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A Case of Late Implantable Cardiac Device Infection with *Aspergillus* in an Immunocompetent Host

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Patient: Female, 67
Final Diagnosis: Infected pacemaker device secondary to *Aspergillus fumigatus*
Symptoms: Swelling over the left pectoral region
Medication: Voriconazole
Clinical Procedure: Pacemaker explantation
Specialty: Cardiology

Objective: Unusual clinical course

Background: With the increasing use of cardiac implantable electronic devices (CIED), there has been an associated increase in rate of complications. Infection accounts for about 1% of these, of which only a handful were reported secondary to *Aspergillus fumigatus*. All of these were seen in chronically-ill patients with several co-morbid conditions within a few years of implantation. None have been reported in an otherwise immunocompetent patient at 7 years after CIED implantation.

Case Report: A 67-year-old woman with symptomatic sick sinus syndrome required a pacemaker 15 years ago with subsequent revision 7 years prior due to battery depletion. She now presented with a left pectoral non-tender mass that developed over several weeks. She denied history of recent fever, trauma, or infection. An elective pacemaker revision and pocket exploration led to the drainage of 150 cc of serosanguineous discharge from the pocket. She received peri-procedural prophylaxis with Vancomycin, but later, wound cultures grew *Aspergillus fumigatus*. She underwent complete removal of the pacemaker system along with a 6-week course of voriconazole and is doing well.

Conclusions: Even though *Staphylococcus aureus* causes most CIED infections, there should be a suspicion for fungal organisms, especially in culture-negative infections, in immunocompromised states like diabetes mellitus or with minimal improvement on antibiotics. If not treated appropriately, aspergillosis may have catastrophic outcomes, including endocarditis, often leading to death. Appropriate treatment should include immediate initiation of antifungals and removal of the CIED. It is still unclear why an immunocompetent patient developed aspergillosis, but appropriate management helped avoid a grave outcome.

MeSH Keywords: Aspergillosis • Cardiac Resynchronization Therapy Devices • Mycoses • Pacemaker, Artificial

Full-text PDF: http://www.amjcaserep.com/abstract/index/idArt/893413

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Background

Infections account for about 1% of the complications associated with the use of cardiovascular implantable electronic devices (CIED), in spite of aggressive precautions [1]. The most common organism implicated is *Staphylococcus aureus*, with 50% being MRSA (methicillin resistant *Staphylococcus aureus*) followed by *Escherichia coli* and *Staphylococcus epidermidis* [2]. Only about 2% of these are secondary to a fungal infection [3]. The majority of these latter cases were lead infections with a few complicated with endocarditis. Only 5 cases were reported who had a generator pocket infection [4–7]. Most commonly seen were the *Aspergillus* species with one case reporting Candida8, but all of them had chronic disease which could have caused the patient to be vulnerable to a fungal infection. We report a patient with immunocompetent status having a pacemaker pocket infection with Aspergillosis, after over 7-years post-implantation which was successfully treated with appropriate antifungals and removal of the entire pacing system.

Case Report

A 67-year-old woman had a history of hypertension, atrial tachycardia, and symptomatic sick sinus syndrome requiring a pacemaker insertion almost 16 years ago had subsequent uneventful revision 7 years ago due to battery repletion. She had presented in the out-patient setting about 6 months prior for swelling on the left side of the chest.

On examination, it was presumed to be a hematoma near the pacemaker pocket site. She had denied any trauma or injury. She had no fever, recent infection or any other signs suggestive of infection elsewhere. The site was non-tender and had no features suggestive of cellulitis. Conservative management with warm-compresses was started which helped decrease the swelling, only to have it recur again. Given the location of the presumed hematoma and the recurrence, there was a concern for fluid collection in the pacemaker pocket. As her pacemaker had reached ERI (elective replacement interval) due to battery depletion, she was scheduled for a pacemaker revision.

On admission, she had no complaints apart from the swelling. She was afebrile and her white blood cell count was also normal at 8300 cells/mcL. After the incision was done, there was drainage of about 150 cc of serosanguineous fluid from the pocket which was sent for laboratory analysis, including gram stain, culture and sensitivity and cytology. She underwent standard peri-operative antibiotics therapy with Vancomycin due to a history of penicillin sensitivity. Later, the pocket site fluid culture grew *Aspergillosis fumigatus*.

She has no history of diabetes mellitus, kidney disease, malignancies or HIV exposure. Infectious disease work-up including panculture (blood culture, urine culture and sputum cultures), HIV titers, hepatitis viral panel, chest X-ray and CT scan of the chest and abdomen were performed and they were within normal limits. In addition, she had an out-patient mammogram which showed no evidence for breast cancer. Social history and exposure history (inclusive of mold) was also reviewed to rule out any potential cause or source of the fungal infection.

She underwent extraction of the entire pacemaker system with debridement of the pocket, and completed six weeks course of anti-fungal therapy with Voriconazole and has been doing well. She underwent a right pectoral pacemaker implantation once she was cleared from her acute infection.

Discussion

With the increasing use of cardiovascular implantable electrophysiological devices (CIED) there has also been a rise in the rate of associated complications. Most commonly seen are bleeding, infections, lead dislodgement, pneumothorax, cardiac perforation, and, rarely, death. Infection rates are variable, but there has been an increase in the recent incidence of infections, ranging from 1% to 7% [1]. In a prospective study [8] of over 1008 patients undergoing CIEDs at our facility, only 1.4% patients developed wound-culture-positive superficial infection, with the rate of bacteremia and pocket infection of only 0.1%. Despite sterile precautions and the use of antibiotic prophylaxis at the time of device placement or revision, the rate of device-related infections may have increased, according to reports from several national databases [3,9]. It is hypothesized that the rise in infection rates could be due to the older and sicker population that required the implantation of cardiac devices.

Classifying

- Infections after device implant can be classified into early and late based on the time since the implant (within 60 days or beyond) [2].
- They can also be considered in two categories:

Pocket infections

Deeper infections – which include device-related endocarditis.

- Alternatively, device infections may be classified by the mode of infection:

Primary infections – when the source of infection is from the device due to contamination at the time of implant

Secondary infection – where the leads get infected due to bacteremia from a different source and can also progress to pocket or generator infection.

- Source of infection can be exogenous (from infected devices) or endogenous.

In support of endogenous acquisition, an association has been noted between the presence of preaxillary skin flora and the pathogens isolated from pacemaker infection. Therefore, aggressive peri-operative wound care has shown to reduce the incidence of infections in patients undergoing CIED implants.

Etiology

Early infections are most commonly caused by *Staphylococcus aureus* [2] of which methicillin-resistant *Staphylococcus aureus* (MRSA) would account for about half. Late infections are most commonly by Streptococcus5. *Corynebacterium* species, *Propionibacterium acnes*, Gram-negative bacilli including *Pseudomonas aeruginosa*, and *Candida* species account for a minority of CIED infections [2,4]. Fungi other than *Candida* and non-tuberculosis mycobacteria are rarely identified as pathogens in CIED infection with the incidence being less than 2% [3].

Aspergillus

Aspergillus fumigatus is a significant and potentially life-threatening fungus, seen especially in an immunocompromised host. It is particularly abundant in the air of buildings with deficient ventilation systems and near construction sites. It most commonly affects the respiratory tract, but other sites, including skin, have also been identified as portals of entry [4] and many times, the source of infection remains unknown [10].

Only a handful of cases have been reported with *Aspergillus* as the cause for CIED infections. One of the first cases reported was back in the 1980s and almost all of them in that era resulted in death with diagnosis being made post-mortem [5,11]. Commonly seen risk factors include immunosuppression, long term antibiotic or corticosteroid use, diabetes mellitus, heart failure or chronic kidney disease, prolonged hospitalization or cardiothoracic surgery [12].

The majority of these cases have been seen with lead infections and endocarditis often with tricuspid valve vegetations [4]. An article published in 2007 [6] reviewed 15 cases of *Aspergillus* associated pacemaker and ICD infections, of which only two had pocket infections. So far only four cases have been reported in association with pacemaker pocket infection and all of these occurred either acutely or sub-acutely.

Pincus et al. [4] described a 54-year-old man who developed an infection at the pacemaker site just within a few days of having multiple procedures/revisions of the pacemaker. Even though he had no systemic signs of infection, the pacemaker site looked visibly infected with cultures of the pocket and lead eventually growing *Aspergillus fumigatus*. He was effectively treated with voriconazole and linezolid. In contrast, Izquierdo et al. [7] described two patients who developed pocket infections secondary to *A. fumigatus* but almost 1.5 to 2 years after device manipulation. Like Pincus et al., their cases also had risk factors like diabetes, but eventually did well with surgical and medical treatment. Cobo et al. [6] reported a 74-year-old woman presenting with pocket infection, which was later found to be from *Aspergillus favus*. An Echocardiogram in addition showed vegetations in the cardiac leads. She also did well after removal of the pacemaker system and with anti-fungal therapy.

The four cases described above had multiple manipulations of the pacemaker device and also had chronic disease like diabetes, which rendered the patient vulnerable to fungal infection. In addition, the time since implant to presentation varied from a few weeks to two years. In contrast, our patient had no chronic disease, nor any malignancy. Extensive investigations were done to rule out any occult malignancy and even HIV was tested. There was no history suggestive of exposure to mold either. She was healthy and was immunocompetent, yet she developed *Aspergillus fungal* infection, that too almost seven years after pacemaker implant making the source of infection, the pacemaker generator, less likely.

If not diagnosed early and treated appropriately, fungal infections are associated with a high mortality because of lead involvement and thrombus formation. Pocket infections can be identified by cultures. But most often, they have a prolonged incubation period ranging anywhere from one day to two weeks. Diagnosing fungal endocarditis remains elusive because of negative blood cultures [13,14]. It has been reported that they are positive only in about 11% of cases [15], thus accounting for the high mortality. Once there is suspicion of *Aspergillus infection*, or when confirmed, immediate anti-fungal therapy should be initiated. As mentioned above, as it most often involves the leads and endocarditis, an echocardiogram is almost always recommended to evaluate the presence of lead and/or valve vegetations. Transthoracic echocardiograms may not be solely enough to identify the vegetations or thrombus so a transesophageal echocardiogram is suggested [13].

Treatment includes appropriate anti-fungal therapy, even before confirming the diagnosis with culture results. Anti-fungal agents like Amphotericin B, flucytosine and itraconazole have been used, but Voriconazole remains the first-choice [10]. Additionally, removal of the CIED system is strongly

recommended, because of the possibility of large intravascular vegetations, for which plain medical therapy may be insufficient [13]. The procedure must be performed with caution in patients who are dependent on the pacemaker or ICD as mortality can be high, but patients tend to do well.

Conclusions

Even though the most commonly seen pathogens for CIED infections are *Staphylococcus aureus* and *Streptococcus*, fungal infections, especially Aspergillosis, have been found to have occurred only acutely or sub-acutely. To the best of our knowledge, there have been no cases of *Aspergillus* infection reported beyond two years after device implantation or manipulation. In addition, fungal infections were only found to have occurred in patients with kidney disease, diabetes, or in an immunocompromised state. We report for the first time a CIED pocket infection by *Aspergillus* almost 7 years after device manipulation in a patient with no risk factors which is an unusual presentation of an unusual complication. So far, in a follow-up period of nine months, we have yet to find a reason why she developed a fungal infection, but she responded well to treatment and has been doing well.

We should be aware that *Aspergillus* can be found anywhere and can cause early or delayed infection, involving the CIED pocket, leads, or both. Although usually associated with an immunocompromised host, it should also be suspected in immunocompetent patients, especially when there is minimal improvement with conventional therapy alone.

Conflict of interest

The authors have no conflict of interest to report. There is no source of funding for this report.

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