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Nickel hypersensitivity reaction following Amplatzer atrial septal defect occluder device deployment successfully treated by explantation of the device

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Trans-catheter atrial septal defect (ASD) or patent foramen ovale (PFO) closure is an established, safe and effective procedure. Most ASD and PFO occlusion devices contain nitinol, an alloy consisting of nickel and titanium. Systemic hypersensitivity reactions to nickel-containing ASD or PFO closure devices have been documented in patients with confirmed cutaneous nickel allergy, but are uncommon. In most reported cases, symptoms have abated spontaneously or in response to medical therapy. In some circumstances, however, device explantation has been necessary, with invariable resolution of symptoms.

A 41 year old lady with a secundum ASD with left-to-right shunt and associated right ventricular dilatation underwent trans-catheter ASD occlusion with a 14 mm Amplatzer occluder device (AGA Medical Corporation, Golden Valley, MN, USA) in July 2012. She had a background of a pituitary prolactin-secreting tumor treated with cabergoline, migraine syndrome, and thoracic spine scoliosis. Immediately postoperatively, she developed transient, mild right hand weakness and paresthesiae with depressed brachial reflexes. Magnetic resonance imaging (MRI) of the brain and the spinal cord did not reveal any abnormality to account for these symptoms, and the paresthesiae and weakness resolved spontaneously within two weeks. In the weeks to months following the procedure, she developed increasingly frequent, and increasingly severe, migraine headaches, sometimes

associated with aura, with inconsistent response to medical therapy, including botulinum toxin injection. In addition, she developed recurrent retrosternal chest discomfort described as sharp, occurring daily, lasting up to 10 min, without precipitant or aggravating or relieving factors, and without tenderness on palpation of the chest wall. Transthoracic and transesophageal echocardiography, invasive coronary angiography, computed tomography (CT) pulmonary angiogram, CT of the chest, abdomen and pelvis, and technetium-99m radionuclide bone scan failed to identify a cause of her symptoms. A systemic hypersensitivity reaction to the implanted device was suspected. Epicutaneous patch allergy testing was strongly positive to nickel on repeated testing (3+, on a scale of 1+ to 3+, where 1+ is a weak positive reaction, and 3+ is an extreme positive reaction), thus confirming definite nickel allergy. Her symptoms did not abate after a trial of oral corticosteroids and clopidogrel. The patient was adamant she wanted to have her ASD closure device removed. She underwent minimally invasive extraction of the Amplatzer device under cardiopulmonary bypass via a right-sided mini-thoracotomy in December 2015. The atrial septal defect was repaired with an autologous pericardial patch. Six months post-hospital discharge, she reported complete resolution of her chest discomfort and migraines.

Most modern endovascular prostheses utilized in interventional cardiology field contain nitinol, a widely used material because of its superelasticity, radiopacity, shape retention properties, and resistance to fatigue and corrosion. Nitinol (an acronym for “nickel titanium naval ordnance laboratory”) is an alloy composed of 45% titanium and 55% nickel. The Amplatzer ASD and PFO occluder devices consist of nitinol wire mesh shaped into two round disks connected by a short waist.

The prevalence of nickel hypersensitivity is estimated to be around 10% in the general adult population [1]. The purported immunological mechanism underlying nickel allergy is a type IV, or cell-mediated, hypersensitivity reaction [1]. Hypersensitivity to nickel may include localized and systemic reactions. Localized cutaneous reactions include dermatitis and urticaria [1]. The clinical manifestations of systemic nickel hypersensitivity reactions are protean. Nickel allergy has been implicated in hypersensitivity reactions to cerebral aneurysm clips manifesting as cerebral edema and eosinophilic cerebral vasculitis. Other manifestations of systemic nickel reactions include fulminant eosinophilic myocarditis following implantable cardioverter-defibrillator implantation, and failure of prosthetic heart valves. Coronary bare

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metal stent in-stent restenosis has been inconclusively linked to nickel allergy.

Direct exposure to nickel through nitinol-containing prosthetic implants such as ASD or PFO occlusion devices may cause chest discomfort [2–4], dyspnea [4–5], fever [5], edema [5], palpitations [4], migraines [6–7] and pericarditis with effusion [3,7]. Two studies have established that systemic nickel levels rise, and then return to baseline, following Amplatzer device implantation. Ries et al. analyzed serum nickel concentration in 67 patients, and found that mean serum nickel concentration rose to a peak at one month post-implantation, and then returned to baseline 12 months later [8]. Similarly, Burian et al. found that during the 6-week period post ASD closure, mean serum and urine levels nickel levels in 24 patients increased 5-fold, and returned to baseline within 6 months post-implantation [9]. A possible mechanism mediating systemic hypersensitivity to implanted nitinol-containing devices consists of a local inflammatory reaction to the implanted device resulting in the formation of either platelet adhesions or inflammatory mediators, or both. Microemboli or inflammatory mediators may spread systemically through the arterial circulation, causing end-organ insult. However, despite anecdotal case reports suggesting a link between nickel-containing intravascular devices and systemic hypersensitivity reactions, the evidence to support of such link is scant. Wertman et al. analyzed the outcomes of 108 patients who underwent transcatheter ASD or PFO closure with a nitinol-containing device [6]. Out of these, 37 had cutaneous nickel patch testing. New onset or worsening migraine with or without aura was significantly associated with nickel allergy [$p = 0.028$]. In a prospective study of 46 patients undergoing ASD closure and tested for nickel hypersensitivity, 8/9 nickel-allergic patients developed a “device syndrome” consisting of chest discomfort, exertional dyspnea, asthenia, and mild leucocytosis, whereas only 2 of the 37 non-nickel-allergic patients developed symptoms [4]. On the other hand, in a retrospective study of 38 patients undergoing ASD closure with an Amplatzer device the incidence of chest discomfort, palpitations, and migraine was similar between the nickel-allergic and the non-nickel-allergic groups [10]. Nickel allergy is diagnosed with a standard epicutaneous patch test, which assesses hypersensitivity to the most common allergenic metals, such as nickel, chrome, and cobalt salts [1]. Prognosis of nickel-hypersensitivity syndromes post-ASD or PFO closure is generally benign. Most patients report spontaneous symptom improvement or resolution within months. The administration of a P2Y₁₂ inhibitor such as clopidogrel or corticosteroids [4,6] has been reported to be effective. Rarely, symptoms do not resolve in response to medical therapy. In such cases, explantation of the device has been successful in terminating symptoms [2,5,11]. The usefulness of patch testing prior to device implantation is controversial, given the lack of evidence underlying the link between ASD closure and nickel allergy. In patients with proven nickel allergy, non-nitinol containing ASD/PFO closure devices such as the Helex (W.L. Gore & Associates, Flagstaff, AZ, USA) [12–13], or the

Atriasept II (Cardia Egan, Minnesota, USA) [14] have been successfully deployed without symptoms during follow-up.

Although the prevalence of nickel hypersensitivity is estimated to be around 10% in the general adult population, systemic hypersensitivity reactions to nickel-containing ASD closure devices are uncommon. In most reported cases, symptoms resolve spontaneously. In rare circumstances, however, device explantation has been necessary.

Disclosures and conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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