Disseminated Aspergillosis and Pacemaker Endocarditis

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KRAMER, L., ET AL.: Disseminated aspergillosis and pacemaker endocarditis. Clinical and pathologic findings in a 65-year old woman with fever of unknown origin are described in this report. Generalized aspergillosis with endocarditis was demonstrated at autopsy. The patient had no recognized risk factors for the development of fungal infection. A functional transvenous pacemaker lead, inserted 2 years previously, was completely encased in a large infected thrombus and may have been the initial site of infection. Septicemia and endocarditis are rare but well-described complications of cardiac pacing, and should be considered in the differential diagnosis of fever of unknown origin in patients with pacemakers. (PACE, Vol. 8, March-April, 1985)

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Introduction

Implantation of a permanent transvenous pacemaker is a well-accepted procedure for the treatment of cardiac conduction disturbances and arrhythmias. Though uncommon, infection associated with these permanently indwelling intravascular prostheses may occur with little local evidence of inflammation. To our knowledge, this is the first reported case of endocarditis and disseminated infection due to Aspergillus species associated with a permanent transvenous pacemaker.

Case Report

A 65-year-old woman was admitted to the hospital complaining of fever of three weeks’ duration. She had been in excellent health all her life until the age of 63 years when syncopal episodes, due to sick sinus syndrome, prompted the implantation of a permanent transvenous pacemaker.

In June, 1983, she underwent elective repair of bilateral hammer toe deformity without complication, and was discharged after 3 days. That night the patient experienced fever to 39°C and shaking chills. Over the ensuing 3 weeks, dry cough was noted with recurrent fever. The patient received oral erythromycin for 10 days without response and was admitted for evaluation. Physical examination was unremarkable except for a fever of 39°C. Laboratory examination revealed a leukocytosis with polymorph predominance and an elevated serum lactic dehydrogenase level. The patient was treated with intravenous penicillin, gentamicin, and oxacillin. Multiple blood cultures were negative. Extensive serologic, radiologic, computerized tomography, ultrasonography, and radionuclide imaging examinations were unrevealing. An intermediate strength PPD was positive to 13 mm of induration. Left-sided cardiac ultrasound revealed no vegetations. A pulmonary ventilation and perfusion scan was interpreted as normal. Plain films of the feet and a bone scan did not suggest infection at the operative sites. Bone marrow biopsy was read as normal. Bronchoscopic biopsy revealed an acute inflammatory exudate without granulomata. Stains and culture for bacteria, fungi, and mycobacteria were negative. Fever persisted despite 2 weeks of antibiotic therapy and the patient was next treated with hydrocortisone, rifampin, isoniazid, and ethambutol.

The patient became confused. A lumbar...
puncture revealed normal cerebrospinal fluid. Computerized tomography of the head was normal. The patient's hemoglobin fell from 14 to 8 grams percent. Platelet count dropped to 16,000 per mm³, serum creatinin rose to 2.2 mg percent and bilirubin rose to 2.9 mg percent. Rapid atrial fibrillation and hypotension developed, and the chest x-ray revealed infiltrates in the right upper and left lower lobes. The patient responded to supportive measures, and antibiotic therapy with cefoxitin, amikacin, and tetracycline was added to the antituberculous medications. Despite this, the

Figure 1A. Gross transverse section halfway along vegetation surrounding pacemaker lead. (hematoxylin and eosin; × 12.5.)
patient continued to deteriorate and developed hypotension and acidosis. She died 6 weeks after hospitalization (9 weeks after the onset of fever).

**Postmortem Examination**

Autopsy showed generalized aspergillosis with involvement of the heart, lungs, liver, spleen, kidneys, and stomach. The end of the pacemaker lead was surrounded by a large (4 × 2.5 × 2 cm) infected thrombus (Fig. 1, A and B). This spread within the right heart and involved the inferior vena cava and the left hepatic vein, causing a focal Budd-Chiari syndrome with acute hepatic and gastrointestinal congestion. Additionally, there were

![Figure 1B. Microphotograph of free edge of vegetation in Figure 1 (Hematoxylin and eosin; ×550.)](image)
partially endothelialized infected mural thrombi in the right atrium and ventricle and in the left ventricle.

Immunodiffusion and counterimmunoelectrophoresis studies performed by the New York State Department of Health on blood obtained antemortem were diagnostic for aspergillosis (two and three bands of identity, respectively).

Discussion

The first known case of disseminated aspergillosis associated with a permanently implanted transvenous pacemaker is presented. Disseminated infection due to *Aspergillus* species is rare, and has been reported only in patients who have had compromise of some host defense system. It has been associated with patients receiving immunosuppressive therapy for malignancy or organ transplant, and in patients with multisystem failure receiving intensive cardiorespiratory support. The relationship between prior corticosteroid therapy and disseminated aspergillosis has been particularly striking. Reported cases of *Aspergillus* species endocarditis have been associated, almost invariably, with prior damage to heart valves, cardiac valvular surgery, and valve prostheses.

The difficulty in diagnosing this disease is illustrated by the fact that in the majority of cases reported, the diagnosis was made at necropsy. Clinical features are entirely nonspecific and include unremitting fever, leukocytosis, pulmonary infiltrates, hepatic dysfunction, and mental status changes.

Blood and urine cultures are rarely positive. Cultures from other sites have occasionally been helpful. Gurwith described five patients with pulmonary aspergillosis after cardiac transplantation. Four of these had *Aspergillus* grown from sputum culture. Only 12 of 34 cases of disseminated aspergillosis reviewed by Young had any cultures positive for the fungus antemortem.

Serology has also been used to aid in the diagnosis. Meyer reported that of six patients with hematologic malignancy in whom the diagnosis of invasive aspergillosis was made antemortem and who received antifungal therapy. Seven of 10 patients who developed precipitins to *Aspergillus* survived their infection, whereas only four of 19 patients with negative serology survived. It is suggested that patients who manifest a serologic response to their disease have a better outcome with therapy.

Infections involving permanently implanted endocardial pacemakers are uncommon; the reported frequency is less than 6% of all units implanted. When infection does occur, local signs are often present, as in 33 of the 46 patients reported by Choo, who had a generator pocket abscess at the time of presentation. Most patients had their infection more than 6 months after pacemaker implantation.

Septicemia and endocarditis have been associated with permanent cardiac pacing. Bluhm described 14 cases of septicemia and endocarditis in patients with permanent pacemakers, five of whom had signs of local infection at the time of diagnosis. The etiologic agents in the vast majority of pacemaker infections are staphylococcal species.

Pacemaker-related fungal infection is extremely rare. Disseminated *Petricillium boydii* infection and pacemaker endocarditis has been described in a 62-year-old woman on chronic high dose steroid therapy for mixed connective tissue disease. Tri-cuspid valve and pacemaker endocarditis due to *Candida* species, with spread to the myocardium, kidney, and lung of an elderly debilitated patient who received multiple courses of antibiotics was reported by Davis et al. In each of these patients, recognized risk factors for the development of invasive fungal disease were present. Each died without the diagnosis suspected antemortem, and at autopsy both had large fungal endocardial vegetations. In his study of permanent pacemaker infections, Choo lists two isolates of *Candida* species. However, the site of isolation (generator pocket, pacing electrode, or blood) is not specified.

It is unclear whether invasive aspergillosis was responsible for the entire 9-week course of this patient's fever of unknown origin, or if she acquired this lethal infection during the prolonged hospitalization. No other source of fever was identified. It can be argued that brief courses of anti-
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biotics, antituberculous medications, and steroids predisposed this patient to fungal infection. However, literature review suggests that these factors are not, in themselves, sufficient. In all likelihood the pacemaker lead itself was the necessary factor permitting infection with Aspergillus.

Infection associated with permanently indwelling intravascular prostheses, though uncommon, may occur with little local evidence of inflammation. In none of the three reported cases of fungal pacemaker endocarditis was infection of the pacemaker considered. It is clear from the autopsy in each case that bulky vegetations would have been easily detected by right heart echocardiography, and that, in conjunction with a compatible clinical syndrome and negative blood cultures, a diagnosis of fungal endocarditis would have been suggested.

Most importantly, despite a low incidence of serious infectious complications, the permanent indwelling transvenous cardiac pacemaker may serve as a nidus of infection that may remain cryptic and may be due to organisms not ordinarily considered pathogenic.

References