Allergic reaction to pacemaker compounds: Case Reports

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Introduction

Allergic reaction to permanent pacemakers or other cardiac implantable electronic devices (CIED) is extremely rare and is usually dismissed confounding with an infectious process.\(^1\) The components of the CIED most frequently involved are titanium, nickel, and epoxy resin.\(^2\) A solution to this problem is the implantation of a new device covered in hypoallergenic material or one that does not contain the identified allergen. We report three cases of allergy to pacemaker components and final outcomes after implantation of covered generators: one with gold coating and the other two with a polytetrafluoroethylene (PTFE) membrane.

Case report

Patient 1

A 47-year-old man with a history of mechanical aortic valve implantation 26 years ago due to a double aortic injury was admitted to our hospital in February 2008 for symptomatic Mobitz type II second-degree atrioventricular (AV) block. An Axios D bicameral pacemaker (Biotronik Co, Berlin, Germany. Components of pacemaker: Titanium and epoxy resin) was implanted via right subclavian vein. Three weeks later, the patient developed erythema and local swelling around the surgical wound without purulent discharge, fever, or leukocytosis. Treatment was based on intravenous antibiotics and removal of the pacemaker and leads. After two weeks, an identical generator was placed on the contralateral side. After a couple of months, the pacemaker generator exteriorized. The same generator model was implanted on the sub-muscular plane. After a month and a half, a vesicle was developed on the implant zone which remitted after management with oral antibiotics, however, in March 2011 it was exteriorized once more. After completely removing the device, an epicardial bicameral
pacemaker (Vitatron T70 DR, Medtronic Inc., Minneapolis, MN, USA. Components of pacemaker: Titanium and polyurethane) was implanted, however, it was exteriorized after four months.

Skin tests were performed on all pacemaker components, including titanium, which reported negative at 72 hours. Biopsies of the lesions were also taken during the device removal procedure, showing giant Langerhans cells and chronic granulomatous inflammation due to foreign body (type IV reaction) (figure 1, panel A).

A new implant was successfully done in March 2012, an endocardial bicameral pacemaker (Medtronic Adapta DR PVV, 24 karat gold, 0.45 mm minimum coating thickness) (figure 2, panel A) in the left subclavian region. No complications reported after a 9-year follow-up.

Patient 2

A 33-year-old woman with congenitally corrected transposition of the great arteries was implanted with a bicameral pacemaker (St Jude, Regency™ model covered with parylene) in 2009 via right subclavian vein due to complete AV block. After 10 years, the patient had a generator replacement (Medtronic, Ensura DR MRI. Components of pacemaker: Titanium and polyurethane). After 5 months, the pacemaker generator exteriorized and an erythema appeared on the pocket zone, without clinical evidence of systemic inflammatory response. The device was removed and a new one (same model) was implanted on the left subclavian region, leaving the two original leads. A month later, the patient developed fever, redness at the pocket zone and exteriorization, a CT angiography was performed which revealed a wide interventricular communication. All four pacemaker leads migrated to different locations: one from the right subclavian crossed the interatrial septum and anchored to the morphologically right ventricle (located on the left), the second lead also from the right subclavian was in the right appendage; the other two leads migrated through the
brachiocephalic venous trunk, one to the right atrium and the other to the apex of the morphologically left ventricle (located on the right). The echocardiogram reported both ventricles with preserved systolic function, was opted for the complete extraction of the device. In December 2019, the four leads were extracted, and an external permanent pacemaker with active fixation lead placed via the right jugular vein.

Dermal tests of the pacemaker components were negative. The biopsy of the pocket lesions demonstrated chronic granulomatous inflammation and multinucleated giant cells (figure 1, panel B). After analyzing the results, it was decided to implant an epicardial pacemaker covered with an expanded polytetrafluoroethylene (ePTFE) bag (Gore-Tex cardiovascular patch) made by the surgery team (figure 2, panel B). No complications or symptoms reported after two years of follow-up.

**Patient 3**

A 17-year-old female, at 4 years of age (2008), an epicardial unicameral pacemaker (St Jude, Regency™ model covered with parylene) was implanted due to complete congenital AV block. In July 2018, the generator was changed by depletion and upgraded to a dual-chamber endocardial pacemaker (St Jude, Endurity Core™ Components of pacemaker: Titanium, epoxy resin and polysulfone) via left subclavian. Fifteen days post sutures removal she developed erythema around the pacemaker pocket and dehiscence of the surgical wound with exposure of the generator, white blood cell count was normal and no fever. The patient was treated with antibiotic regimen and wound care for a year and a half. In January 2020, the entire system was removed and treated with antibiotics to implant a new contralateral submuscular pacemaker (St Jude, Endurity Core™). One month later the system exteriorized, it was removed, and a different scheme of intravenous antibiotics was applied, a bicameral epicardial pacemaker (Biotronik, Effecta® DR. Components of
pacemaker: Titanium, epoxy resin and silicone) was implanted after completing 15 days of medication. Dehiscence of the surgical wound and a third exteriorization occurred. In May 2020, the device was removed and implanted a new pacemaker (same model as the previous one) via right subclavian. Fifteen days later, similar complications from previous implants were observed, erythema, dehiscence of the surgical wound and a fourth exteriorization.

The dermal tests concluded rejection to nickel, therefore in August 2020 the implantation of an epicardial pacemaker was chosen with the casing covered by a PTFE bag. The leads (The Greatbatch Medical Myopore® Bipolar Sutureless Myocardial Pacing Lead) were fixed in the right atrium and in the anterior face of the right ventricle. The bicameral generator used (Endurity Core St Jude) was wrapped in an ePTFE bag made by the surgical team. At a 10-month follow-up, the patient has remained with the surgical wound adequately healed with satisfactory outcomes. The pocket tissue biopsy reported findings consistent with the two previous cases (figure 1, panel C).

Discussion

As previously mentioned, allergy to any permanent pacemaker component is extremely rare.\(^1\) To our knowledge, this is the first series of cases published in the literature with medium and long-term follow-up.

The diagnostic approach is challenging, as it is commonly mistaken for an infection process, and this last complication is seen much more frequently in clinical practice.\(^2\) In a case-control study that included 2,417 patients who underwent CIED implantation over a 4-year period, Nery et al.\(^3\) reported an incidence of infection of 1%. While the incidence of allergy to some one specific component of the pacemaker still unkown.
The data in our case series are based on two centers with a high volume of device implants; since 2008 to date a total of 5,526 pacemakers have been implanted in both centers, resulting in an estimated incidence of allergic reaction of 0.05%.

The dermal signs that occur in infection and allergy to pacemakers are similar; in infection, erythema occurs in 41% and skin erosion in 21%. These signs are common in Titanium allergy or other CIED components and therefore making an accurate diagnosis is more difficult. In all three cases presented in this case reports, dermal lesions appeared, and the exteriorizations of the pacemaker generator occurred in the first weeks following the device implant.

The first case of allergy associated with pacemaker components was documented in 1970 by Raque et al. In this patient, silicone was the allergen reported by the tests performed. Since then, several cases have been reported, in 2002 Dery et al. analyzed 21 cases reported worldwide up to that time, 5 of them had presented allergies to nickel, 4 to titanium, 3 to epoxy and the other cases were related to cobalt, chromium, mercury, silicone, cadmium and parylene; however, in 6 patients the dermal tests were negative. The latter is not surprising, as dermal tests with titanium and other CIED components have low sensitivity and therefore can lead to false negative results.

In other words, the fact that these tests are negative does not exclude the possibility of allergic reaction to some CIED material. In the first two patients that we showed the dermal tests were reported with negative results and in the third case positive for nickel. It is worth mentioning that in case number 2 and 3 the allergic reaction occurred until the second implant. We consider that the device (St Jude, Regency™ model covered with parylene) used in both cases initially played a particularly important protective role.

The definitive treatment of this pathology is the removal of the allergenic material, but this is not possible in patients with an indication for a pacemaker. In some cases, partial resolution has been achieved with topical steroids, but their long-term use may have other
complications.\textsuperscript{5,9} To date in most of the case reports, the definitive treatment has been the implantation of a pacemaker generator covered with gold, silicone or PTFE manufactured during the procedure.\textsuperscript{1-2,6,8-14}

Of the cases we report here, the first one was implanted with a gold-covered pacemaker generator and the other two were wrapped in ePTFE; none of them have shown allergy data again during their follow-up. In our experience, the use of PTFE has provided an adequate alternative since it is a much more viable material and no allergic reactions have been reported despite its greater use in other surgical procedures.\textsuperscript{15} It is also much more difficult to get a device covered with gold since there is only one manufacturer in the world and silicone is a material with little use in surgeries today.

**Diagnostic criteria for allergic reaction to pacemaker**

We recommend the following strategy based on the literature and our case series (see Table 1): 1) The appearance of erythema or eczema over the pacemaker area accompanied by local inflammation but without evidence of systemic infection, 2) exteriorization of the device within the first 6 months post-implantation is highly suggestive 3) exteriorization repeatedly on two or more occasions 4) cultures of blood, pocket tissue, and of the device material are negative 5) the presence of multinucleated giant cells in the pacemaker pocket tissue biopsy 6) No recurrence of exteriorization after implantation of a generator covered with gold or PTFE.

**Conclusion**

There is a growing in the indications of CIED, which forces the clinician to be aware of complications; an unusual condition is allergy to the components of the device, that is
confirm when the dermal tests are positive, but when they are not, and strong clinical suspicion remain we suggest several data that support an allergic reaction to some component of the pacemaker. A good treatment option in our experience due to its greater availability is the implantation of the device wrapped in PTFE.

References


Figure 1. Pacemaker pocket tissue biopsy

Classic type IV reaction is shown, characterized by chronic granulomatous inflammation and Langerhans cells (yellow arrows). Pathology findings were consistent in the three reported cases (Panel A - Case 1, Panel B – Case 2 and Panel C – Case 3).

Figure 2. Pacemaker generators covered

Panel A shows the gold-coated pacemaker generator, implanted in the first case. Panel B shows the polytetrafluoroethylene (PTFE) wrapped generator used in the second case.
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
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<tbody>
<tr>
<td>Sex</td>
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<tr>
<td>Time to rejection</td>
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<td>Local erythema Local inflammation</td>
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<td>Peripheral blood and pocket tissue cultures ‡</td>
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Note: CHB: Complete Heart Block; ePTFE: expanded polytetrafluoroethylene.
▲ Involves only the first device related to the reaction.
† Included all components of the pacemaker.
□ No history of previous dermatological hypersensitivities.
‡ Include aerobic, anaerobic, and atypical microorganisms.
“Key Teaching Points”

- An allergic reaction to a pacemaker should be suspected after repeated exteriorizations without other evidence of a systemic inflammatory response.

- Type IV allergic reaction on tissue biopsy from the pacemaker pocket is the most characteristic finding of an allergic reaction to the pacemaker compounds.

- Covering the device with polytetrafluoroethylene, a widely available material, offers good results as treatment.