

Systemic Hypersensitivity Reaction (without Cutaneous Manifestations) to an Implantable Cardioverter-Defibrillator

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Implantable cardiac devices play a significant role in decreasing the morbidity and mortality in patients with cardiovascular disease. Tissue-device interactions leading to systemic hypersensitivity are rarely reported or are perhaps misdiagnosed as infectious in origin. We report the case of a 51-year-old female who underwent placement of an implantable cardiac defibrillator (ICD) and a biventricular pacemaker and who immediately postoperatively experienced sepsislike symptoms without any identifiable causative pathogens and without any dermatitis. Patch testing revealed an extreme reaction to cobalt confirmed as present in the defibrillator. Removal of the ICD led to the complete resolution of her symptoms. Patch testing helped guide the construction of a gold-coated ICD, which was implanted in the patient. The patient has remained symptom free after implantation of this gilded ICD.

SKIN INVOLVEMENT as a sign of an allergic reaction to an implantable cardiac defibrillator (ICD) or pacemaker typically manifests as localized erythema with dermatitis on or near the site of implantation. A review of the literature finds at least 30 reported cases of allergy to an ICD or pacemaker component manifesting with localized skin findings.¹ However, no case report has detailed noninfectious systemic reactions without skin findings to pacemaker or ICD components. Allergens reported as causing ICD-related dermatitis include titanium, silicone, cobalt, epoxy, polyurethane, and thiuram mix.¹ We report the case of a patient who developed a systemic sepsislike reaction without skin manifestations after the placement of an ICD and a biventricular pacemaker. Patch testing showed that the patient had a contact allergy to metals present in her ICD. She experienced a complete resolution of symptoms with the removal of the allergenic ICD and has remained symptom free after the placement of a new ICD containing none of her allergens.

Case Report

A 51-year-old female with a medical history of nonischemic cardiomyopathy developed heart failure symptoms, left

bundle branch block, and decreased ejection fraction, leading to the placement of an ICD with a biventricular pacemaker. Immediately after the defibrillator placement (and despite an improvement in energy level and breathing), she experienced pocket-site pain, which migrated to her left axilla. She then developed significant hypotension, malaise, nausea, and vomiting while hospitalized and became febrile on discharge. The patient continued to experience fevers, rigors, and hypotension and was readmitted for evaluation.

On re-admission, results of blood cultures taken repeatedly over a course of 3 weeks were negative. However, the patient was empirically started on an 8-week course of intravenous vancomycin (800 mg every 12 hours). A trans-esophageal echo revealed echo densities on the right lead, possibly due to thrombus formation without the exclusion of vegetative growth. She also developed a swollen left neck and a venous pattern on her left chest, consistent with obstructed flow in the left subclavian vein. The systemic sepsislike picture, coupled with echocardiographic findings, justified the explantation of the device. After the removal of the device, her symptoms resolved and there was complete cessation of chest pain, fever, nausea, and hypotension.

Results of laboratory examination (including culture of the explanted device) were negative and failed to elucidate any source of infection. Because of the lack of bacteriologic findings and her need for another ICD, patch testing was performed to see if any allergens in the ICD could have caused her symptoms. She had a history of scalp itching after using hair dye and had periodically developed eyelid and axillary dermatitis. She also had a history of rash associated with wearing costume jewelry.

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The patient was tested with a modified North American Contact Dermatitis Group (NACDG) standard series and with preservative, epoxy, isocyanate, rubber, and metal series (all allergens from Chemotechnique, Toronto, Ontario, Canada) based on the composition of the ICD and her allergic history. Allergens were placed on Finn Chambers (Epitest Ltd Oy, Tuusula, Finland) on Scanpor tape (Norgesplaster A/S, Vennesla, Norway). Readings were performed at 48 and 72 hours. Reactions were graded according to the NACDG grading system. At 72 hours, the patient showed the following positive reactions: +++ to cobalt chloride, + to nickel sulfate, + to palladium chloride, ++ to p-phenylenediamine, + to benzocaine, +++ to diaminodiphenylmethane (methylenedianiline [MDA]), + to toluene diisocyanate (TDI), + to balsam of Peru, + to fragrance mix I, + to chlorhexidine, and + to methylchloroisothiazolinone/methylisothiazolinone.

The manufacturer's ICD components were left in place for 1 week under occlusion, and patches were read 7 and 9 days after placement. At day 9, the patient showed questionable reactions (macular erythema only) to a titanium square, soft silicone adhesive, and medical-grade epoxy. The manufacturer would not confirm whether MDA, TDI, or any material cross-reacting with these compounds was present in the coating material of the ICD. However, the manufacturer did confirm that the pacemaker leads contained a "significant amount" of MP35N metal, a cobalt-chromium-molybdenum alloy. The company also disclosed that MP35N contained 35% nickel.

Our patch-test results guided the manufacturing (by another company) of a gold-coated pacemaker with leads composed of iridium and platinum. This second pacemaker has been tolerated by the patient without any complications.

Discussion

Contact sensitivity to an ICD presents a particular challenge to clinicians as the use of ICDs has evolved into first-line therapy and prophylaxis for cardiac arrhythmias such as ventricular tachycardia and ventricular fibrillation.² Although relatively rare, cutaneous reactions to implantable cardiac devices have been documented.^{3,4} A review of the literature found, in the past 35 years, no fewer than 30 reported cases of hypersensitivity to components of pacemakers leading to adverse reactions manifesting in the skin.^{1,4,5} The perceived rarity of pacemaker hypersensitivity reports in the literature may be due to misdiagnosis as infection.

Most such hypersensitivity reactions occur within 2 days to 2 years of implantation, but in all reported cases, the average onset is approximately several weeks to a few months after implantation.^{1,5} It has been suggested that the timing of an initial reaction could depend on prior sensitization. One report describes a hypersensitivity reaction to nickel in an ICD that occurred immediately after implantation in a patient with a history of nickel allergy.⁶ Hypersensitivity reactions to various ICD components (including titanium,^{1,7} polychloroparaxylene,⁸ epoxy resin,⁹ epoxy hardener,¹⁰ nickel,⁶ chromium, cobalt, mercury,^{11,12} and polyurethane¹³) have been documented in the literature. Cutaneous reactions generally manifest as well-circumscribed erythema, plaques, vesicles, bullae, and edema localized to the implantation site.⁵ However, generalized dermatitis (including pruritus), limited dermatitis at different sites, and nonallergic cutaneous findings (such as pressure dermatitis) have also been reported.^{1,3,5,14}

Diagnosing contact sensitivity to an ICD can be challenging because many patients are first suspected of having an infection, due to cutaneous involvement primarily at or near the site of implantation. However, when infection is ruled out by negative results of cultures of tissue, blood, and pacemaker components, pacemaker allergy should be considered a possibility. Mild cases are managed with topical corticosteroids to control local dermatitis. Cases that are more severe and prolonged are resolved by removing the device and implanting a device that is allergen free for the patient (as much as is technically possible).

This case illustrates the unique presentation of a patient with contact sensitivity to an ICD. Her symptoms appeared to be consistent with a sepsislike reaction (fever, rigors, hypotension, and nausea), favoring an infectious etiology. However, numerous blood cultures and skin swabs following implantation, as well as cultures taken from ICD components following explantation, remained negative. Furthermore, the removal of the ICD resulted in an immediate cessation of all symptoms. The lack of infectious organisms, the presence of proven contact allergens for the patient in the ICD, and the resolution of symptoms upon pacemaker explantation strongly suggest a diagnosis of pacemaker hypersensitivity.

The patient's patch tests revealed an extreme reaction to the metal cobalt and a weak reaction to nickel, both of which were present in the pacemaker leads. Additionally, she showed a strong reaction to the main hair dye sensitizer para-phenylenediamine (PPD), which can

cross-react with the aromatic epoxy hardener MDA. Theoretically, MDA could have been present in the medical-grade epoxy. TDI or cross-reacting chemicals also could theoretically have been present in the coating of the original ICD although the manufacturer refused to confirm this. The patient also reacted to benzocaine, which is structurally similar to PPD and MDA, thus confirming her allergy to para-amino compounds. Her history of pruritus of the scalp after using hair dye is consistent with her reaction to PPD.

The patient's contact allergens, some definitively proven to be present in the ICD and others possibly present in the ICD, could explain her symptoms after ICD placement. The systemic symptoms she experienced (fever, rigors, hypotension, and nausea) have not been detailed in other reports of ICD hypersensitivity. Mechanisms explaining this sepsislike reaction in the absence of overt infection could be attributed to endogenous pyrogen-activating factor (EPAF).^{15,16} Studies performed in both animal and human lymphocyte models have found a nonpyrogenic lymphokine responsible for stimulating the release of endogenous pyrogen from monocytes and macrophages while having no effect on neutrophils in delayed hypersensitivity reactions.^{17,18} Contact with an allergen or allergens in the patient's ICD could theoretically cause the continuous release of EPAF, leading to her symptoms. This hypothesis may be supported further by the cessation of symptoms upon ICD removal.

Conclusions

Hypersensitivity reactions should be considered in the differential diagnosis of patients with systemic symptoms such as fever, hypotension, and nausea after ICD implantation, even in the absence of skin manifestations.

Patch testing with manufacturer-supplied components and testing with allergen series based on ICD components and the patient's prior medical history should be carried out by those with expertise in the field. Implantation of future ICDs should be guided by patch-test results. It is important to highlight the challenges to physicians regarding the makeup of implanted devices from certain manufacturers who may be concerned about legal liability or divulging formulation secrets. Patients with known extreme hypersensitivity to metals may benefit from patch testing prior to ICD implantation. The value of patch testing as a preventive measure in patients with an unknown history of contact allergens remains unclear.

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