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Case Report

Internal Medicine Section

Infective Endocarditis of Native Valves due to Aspergillus in an Immunocompetent Host: A Rare Presentation

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ABSTRACT

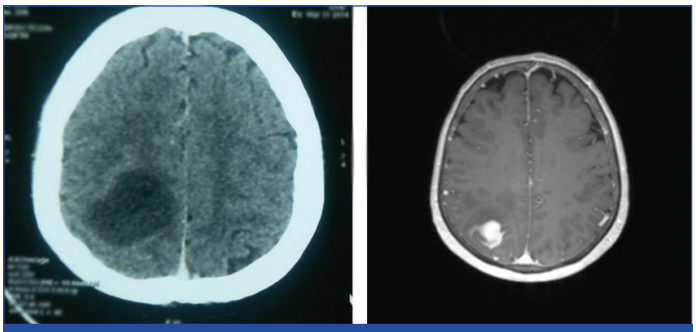
Aspergillus endocarditis is a rare entity in an immunocompetent host with native valves. Late or misdiagnosis leads to increased morbidity and mortality. In this report authors present a case of native valve Aspergillus endocarditis, in 30-year-old male immunocompetent patient with no co-morbidities. The patient also had a parietal glioma. He underwent four surgeries including valve replacement during the course of illness. Patient improved with appropriate antifungal therapy and surgeries. He was on suppressive antifungals and continued to do well. Aspergillus endocarditis is to be considered in culture negative endocarditis. The optimal management includes adequate surgical debridement in conjunction with prolonged antifungal therapy.

Keywords: Fungal endocarditis, Metastatic complications, Suppressive antifungal therapy, Valve replacement

CASE REPORT

A 30-year-old male patient presented with chief complaints of sudden onset of generalised tonic clonic seizures of few-hours duration. He had five episodes of seizures, each lasting for 1-5 minutes duration. There was no preceding history of fever or headache. He had complaints of fatiguability. No significant medical or surgical history was there. There was no history of smoking, consumption of alcohol or intravenous (i.v.) drug abuse. There were no history similar complaints or any other significant medical conditions in the family.

On physical examination, vitals were stable and there was left hemiparesis with no cranial nerve involvement. Other systems examination was also normal. Computed Tomography (CT) scan followed by Magnetic Resonance Imaging (MRI) of the brain revealed an enhancing space occupying lesion of size 33×41×36 mm in right parietal region [Table/Fig-1,2]. The differentials include glioma and cerebral metastasis. During the hospitalisation, his urea and creatinine worsened gradually along with decreased urine output over four days. Haemodialysis was started through an internal jugular venous access. Progressive transaminitis was noted along with lactate dehydrogenase of 42000 IU/L [Table/Fig-3].



[Table/Fig-1]: Computed tomography of brain showing well-defined hypodense lesion in right parieto-occipital region. **[Table/Fig-2]:** Contrast enhanced T1 weighted magnetic resonance imaging showing enhancing space occupying lesion in right parieto-occipital region. (Images from left to right)

After five days he was haemodynamically stable, however in view of worsening renal and liver parameters, he was transferred to another hospital with all super specialties for better care. He was afebrile. There was leukocytosis with thrombocytopenia (white blood count were 14000/mm^3, platelets were 70000/mm^3). Tests for dengue, malaria, leptospirosis, and scrub typhus were negative. Human immunodeficiency virus-enzyme-linked immunoassay, Hepatitis B surface antigen (HbsAg) and anti-hepatisis C virus were non reactive. Screening for autoimmune diseases {Antinuclear antibody (ANA), Antineutrophil Cytoplasmic Antibodies (ANCA)} was negative. His central venous catheter was re-sited. Empiric antibiotics (meropenem, teicoplanin) were started in view of suspected sepsis and steroids were initiated for cerebral oedema. A 2D echo was normal. Blood and urine cultures were non significant. Renal biopsy was done, and features were suggestive of acute tubular necrosis [Table/Fig-4]. Liver enzymes and renal function normalised over next five days and dialysis was stopped [Table/Fig-3].

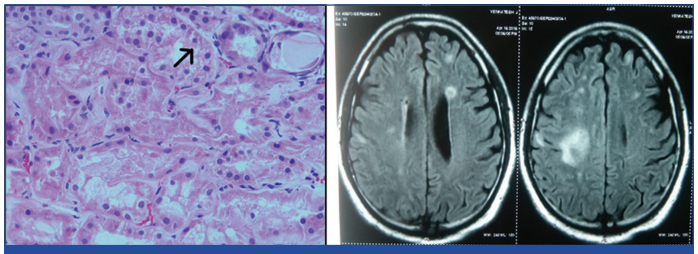
Parameter	Day 1	Day 4	Day 10	Day 15
Total white blood cell	12000	11600	14000	11,098
Platelets	2,05,000	1,89,000	70,000	1,16,000
Urea (mg/dL)	106	223	216	79
Creatinine (mg/dL)	2	7	4	2.6
AST (IU/L)	152	4032	3540	459
ALT (IU/L)	264	7182	4321	268

[Table/Fig-3]: Investigation findings.

On the 10th day of illness, he had a fever with pain and redness in the left eye with progressive loss of vision over the next two days. Intravitreal fluid aspiration showed thin branched, septate filamentous fungus. He was given intravitreal Liposomal Amphotericin B (LipAmB) at dose of 10 mcg/0.1 mL along with systemic LipAmB (3 mg/kg/day) and caspofungin (50 mg once a day). Computed tomography scan of paranasal sinuses showed maxillary sinusitis. Evisceration of the eye was done on day 15 of illness.

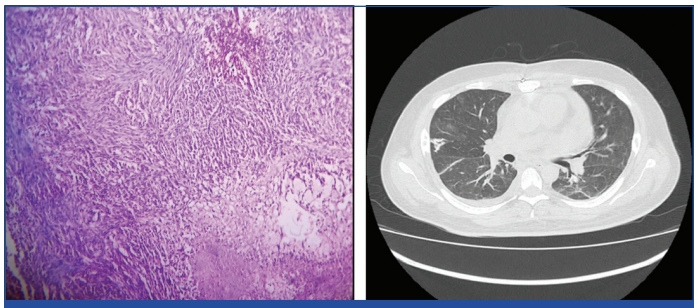
Repeat MRI of the brain showed new areas of diffusion restriction and high signal intensities on T2W and Fluid Attenuated Inversion Recovery (FLAIR) suggestive of infarcts [Table/Fig-5]. He underwent craniotomy and excision of the glioma on day 18 of illness. A day later his fever recurred with new onset dyspnea. Blood cultures were repeated. Repeat 2D echo revealed vegetation on the posterior mitral leaflet with mitral regurgitation. Meropenem 1gm i.v. BD, teicoplanin 400 mg i.v. OD, LipAmB 3 mg/kg/day and caspofungin 50 mg OD were continued with diuretics. The histopathological examination of the brain glioma showed diffuse astrocytoma of grade III without any fungal elements [Table/Fig-6]. After four days, fever and dyspnea subsided. Repeat 2D echo showed reduction in size of vegetation

and reduced mitral regurgitation. He was discharged on 42nd day of illness, with an advice to continue same i.v. antibiotics at home.



[Table/Fig-4]: Histopathology of renal biopsy showing renal tubular necrosis with sloughing of epithelial cells {Haematoxylin and Eosin stain (H&E)-10X}.
[Table/Fig-5]: Magnetic resonance imaging of brain showing features of acute infarcts. (Images from left to right)

Within two days of discharge, his fever, dyspnea recurred. He presented with signs of heart failure. Transthoracic echocardiogram showed 2.1×1.0 cm vegetation on posterior mitral leaflet with grade III mitral valve prolapse and severe mitral regurgitation. Transesophageal Echocardiogram (TEE) showed large vegetation on posterior mitral leaflet with additional vegetation on anterior mitral leaflet, severe mitral regurgitation, and vegetation on tricuspid leaflet and chordae. Computed tomography scan of the chest showed wedge shape hyperdense lesion in superior segment of right lower lobe suggestive of septic pulmonary embolisation [Table/Fig-7]. Till this point he had already received six weeks of meropenem and teicoplanin, five weeks of LipAmB and caspofungin. Meropenem, teicoplanin and caspofungin were stopped. He was started on intravenous voriconazole with LipAmB along with treatment for cardiac failure.



[Table/Fig-6]: Histopathology of brain showing astrocytoma (H&E 10X).
[Table/Fig-7]: Computed tomography chest showing wedge shaped lesion suggestive of septic emboli. (Images from left to right)

Patient underwent Double Valve Replacement (DVR: mitral and tricuspid) six weeks after the neurosurgery. Large vegetations were noted on mitral and tricuspid valve [Table/Fig-8] and both valves were replaced with St Jude Medical Epic porcine bioprosthesis valves. Intra and postoperative periods were uneventful. He was given anticoagulation for one month postoperatively with target International Normalised Ratio (INR) of 2.5. Histopathological examination of the excised valve showed acute branching septate hyphae [Table/Fig-9]. Valve culture grew *Aspergillus flavus* which was sensitive to AmB, voriconazole, itraconazole and posaconazole. LipAmB was stopped three weeks after surgery due to suspected drug fever. He was discharged in a stable condition after one month of surgery. Intravenous voriconazole was given for six weeks from the date of surgery with regular monitoring of voriconazole trough levels. Follow-up TEE after two weeks did not show any vegetation.

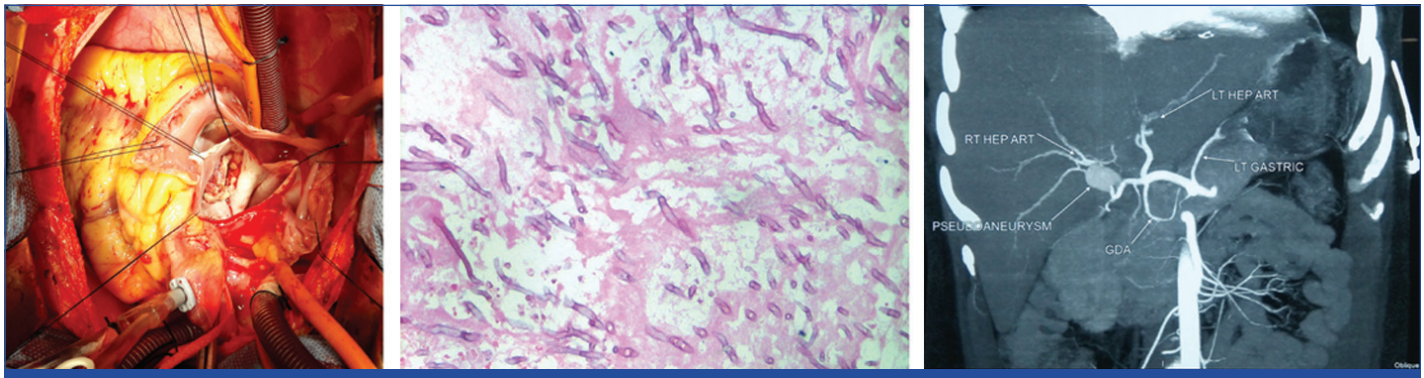
A day after he finished six weeks of intravenous voriconazole, he was admitted again in hypovolemic shock following complaints of melena of five days duration and haematemesis of two days duration. He was resuscitated with blood products. Ultrasound of the abdomen showed dilated proximal common bile duct with intrahepatic biliary radicular dilatation and splenomegaly. Voriconazole was withheld in view of deranged liver functions {Aspartate transaminase (AST) and Alanine Transaminase (ALT) of 180 and 230 IU/L respectively} and LipAmB was started again. CT angiogram of abdomen showed right hepatic artery leaking pseudoaneurysm with the aneurysmal extension into common bile duct [Table/Fig-10]. Coiling of the pseudoaneurysm was done. Haematemesis and melena stopped. He improved over 1 week and voriconazole was restarted as liver function were normalised (AST was 34 and ALT was 52 IU/L).

Whole body Positron Emission Tomography-Computed Tomography (PET/CT) scan was done, and it did not show any residual lesion in the brain or else where. Work up for primary immune deficiencies like flow cytometry for T cell markers, immunoglobulin profile and Nitroblue Tetrazolium Test (NBT) were negative. The patient is now nearly 4-year postvalve replacement surgery and is doing well on voriconazole suppression therapy of 200 mg 1 BD dose, which is planned to be continued lifelong.

DISCUSSION

Aspergillus species cause approximately 20-30% of all fungal endocarditis cases [1,2]. Of all aspergillus infective endocarditis cases, *A.flavus* contributes approximately 7% cases [2]. The various risk factors that have been described include underlying cardiac abnormalities, prosthetic valves, malignancy, solid-organ transplants, bone marrow transplants, steroid treatment, prolonged antibiotic exposure, haematological malignancy and chemotherapy and cytotoxic therapy [2,3].

The definitive diagnosis requires confirmation with histopathology and speciation from microbiological cultures. The treatment includes antifungal therapy with surgical debridement. Voriconazole is the preferred antifungal [4] and its superiority over amphotericin B has been shown in a large, randomised control trial. Aspergillus endocarditis is associated with 50-90% mortality [5].This case has been reported as this patient had two different pathologies with overlapping clinical features. Patient initially presented with seizures because of glioma and later found to have invasive fungal infection in form of endophthalmitis earlier and endocarditis later. He did not have any of the traditional risk factors for aspergillus endocarditis. Very few case reports of aspergillus endocarditis



[Table/Fig-8]: Intraoperative picture showing vegetations. **[Table/Fig-9]:** Histopathology of valve tissue stain showing acute branching septate hyphae (H&E) 40X Periodic Acid Schiff).
[Table/Fig-10]: Pseudoaneurysm of right hepatic artery. (Images from left to right)

have been reported in immunocompetent hosts. One case report was of a young immunocompetent female who presented with complaints of progressive dyspnea in shock she had extensive invasive aspergillosis with fulminant mediastinal involvement along with endocarditis. Like the index case, she also had red eye and painful visual loss due to aspergillusendophthalmitis. She succumbed to illness [6]. A similar case of a 65-year-old immunocompetent man presented with a three-month history of chest pain, dyspnoea and fatigue, found to have aortic regurgitation and a medium-sized sessile vegetation on the mitral valve, with mild mitral regurgitation underwent radical reconstruction of the aortic root, mitral valve replacement. Valvular tissue sent for culture grew *A. fumigatus*. He completed four weeks of dual antifungal therapy with intravenous voriconazole and amphotericin B and was discharged home on life-long oral voriconazole. Two months later he presented with dyspnoea on exertion and was found to have new dehiscence of the aortic valve from the previously placed patch and significant perivalvular aortic regurgitation and died three days later from cardiogenic shock [7]. In another report, 64-year-old lady who underwent aortic valve replacement for severe stenosis of a bicuspid aortic valve presents later with aortic root vegetation sparing the prosthetic valve. Aortic root was resected and replaced with an aortic homograft. Culture of the aortic root sample showed aspergillus. She was discharged well on long term voriconazole therapy [8]. A case series of fungal endophthalmitis in immunocompetent hosts following presumed contaminated intravenous infusion has been reported from India [9].

In the present case, the patient initially did not receive voriconazole (which is the drug of choice for aspergillus) probably due to deranged liver function (severe transaminitis) however he improved with liposome-encapsulated amphotericin B (Lip Am B). Patient and attendants were counselled by our team of doctors regarding the need of cardiac valve replacement for recurrent cardiac failure symptoms. Risk of cardiac arrhythmias and systemic embolisation of the vegetations during the surgery, intracerebral haemorrhage risk associated with post operation anticoagulation were all informed [10].

In the index patient, pseudoaneurysm of the right hepatic artery was attributed to mycotic aneurysm due to underlying aspergillus infection itself. This happened despite being on antifungal treatment for more than 12 weeks in total. This patient with good functional outcomes despite many life-threatening events. Despite the surgeries and antifungal treatment, the long-term course of the disease and outcome remains unclear [11].

CONCLUSION(S)

Aspergillus endocarditis, in an immunocompetent host without any risk factors for fungal infection is very rare. A high index of suspicion in culture negative endocarditis is necessary. Tissue histology and culture are required for confirmative diagnosis. Valve replacement combined with antifungal treatment is the optimal treatment approach. These patients usually require long term therapy with voriconazole.

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