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Pericarditis Associated With Nickel Hypersensitivity to the Amplatzer Occluder Device: A Case Report

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A 38-year-old man with a history of migraine headaches with aura and one episode of ischemic stroke was found to have a patent foramen ovale (PFO). After percutaneous closure with the nickel-containing Amplatzer PFO occluder, the patient developed pericarditis, atrial fibrillation, and increased migraine headaches with aura that abated with oral prednisone. He tested positive for nickel hypersensitivity, which we conclude is the likely etiology of his pericarditis. © 2005 Wiley-Liss, Inc.

Key words: Amplatzer; patent foramen ovale; nickel hypersensitivity; pericarditis; migraine headache

INTRODUCTION

Several new devices are available that permit percutaneous closure of patent foramen ovale (PFO) or secundum atrial septal defects (ASD). These devices have been extremely well tolerated, with an estimated worldwide experience of close to 40,000 cases with the Amplatzer devices and 15,000 cases with the CardioSEAL/STARFlex devices. Components of these devices consist of metal alloys that contain nickel. The incidence of dermal sensitivity to nickel is approximately 15% of the population [1], yet the incidence of adverse events with these devices that has been attributed to nickel allergy remains extremely small. The companies that make these devices are not aware of any reports of adverse events in patients who are allergic to nickel.

This report documents a presumed type IV hypersensitivity reaction to an Amplatzer PFO occluder device and discusses the implications for closure devices.

CASE REPORT

A 38-year-old man with migraine headaches with aura since the age of 22 developed a 6-hr episode of severe headache associated with right-sided visual loss and paraphasic speech. A brain MRI study demonstrated a small ischemic stroke in the left middle cerebral artery distribution. A hypercoagulability workup revealed antibodies for cardiolipin and β2 glycoprotein I. He was found to have a PFO during a transesophageal echocardiogram (TEE). Paradoxical embolism through the PFO was thought to be the etiology of the stroke. A 35 mm Amplatzer PFO occluder device was inserted percutaneously without complications.

Several days after the procedure, the patient complained of intermittent episodes of substernal chest pressure and tingling sensation in the left arm. The pain progressed to severe left scapular discomfort that was exacerbated with inspiration or movement. The quality of his migraines also changed postclosure: the headaches were more frequent and he had more visual auras without headache. On ECG, there was J-point elevation, which was unchanged from the electrocardiogram prior to the procedure. There was no audible rub. He had no history of allergies. A computed tomography angiogram revealed no pulmonary embolism but did show a small pericardial effusion. A repeat TEE showed no erosion or positional change of the device and confirmed the small pericardial effusion. There were two episodes of atrial fibrillation, which responded to β-blocker therapy. An MRI did not reveal any new lesions indicative of stroke. The patient was begun on prednisone 40 mg/day for a clinical diagnosis of pericarditis. Allergy patch testing showed a 2+ reaction to nickel (erythema,

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infiltration, papules, and vesicles [2]) consistent with a type IV hypersensitivity reaction to nickel. The chest discomfort improved over a 3-week period while on prednisone. Follow-up TEE 3 weeks and transthoracic echo 2 months after the procedure showed resolution of the pericardial effusion and a stable position of the device without thrombus or interatrial shunt.

DISCUSSION

The Amplatzer PFO occluder device consists of nitinol wire mesh shaped into two round disks connected by a short waist. Nitinol (an acronym for "nickel titanium naval ordnance laboratory") is a metallic alloy composed of 55% nickel and 45% titanium, giving it superb elasticity and shape memory. Since 15% of the population demonstrates skin sensitivity to nickel, the issue of biocompatibility of nitinol implants is pertinent and controversial. An orthopedic study analyzed in vitro nickel leakage and found undetectable release of nickel after 10 days [3]. In contrast, cardiac devices are exposed to the bloodstream and are more likely to release nickel systemically. Ries et al. [4] analyzed the release of nickel after implantation of Amplatzer occluders. They found that serum levels rose to a mean peak of 1.50 ng/mL at 1 month after implantation from a mean baseline level of 0.47 ng/mL. None of the 67 patients followed by Ries et al. [4] had a history of nickel sensitivity, nor did any demonstrate it after implantation. At 12 months, nickel serum levels fell to preimplantation levels.

A PubMed search revealed no previously reported hypersensitivity reactions to the Amplatzer device. There is one report of a woman who reacted to a nitinol-containing PFO occluder (PFO-Star; Cardia, Burnsville, MN) [5]. Two months after deployment of the device, she experienced dyspnea, high-grade fever, and dependent edema. Skin patch testing demonstrated hypersensitivity for nickel. Her symptoms persisted until the device was explanted 4 months after transcatheter closure. Other reports of nitinol allergy include an 11-year-old boy allergic to a HELEX Septal Occluder (W.L. Gore, Flagstaff, AZ) and sternal stainless steel wires [6] and patients allergic to orthodontic appliances [7,8]. In addition, a patient developed a generalized eczematous dermatitis consistent with a systemic nickel hypersensitivity reaction following placement of an endovascular stent graft for abdominal aortic aneurysm (AAA) [9]. Stainless steel coronary artery stents contain 2–3% nickel and in-stent restenosis has been associated with patients who demonstrate skin sensitivity to nickel [10].

Our patient had a localized pericardial reaction and did not demonstrate any systemic allergic phenomena. Certain processes may prevent nickel release and minimize the risk of an allergic response. After immersion of a nickel-titanium alloy in physiologic Hank's solution, X-ray photoelectron spectroscopy showed a titanium oxide coating with minimal amounts of nickel in the outermost surface layers while scanning electron microscopy showed growth of a calcium-phosphate layer with varying thickness on the surface [3]. Either of these chemical processes plus endothelization may prevent systemic exposure to nickel. If the occluder is eventually surrounded by fibrous tissue and not exposed to inflammatory cells, then the hypersensitivity reaction may eventually cease. Explantation should only be necessary for fulminant hypersensitivity reactions that are unresponsive to steroid therapy.

Definitive proof of a type IV hypersensitivity reaction requires a biopsy of the affected tissue to demonstrate effector T-cells and macrophages. Nickel allergies are typically type IV hypersensitivity reactions via skin contact [11]. The delayed-type hypersensitivity that nickel elicits is mediated by antigen-specific effector T_H1 cells [11]. It is thought that divalent cations such as nickel alter the conformation or the peptide binding of MHC class II molecules and thus provoke a T-cell response. Upon subsequent reexposure, the T_H1 cell recognizes the antigen and releases cytokines, which act on vascular endothelium, activating local endothelial cells. This activation results in an inflammatory cell infiltrate of macrophages predominantly, causing fluid and protein to accumulate. Wataha et al. [12] were able to show that nitinol caused a significant secretion of interleukin-1β (IL-1β) from monocytes. The levels of IL-1β were enough to induce intercellular adhesion molecules (specifically ICAM-1) from vascular endothelial cells. Adhesion molecules then recruit macrophages and other inflammatory cells. Treatment options include topical corticosteroids or tacrolimus for patients with contact dermatitis [13–16] and oral administration of prednisone for systemic allergic reactions.

Although it is impossible to prove without a biopsy, our patient's symptoms are consistent with a type IV hypersensitivity reaction to the nickel component in the Amplatzer PFO occlusion device. The symptoms of pericarditis, atrial fibrillation, and increase in migraine headaches with visual aura abated with corticosteroid administration. We did not know if the size of the implant had any effect on these adverse events. A 35 mm device was chosen because of the length of the PFO and an associated atrial septal aneurysm. If symptoms persist, surgical explantation of the device should be considered. Patients with similar symptoms who have undergone an Amplatzer or other nitinol device implantation should be tested for possible nickel hypersensitivity. Although the risk of a significant allergic reaction to nickel in these devices is extremely small ($\sim$ 1 in 17,000), this case underscores the potential risks asso-

ciated with inserting a permanent cardiac device. Awareness of this potential problem may increase the reports of this occurrence so that patients and physicians may have an improved understanding of the risk associated with implantation of these devices in patients who are sensitive to nickel.

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