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BEGINNER

CASE REPORT: CLINICAL CASE

Systemic Allergic Contact Dermatitis Due to a GORE CARDIOFORM Septal Occluder Device

A Case Report and Literature Review

Charles D. Resor, MD,[a] Ari M. Goldminz, MD,[b] Prem Shekar, MD,[c] Robert Padera, MD, PhD,[d] Patrick T. O'Gara, MD,[e] Pinak B. Shah, MD[e]

ABSTRACT

Nickel hypersensitivity is a rarely reported complication of percutaneous patent foramen ovale/atrial septal defect closure. Herein, we report a case of systemic allergic contact dermatitis to nickel present in a GORE CARDIOFORM (W.L. Gore, Flagstaff, Arizona) septal occluder that resolved following explanation. To our knowledge this is the first published case of nickel hypersensitivity associated with this device. (**Level of Difficulty: Beginner.**) (J Am Coll Cardiol Case Rep 2020;2:1867–71) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Nickel hypersensitivity is a rarely reported complication of patent foramen ovale (PFO)/atrial septal defect (ASD) closure with percutaneous occluder devices. Herein, we report a case of systemic allergic contact dermatitis to nickel present in a GORE CARDIOFORM septal occluder (GSO) device (W.L. Gore, Flagstaff, Arizona) that completely resolved following explanation. To our knowledge this is the first published case of nickel hypersensitivity associated with this device.

LEARNING OBJECTIVES

- To understand the low incidence of systemic allergic reaction due to nickel hypersensitivity related to PFO/ASD occluder devices.
- To understand the appropriate workup in patients presenting with allergic symptoms following device implantation.

HISTORY OF PRESENTATION

A 37-year-old female patient initially presented to our institution for evaluation of right-sided chamber enlargement detected by transthoracic echocardiography performed for evaluation of palpitations. A cardiac magnetic resonance imaging study was performed which revealed a septum secundum defect with Qp/Qs of 1.15 and borderline right-sided chamber enlargement (right ventricular end-diastolic volume index [RVEDVi], 90 ml/m^2). Follow-up at 1 year with repeat magnetic resonance imaging revealed a mildly dilated right atrium and right ventricle (RVEDVi, 119 ml/m^2) with Qp/Qs of 1.4. Given the mild but

From [a]The CardioVascular Center, Tufts Medical Center, Boston, Massachusetts; [b]Department of Dermatology, Brigham and Women's Hospital, Boston, Massachusetts; [c]Department of Cardiac Surgery, Brigham and Women's Hospital, Boston, Massachusetts; [d]Department of Pathology, Brigham and Women's Hosptial, Boston, Massachusetts; and the [e]Department of Cardiology, Brigham and Women's Hospital, Boston, Massachusetts.

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ABBREVIATIONS AND ACRONYMS

ASD = atrial septal defect

GSO = Gore Septal Occluder

PFO = patent foramen ovale

progressive right-sided chamber enlargement, the patient was referred for percutaneous ASD closure.

She underwent uncomplicated implantation of a 30-mm GSO device under transesophageal echocardiographic guidance. She was administered a single dose of perioperative cefazolin and started on aspirin monotherapy post-procedure. She did well clinically post-procedure without any cardiovascular symptoms, but after 7 days began to develop generalized pruritus and diffuse urticaria over her torso and extremities (**Figure 1**). The patient's medical history was notable only for palpitations and the above evaluation and treatment.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis included possible drug reaction and allergic reaction to the recently implanted device or other contact allergens.

INVESTIGATIONS

Given the suspicion of a possible drug reaction, aspirin was discontinued and replaced temporarily with clopidogrel. She was seen in the Dermatology Clinic where a systemic allergic contact dermatitis was among the diagnoses considered. The GSO contains nitinol (55% nickel and 45% titanium) and expanded polytetrafluoroethylene material. She underwent patch testing with allergens (Chemotechnique Diagnostics, Malmö, Sweden) placed in Finn Chambers (Smart Practice, Phoenix, Arizona) on Scanpore tape (Medline Industries, Inc., Northfield, Illinois). Allergens were adhered to the skin for 48 h. A first read was performed at the time of patch removal, showing a questionable reaction to nickel sulfate 5%. At the delayed, 72-h reading, the only positive reaction was to nickel sulfate 5% which showed an extreme (3+) reaction. Of note, testing to 4 titanium allergens as well as nickel sulfate 2.5% was negative. Direct skin testing to the device itself under occlusion on the skin for 7 days was negative. Laboratory testing including tryptase, erythrocyte sedimentation rate, complete blood count, serum immunoglobulin E as well as serum and urine nickel levels were within normal limits. A nickel spot test (dimethylglyoxime) was performed and did not detect nickel release from the device.

Over the ensuing 8 weeks, she followed allergen avoidance strategies, which included changes to her skin care products, a low-nickel diet, as well as antihistamines. However, her symptoms and urticaria continued to worsen.

MANAGEMENT

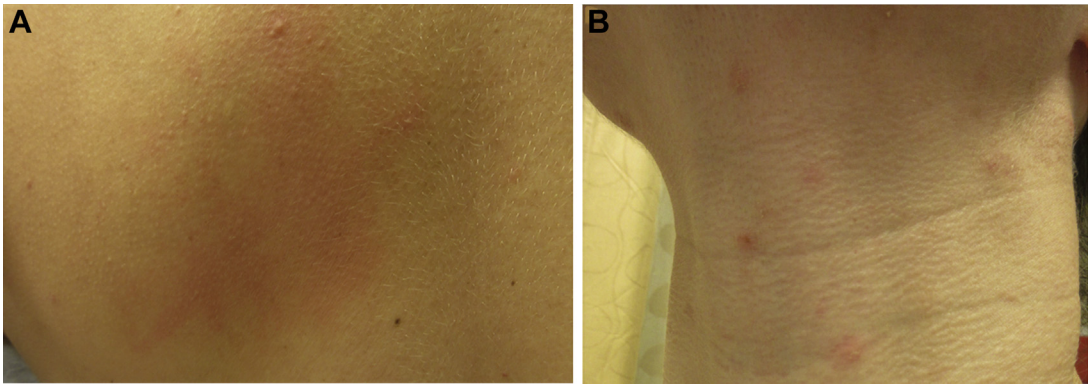
Given the extreme reaction to nickel on patch testing and persistent, severe urticaria despite allergen avoidance strategies, conservative therapy, and workup for other potential causes of her urticaria, the patient decided to undergo device explantation and bovine patch ASD repair via midline sternotomy. A polymer ZIPFIX system (DePuy Synthes, West Chester, Pennsylvania) was used as an alternative to metal sternotomy wires. She experienced an uneventful post-operative course. Her symptoms and urticaria resolved within 7 days of explantation and had not recurred as of her 1-month and 3-month follow-up visits. Histologic evaluation of the tissue surrounding the device showed a mixed chronic inflammatory infiltrate consisting of lymphocytes, plasma cells, and macrophages with a prominent eosinophilic component (**Figure 2**).

DISCUSSION

Nickel is the most prevalent contact allergen, with positive reactions occurring in approximately 20% of patients who undergo patch testing (1). Whereas rates of nickel sensitization are decreasing in Europe possibly due to regulations on nickel release from consumer items, sensitization rates may be increasing in North America (2). Despite the significant nickel content of all United States Food and Drug Administration-approved PFO/ASD closure devices, documented allergic reactions to these devices after implantation are relatively rare. One review estimated the rate of device-related allergic events at 1 per 17,000 (3).

In the current case, the diagnosis of allergic contact dermatitis secondary to the device is supported by the onset of urticaria 1 week after implantation, confirmation of contact allergy to one of the materials present in the device, and resolution within a week of explantation. Additionally, histologic evaluation of the tissue surrounding the device showed chronic inflammation with eosinophilia, also supporting the diagnosis of a hypersensitivity reaction. Although we did not specifically evaluate for polytetrafluoroethylene (PTFE) sensitization beyond skin testing to the device itself, PTFE is a rare contact allergen and the patient's positive reaction to nickel allergen testing was extreme. To our knowledge, this is the

FIGURE 1 Dermatologic Findings



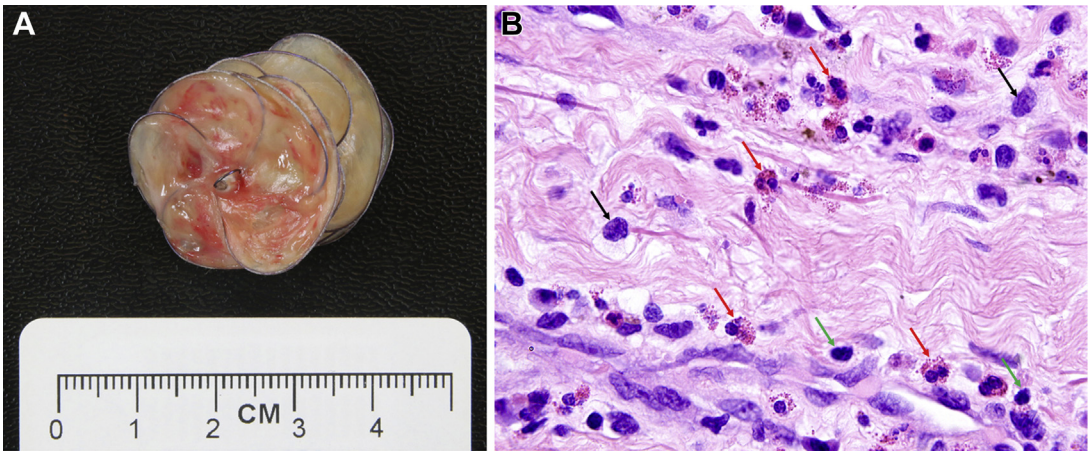
(A) Urticaria-torso. **(B)** Urticaria-neck.

first reported case of nickel hypersensitivity associated with the GSO device.

Contact allergy secondary to the Amplatzer (St. Jude Medical, Inc., St. Paul, Minnesota) (4–6), PFO-Star (Cardia Inc., Burnsville, Minnesota) (7), and Gore Helex (8) devices have been described previously. The GSO, which has less exposed nickel than other approved devices, was shown to have in vitro nickel elution similar to placebo and significantly lower than the Amplatzer septal occlude (9). Therefore, the GSO has been thought to be a good alternative for percutaneous PFO/ASD closure in patients with nickel contact allergy.

In the 3 pivotal randomized trials on PFO closure published in 2017, which included more than 2,000 patients, only 1 device-related allergic reaction was reported among the adverse events (10–12). This occurred in a patient randomized to medical therapy in the RESPECT (Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment) trial of the Amplatzer device. Whether this patient crossed over to the device arm, received off label device implantation, or had an allergic reaction to an unrelated device is not clear. No device explantation was reported in any of the trials. Of note, patch testing to nickel was not

FIGURE 2 Histopathology



(A) Gross specimen of explanted Gore Septal Occluder device. **(B)** Photomicrograph of tissue surrounding the implant showing fibrosis and chronic inflammation including lymphocytes **(green arrows),** macrophages **(black arrows),** and prominent eosinophils **(red arrows)** (hematoxylin and eosin–stained section, original magnification ×200).

required in the studies and patient reported history of nickel allergy was not an exclusion criterion for any of the trials.

Nickel exposure is known to induce urticaria in a subset of patients with nickel allergy, and has been previously reported in association with various implants (13). As in the current case, systemic allergic contact dermatitis to nickel following implantation of an intracardiac device that resolved with explantation has been described (14). In this prior report, patch testing showed a 3+ reaction to nickel sulfate, whereas other investigations such as serum nickel testing and an evaluation of in vitro nickel elution from the device did not show elevated nickel levels.

Rates of device-related allergic reactions are difficult to estimate as the entity is poorly defined, not well understood mechanistically, and apparently rare (15). Previous case reports note signs or symptoms of nickel allergy related to PFO/ASD closure devices covering a wide range of symptomatology including chest pain, palpitations, pericarditis/effusion, dyspnea, bronchospasm, headache, rash, and fever. Medical treatments used in these cases have included antihistamines, steroids, and clopidogrel (16).

In a retrospective analysis of explantation rates for PFO/ASD occluder devices, 38 of 13,736 (0.28%) of patients undergoing percutaneous closure had device removal (17). Allergy was not listed as the primary cause of explantation in any cases, but among the 14 patients who required device explantation for chest pain, 7 were found to have a positive patch test for nickel. Additional reasons for device explantation included residual shunt, thrombus, effusion, and perforation.

Investigations of symptoms or other adverse events following percutaneous PFO/ASD closure with nickel-containing devices in patients with known nickel allergy have yielded conflicting results (18–20). Although these studies are limited by small sample sizes and generalizability, none reported cases of device failure or explantation. One study described a "device syndrome" marked by chest pain, dyspnea, fatigue, and mild leukocytosis that developed in 8 of 9 nickel-allergic patients within several days of implantation and resolved with prednisone and clopidogrel. The actual prevalence of these symptoms among nickel-allergic patients who receive percutaneous PFO/ASD closure with nickel-containing devices is unknown. Despite the high prevalence of nickel allergy among the general population, the current literature suggests low rates of allergic reactions to PFO/ASD closure devices. The current North American standard concentration for nickel patch testing of 2.5% may even underestimate the true prevalence of nickel allergy (2). In Europe, a 5% nickel concentration is typically used for screening. Some investigators have also advocated the use cobalt-chromium or stainless steel devices for use with other intracardiac devices in the setting of nickel allergy. However, intracoronary cobalt-chromium and stainless steel stents are thought to elute a greater amount of nickel than the nitinol-containing alternatives (21). Currently, all the approved PFO/ASD occluder devices contain nitinol.

The role of pre-implantation screening is a controversial topic given the currently low-reported incidence of device-related allergic syndromes particularly with the newer devices, uncertain relevance of positive patch test results, and presently limited alternative options for device materials. In patients with known nickel allergy under consideration for PFO/ASD closure, a discussion of the risks and benefits should include device-related allergic reactions. Post-implantation workup is also complicated by atypical presentations and symptomatology, the lack of evaluation techniques that establish definitive causation, and the potential risks of explantation without a guarantee of symptom resolution. Further research is required to help guide the decision process particularly for patients with known nickel hypersensitivity and to stratify risk for the development of device-related reactions during the pre-operative evaluation process.

FOLLOW-UP

As of 3 months post-procedure, the patient has done well clinically and has remained free of urticaria or any allergic or cardiovascular symptoms.

CONCLUSIONS

Nickel hypersensitivity is a rarely reported complication of PFO/ASD closure with percutaneous occluder devices. To our knowledge this is the first published case of nickel hypersensitivity associated with the GSO device.

AUTHOR RELATIONSHIP WITH INDUSTRY

Dr. Goldminz's wife owns stock in Johnson and Johnson. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr. Charles D. Resor, The CardioVascular Center, Tufts Medical Center, 800 Washington Street, South 6, Boston, Massachusetts 02111. E-mail: cresor@TuftsMedicalCenter.org. Twitter: @CDResorMD.

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