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Use of the 1,3- β -D-Glucan Assay for the Early Detection of Fungal Endocarditis in a 45-Year-Old Man

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Conflict of interest: None declared

Patient: Male, 45-year-old
Final Diagnosis: Fungal endocarditis
Symptoms: Cough • fever • hemiplegia • malaise • shortness of breath
Medication: —
Clinical Procedure: Endarterectomy • valve replacement surgery
Specialty: Cardiology

Objective: Challenging differential diagnosis

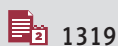
Background: The management of fungal endocarditis is difficult due to high mortality and incidence of embolization. Fungal blood cultures are the criterion standard for diagnosis but show slow growth or remain negative in more than 50% of cases. We present a case in which the 1,3- β -D-glucan (BG) assay was used to initiate antifungal treatment prior to growth in blood culture.

Case Report: A 45-year-old man with known intravenous drug use presented to the Emergency Department in acute hypoxic respiratory failure with a prominent aortic regurgitation murmur. Imaging findings were suggestive of endocarditis. In the Intensive Care Unit, investigations confirmed aortic valve infective endocarditis with abscess. Evidence of widespread embolization, including a shin abscess positive for *Candida albicans* combined with a positive BG assay prompted treatment with antifungal medication prior to positive fungal cultures. The patient underwent valve replacement and during recovery was incidentally found to have subclinical cerebral infarctions caused by a septic thrombus positive for *C. albicans* in the right carotid artery despite weeks of antifungal treatment. Carotid endarterectomy successfully removed the thrombus, but the patient developed a right-sided stroke. Four months later, the patient has no evidence of aortic insufficiency on echocardiogram and has made a nearly full recovery from the stroke.

Conclusions: We report a case of left-sided fungal endocarditis in which the BG assay was used for timely medical and surgical management leading to a successful cardiac outcome. Stroke from septic emboli is a potential complication even after weeks of antifungal therapy and valvular replacement.

MeSH Keywords: beta-Glucans • Early Diagnosis • Endocarditis • Stroke

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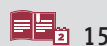
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Background

Fungal endocarditis (FE) is a rare cause of infective endocarditis, representing less than 2% of all cases [1]. Due to its high mortality rate, high incidence of embolism, and differing management from bacterial infective endocarditis, establishing the diagnosis of FE as early as possible is important. Differentiating FE from bacterial endocarditis can be a diagnostic challenge, with blood cultures often having no growth throughout the clinical course. We present a case in which the 1,3- β -D-glucan (BG) assay was used to initiate treatment prior to fungal blood cultures becoming positive, leading to a successful cardiac outcome; however, the patient encountered an unexpected late complication.

Case Report

A 45-year-old man with known intravenous drug use (IVDU) presented to our hospital with 1 week of fever, cough, and malaise. His symptoms had worsened over the previous 2 days with increasing shortness of breath.

On presentation to the Emergency Department, he was hypoxic with examination remarkable for a prominent aortic regurgitation murmur. A chest radiograph revealed pulmonary edema. A transthoracic echocardiogram confirmed a large aortic valvular vegetation involving predominantly the right and left coronary cusps, approximately 1×0.6 cm in size, and severe aortic regurgitation. Bacterial and fungal blood cultures were collected prior to the initiation of broad-spectrum antibiotics. He was intubated and admitted for presumed infective endocarditis with acute heart failure. Treatment with diuretics and afterload reduction improved his respiratory status allowing for extubation on day 2, but he remained febrile.

During the first week of admission, the patient was treated empirically for bacterial endocarditis with concurrent multifocal pneumonia. Transesophageal echocardiography revealed multiple mobile aortic valve vegetations extending from the right and left coronary cusps measuring 1.8×1.1 cm (Figure 1) and a newly found 0.9×2.5-cm valve ring abscess. An aortogram showed aortic root abscess along with evidence of septic pulmonary emboli and possible right coronary artery embolus (Figure 2). Liver and splenic infarcts were identified on computed tomography (CT) of the abdomen, showing widespread embolization. Blood cultures remained without growth. At the end of the first week of admission, a BG assay returned elevated to 135 pg/mL (normal <60 pg/mL) and a left shin abscess developed, with cultures growing *Candida albicans*. Intravenous caspofungin was started for presumed FE. On hospital day 10, a single blood culture acquired on the second day of hospital admission showed a positive result for *C. albicans*, confirming

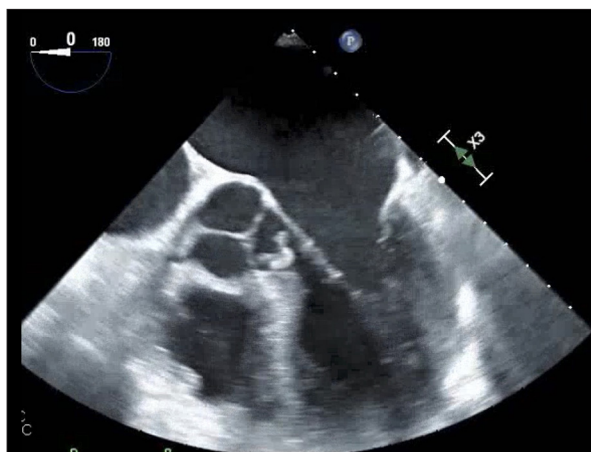


Figure 1. Transesophageal echocardiogram showing aortic valve vegetations seen in midesophageal short axis view.



Figure 2. Computed tomography aortogram showing likely right coronary artery septal embolus.

the diagnosis. A second BG assay collected prior to initiation of antifungal therapy returned elevated to 131 pg/mL (normal <60 pg/mL) as well.

The patient underwent aortic valve replacement with a 23-mm Inspiris pericardial valve, tricuspid valve repair with 28-mm triad ring, and repair of abscess cavity and aortic annulus with a bovine pericardial patch. During recovery, the patient developed right jaw pain. CT incidentally showed thrombus in the right carotid artery. Magnetic resonance (MR) angiography demonstrated 50% occlusion of the right internal carotid artery with thrombus likely infectious in origin. The external carotid artery was completely occluded. MR brain showed new subclinical right cerebral infarction. To reduce ongoing embolization, the patient underwent an open carotid endarterectomy. Thrombectomy resulted in the resumption of carotid flow; however, the patient showed signs of dense left hemiparesis postoperatively. CT angiography showed occlusion of the M2

segment of the right middle cerebral artery with corresponding infarction seen on MR brain (Figure 3). *Candida albicans* growth was confirmed in the thrombus culture.

At 4 months after admission, the patient was on suppressive oral fluconazole 800 mg once daily. He had no cardiac signs or symptoms, with no evidence of aortic valve dysfunction on echocardiogram. He has regained 4/5 strength in the left extremities.

Discussion

This report describes a case of FE with aortic valve abscess in a man with IVDU. A decision to initiate antifungal treatment was made prior to culture confirmation based on a combination of clinical findings and elevated BG.

FE is a rare cause of infective endocarditis, representing <2% of cases [1]. *Candida* and *Aspergillus* species are responsible for over 75% of cases. Mortality is especially high, at >50%, emphasizing the need for accurate and timely diagnosis [2]. In the IVDU population, right-sided bacterial endocarditis is the predominant subtype (95%), while FE is more common in immune-compromised hosts [3].

FE presents with subacute, systemic signs of infection with higher involvement of the aortic valve, and a 34% to 46% incidence of peripheral embolization [2,4,5]. Positive fungal blood cultures are the criterion standard method for definitive diagnosis of fungemia, but they can be challenging because fungal blood cultures are negative in over 50% of cases or slow to show growth as in our case [5–7]. Newer and quicker nonculture tests such as the BG quantitative assay can aid clinicians in early diagnosis and intervention [8]. The BG assay (Fungitell®) detects glucan, a protein in fungal cell walls. The BG assay is recommended for the diagnosis of invasive fungal infections, with a 90% sensitivity [8]. This assay can be positive far earlier than fungal blood culture, allowing early initiation of antifungal treatment [9]. Other tests such as mannan antigen or antibody are also available as an adjunct, but sensitivities are far lower [10]. In our case, a BG assay showed double the normal value on 2 occasions. Additionally, the patient had widespread dissemination of presumed *C. albicans* infection with embolization to heart, lung, liver, and spleen. Drainage of a skin abscess positive for *C. albicans* further suggested septic embolization. The constellation of findings along with a lack of clinical improvement on antibiotic therapy prompted the initiation of antifungal medication prior to a fungal culture positive for *C. albicans*.

The BG assay can be positive in certain situations such as hemodialysis with cellulose membranes, during the administration of specific antibiotics manufactured with glucan-like

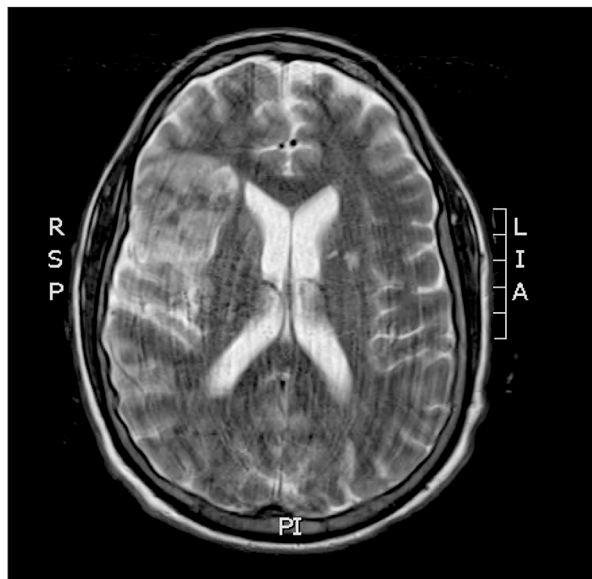


Figure 3. Magnetic resonance image of the brain showing right middle cerebral artery infarction on 2-week follow-up imaging.

components, or extensive exposure to glucan-containing materials (e.g., gauze) [8]. However, in invasive fungal infections, repeating the BG assay will show a persistent abnormal level. In our case, a repeat BG assay was again above normal at 131 pg/mL (normal <60 pg/mL) [9]. Along with a clinical course and risk factors suggestive of fungal infection, repeat measurements can raise the positive predictive value of the BG assay to 99% for 3 sequential positive samples.

Surgical intervention is nearly universally required, with a 44% reduction in mortality after valvular replacement and maintenance treatment with antifungal agents [11]. Early surgery has been shown to be beneficial, emphasizing the importance of early diagnosis [12]. Current guidelines recommend treating FE caused by *Candida* species with liposomal amphotericin B with or without flucytosine or a high-dose echinocandin (e.g., caspofungin) [1]. Due to a high rate of reoccurrence, sometimes years later, lifelong suppressive oral fluconazole is recommended [11]. This treatment was recommended to our patient.

Stroke occurs in about 20% of FE cases [2,13]. Left-sided infective endocarditis is associated with a higher risk of stroke, which is typically ischemic in nature and caused by septic emboli in a multifocal pattern [14]. Ninety percent of ischemic strokes are evident on admission or occur within the first 48 hours afterward [15]. Our patient was noted to have evidence of stroke in the fifth week of presentation with no prior evidence of stroke on examination or imaging. Treating endocarditis-related ischemic stroke with thrombolysis must be done with caution due to the high risk of hemorrhagic conversion [14]. Therefore, it was not done in our case.

Conclusions

We present a case of 45-year-old man with IVDU with several clinical findings suggestive of FE: aortic valve involvement and widespread embolization including culture-positive left shin abscess. An elevated BG assay prompted the initiation of antifungal treatment prior to a positive result from fungal

blood culture, demonstrating the utility of the test (especially when used in series) for earlier detection of FE. Surgical valvular replacement had a successful cardiac outcome, but the patient suffered an unusually late embolic stroke secondary to a *C. albicans*-positive thrombus. Embolic stroke should be viewed as a potential complication even weeks after initiation of antifungal therapy and valvular replacement.

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