Case report

# *Aspergillus* endocarditis presenting as femoral artery embolism

# Fallberichte. *Aspergillus*-Endokarditis mit Femoralarterien-Embolie

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**Summary**

Fungal valvular endocarditis is an unusual cause of endocarditis, yet very important because of its historically poor prognosis. We report two fatal cases of fungal valvular endocarditis following cardiovascular surgery, presenting as femoral artery embolism. *Aspergillus terreus* and *A. flavus* were the causative agents of endocarditis in the two patients. Diagnosis was established very early by culture of the emboli and was confirmed later by isolation of the same *Aspergillus* species from the resected valve tissue.

**Zusammenfassung**

Pilzbedingte Herzklappen-Endokarditis ist eine ungewöhnliche Endokarditisform, die jedoch besondere Aufmerksamkeit erfordert wegen ihrer historisch schlechten Prognose. Wir berichten über zwei fatale Fälle von Herzklappen-Embolie. *Aspergillus terreus* und *A. flavus* waren die Erreger. Die Diagnose wurde früh durch Kultur der Emboli gestellt und später durch Isolierung der gleichen *Aspergillus*-Arten aus dem resezierten Klappengewebe bestätigt.

**Key words:** *Aspergillus terreus*, *Aspergillus flavus*, endocarditis, embolism.

**Schlüsselwörter:** *Aspergillus terreus*, *Aspergillus flavus*, Endokarditis, Embolie.

## Introduction

Fungal infections have emerged as the important agents of opportunistic infections all over the world. Various *Aspergillus* spp. and *Candida* spp. account for the majority of such infections. Invasive aspergillosis is the most common mold infection occurring in immunocompromised patients[1] and the second most common agent after *Candida* species to cause fungal endocarditis.[2] *Aspergillus* species may often contaminate hospital rooms and supplies and may inadvertently gain entrance into susceptible patients through many portals. The anamorphic genus *Aspergillus* contains over 180 recognized species.[3] Many of the species are quite rare and only five to six species are known etiological agents of aspergillosis in humans and lower animals.[4] *Aspergillus fumigatus* and *A. flavus* are the species most commonly involved in invasive mold infections. Other species involved in human aspergillosis are *A. niger*, *A. nidulans*, *A. ustus*, *A. versicolor*, and *A. terreus*.[5] Mycotic infections of the heart, however, are relatively uncommon but may be increasing in frequency.[6] These are usually associated with disseminated fungemia and are usually fatal.[2] Here, we report two cases of postoperative *Aspergillus* endocarditis presenting as femoral artery embolism.

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## Case reports

### Case no. 1

A 34-year-old euglycemic, normotensive male with a prior history of subaortic membrane excision done 3 years earlier at another hospital was admitted with



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symptoms of acute onset of pain in both legs of 2 weeks duration and with the pain in the right leg increasing gradually for the past 1 week. His investigations at the time of admission revealed normal hemoglobin of 11.5 g%, urea of 25 mg $dl^{-1}$, creatinine 0.7 mg $dl^{-1}$, and glucose was 95 mg $dl^{-1}$. His total WBC count was 20 300 $cmm^{-1}$, with polymorphonuclear leukocytes of 71%, lymphocytes of 25%, and eosinophils of 4%. The erythrocyte sedimentation rate (ESR) level was raised and was 80 mm at the end of 1 h. An echocardiography (ECHO) revealed rheumatic heart disease, thickened mitral leaflets with grade II mitral regurgitation (MR), moderately severe aortic regurgitation and moderately severe pulmonary artery hypertension (PAH). No clot or vegetations were seen on ECHO. Three sets of blood cultures, cultured onto multiple media were sterile at the end of 2 weeks of incubation. An aortogram undergone on the first day after admission revealed total occlusion of right common iliac artery and left common femoral arteries, following which he underwent a bilateral femoral embolectomy on the second postadmission day. The clot from the femoral artery was sent to the microbiology laboratory for culture, which grew *A. terreus* on all broth and solid media after 48 h of incubation. On the first postoperative day (POD) he was started on amphotericin B 1 mg $kg^{-1}$ body weight as an intravenous infusion which, however, had to be withheld from the second POD because of elevated renal parameters and nephrotoxicity. Due to reoccurrence of embolization to the left femoral artery a repeat left femoral embolectomy was performed 4 days later. The transthoracic echocardiography underwent initially did not show any vegetation, however, a transesophageal echocardiography (TEE) revealed a vegetation on the aortic valve which was mildly thickened and which was attached to left coronary cusp (LCC) and measured 1.8 cm.[2] The TEE performed also revealed severe aortic regurgitation, septal hypertrophy and mild to moderate mitral stenosis. An emergency homograft aortic valve replacement was performed on the eigth day after admission. Embolectomy specimen and the native aortic valve was also then sent to the microbiology laboratory for culture. All the specimens cultured grew the same *A. terreus* on all broth and agar media. The patient was afebrile and ambulant and the wound was healing well at the time of being discharged on the 10th POD. He was receiving amphotericin B at the time of discharge at 1 mg $kg^{-1}$ $day^{-1}$. He was, however, readmitted after a month with dyspnea, marked pallor and acute atrial flutter with rapid ventricular rate. The chest X-ray was suggestive of acute pulmonary edema. The patient suddenly developed ventricular tachycardia and ventricular fibrillation and had a sudden cardiac arrest and was immediately intubated and put on ventilatory support. In spite of all efforts, the patient continued to deteriorate and expired within 24 h after being readmitted.

### Case no. 2

A 45-year-old male, non-diabetic who underwent mitral valve replacement (MVR) at our hospital 6 months prior to his admission presented with high grade fever of 3 weeks duration, symptoms of transient ischemic attack followed by left hemiparesis. At admission his hemoglobin was 8.8 g%, total count was 16 000 $cmm^{-1}$ with a differential count of 80% polymorphonuclear leukocytes, 18% lymphocytes, and 2% eosinophils. His urea was 47 mg $dl^{-1}$, creatinine was 1.5 mg $dl^{-1}$, bilirubin was 0.7%. He was empirically started on vancomycin and rifampicin for infective endocarditis. A Doppler done showed a block at the common femoral artery. On the second day after admission he developed embolic occlusion of the right femoral artery for which femoral embolectomy was performed. The embolectomy specimen was sent to the microbiology laboratory for culture which grew *A. flavus* on all media after 48 h. He was started on amphotericin B at 0.25 mg $kg^{-1}$ $day^{-1}$ gradually increasing to 1 mg $kg^{-1}$ $day^{-1}$. His ECHO findings showed normal functioning mitral prosthetic valve with vegetations and a paravalvular leak, grade II aortic regurgitation with vegetation on the non-coronary cusp measuring $18 \times 14$ mm, prolapsing into the aorta (Fig. 1). Three sets of blood culture which were sent at the time of admission were sterile. The patient underwent a redo MVR and AVR on the fourth day after admission. Specimens such as the previous mitral prosthetic valve, aortic leaflet and tissue from aorto mitral continuity were sent to microbiology laboratory for culture. All the above specimens grew a heavy growth of *A. flavus*. Following surgery he was continued on injection amphotericin B at 1 mg $kg^{-1}$ as an intravenous infusion. The patient was extubated on the second POD. His blood urea level which was high preoperatively gradually settled over the first postoperative week. However, on the 10th POD his echocardiogram showed an aortic paravalvular leak. He developed aphasia followed by bilateral hemiplegia. The patient deteriorated rapidly showing signs of fungal sepsis, including massive increase in leukocyte count, acute phase parameters and abnormal liver function tests. A CT scan was performed which revealed infarcts in the left centriform nucleus and internal capsule bilaterally. On the 17th POD he developed tachypnea and respiratory distress.

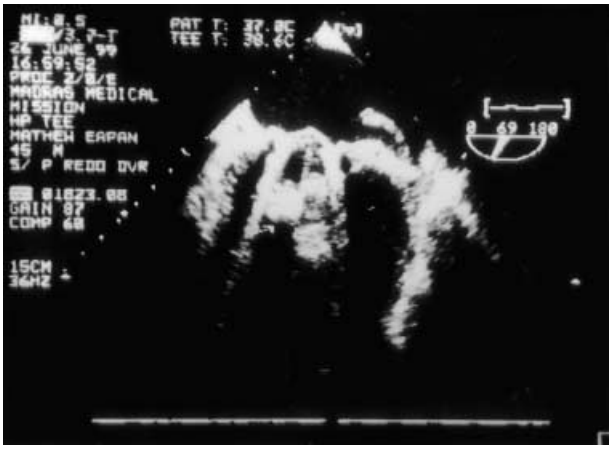


**Figure 1** Transesophageal echocardiography (TEE) of case 2: done 2 days prior to mitral and aortic valve replacement showing a vegetation on the mitral prosthesis.

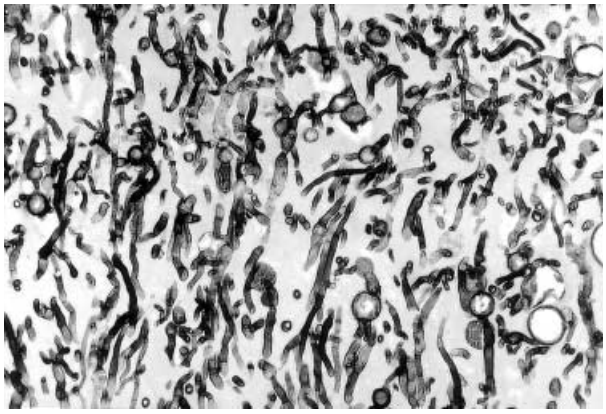

**Figure 2** Case 1: femoral embolectomy specimen. Gomori's methenamine silver stain showing septate dichotomously branching hyphae of *Aspergillus terreus* (×400).

His hemodynamic parameters were unsatisfactory and he developed metabolic acidosis and was reintubated. He later developed features of low cardiac output with multiorgan failure and expired on the same day. Postmortem was not performed on either of the patients.

### Microbiological investigation of the embolus from case 1

A gram-stained smear from the ground embolectomy specimen showed numerous RBC's and pus cells and many partially stained dichotomously branched, broad, septate hyphae. No bacteria were seen. A 10% KOH preparation revealed broad septate dichotomously branched hyphae. Small portions of the specimen were inoculated on routine media such as blood aga r(BA), MacConkey agar (MA), and Sabouraud glucose agar (SDA). Cultures were incubated at room temperature (25–30 °C) and at 37 °C, as well as into liquid media such as thioglycollate broth (TB) and Sabouraud glucose broth (SDB) at room temperature and at 37 °C. Heavy growth of *Aspergillus* species was obtained on all media. Detailed study of the isolate revealed that the isolate grew at both temperatures of incubation within 48–72 h. On SDA, the colonies were initially white and cottony to velvety and gradually became powdery to granular and turned cinnamon brown in color with a characteristic amber colored pigment which exuded into the medium. Slide culture on Czapek's agar of the isolate showed conidial heads which were compactly columnar in buff or cinnamon colour; the conidiophores were smooth and colorless bearing hemispherical vesicles terminally. Vesicles bore biseriate phialides producing chains of globose conidia. Conidia were globose to subglobose, smooth and smaller in size. Many submerged hyphae showed globose to ovate hyaline conidia (aleurioconidia) borne directly on the hyphae, sessile or on short stalks. The embolectomy specimen stained with Gomori's methenamine silver stain showed numerous septate dichotomously branching hyphae. Few broad, septate hyphae suggestive of *Aspergillus* spp. were observed (Fig. 2).

### Microbiological investigation from case 2

The ground embolectomy specimen showed numerous septate hyphae showing dichotomous branching in KOH mounts. The gram-stained smear from the ground embolectomy specimen showed numerous RBC's and pus cells and many partially stained dichotomously branching fungal filaments. No bacteria were seen. Small portions of the specimen were inoculated on media previously mentioned. Cultures were incubated at room temperature and at 37 °C. Liquid media such as TB and SDB were also inoculated and were incubated at room temperature and at 37 °C. Heavy growth of *Aspergillus* species was obtained at the inoculum sites on all media. Detailed study of the isolate revealed that the organism grew at both temperatures within 48–72 h of incubation. The surface of the colony turned from white to yellow-green on further incubation. Slide cultures on Czapek's agar revealed conidial heads which were globose, radiating or columnar light yellow-green in color. Conidiophores were colorless with outer wall roughened to coarsely roughened bearing globose to subglobose vesicles and fertile over most of their surface. Both uniseriate and biseriate phialidic arrangement was observed among the conidial heads. Conidia were


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globose to subglobose, smooth when young becoming conspicuously rough walled. Based on the characteristic yellow-green colored colonies, growth at higher temperatures (up to 45 °C), roughened conidiophores and both uniseriate and biseriate phialiic arrangement, the isolate was identified as *A. flavus*.

## Discussion

Severely debilitated patients are vulnerable to a variety of opportunistic fungal infections, and *Aspergillus* spp. are the second most common opportunistic fungi after *Candida* spp. causing serious infections. True *Aspergillus* valvular endocarditis is extremely rare and mainly occurs after heart surgery over prosthetic valves.[6] Diagnosing fungal prosthetic valve endocarditis can be difficult as according to past reports persons suffering rarely have positive blood cultures and only half of these patients present with fever.[7] *Aspergillus* spp. are ubiquitous and one of the most common fungi in the environment and often contaminate the laboratory environment. However, in the above cases the demonstration of characteristic broad, septate dichotomously branched hyphal elements in the wet mounts of the specimen and subsequent isolation of the causative *Aspergillus* spp. on all media as well as the failure of growth of any other aerobic or anaerobic organisms from the specimens conclusively proved the etiological role of the two species. Both patients in the above cases presented with embolic events in the extremities with vegetation on the valves, which accounted for the incidence of embolic events. Fungal endocarditis has been seen to affect aortic valve prosthesis most commonly and to occur soon after valve surgery.[8] Our first patient developed *A. terreus* endocarditis 3 years after subaortic resection, which is unusual. The second patient developed fungal endocarditis of the mitral prosthesis 6 months after surgery. Although, it is likely that the aspergilli could have gained entry from the environment during surgery we could not establish the source of the infection due to the lapse in the time between surgery and the presentation of the symptoms. Also both the patients had normal chest X-rays ruling out a primary pulmonary site of infection. The use of echocardiography and especially TEE has improved the detection rate of fungal vegetations. Definite diagnosis of fungal endocarditis requires identification of the fungal emboli or isolation of fungus from blood or from the previously infected valve. In the above cases, diagnosis was made after the patients presented with constitutional symptoms and embolic episodes and the *Aspergillus* spp. were cultured from the embolectomy specimens. The same species were recultured from excised native and prosthetic valves respectively. Identity of both the species was confirmed by one of us (AAP). In both patients, despite treatment the outcome was fatal.

*Aspergillus terreus* is widespread in the environment. However, it has been reported rarely to cause cutaneous, subcutaneous and disseminated infections in immunosuppressed patients.[9] Sutton *et al.*[10] reported on the antifungal susceptibility for 101 clinical isolates of *A. terreus* to various antifungal agents and compared it with voriconazole. Only 1.98% of the strains appeared susceptible to amphotericin B with an MIC of $<1$ μg ml$^{-1}$. All the other strains had MICs ranging between 2 and 16 μg ml$^{-1}$. Conversely at 48 h, voriconazole MICs were within the therapeutic range of 2–10 μg ml$^{-1}$. Unfortunately voriconazole is not available in the Indian market. Special localization of the fungus on the valve endothelium as a large vegetation leads to persistent detachment during blood flow and embolization affecting major blood vessels.

Since dissemination of fungal endocarditis invariably occurs in cases of valve endocarditis, it is necessary to adopt a combined approach of early diagnosis, surgical removal of the infected valve and lifelong therapy which could change the otherwise bleak scenario of survival rates of only 20–45% and lead to a better diagnosis and effective treatment for the historically poor prognosis of this condition.

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