ESC European Society of Cardiology

European Heart Journal - Case Reports (2023) **7**, 1–6
https://doi.org/10.1093/ehjcr/ytad218

**CASE REPORT**
*Valvular heart disease*

# Rare case of infective endocarditis from invasive aspergillosis encasing the pulmonary valve: a case report

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*Received 13 December 2022; first decision 20 February 2023; accepted 21 April 2023; online publish-ahead-of-print 24 April 2023*

**Background** *Aspergillus* endocarditis is a rare cause of infective endocarditis and requires high index of suspicion for diagnosis.

**Case summary** We describe a case of a 50-year-old man with history of metastatic thymoma on immunosuppression (gemcitabine and capecitabine) who presented with progressive dyspnoea. Echocardiography and computed tomography (CT) of chest showed filling defect in the pulmonary artery. The initial differential diagnosis was of pulmonary embolism and metastatic disease. The mass was subsequently excised, which revealed a diagnosis of *Aspergillus* endocarditis of the pulmonary valve. Unfortunately, he passed away despite medical treatment with antifungal therapy after surgery.

**Discussion** *Aspergillus* endocarditis should be suspected in immunosuppressed hosts with negative blood cultures and large vegetations on echocardiography. Diagnosis is made by tissue histology but may be difficult or delayed. Optimal treatment involves aggressive surgical debridement and prolonged antifungal therapy; prognosis is poor with high mortality.

**Keywords** *Aspergillus* • Endocarditis • Fungal endocarditis • Immunosuppression • Case report

**ESC Curriculum** 2.1 Imaging modalities • 2.2 Echocardiography • 4.11 Endocarditis

## Learning points

- To identify risk factors and clinical presentation of *Aspergillus* endocarditis
- To learn specific features to diagnose *Aspergillus* endocarditis, which include early index of suspicion in immunocompromised patients and use of non-invasive serum markers and tissue diagnosis in high-risk patients
- To understand the diagnostic testing and treatment approach of *Aspergillus* endocarditis

## Introduction

Infective endocarditis (IE) is a serious disease with incidence of 30 to 100 episodes per million patient years. Fungal endocarditis is thought to represent <10% of all cases of IE, with most of the cases due to *Candida* (50–80%) and *Aspergillus* (20–25%).[1–4] Although rare, fungal endocarditis is usually associated with high rates of morbidity and mortality, with higher rates for *Aspergillus* endocarditis.[5] Fungal endocarditis should be suspected as a possible cause of endocarditis in presence of a central line, long-term parenteral nutrition, and immunosuppressed states such as cancer patients, and prolonged use of steroids.[6]

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Handling Editor: Amir Khalifa
Peer-reviewers: Rita Pavasini; Julio Echarte
Compliance Editor: Pok-Tin Tang
Supplementary Material Editor: Elton Luo

## Timeline

| Day | Event |
|---|---|
| 17 years prior to presentation | Diagnosed with myasthenia gravis and mediastinal thymoma |
| | Underwent radical thymectomy with adjuvant mediastinal radiotherapy |
| 14 years prior to presentation | Recurrent metastatic lung lesions |
| | Underwent left lower lobectomy, pleurectomy, and resection and reconstruction of the diaphragm |
| | Post-operative pulmonary embolism |
| 3 years prior to presentation | Recurrent of metastatic thymoma on positron emission tomography (PET)/CT |
| | Treated with carboplatin, etoposide, pemetrexed, selinexor, and everolimus |
| | Started on eculizumab |
| Two months prior to presentation | Evaluated for worsening shortness of breath |
| | Computed tomography angiography (CTA) showed filling defect in main pulmonary artery (PA) and cancer progression |
| | Treated for pulmonary embolism with enoxaparin 80 mg twice a day |
| Two weeks prior to presentation | Admitted at outside hospital with dyspnoea and weakness, treated for pneumonia with antibiotics |
| Day 1 | Presents with progressive dyspnoea, fatigue and palpitations |
| Day 2 | CTA showed interval enlargement of large central filling defect in main pulmonary arteries |
| Day 3 | Echocardiogram showed echogenic mass in the main PA and right ventricle dysfunction |
| Day 4 | Multidisciplinary discussion, cardiothoracic surgery consulted |
| Day 6 | Excision of PA mass and pulmonary valve replacement. Veno-arterial extracorporeal membrane oxygenation (VA-ECMO) support required for cardiogenic shock. Post-operative bleeding and coagulopathy requiring multiple transfusions |
| Day 9 | Intraoperative cultures grow *Aspergillus tereus*, and amphotericin B treatment was initiated. |
| Day 11 | Progressive respiratory failure, bronchoscopy revealed mucus plugging |
| Day 13 | Ischaemic bowel and pneumoperitoneum |
| Day 15 | Underwent exploratory laparotomy for worsening pneumoperitoneum and shock, revealed a perforated rectal ulcer |
| Day 16 | Due to progressive multiorgan failure, transitioned to comfort care |

## Case presentation

A 50-year-old Caucasian man presented with progressive dyspnoea and palpitations for two days. He also complained of lower extremity swelling for a week and fatigue, anorexia, and weakness for two months. He denied fever, chills, and cough. Two months prior to his current presentation, he was evaluated for worsening shortness of breath. Chest computed tomography angiography (CTA) at that time showed a filling defect in the main pulmonary artery (*Figure 1*) which was thought to be pulmonary embolism (PE), as well as evidence of cancer progression with development of bilateral pulmonary metastases and left pleural metastases. Rivaroxaban was switched to enoxaparin 80 mg BID due to concern for rivaroxaban failure. Two weeks prior to current presentation, he had presented at an outside hospital with shortness of breath and weakness and was treated for presumed pneumonia with oral amoxicillin clavulanic acid. His symptoms got progressively worse, and he presented to the emergency room.

On admission, he had a temperature of 37°C, heart rate of 147 beats per minute, blood pressure of 115/80 mmHg, and respiratory rate of 22 breaths per minute. Examination was notable for uncomfortable appearance, tachypnoea, irregularly irregular rhythm, tachycardia, bilateral pitting oedema, and elevated jugular venous pressure of 12 cm water above right atrium. There was no murmur, cyanosis, clubbing, or peripheral stigmata of endocarditis.

The patient's past medical history was notable for a mediastinal thymoma diagnosed 17 years prior to presentation, which was detected during work-up of myasthenia gravis (please see Timeline for details). He continued to develop progressive metastatic disease and was treated with various chemotherapeutic agents (carboplatin, etoposide, pemetrexed, selinexor, and everolimus), most recently with gemcitabine and capecitabine. He was also being treated with eculizumab for myasthenia gravis, and he was on rivaroxaban for paroxysmal atrial fibrillation.

Differential diagnosis for the current presentation included evolving pulmonary embolism despite anticoagulation, further progression of metastatic disease or endocarditis. Laboratory investigation revealed white blood cell count 26.5 K/μL (neutrophils 85%) (normal 4–10.8 K/μL), haemoglobin 10.7 g/dL (normal 12.5–16.5 g/dL), platelets 162 K/μL (normal 145–400 K/μL), creatinine 1.32 mg/dL (normal 0.6–1.1 mg/dL), total bilirubin 3.3 mg/dL (normal 0.3–1.2 mg/dL), direct bilirubin 1.5 mg/dL (normal 0–0.3 mg/dL), aspartate transaminase 175 units/L (normal 0–33 units/L), alanine transaminase 45 units/L (normal 10–49 units/L), B-natriuretic peptide 1070 pg/mL (normal 0–99 pg/mL), and international normalized ratio of 1.3 (normal 0.8–1.2). Electrocardiogram showed atrial fibrillation with rapid ventricular response and right bundle branch block. Two sets of blood cultures were obtained at admission before administration of antibiotics. He was then treated empirically with intravenous cefepime while awaiting culture results, which were negative. Chest CTA showed interval enlargement of a large central filling defect within the main pulmonary artery (PA) in the expected region of the pulmonic valve, multiple focal opacities with peripheral distribution in the left upper lobe of the lung, patchy ground glass opacities in right lung, and small bilateral pleural effusions (*Figures 1* and *2*). The filling defect was thought to be atypical for PE given progression despite anticoagulation and location in the region of pulmonary valve, hence alternate imaging modality was sought. Transthoracic echocardiogram revealed an echogenic mass measuring 3.5 × 1.4 cm, extending from the right ventricular outflow tract (RVOT) into the main PA encasing the pulmonic valve, mild to moderately dilated right ventricle (RV) with moderate RV dysfunction, moderate to severe tricuspid regurgitation, and severely elevated RV systolic pressure due to RVOT obstruction (*Figure 3*, Supplementary material online, *Figure*, and Supplementary material online, *video*). The

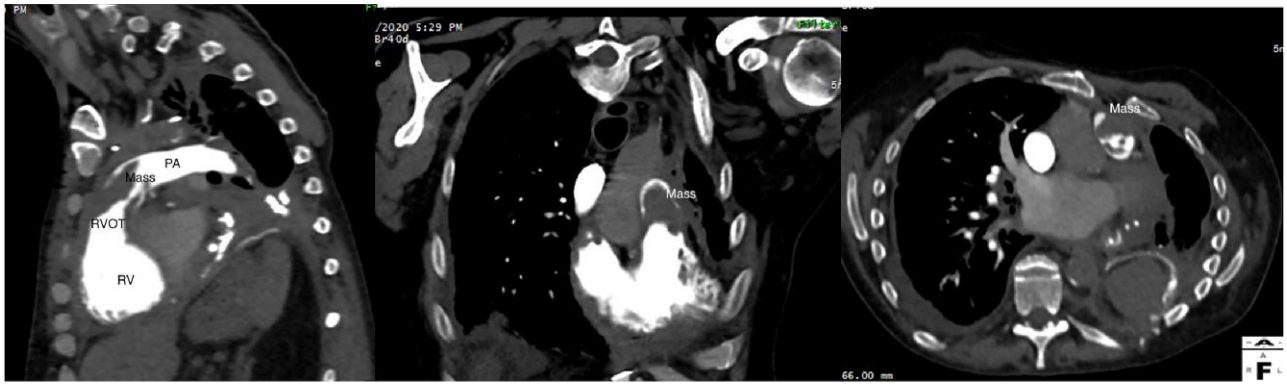


**Figure 1** Computed tomography angiography chest at presentation showed interval enlargement of the large central filling defect in the main pulmonary artery.

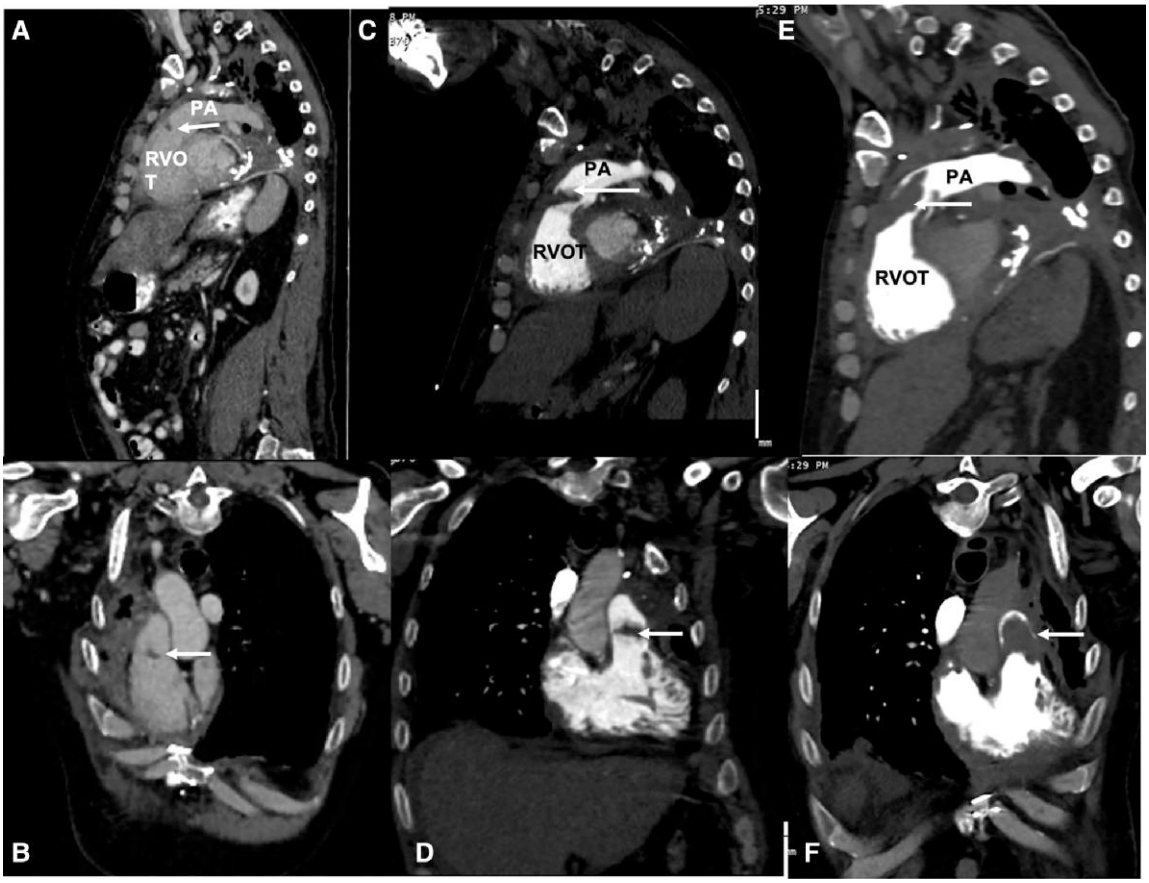


**Figure 2** Computed tomography angiography chest showing pulmonary mass at various timepoints—two months prior to presentation (*A* and *B*), two weeks prior to presentation (*C* and *D*), and at presentation (*E* and *F*).

patient was treated with enoxaparin 80 mg BID. Despite therapeutic anticoagulation, antibiotic administration, adequate rate control and diuresis, he remained dyspnoeic, and the pulmonary mass persisted. Due to high suspicion of malignancy and RVOT obstruction resulting in RV dilatation and dysfunction, he was referred for cardiac surgery, and he underwent excision of the pulmonary artery mass and pulmonary valve replacement with a 25 mm Magna Ease bioprosthetic valve (*Figure 4*). Due to persistent RV dysfunction, he required haemodynamic support

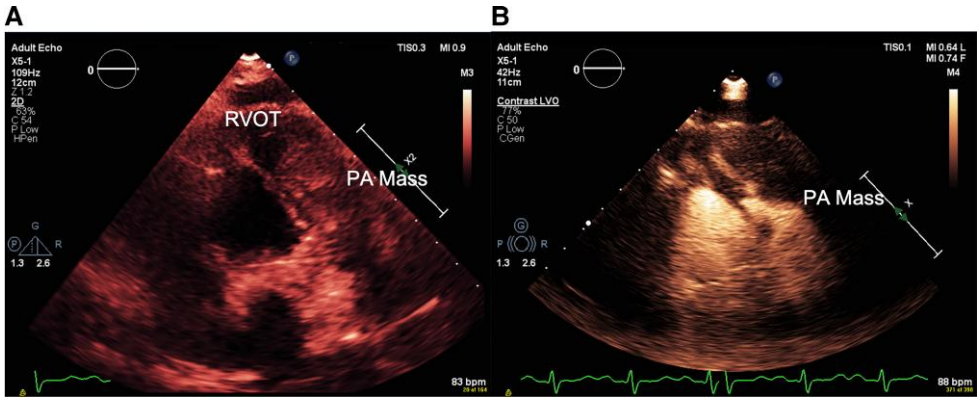


**Figure 3** Transthoracic echocardiogram showed a large echogenic mass in right ventricular outflow tract encasing pulmonary valve. (*A*) Without ultrasound enhancing agent; (*B*) with ultrasound enhancing agent. RVOT, right ventricular outflow tract.

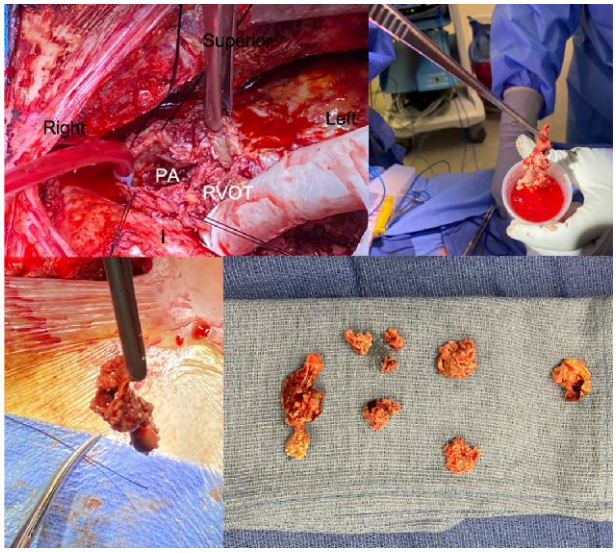


**Figure 4** Intraoperative findings. Pulmonary artery mass resected. PA, pulmonary artery.

with venoarterial extracorporeal membrane oxygenation post-operatively. His post-operative course was also complicated by severe coagulopathy and bleeding requiring multiple transfusions. Follow-up echocardiogram on post-operative Day 3 showed severe biventricular dysfunction. Intraoperative cultures of the mass grew *Aspergillus terreus*, and histologic evaluation revealed a fungal ball with fibrin and acute inflammation consistent with aspergillosis (*Figure 5*). He was treated with amphotericin B after the intraoperative cultures grew *Aspergillus* (Day 9 of presentation). Despite surgical and antifungal treatment, his hospital course was complicated by respiratory failure, renal failure, bowel ischaemia, perforation and pneumomediastinum, and lower extremity ischaemia. Unfortunately, he died from multisystem organ failure due to invasive *Aspergillus* infection. Sensitivity results were available after he died and showed that minimum inhibitory concentration (MIC) for amphotericin B was 4 μg/mL suggesting that the organism was not sensitive to amphotericin B (MIC > 2 μg/mL associated with treatment failure). The organism was sensitive to other antifungals like itraconazole, voriconazole, micafungin, and caspofungin (MIC < 0.06 μg/mL).

## Discussion

We describe a rare case of invasive *Aspergillus* endocarditis involving the pulmonary valve, which presented as a pulmonary artery mass mistaken as pulmonary embolism. Fungal endocarditis is rare, although recent studies have suggested a rise in incidence of fungal endocarditis. This is likely due to increase in number of invasive procedures, greater use of cardiac valves and devices, and prolonged used of intravenous catheters and broad-spectrum antibiotics.[2,7]

*Aspergillus* spores are ubiquitous in the environment, and illness due to exposure or infection can present in different forms after inhalation, largely influenced by immunity of the host. Allergic bronchopulmonary aspergillosis and chronic (non-invasive) pulmonary aspergillosis are more typical for immunocompetent patients, whereas invasive aspergillosis occurs in immunocompromised patients.[8] *Aspergillus* species are an important cause of life-threatening infection in immunocompromised patients, which includes patients with prolonged neutropenia, allogenic haematopoietic stem cell transplantation, solid organ transplant, inherited or acquired immunodeficiencies, corticosteroid use, and prior surgery (cardiac or non-cardiac).[6] Invasive aspergillosis, characterized by invasion of blood vessels with obstruction and haemorrhagic infarction, can cause severe invasive infections in almost any organ system, including the sinuses, lungs, heart, and central nervous system.[9] It most commonly involves the respiratory tract; endocarditis is rare, with mitral and aortic valves being the most involved valves in such cases.[3]

The diagnosis of *Aspergillus* endocarditis is difficult and often delayed, with diagnosis made post-mortem in up to one-third of cases as the disease lacks most of the clinical criteria used for diagnosis of IE. Blood cultures are almost always negative, and fever may be absent.[5] Fever, new cardiac murmur, clinical features of peripheral emboli such as new neurologic defects, heart failure, and dyspnoea are the most commonly seen clinical features, but are non-specific and do not help distinguish from bacterial endocarditis.[6] Vegetations secondary to *Aspergillus* species are often large and pedunculated; therefore, embolic complications are common, particularly to large arteries.[4] Definitive diagnosis is made by histologic demonstration of invasive hyphae or positive culture from a normally sterile

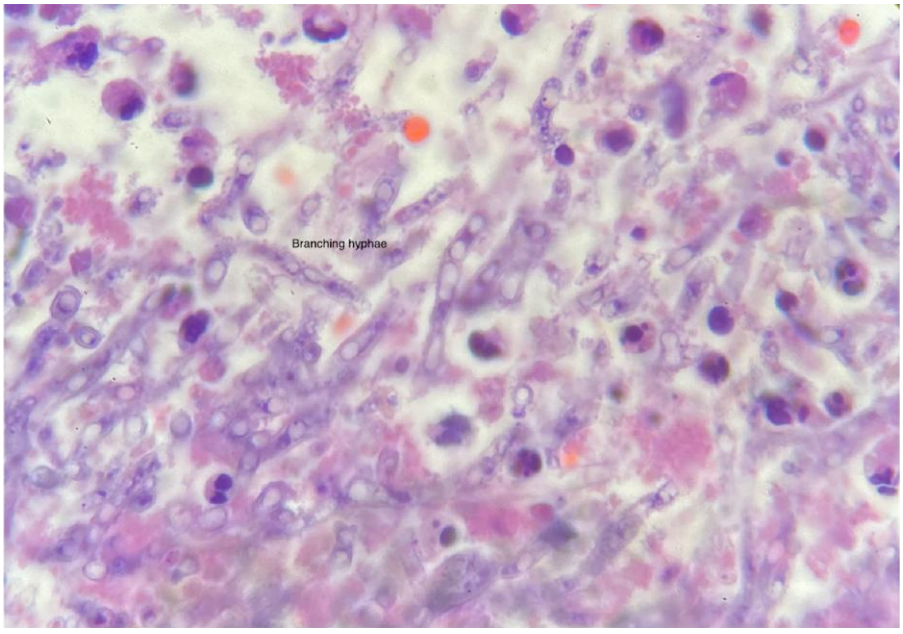


**Figure 5** Pathology from the mass in the pulmonary artery showed fungal elements at 400× magnification. PA, pulmonary artery.

environment.[8] Non-invasive serum markers such as galactomannan and (1→3)-β-D-glucan may be positive and are helpful in cases of IE with negative blood cultures. However, false positive results can occur and are not species specific.[6,9]

Unfortunately, there are no specific clinical features, imaging appearances, or biomarkers to differentiate fungal endocarditis from other differentials such as tumour or thrombus. Hence, high index of suspicion is required for diagnosis, which is made by histology. Some clues to the presence of fungal endocarditis may be endocarditis in an atypical location (such as pulmonary valve), large size of vegetation, increase in size of thrombus despite treatment with anticoagulation, and immunosuppressed state.

Treatment of *Aspergillus* endocarditis involves a combination of surgical debridement and antifungal therapy to prevent embolic complications and valvular decompensation.[6] The recommended antifungal therapy for invasive *Aspergillus* infections is voriconazole or liposomal amphotericin B.[6] Despite treatment, the prognosis of *Aspergillus* endocarditis is poor, with overall mortality rates of 50–90%, mean survival period of 11 days, and 32% survival rate from the acute episode; mortality rates are higher in patients treated with medical therapy alone.[3,10] Poor outcomes may be due to difficulty in diagnosis with lack of clinical and laboratory criteria, as well as the immunocompromised nature of the host.[10] Long duration of therapy (>2 years) with combined clinical and echocardiographic surveillance is recommended after surgical replacement of the infected valve, and lifelong antifungal therapy should be considered in such cases.[5]

## Conclusion

Invasive fungal infections of the heart are rare and difficult to differentiate from tumours and thrombus on imaging. A high index of suspicion is necessary in immunocompromised patients to diagnose and treat this frequently fatal condition.

## Lead author biography

Binaya Basyal is a cardiology fellow at Medstar Georgetown University, Washington Hospital Center. He graduated MBBS in Manipal College of Medical Sciences, Nepal. Whereafter, he completed his training in Internal Medicine at Medstar Washington Hospital Center. Binaya will pursue a career in cardiac electrophysiology.

## Supplementary material

Supplementary material is available at *European Heart Journal – Case Reports*.

**Slide sets:** A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

**Consent:** The authors confirm that the written consent for submission and publication of this case report, including images and associated text, has been obtained from the patient representative in line with COPE guidance.

**Conflict of interest:** None declared.

**Funding:** None.

### Data availability

The data underlying this article are available in the article and in its online Supplementary material.

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