence of typical findings of said microorganism in the pathology piece, the polymerase chain reaction test was negative. Some authors suggest that transthoracic and/or transesophageal echocardiography is a useful tool in the identification of FE, because it is very specific and it reaches a sensitivity greater than 70% by identifying large, friable and mobile vegetation that have an increased risk of peripheral embolization [1]. Regarding treatment, the recommendation is to perform a surgical debridement along with the application of antifungal therapy in the vast majority of patients, since success rates with antifungal therapy in isolation only reaches 4% [3]. There is no data regarding the total duration of such therapy although most authors suggest suppressive treatment for at least 2 years or even for life considering that [3] recurrence rates reach up to 50% [6,7].

Finally, fungal endocarditis due to *Aspergillus* continues to be a diagnostic challenge in pediatrics, since it requires a high index of clinical suspicion and it is based on the microscopic, histopathological and microbiological documentation of said microorganism in samples of cardiac origin [1,5]. FE should be considered as a differential diagnosis in cases of endocarditis with negative cultures [1]. Its current prognosis is not very favorable, reaching a mortality level higher than 90% of the cases regardless of the treatment modality [3]. The possibility of different clinical outcomes regarding fungal endocarditis due to *Aspergillus* in immunosuppressed patients or those in patients without this condition might be considered.

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## Conflict of interest

The authors have no conflicts of interest to declare.

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