Aspergillus fumigatus pacemaker lead endocarditis: A case report and review of the literature

Roger Leong MD¹, Brian R Gannon MSc MD², Tim J Childs PhD MD FRCPC²,
Phillip A Isotalo MD FRCPC², Hoshier Abdollah MB ChB³

R Leong, BR Gannon, TJ Childs, PA Isotalo, H Abdollah.
Aspergillus fumigatus pacemaker lead endocarditis: A case report
and review of the literature. Can J Cardiol 2006;22(4):337-340.

The diagnosis of fungal endocarditis requires a high index of clinical suspicion. Rarely, pacemaker implantation may be a risk factor for the development of fungal endocarditis. A 71-year-old man with a history of multiple transvenous pacemaker manipulations and fever of an uncertain source is described. A diagnosis of culture-negative pacemaker endocarditis was established only after repeat transthoracic echocardiography. Amphotericin B was instituted; however, the patient developed a cerebral infarct and died. Postmortem examination demonstrated *Aspergillus fumigatus* within a large pacemaker lead thrombus, tricuspid and aortic valve vegetations, and septic pulmonary and renal emboli. The present report describes the clinical and pathological features of a rare case of *Aspergillus fumigatus* pacemaker lead endocarditis and suggests that serial echocardiograms may be effective in the early detection of pacemaker lead vegetations. The diagnostic features and therapeutic management of pacemaker lead endocarditis are reviewed.

Key Words: *Aspergillus fumigatus*; Echocardiography; Endocarditis; Fungus; Pacemaker

Fungal endocarditis is an uncommon complication of pacemaker implantation and is associated with high mortality rates (1). Survival is largely dependent on early diagnosis and treatment. However, late diagnosis is common due to the frequency of nonspecific clinical symptoms, negative blood cultures and delays in obtaining appropriate imaging studies. A high index of suspicion for fungal endocarditis should be maintained in individuals with implantable pacemakers and fever of an uncertain source, especially in the context of negative blood cultures. We report a patient with rare pacemaker lead endocarditis due to *Aspergillus fumigatus*, and review the diagnostic and treatment considerations.

CASE PRESENTATION

A 71-year-old man was admitted with a two-week history of chest pain and a one-week history of low-grade fever (less than 39°C). His medical history was significant for myocardial infarction, atrial fibrillation and asystolic arrest, leading to pacemaker insertion 23 years previously. Numerous pacemaker-related complications had led to five pacemaker revisions. Superior vena cava (SVC) syndrome, secondary to pacemaker lead fibrosis, was treated on two separate occasions with

Endocardite à *Aspergillus fumigatus* liée à une électrode de stimulateur cardiaque : Rapport de cas et revue de la littérature

Le diagnostic de l'endocardite fongique requiert un fort indice de suspicion clinique. Il est rare que l'implantation d'un stimulateur cardiaque constitue un facteur de risque à l'égard d'une endocardite fongique. On décrit ici le cas d'un homme de 71 ans ayant de multiples antécédents de manipulations transveineuses pour implantation de stimulateur cardiaque et présentant une pyrexie d'étiologie inconnue. Un diagnostic d'endocardite liée au stimulateur cardiaque négative à la culture a été posé, uniquement après la reprise de l'échocardiographie transthoracique. De l'amphotéricine B a été débutée, mais le patient a subi un infarctus cérébral et est décédé. À l'autopsie, la présence d'*Aspergillus fumigatus* a été confirmée dans un volumineux thrombus lié à une électrode de stimulateur cardiaque, dans des végétations des valvules tricuspidiennes et aortiques et des embolies septiques pulmonaires et rénales. Le présent rapport décrit les caractéristiques cliniques et pathologiques d'un cas rare d'endocardite à *Aspergillus fumigatus* impliquant une électrode de stimulateur cardiaque et propose la réalisation d'échocardiogrammes en série pour permettre le dépistage précoce et efficace des végétations affectant les électrodes des stimulateurs cardiaques. On passe en outre en revue les caractéristiques diagnostiques et le traitement de l'endocardite liée à une électrode de stimulateur cardiaque.

percutaneous catheter dilation and stenting, most recently performed four months before presentation. He was receiving chronic anticoagulation with warfarin, and antiplatelet therapy consisting of acetylsalicylic acid and clopidogrel. He had no history of being immunocompromised.

Physical examination revealed a temperature of 38.5°C. Chronic plethora due to longstanding SVC obstruction was observed. There were no cardiac murmurs or extra heart sounds. No stigmata of infectious endocarditis were observed. The remainder of the physical examination was unremarkable. Pertinent laboratory data included a hemoglobin count of 113 g/L, white blood cell count of $3.8 \times 10^9/L$, platelet count of $153 \times 10^9/L$, erythrocyte sedimentation rate of 102 mm/h, C-reactive protein concentration of 163 mg/L and international normalized ratio of 2.8. There was no biochemical or electrocardiographic evidence of myocardial infarction. Multiple blood cultures performed during the patient's six-week admission were negative and no antimicrobial therapy was initiated.

Transthoracic echocardiography (TTE) demonstrated normal left ventricular function, impaired diastolic function, estimated right ventricular systolic pressures of 48 mmHg and no

¹Department of Medicine; ²Department of Pathology and Molecular Medicine; ³Division of Cardiology, Department of Medicine, Kingston General Hospital and Queen's University, Kingston, Ontario

Correspondence: Dr Phillip A Isotalo, Department of Pathology and Molecular Medicine, Kingston General Hospital, 76 Stuart Street, Kingston, Ontario K7L 2V7. Telephone 613-549-6666 ext 4169, fax 613-548-6076, e-mail isotalo@cliff.path.queensu.ca

Received for publication October 29, 2004. Accepted June 1, 2005

Figure 1) A Transthoracic echocardiogram of the right atrium (RA), tricuspid valve (TV) and right ventricle (RV) demonstrating a pacemaker lead (P) and no valvular vegetations. **B** Second transthoracic echocardiogram of the right heart, seven weeks after the initial echocardiogram, demonstrating a right ventricular pacemaker lead thrombus (Th)

valvular vegetations (Figure 1A). A pulmonary angiogram revealed left posterobasal and right apical pulmonary artery aneurysms, and multiple, small bilateral pulmonary emboli. Computed tomography (CT) of the chest confirmed the pulmonary artery aneurysms. Mediastinal and paratracheal lymphadenopathy was also noted. The largest node was 1.5 cm, which was deemed too small to biopsy. The radiographic findings, persistently elevated erythrocyte sedimentation rate and C-reactive protein, and cyclical fever raised clinical suspicions of neoplasm and vasculitis. However, extensive investigations, including CT of the abdomen, bone marrow biopsy and temporal artery biopsy were all unremarkable. The patient's clinical condition improved during his six-week admission. His fever remitted the day following admission, returned for seven days 14 days later and was followed by no further fever for four weeks. He was discharged with no definitive diagnosis, although clinical suspicion of occult malignancy was high. Warfarin was continued for pulmonary emboli, and close follow-up, including chest CT, was arranged.

The patient was admitted one week after discharge with fatigue and dyspnea. Physical examination revealed an afebrile patient requiring supplemental oxygen. Again, there was no stigmata of endocarditis or new heart murmurs. Laboratory investigations revealed a hemoglobin count of 96 g/L, a white blood cell count of $6.7 \times 10^9/L$ and severe thrombocytopenia of $27 \times 10^9/L$. A TTE identified a 4 cm by 2 cm mass attached to a pacemaker electrode that was freely mobile between the right ventricle and right atrium and that was associated with tricuspid regurgitation (Figure 1B). No cardiac valve masses were demonstrated. Chest radiograph revealed a new right lower lobe pulmonary infarct. Surgery to remove the thrombus, pacemaker and SVC stent was delayed due to thrombocytopenia. Empirical antimicrobial therapy was initiated, and included gentamicin, vancomycin, rifampin and amphotericin B. Seven days after admission, the patient developed a large hemorrhagic cerebral infarct. Palliative therapy was instituted and the patient died the next day.

Postmortem examination revealed a large, 6 cm $\times$ 3 cm $\times$ 3 cm thrombus encasing the right ventricular pacemaker lead, with thrombus extending into the right atrium and SVC (Figure 2). There was contiguous and extensive involvement of an SVC stent by this thrombus. Large friable thrombi were identified on both the tricuspid and aortic valves. There was

Figure 2) Gross photograph of a heart depicting a 6 cm $\times$ 3 cm $\times$ 3 cm thrombus (long arrow) around the pacemaker lead (short arrow), extending from the right ventricle to the superior vena cava

no evidence of infection of the pacemaker pocket. Microscopy of the pacemaker lead thrombus demonstrated numerous septate and branched fungal hyphae (Figure 3), and postmortem thrombus cultures grew *Aspergillus fumigatus*. Fungal organisms were identified in tricuspid valve thrombi but were not observed in aortic valve thrombi. No other underlying cardiac valve pathology was identified; however, a patent foramen ovale was present. Infected pulmonary and left renal thromboemboli were identified, in association with tissue infarction. The brain demonstrated multiple hemorrhagic cerebral infarcts with no evidence of fungal invasion.

DISCUSSION

The present case describes a rare occurrence of pacemaker lead endocarditis due to *Aspergillus fumigatus*. Fungal organisms account for 1% to 10% of cases of infective endocarditis (1,2). A recent review of 152 cases of fungal endocarditis attributed 39 (25%) to molds and 28 (18%) to *Aspergillus* species (1). Endocarditis develops in approximately 10% of pacemaker implantations that are complicated by infection (3). Although bacterial infections with *Staphylococcus* species constitute the majority of reported pacemaker lead endocarditis cases (3-8), fungal etiologies comprise an important subgroup (6). To our

knowledge, there have only been two reported cases of *Aspergillus fumigatus* (9,10) and one case of *Aspergillus niger* pacemaker lead endocarditis (5). *Aspergillus fumigatus* infection of implantable cardioverter defibrillator leads has also been recently described (11).

Common risk factors for fungal endocarditis include anatomical cardiac abnormalities, cardiothoracic surgery, intravenous drug use, use of indwelling vascular catheters and other invasive monitoring devices, prior antibiotic therapy, prolonged hospitalization and decreased immunocompetence (1,12,13). Repeated surgical procedures on pacemaker systems are the single most important risk factor contributing to pacemaker lead endocarditis (14). Outbreaks of fungal endocarditis have been associated with defective hospital ventilation and air conditioning systems, bird droppings deposited near windows and air vents, and building renovations (2,15), illustrating the ubiquitous nature of fungi. The early diagnosis of fungal endocarditis is often elusive because blood cultures are commonly negative and classic physical findings are rare (13). Thus, unacceptably high mortality rates persist. Despite aggressive surgical and antimycotic therapy, the overall mortality rates for fungal endocarditis range from 50% to 94% (1,2,16,17). *Aspergillus* species endocarditis mortality rates are greater than 90%, regardless of treatment modality (1,10). There is also wide variation in the timing of the diagnosis of fungal endocarditis. The interval between cardiac valve replacement and onset of fungal infection in 54 cases has been reported to be between one day and 24 years (1).

The most common presentations of fungal endocarditis are fever, changing cardiac murmurs, heart failure, sepsis and systemic emboli (1,2,16). These findings are often inconsistent and rarely occur together. Blood cultures for *Aspergillus* species endocarditis have been reported to be positive in only 11% of cases, whereas *Candida* species-positive blood cultures range from 83% to 95% (16,17). Major emboli are present in approximately 68% of all fungal endocarditis cases and up to 83% of *Aspergillus* species cases (16,17). Culture of these peripheral emboli, when present, may be an effective method of establishing a diagnosis. Echocardiography has reported sensitivities of between 54% and 80% (2,3) in detecting fungal endocarditis. False-negative echocardiographic results may occur due to mural endocarditis, most frequently observed in immunocompromised patients and *Aspergillus* species infections (17). Transesophageal echocardiography (TEE) has superior sensitivity in detecting pacemaker lead vegetations, and a recent review (8) cites the sensitivity of TEE to be in excess of 90% when compared with TTE (less than 30%). These findings are largely due to the inability of TTE to adequately visualize the right atrium and SVC, and to resolve vegetations on reverberating pacer electrodes. The low sensitivity of TTE in comparison with TEE is a possible explanation for our patient's negative TTE at initial clinical presentation. Although rare cases of fungal endocarditis have been effectively treated with antimycotic therapy alone (17), combined medical therapy and surgical removal of infected valves and any accompanying hardware are the mainstay of treatment (7-8,16,17). Amphotericin B is the antimycotic of choice, with recommended total doses of 2 g to 3 g (50 mg/kg) (16,17). For pacemaker lead endocarditis, most authors advocate thoracotomy when vegetations exceed 1.0 cm in size because the risk of embolization is significantly increased with intravascular traction methods (8,18). Life-long antifungal prophylaxis has been advocated in numerous series, because

Figure 3) Gomori's methenamine silver stain of infected pacemaker lead thrombus, demonstrating numerous septate fungal hyphae morphologically resembling *Aspergillus* species (original magnification $\times 200$)

late recurrent fungal endocarditis is common (2); however, further evaluation of this approach is required.

We report a rare case of pacemaker lead endocarditis due to *Aspergillus fumigatus* infection. Diagnosis was delayed due to multiple negative blood cultures, and nonspecific clinical and laboratory findings. The most notable finding was the absence of vegetations on initial two-dimensional TTE and the subsequent identification of a large pacemaker lead thrombus by TTE seven weeks later. Because of the limits of TTE in visualizing right-sided masses, TEE is considered the imaging technique of choice if the clinical suspicion for pacemaker endocarditis is high.

CONCLUSIONS

Although pacemaker lead endocarditis is a rare complication of pacemaker implantation, a high index of clinical suspicion for endocarditis is required in individuals with transvenous pacemakers and fever of an undetermined origin. Suspicion of a fungal etiology must be considered when negative blood cultures are encountered. Early and serial echocardiography is vital for early diagnosis of pacemaker lead endocarditis. When feasible, TEE is the best method to detect vegetations on pacemaker leads and cardiac valves. Patients with fungal pacemaker lead endocarditis require aggressive surgical management, including explantation of all hardware, and appropriate antimycotic therapy.

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