Aspergillus Infection of Implantable Cardioverter-Defibrillator

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The use of pacemakers and implantable cardioverter-defibrillators (ICDs) continues to increase for the management of cardiac dysrhythmias and, more recently, heart failure.1-3 The implantation of artificial cardiac devices, however, is not without risk, and potentially fatal consequences may occur. Long-term complications associated with pacemaker and ICD therapy include infection, lead failure, and spurious shocks.1,4 The incidence of ICD and pacemaker infection ranges from 0.13% to 8.0%.2,4-7 Late-onset infections (>60 days after implantation) tend to be more indolent and variable in clinical presentation than earlier-onset infections.

REPORT OF A CASE

A 55-year-old man with a history of coronary artery disease was referred to our institution for evaluation of progressive pulmonary infiltrates and worsening anemia. He had been in good general health until 4 months previously, when he was diagnosed as having pneumonia. The illness occurred several weeks after he had cleaned out his “moldy” cabin. The lung infiltrates persisted, and the patient had intermittent fever, persistent fatigue, and a 9-kg weight loss during the subsequent 3 months. Several courses of broad-spectrum antibiotic therapy with azithromycin and levofloxacin provided minimal clinical or radiological improvement. One month before the current presentation, he underwent computed tomography (CT) of the chest that revealed bilateral infiltrates and cavitary lesions, some of which were peripheral. Pulmonary embolism was suspected, and anticoagulant therapy with heparin was begun, followed by warfarin therapy. The patient’s fatigue continued to worsen, and his cough became productive of brownish sputum with occasional flecks of blood.

During his 4-month illness, the patient had worsening anemia with no identifiable cause. Esophagogastroduodenoscopy and colonoscopy revealed no potential source of gastrointestinal bleeding. Bone marrow biopsy yielded findings consistent with anemia of chronic disease. The patient was admitted to our hospital for evaluation of recurrent fever, fatigue, worsening lung infiltrates, and anemia.

The patient’s medical history was remarkable for coronary artery disease, including myocardial infarction and percutaneous coronary stenting. An ICD had been placed for management of postinfarction arrhythmia 28 months before admission but had been turned off when improper sensing was noted and ICD therapy was no longer believed necessary. Tentative plans had been made for removal of the ICD. The patient had no history of malignancy or immunosuppression. He had discontinued using tobacco and alcohol at the time of his myocardial infarction.

On physical examination, the patient appeared fatigued but not acutely ill. His temperature was 37.1°C, blood pressure was 112/80 mm Hg, and pulse rate was 96/min. His lungs sounded clear. Cardiac examination revealed a grade 2/6 systolic murmur over the left sternal border but no peripheral signs of infective endocarditis. Laboratory
test results were as follows: hemoglobin level, 8.0 g/dL; leukocyte count, 14.7 × 10^9/L; and platelet count, 145 × 10^9/L. The erythrocyte sedimentation rate (ESR) was elevated at 84 mm/h, and the chemistry panel was notable only for a creatinine level of 1.6 mg/dL. Urinalysis revealed 1 to 3 erythrocytes per high-power field but otherwise normal findings. Antineutrophil cytoplasmic antibody assay yielded normal results. Chest radiography revealed patchy infiltrates involving both lungs, along with the ICD and pacer leads (Figure 1). Chest CT showed patchy nodular infiltrates throughout both lungs, many of which were cavitated (Figure 2). Transesophageal echocardiography revealed multiple large and small vegetations on both ICD leads (Figure 3, left) and possibly on the tricuspid valve leaflets (imaging was obscured by the ICD leads). The largest vegetation was 3.5 × 1.0 cm.

The patient underwent extraction of the ICD. Cultures from the ICD leads grew Aspergillus fumigatus, and amphotericin B liposome therapy was begun. Two days after removal of the device, repeated echocardiography revealed multiple masses on the atrial aspect of the tricuspid valve, the septal leaflet body, and the base of the posterior leaflet and moderate to severe tricuspid regurgitation (Figure 3, right). In addition, a 4.0 × 1.5-cm mass was attached to the free wall of the right atrium. The patient underwent concomitant tricuspid valve replacement (Figure 4), coronary artery bypass grafting, evacuation of vegetations from the wall of the right atrium, and right upper lobe surgical biopsy. Tissue from the tricuspid valve and atrial free wall grew A. fumigatus in culture. Examination of the lung biopsy tissue revealed chronic cavitary aspergillosis. However, multiple blood cultures obtained during hospitalization yielded no microbial growth.

The patient’s postoperative course was uncomplicated, and he was discharged from the hospital 13 days after surgery. Intravenous amphotericin B liposome therapy was initiated preoperatively and continued for 3 weeks after hospital dismissal until a total of 20 g had been administered, followed by initiation of itraconazole therapy. Fever recurred while the patient was taking itraconazole but resolved when it was replaced with voriconazole. Two months after hospital dismissal, transesophageal echocardiography showed no evidence of endocarditis, and CT of the chest revealed a marked decrease in the size and number of cavitary lesions.

DISCUSSION
With the ever-increasing use of intracardiac devices, clinicians are likely to encounter more patients experiencing complications related to the devices. Infectious complications, in particular, cause considerable morbidity and mortality. Although the association of infections with intracardiac devices is well known, their clinical presentations may vary and make diagnosis difficult.

In our patient, the onset of symptoms related to his ICD system infection was delayed, as has been noted in other reported cases of infective endocarditis related to intracardiac devices. For example, Cacoub et al reported 33 patients with pacemaker endocarditis in whom the average interval from first symptoms to diagnosis was 5 months. Furthermore, the mean interval from the last procedure to the diagnosis of endocarditis in their study was 20 months. Our patient’s initial episode of pneumonia 4 months before diagnosis likely represented septic pulmonary embolism of vegetations present in the right
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side of the heart. This episode occurred more than 2 years after placement of his ICD. This long interval caused the potential association of his illness with the intracardiac device to be overlooked despite persistent lung infiltrates and symptoms. Klug et al described clinical or radiological evidence of pulmonary involvement in 38% of their 52 patients with endocarditis related to an infected pacemaker lead. Thus, pulmonary manifestations are common among patients with endocarditis related to intracardiac devices.

Septic pulmonary embolisms typically produce abnormalities on chest radiography, but their appearance is not uniform; multiple bilateral cavitary nodules at the lung periphery are most typical. Characteristic CT findings are discrete nodules in various stages of cavitation with visible feeding vessels. However, multifocal cavitary lesions in the lung can also be associated with neoplasms, pulmonary infarctions, abscesses, vasculitides, congenital abnormalities, rheumatoid nodules, and pneumoconioses. Consequently, correlation with the clinical context is important to narrow the broad differential diagnosis. In our patient, the presence of a murmur directed further investigation toward a potential cardioembolic source and increased the likelihood of septic pulmonary embolism.

The presence of persistent anemia and an elevated ESR in our patient also served as markers for an inflammatory state related to underlying chronic infection. In patients with pacemaker-related mural endocarditis, anemia has

Figure 3. Transesophageal echocardiographic images. Left, Vegetations (arrows) attached to implantable cardioverter-defibrillator leads (arrowheads). Right, Vegetations attached to right atrial free wall (arrow 1) and tricuspid valve (arrow 2). LA = left atrium; RA = right atrium; RV = right ventricle.

Figure 4. Photomicrographs from resected tricuspid valve. Left, Valvular vegetation shows numerous fungi (Grocott methenamine silver, original magnification ×90). Right, Branching at 45° angles is typical for aspergillus (Grocott methenamine silver, original magnification ×540).
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been cited as one of the most frequently identified laboratory findings, in addition to elevated ESR, leukocytosis, and microscopic hematuria.5,13

Fungi are uncommon causes of infective endocarditis, and tricuspid valve involvement, as seen in our patient, accounts for less than 10% of such cases.14 The mortality rate for fungal endocarditis is high, ranging from 56% to 72%.14,15 Predisposing factors for fungal endocarditis include structural cardiac abnormalities, prosthetic cardiac devices, central venous catheters, prior antibiotic use, and immunocompromised conditions.14

Aspergillus species account for 20% to 30% of fungal endocarditis and are less common than Candida species as causative pathogens.14,15 Aspergillus endocarditis, most commonly involving A fumigatus, is a rare infection found most frequently in patients who have recently undergone open heart surgery or are immunocompromised, although its frequency is increasing.14,15 It is unclear whether the higher incidence is due to the increasing use of immunosuppressive therapy and intravascular devices or simply to better recognition with use of transesophageal echocardiography and improved culture techniques.16 The ubiquitous presence of Aspergillus species in the environment makes it difficult to avoid exposure.17 Our patient may have inhaled A fumigatus when cleaning out his moldy cabin.

Infections related to intracardiac devices should be treated with removal of the infected hardware and appropriate antimicrobial therapy.4,5,7,13 The latter aspect obviously requires identification of the offending microbial agent(s). One of the difficulties in diagnosing fungal endocarditis is the relatively low sensitivity of blood cultures,18 as demonstrated in our patient. Blood culture results are negative in nearly one half of patients with fungal endocarditis.15 In our patient, transesophageal echocardiography provided sound evidence of the presence of an infected intracardiac device.19 Transesophageal echocardiography is superior to thoracic echocardiography for detecting infective vegetations associated with transvenous pacemakers or ICDs because of its higher resolution. Reverberations and artifacts from pacemaker or ICD leads impair transthoracic echocardiographic visualization of vegetations attached to or near the leads.20,21 Culture and histological examination of vegetations yield a higher rate of mycological diagnosis and, in our case, confirmed the diagnosis of ICD-related aspergillus endocarditis.

CONCLUSIONS

With the increasing use of intracardiac devices, clinicians are likely to encounter more patients with infectious complications related to these devices. In a patient with symptoms suggestive of infection, especially in the setting of a chronic or worsening clinical course, all hardware should be subjected to rigorous evaluation for possible infection. Pulmonary and systemic manifestations resulting from infected intracardiac devices may have an insidious onset. In addition, the interval between implantation of the device and clinical manifestations related to device infections may be lengthy. Although results of blood cultures may be negative, currently available imaging techniques, including echocardiography and CT, usually yield valuable clues to an infectious process.

REFERENCES