Aspergillus flavus Endocarditis – To Prevaricate is to Posture

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ABSTRACT

Fungal endocarditis represents both a diagnostic and therapeutic challenge to the treating team. The critical care physician will see a rising incidence as older and more immuno-compromised patients are being supported in their intensive care units. Aspergillus sp. endocarditis represents less than 25% of all cases of fungal endocarditis and is associated with a mortality of around 80%. Early diagnosis may assist with definitive management. We review a case of Aspergillus endocarditis, and review the literature as to optimal methods of detection, imaging modalities of choice, and management, both surgical and medical.
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Key words: Aspergillus flavus, endocarditis, thromboembolism

The incidence of native valve endocarditis in the general population is estimated to be about 3.8 cases per 100,000 per year.[1] Fungal endocarditis (FE) is much rarer accounting for 1.3% to 6% of total cases.[2-4] The incidence of FE is rising due to the increasing use of intravascular devices, prevalence of patients with prosthetic heart valves and prolonged survival of immunocompromised patients.[5-7] Aspergillus remains an uncommon cause of native valve endocarditis, accounting for less than 25% of cases of FE.[3,4] Outcomes in FE are poor with case series reporting a mortality of 56 - 94% overall and 80% for aspergillus endocarditis.[3,4]

We describe a case of mitral valve *Aspergillus flavus* endocarditis in a patient with a history of intravenous drug use, which resulted in fatal arterial and cerebral embolisation.

CASE REPORT

A 51 year old female presented from another hospital with a 2 week history of diarrhoea, weight loss of 6 kilograms and lethargy. She was known to use intravenous drugs, and was a carrier of hepatitis B and C. She was receiving treatment for a bipolar affective disorder, was an asymptomatic carrier of haemochromatosis and had a past history of pulmonary tuberculosis.

On presentation, the patient was afebrile, haemodynamically-stable and there were no embolic stigmata of infective endocarditis (IE). Cardiac auscultation revealed a loud pan-systolic murmur radiating to axilla. Initial laboratory results indicated a raised white cell count (WCC) of 13.7 X 10^9/L (neutrophils 9.0 X10^9/L), CRP 87 (reference range <5) and ESR 15 mm/hr (reference range <20). Trans-thoracic echocardiography (TTE) demonstrated a mass measuring 1.7 cm by 1.6 cm on the posterior leaflet of the mitral valve. Six sets of blood cultures, taken prior to the commencement of antibiotics, were sterile. Subsequent TTE performed two days later showed the cardiac lesion had increased in size to 2.6 cm by 1.6 cm. The differential diagnosis included mxyoma and endocarditis. A cardiac MRI showed a 2.5 cm diameter well-defined mass attached to the posterior leaflet of the mitral valve (Figure 1). The mass contained several areas of increased signal, suggestive of fatty tissue. No enhancement was observed with Gadolinium, which made the diagnosis of mxyoma less likely.

Subsequently, the patient developed hypotension, a decreased conscious state (Glasgow coma score of 3) and was transferred to the intensive care unit. After resuscitation, a difference between femoral (BP 30/0

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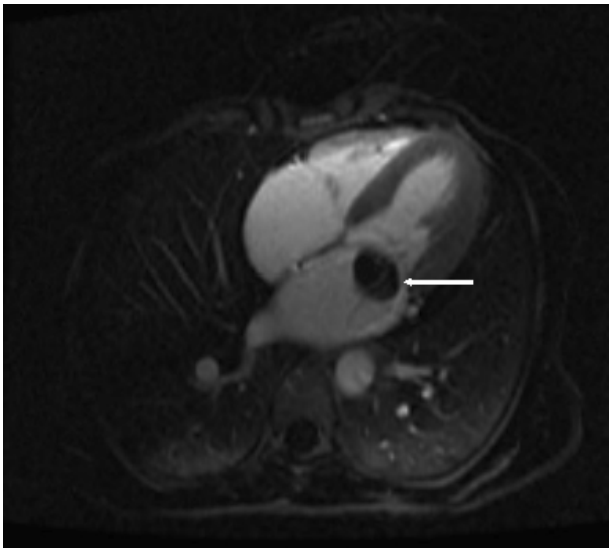

Figure 1. MRI 4 chamber view. The arrow points to the Aspergilloma on the mitral valve.

mmHg) and brachial (BP 70/30 mmHg) arterial pressures was noted. The electrocardiograph (ECG) showed widespread ST and T wave changes. Transoesophageal echocardiography (TOE) was performed, which showed severe left ventricular dysfunction, mild mitral valve regurgitation and a smaller fimbrillated mass on the mitral valve (Figure 2). An abdominal ultrasound scan demonstrated hypo-echoic material within the aorta just distal to the superior mesenteric artery. Liposomal amphotericin was initiated.

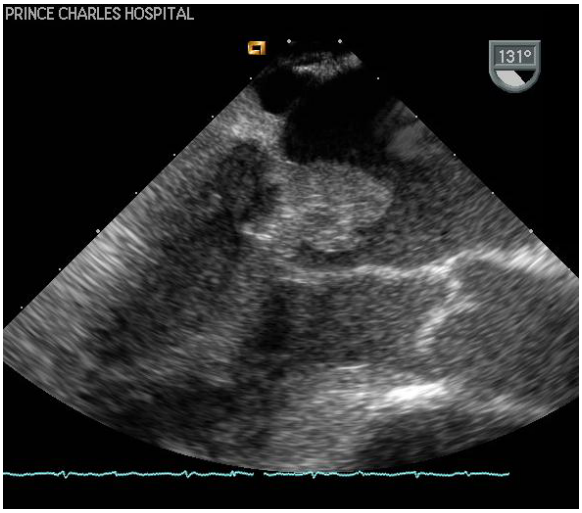

Figure 2. A post collapse transoesophageal echocardiograph showing the fimbrillated mass.

The patient subsequently died of cerebral infarction and multiple organ failure secondary to myocardial dysfunction and bowel ischaemia. Assessment of neutrophil function demonstrated abnormally low levels of CD43, an anti-adhesive molecule and L-selectin (L. Fung, personal communication).

The family consented to a limited postmortem examination of the patients' thorax. The findings were;

1. Aspergillus endocarditis of the mitral valve,
2. Acute myocardial infarction of posterior and lateral walls of the left ventricle, and
3. Pan-acinar pulmonary emphysema.

Further video and still images of cardiac MRI and TOE as well as still post mortem images can be viewed at The Prince Charles Hospital Critical Care Research Group's website: http://tcph-ccrg.org.

DISCUSSION

Aspergillus endocarditis is an uncommon and frequently lethal condition. Important risk factors include previous valve surgery, antibiotic use, immunosuppression and intravenous drug use. The aortic valve is most commonly affected in FE, but the mitral valve is reported to be more frequently involved in aspergillus native valve endocarditis. The duration of symptoms prior to diagnosis in patients who present *de novo* ranges from 1 day to 1 year.[3-5]

Clinical presentation of FE is indistinguishable from bacterial endocarditis in the majority of cases. The most common presenting features are reported (in order of frequency); fever, change in heart murmur; major peripheral embolisation; focal or generalised neurological features, heart failure and dyspnoea. The classical signs of Osler's nodes, splinter haemorrhages, finger clubbing and Roth spots are less common.[3-5]

Positive blood cultures are important diagnostic criteria for IE as described in the Duke criteria.[8] However, the diagnostic yield of blood cultures is not high in FE, and failure to identify a causative agent should prompt consideration of both fungal and fastidious bacterial causes.[9,10] In a review of 290 patients with fungal endocarditis, only 18% had this aetiology considered prior to the eventual diagnosis.[3] The majority of blood culture systems and media can support the growth of fungi in aerobic milieu. Specialised culture systems and stains have been shown to result in identification rates in *Candida* species of between 83 and 95%.[9] Blood cultures have a sensitivity for isolating fungi in only 30% of filamentous fungal infections; however *Aspergillus* can be presumptively identified in 75 - 95% of vegetations often by microscopy of segmented branching hyphae only and 65% of emboli.[9] Antigen testing may be of benefit when cultures are negative.[10]

The rarity of FE with frequently negative blood cultures may prevent early diagnosis. However culture

negative endocarditis with large vegetations in a high risk patient should prompt the clinicians to consider the diagnosis of FE.[2]

Echocardiographic examination cannot distinguish bacterial and fungal endocarditis, although bulky vegetations are associated with *Staphylococcal*, gram negative and fungal endocarditis.[2]

Treatment of FE consists of antifungal drugs and surgery.[2,11,12] Medical therapy alone for aspergillus endocarditis is associated with mortality of 90 - 100%. This may be due to the inability of drugs to achieve adequate high levels within the valve and vegetation. The fungal cell wall provides a unique target for anti-fungal drugs because the cell wall is composed of beta-1,3-d glucan, mannan, and chitin. Classes of antifungal antibiotics with activity against *Aspergillus sp.* include the polyene macrolide amphotericin B deoxycholate (AmB) and its lipid based preparations (AmB lipid complex, AmB colloidal dispersion and liposomal AmB) and newer azoles such as itraconazole, voriconazole and echinocandins (caspofungin).[12,13] Although theoretically attractive, the role of combination therapy is currently unclear.[14]

Surgical intervention in acute IE was first reported in 1961 with the successful repair of a ventricular septal defect and removal of a vegetation from a tricuspid valve, which was subsequently shown to be due to *Candida albicans.*[15] The first successful valve replacement in an acute IE patient occurred in 1965.[16] The timing of surgical intervention in acutely ill patients is guided by general patient status; evidence of cardiovascular instability and failure of medical therapy.[11]

As the cure rate for FE is low, close monitoring of response to treatment is essential. Historically, this has entailed complete blood count, biochemistry, erythrocyte sedimentation rate, C reactive protein, repeat blood cultures and imaging of known foci/emboli. Recently, the availability of quantitative serum *Aspergillus* antigen testing (Gallactomannen assay) may aid in the monitoring of progress as persistently raised assays may indicate treatment failure.[10]

The overall survival rate in patients with aspergillus endocarditis remains poor and is relatively unchanged since 1968. A high index of suspicion is required and delay in diagnosis and therapy is frequently fatal.

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