Original Articles

Diagnostic Challenges in Native Valve Fungal Endocarditis Producing a Massive Septic Pulmonary Embolus

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Diagnosis and treatment of *Candida albicans* endocarditis can be difficult. We report a case of this rare condition in which a patient on oral fluconazole presented with septic pulmonary emboli without initial echocardiographic evidence of vegetation. Rapid attainment of a tissue diagnosis, along with combined medical surgical treatment proved to be effective for this patient.

Key words : *candida albicans*, infectious endocarditis, culture negative endocarditis, septic pulmonary emboli, micafungin

Introduction

Fungal endocarditis, especially of native valves, is rare, with *Candida albicans* being the causative organism in one-fourth of such cases¹⁾. As such, diagnosis can be difficult. Diagnosis is further complicated if a vegetation is not initially seen by echocardiogram or the patient presents with non-specific symptoms such as fever. Ultimately embolic phenomena may occur if not treated promptly enough. We report a case of massive septic pulmonary embolus in the right pulmonary artery caused by *Candida albicans* endocarditis of the tricuspid valve.

Case

An 18 year-old Nigerian female presented to the University Hospital Emergency Department with a 2 day history of fever, right-sided pleuritic chest pain, and progressive dyspnea.

Her past medical history was significant for a localized nasopharyngeal carcinoma which was treated successfully with chemotherapy and local radiation one year earlier. Eleven months prior to presentation she developed septic pulmonary emboli, and a blood culture

drawn from her Broviac catheter grew *Enterococcus faecalis* and *Candida albicans*. The Broviac catheter was removed and a transthoracic echocardiogram (TTE) demonstrated mild tricuspid regurgitation but was otherwise unremarkable. She was treated with ampicillin and gentamicin for the *Enterococcus* and oral fluconazole for the candidemia. Subsequent computed tomography (CT) scans demonstrated resolution of the septic pulmonary emboli; however, empiric daily fluconazole was continued as new focal consolidations were seen.

Two months prior to this admission, the patient developed acute left-sided pleuritic chest pain, and hypotension. Chest CT scan demonstrated a new consolidation of the left lobe with no evidence of pulmonary embolus on CT angiogram. Symptoms resolved over the course of 24 hours, and she continued fluconazole. The patient then flew to Europe for a two week vacation. Eleven days after returning to the US, she developed fever, chest pain and dyspnea. The patient presented two days later.

Initial physical examination revealed an uncomfortable patient with tachycardia, tachypnea, and a new cardiac murmur. Laboratory values demonstrated a WBC of 12,000/uL, BUN/creatinine of 17/1.47 mg/dL and an elevated D-dimer of 4.5 mg/L. A CT pulmonary angiogram revealed embolus in the right branch of the pulmonary artery and a new right hilar soft tissue

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Fig. 1. Computed tomography pulmonary angiogram showed a large filling defect (arrow) in the branch of the right pulmonary artery to the right lower lobe.

density (Fig. 1). The patient was started on a heparin drip for the pulmonary embolism, and empiric antibiotics.

New onset premature atrial contractions were identified and an echocardiogram revealed a small echodense protuberance at the tip of one of the tricuspid valve (TV) leaflets, thought to be a flailtip. There was also mildly increased tricuspid regurgitation compared to the previous echocardiogram. No deep venous thrombosis (DVT) was identified via upper and lower extremity ultrasonography. Fluconazole was changed to voriconazole for broader antifungal coverage; however, no improvement in dyspnea, O_2 requirement, or fever was noted. No infection was identified and all blood cultures were negative. On the hospital day four, core biopsies of the pulmonary embolus were obtained by femoral catheterization for a tissue diagnosis. Pathology revealed fibrinous necrotic tissue without evidence of organisms or hyphae, and a keratin stain to evaluate for recurrence of her nasopharyngeal carcinoma was negative. Cultures of the tissue, however, grew *Candida albicans*. Minimum Inhibitory Concentration (MIC) for fluconazole, amphotericin B, voriconazole, and micafungin for this isolate were < 0.125 $\mu\text{g}/\text{mL}$, 0.5 $\mu\text{g}/\text{mL}$, < 0.03 $\mu\text{g}/\text{mL}$, and < 0.015 $\mu\text{g}/\text{mL}$, respectively. Voriconazole was changed to micafungin to provide better fungicidal activity. Intravenous (IV) antibiotics were discontinued once the *Candida* was identified as all blood cultures were negative.

TTE performed one week after the initial echocardiogram demonstrated an increased size of the TV lesion. Transesophageal echocardiogram (TEE) confirmed the isolated TV lesion. Fungal vegetation on the TV was suspected; therefore, on hospital day 16 the patient had a resection of the TV lesion, valvuloplasty, and removal of the pulmonary artery embolus. Gross purulence was noted within the pulmonary artery when the embolus

Fig. 2. Histological examination of tissue from the excised tricuspid valve showed fungal infection. Pseudohyphae consistent with *Candida albicans* were seen under 400x magnification with Gomori methenamine silver stain.

was removed. No perihilar mass or other valvular lesions were identified at surgery. Samples from both the TV and the arterial embolus were submitted for pathology and culture. Histology of the excised portion of TV showed pseudohyphae (Fig. 2), and tissue cultures from both the TV lesion and the pulmonary embolus grew *Candida albicans*.

Postoperatively, the patient remained afebrile and her symptoms improved. Once the patient was medically stable, she was discharged home on IV micafungin 150mg daily for a four month course then changed to oral fluconazole. Now fourteen months after discharge, the patient continues to do well.

Discussion

This report illustrates an unusual case of native valve fungal endocarditis that developed in a patient with a history of candidemia following treatment for nasopharyngeal carcinoma one year earlier. In retrospect, this patient likely produced recurrent septic pulmonary emboli over an 11 month period despite being on antifungal therapy to which the isolate was susceptible.

Fungi cause less than 10% of cases of infective endocarditis, with native valve fungal endocarditis being even less common¹⁾. Approximately 24% of cases of fungal endocarditis are caused by *Candida albicans*. It is usually seen in patients with valvular disease, intravenous drug use, indwelling vascular lines, or immunocompromised states¹⁾. This patient had no drug history; however, she previously underwent chemotherapy for her nasopharyngeal carcinoma and had a central line. The patient had four of the six most common features of infective endocarditis: fever, new heart

murmur, major peripheral embolization, and dyspnea¹⁾. However, dyspnea and fever could be explained by a large pulmonary embolus resulting from a DVT. Furthermore, pulmonary embolism could also result from hypercoagulability following recurrence of nasopharyngeal carcinoma.

The inability to demonstrate any infectious organism from multiple blood cultures during her hospitalization delayed the diagnosis of infective endocarditis. The use of blood cultures during diagnosis is well established, with the first two sets of blood cultures being positive in over 90% of cases²⁾. However, blood cultures remain negative in 2.5–31% of all cases of infective endocarditis, and is more commonly seen in patients with prior antimicrobial treatment, right-sided endocarditis, fastidious organisms, or fungi such as *Candida albicans*^{2,3)}. Cases of culture negative endocarditis present a diagnostic challenge and may require alternative laboratory methods for diagnosis of a specific pathogen, including evaluation of histology after surgery, electron microscopy, serology, immunochemistry, or PCR-based molecular techniques⁴⁾.

Echocardiography is another crucial component in the diagnosis of infective endocarditis with its inclusion in the Modified Duke Criteria⁵⁾ and it is the best noninvasive method available to visualize cardiac vegetations, with sensitivity between 40–63% for TTE, and 90–100% for TEE⁶⁾. However, the initial TTE identified only mildly increased tricuspid regurgitation without clear cardiac vegetation. Therefore, we were unable to make an immediate diagnosis using either blood cultures or echocardiography.

Rapid diagnosis and initiation of treatment is paramount in infective endocarditis as patients who are febrile for more than one week after starting therapy can have a 50% mortality rate³⁾. The critical point in the diagnosis came with the decision to obtain a core biopsy of the pulmonary embolus, as there was no other clear source of infection. This unusual and aggressive approach allowed us to identify *Candida albicans* as the infectious agent. With this knowledge and the subtle change in the TV seen on echocardiography we suspected that the patient had infective endocarditis.

There are no randomized, prospective trials of medical therapy versus combined medical and surgical therapy for treatment of fungal endocarditis. However, the treatment recommendation for patients with *Candida* endocarditis based on the 2009 Infectious Diseases Society of America guidelines is valve replacement combined with antifungal therapy⁷⁾. Villaquiran et al. reported a patient with tricuspid *Candida albicans* endocarditis who was successfully treated with valve

sparing surgery following a large septic pulmonary embolus⁸⁾. Our patient underwent a similar valve sparing procedure which was well tolerated.

The current initial antifungal recommendation for the treatment of *Candida* endocarditis is amphotericin B with or without 5-flucytosine, or an echinocandin⁷⁾. Antifungal therapy should be continued for at least six weeks after valve replacement⁷⁾. Amphotericin B is a fungicidal medication that has historically been considered the “gold standard” for antifungal medication. However, it fails to penetrate well into fibrin clots and vegetations and has many side effects which can result in premature discontinuation⁹⁾. A recent meta-analysis for the treatment of invasive *Candida* infections showed similar efficacy and mortality between amphotericin B and caspofungin, and caspofungin had fewer side effects than amphotericin B¹⁰⁾. It also showed no difference in mortality, treatment failure, or adverse events between caspofungin and micafungin¹⁰⁾. We chose to treat this patient with IV micafungin because of its fungicidal activity and fewer side effects. The duration of the treatment was extended from 6 weeks to 4 months because the patient was known to be noncompliant with oral medications.

In conclusion, this patient illustrates a rare case of solitary native valve fungal endocarditis, which resulted in a large septic pulmonary embolus. Standard diagnostic techniques including blood cultures and echocardiogram did not yield a diagnosis. Femoral catheterization with tissue biopsy of the pulmonary embolus was the key to a successful diagnosis and treatment of this patient. More rapid and sensitive techniques are necessary to help identify patients with culture negative endocarditis as this condition is associated with significant morbidity and mortality⁴⁾. This case also illustrates a modified approach to the current treatment for infective endocarditis. In this patient, a valve sparing surgical procedure combined with a newer class of fungicidal medications, the echinocandins, was very successful for treating the fungal endocarditis.

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