

Fatal Endocarditis due to *Aspergillus flavus* in Iran

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Infective endocarditis is a rare but potentially devastating infection of the native endocardium and heart valves. The majority cases of infective endocarditis are caused by bacteria, whereas cardiac fungal infections account for 2-4% of all cases of endocarditis.¹ The prevalence of these infections has grown in the last decade due to intravenous drug abusing, malignant neoplasm, solid organ transplantation, long term use of antibiotics as well as open-heart surgery which is a major factor in developing of this infection.^{2,3} Two-thirds of cases of fungal endocarditis are caused by *Candida*, and one third by *Aspergillus*.^{4,5} *Aspergillus* endocarditis is usually associated with high morbidity and mortality, ranging from 80% to 96%, regardless of treatment.⁶ Unfortunately, establishing a definitive diagnosis of fungal endocarditis frequently remains a problem. Thus, rapid and precise diagnosis is an essential factor for appropriate and adequate treatment; whereas postponing of diagnosis, may cause irreversible consequences. Here, we report a case of fatal endocarditis caused by *Aspergillus flavus*.

Case Report**Case Report**

A 19-year old housekeeper female, weighting 40 kg was admitted for fever, vomiting, anorexia, nausea, and chest pain. She had a history of Fallot's Tetralogy, for which she underwent ventricular septal defect (VSD) surgery. She took gentamycine and penicilline with suspicion of bacterial endocarditis two weeks prior to hospitalization. Upon admission to the hospital, the patient's complaints were severe dyspnea, chill, coughing, tachypnea and severe weight loss. Systolic and diastolic murmurs were discovered on physical examination but she had no sign of organomegaly, petechia, clubbing and edema. Peripheral blood examination disclosed anemia (Hb: 8 gr/dl, RBC: $2.9 \times 10^{-6}/\mu\text{l}$, HCT: 28%)

and leukocytosis ($25700/\mu\text{l}$). All of her six blood cultures on the days 1,2,3,5,7,10 were negative.

In her echocardiography, verrucoid vegetation was seen on her right ventricular under tricuspid valve. She underwent surgery to sequester mentioned vegetation over cortex patch, 9 days after admission. Drug therapy with amphotericin B (40 mg/day) and 5-fluorocytosine (100 mg/kg/d) was initiated 1 day later. The examination of histological sections staining with periodic acid-Schiff (PAS) and Hematoxylin-Eosin (H&E) as well as wet mount (KOH 10%) preparation of samples indicated the branched, septated and dichotomous mycelia within the tissue (Figure

[(0)]

1). The remaining specimen was also cultured on Brain Heart Infusion agar (BHI), Sabouraud's dextrose agar (S) and Sabouraud's containing 0.005% chloramphenicol (Sc). The S and Sc culture media were incubated at 25°C and BHI at 37°C. The colonies grew rapidly, attaining a diameter of 5 cm within 5 days and their colour was yellowish-green. Cellophane tape preparations and slide cultures demonstrated septate, branched and hyaline hyphae with rough-walled conidiophores and radiated conidial heads. Based on these histological and mycological findings, *Aspergillus flavus* has been determined as causative agent of fungal endocarditis of this case. Although amphotericin B in combination with 5-fluorocytosine were administered in efficient dosage, they did not influence the course of disease. Furthermore, heart surgery performed to remove fungal vegetations was not helpful. In spite of all intensive-care managements, the patient died on day 15 following brain emboli due to fungal endocarditis.

Discussion

During two last decades, the incidence of fungal endocarditis was dramatically increased and made a diagnostic and therapeutic challenge for physicians.⁷

The most common fungal organisms results in endocarditis are candida and aspergillus with frequency of 62% and 18%, respectively.^{1,8} By contrast, in the study of Pierroti et al, aspergillus species were recovered from 71.8% of mould endocarditis.⁹ Among aspergilli, *A. fumigatus* is the principle aetiological agent, although other species have also been incriminated. The aetiological role of *A. flavus* in this patient is consistent with the other published reports from this region.¹⁰

In the normal human immune system, *Aspergillus* species do not cause systemic disease and invasion is restricted to the immunocompromised host.¹¹ However based on clinical and laboratory examinations, our patient had no signs of immunodeficiency. Furthermore, previous studies indicated that contamination of operating room especially during reconstruction procedures might play a role.¹ Therefore, we evaluate operating room contaminations by plating methods and *A. flavus* were isolated from all media at several intervals. Based on these evidences, the only predisposing factor for aspergillus infection in this patient was the open-heart surgery which is considered as the major risk factor in infective endocarditis.^{7,9}

Clinical manifestations of fungal endocarditis are not specific and similar to those of bacterial endocarditis except large vegetation⁵ on valves and high incidence of embolization. Fever is considered as one of the basic signs of infective endocarditis. Moreover, other studies indicated that fever is also a common sign in aspergillus endocarditis.¹² Our patient had also had persistent fever that was resistant to antibacterial therapy. Thus, fever can not be considered as the pathognomonic sign for diagnosis of aspergillus endocarditis. Transesophageal Echocardiography (TOE) is a powerful diagnostic method, with an established accuracy for vegetations of over 90%.^{8,13} As demonstrated in this case, echocardiography revealed verocoid vegetation on right ventricular tricuspid valve. Moreover, lung embolization which is a common phenomenon in right-sided endocarditis was also observed in this patient.

Common laboratory findings including anemia and leukocytosis which was observed in our patient to a varying extent, are non-characteristic. Isolation of *Aspergillus* species from peripheral blood cultures is highly uncommon.¹³ All of the blood cultures from this patient were also failed to yield aspergillus. Therefore, persistently negative blood culture does not rule out fungal aetiology, whenever the patient has clinical presentation of infective endocarditis. The scarcity of this infection coupled with a negative blood culture results in most mold cases and weaken

our ability to secure early diagnosis. Thus, this entity should be considered in patients with persistent fever and negative blood cultures after open-heart surgery. On the other hand, survival in patients with fungal endocarditis is rather poor, and hardly exceeds 50%. In accordance with the majority of disseminated cases of *A. flavus* infection described previously¹⁴ the outcome in this case was also fatal, despite of surgical procedure and antifungal therapy.

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