Triclosan Allergy Mimicking Recurrent CIED Infections

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October 30, 2023

Abstract

An 80-year-old man had a secondary prevention defibrillator in place for treatment of sustained ventricular tachycardia. After a generator replacement several years later, he developed a series of apparent pulse generator infections requiring extraction. Each purulent appearing pocket eruption was culture negative. Eventually, he was diagnosed with a delayed hypersensitivity reaction to triclosan, an antibacterial that is commonly impregnated in surgical sutures. The evaluation for this is difficult and can be misleading. This entity should be considered in the differential diagnosis of patients with culture negative CIED infections.

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Running Title: Triclosan Allergy mimicking Infection

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Abstract

An 80-year-old man had a secondary prevention defibrillator in place for treatment of sustained ventricular tachycardia. After a generator replacement several years later, he developed a series of apparent pulse generator infections requiring extraction. Each purulent appearing pocket eruption was culture negative.

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An 80-year-old man with mitral valve disease and ischemic cardiomyopathy underwent placement of a dual chamber implantable cardiac defibrillator (ICD) in 2004 with an upgrade to a cardiac resynchronization therapy defibrillator (CRT-D) in 2008. He required infrequent therapy for monomorphic ventricular tachycardia (VT) and he had a generator replacement in 2013. He lost a great deal of weight and had a pocket revision for threatened generator erosion in 2014. The pulse generator was repositioned into the subpectoral plane at that time.

The patient underwent another pulse generator replacement in April 2019. Several weeks later, he developed erythema and tenderness overlying the new generator (Figure 1). He denied fever or chills, had no leukocytosis (white blood cell count 7.6 x 10^3/mcL), and blood cultures prior to initiation of empiric antibiotics were no growth. A pulse generator infection was suspected, and a complete system extraction was performed in July 2019. Frank purulence was noted within the pocket. Bacterial cultures and gram stain obtained intraoperatively remained negative. The patient was intermittently febrile following the procedure without developing leukocytosis, positive culture data, or evidence of vegetation by TEE. He completed a 14-day course of combined intravenous and oral empiric antibiotics, receiving linezolid upon discharge at the recommendation of the infectious disease consult team. Repeat outpatient blood cultures remained negative and a right sided pre-pectoral CRT-D system was implanted in October 2019. He was out of state in December 2019, at which time his pocket again became inflamed. After failing a 10-day course of outpatient clindamycin, the system was extracted at another tertiary care facility and the patient completed a course of antibiotics. Three months later, given his recent extractions from both pre-pectoral regions, a dual chamber ICD was implanted using a right femoral vein approach with lead tunneling to the right lower quadrant for abdominal device placement.

He was readmitted to our facility two months later with erythema and ulceration of the abdominal pocket despite a seven-day trial of cephalexin. TTE was negative for lead or valvular vegetation. CT imaging revealed reactive right inguinal lymph nodes and a fluid collection surrounding the pulse generator and at the site of the lead suture sleeves in the right groin. Once again, he underwent extraction. Blood cultures, gram stains and tissue samples taken from the femoral and abdominal pocket sites were cultured for bacteria, fungi, and mycobacteria. All cultures remained negative. Broad range sequencing for fungal 18S rRNA and bacterial 16S rRNA studies were negative. Serologies for Q fever and Bartonella were also negative. A CT venogram revealed patent vascular access through a right subclavian collateral network. A defibrillator vest was applied and a peripherally inserted central catheter was placed. The patient completed a 14-day course of ceftriaxone and vancomycin at the recommendation of the infectious disease team.

After recurrent culture negative infections, an alternative diagnosis such as a contact hypersensitivity reaction was suspected, and he was referred to Allergy & Immunology. Patch testing was negative out to 12 days for components of the previously utilized CRT-D system, intraoperative antibiotics, and material comprising a commercially available antibacterial envelope: Cobalt 1%, Cobalt Sulfate 2.5%, Titanium Oxide 0.1%, Minocycline 10%, Doxycycline 5%, Rifampin 10 %, Rifampin 30%, and Adhesives. Given his history of sustained VT, he underwent re-implantation of a gold-plated dual chamber ICD system via right axillary venous access in November 2020 and was discharged with a 90-day course of prophylactic doxycycline 100mg daily.

Approximately six weeks later the patient developed erythema and tenderness over the new device pocket. After a decision was made to extract the system, an aspirate of purulent material (Figure 2) was obtained for standard gram and AFB stains and was cultured for bacteria, fungi, and mycobacteria. A PET CT was also performed demonstrating findings consistent with inflammation around the ICD with extension to the superior vena cava.

The patient was taken for a fourth extraction. During the procedure, three commonly utilized surgical sutures (Silk, Vicryl and Ethibond) were placed as single interrupted sutures in the right upper chest (Figure 3) to further evaluate for a hypersensitivity reaction. We also tested a sample of the antibacterial envelope by placing a small wedge of envelope subcutaneously and approximating the fascia by our standard technique (Figure 3). Results of the incubated aspirate and peripheral blood cultures remained negative. Given the low suspicion for an infectious process, the patient was discharged without antibiotics.

Approximately 14 days after placement of interrupted test sutures, the patient presented with erythema and induration at the test site for the antibacterial envelope with standard pocket closure (Figure 4). After another week, the site developed fluctuance and pustular drainage. A similar reaction was not noted at the other suture sites. We also we noted four discrete healing deep ulcerations at the sites of the interrupted fascial sutures placed by the operator during the previously implanted gold-plated ICD. At this point, we realized that our standard technique for fascial closure utilized triclosan-coated antimicrobial sutures (Vicryl Plus). Epidermal patch testing was repeated, this time adding a patch test to triclosan to the same panel of antibiotics, metals, and adhesives. Patch testing was again negative. Intradermal testing for a hypersensitivity reaction to triclosan-coated suture was then performed by placing a single-interrupted Vicryl Plus suture in the right pre-pectoral area. Fourteen days later, the patient presented with erythema and pustular drainage from the suture site (Figure 5). After another week, the site developed superficial erosion.

Upon identifying triclosan-coated suture as the culprit allergen, our team contacted the other two device implanting facilities. They both confirmed employing triclosan-coated suture for fascial closure at the device system pocket and femoral vascular access sites. Given his repeated negative infectious work-up, the details of his procedural history, and the two profound reactions to in-vivo suture placement, the multi-disciplinary team concluded that the patient's rejection of implanted devices was brought on by a type IV hypersensitivity reaction to the antibiotic-impregnated suture.

In the end, the patient was scheduled for a new defibrillator implantation. Sadly, the day before the planned surgery, he removed his defibrillator vest to slide beneath an automobile to perform repairs. There, he suffered sudden cardiac arrest and was found hours later.

DISCUSSION

Triclosan is a compound with broad-spectrum antibacterial and antifungal properties (bacteriostatic and bactericidal) used to inhibit microbial growth on the skin and other surfaces. After becoming licensed for use in 1964, triclosan became a ubiquitous substance to human exposure with its inclusion in personal care items, household products, clothing, and toys.[1] Along with paucity of proven efficacy and potential to develop antimicrobial resistance[1,2], epidemiological studies monitoring long-term triclosan exposure suggested environmental accumulation and potential human health effects with cumulative doses[3-6]. The Food and Drug Administration (FDA) eventually banned widespread use in consumer soaps and antiseptic products in 2016 and 2017, respectively.[7] However, triclosan's antimicrobial properties remain a component in several commercially available surgical sutures, including FDA approved triclosan-coated polyglactin 910 antibacterial suture (Vicryl Plus; Ethicon, Johnson & Johnson, Sommerville, NY, USA), triclosan-coated poliglecaprone 25 antibacterial suture (Monocryl Plus; Ethicon, Johnson & Johnson, Sommerville, NY, USA), and triclosan-coated polydioxanone antibacterial suture (PDS Plus; Ethicon, Johnson & Johnson, Sommerville, NY, USA).

Both in vitro and in vivo animal experiments have shown that triclosan-coated sutures (TCS) attenuate bacterial colonization[8-11] and exhibit inhibitory activity to a wide spectrum of pathogens related to surgical site infections (SSIs)[8-13] without altering the physical properties of sutures or interfering in the wound-healing process.[12,14] Following FDA approval in 2002, incorporation of antibiotic-coated suture material into primary wound closure became a common technique in the multi-disciplinary approach to surgical site infection risk reduction. Randomized control trials published to date have offered mixed outcomes in achieving the primary endpoint of SSI reduction[15-19], with at least a trend toward reduced short- and

longer-term infection. Multiple systematic meta-analyses have demonstrated improved outcomes in specific circumstances, favoring TCS use in adult patients, abdominal procedures and clean or clean-contaminated surgical wounds.[20-22]No currently published data has demonstrated reduction of SSI in the cardiac surgery subgroup and, thus far, no trials have evaluated TCS use in cardiac implantable electronic device placement.

Considering the evidence quality and trial limitations, the Centers for Disease Control (CDC) and World Health Organization (WHO) have issued conditional recommendations to consider antimicrobial-coated suture use in all surgical procedures.[23,24] The American College of Surgeons (ACS) and the Surgical Infection Society (SIS) offer recommendations limited to abdominal cases.[25]Implantable cardiac device pocket infection persists as an important procedure-related complication with the rate of overall CIED infection reported between 1.6 and 5.8 percent.[26,27] As triclosan-coated suture remains a ubiquitous procedural tool to minimize surgical site infection, it becomes increasingly important to recognize the presentation of allergic contact dermatitis masquerading as the very complication we are working to avoid.

Allergic contact dermatitis (ACD) represents a type IV hypersensitivity reaction resulting from contact sensitization to an allergen[28-31] and may be localized to the tissue in contact with the allergen or may present as a systemic reaction.[32] Allergic contact dermatitis from triclosan exposure is an uncommon but recognized phenomenon. Retrospective analyses report a positive reaction rate between 0.32%-0.8% in patients on whom patch testing was performed with triclosan, 2% in petrolatum.[33,34] However, not all positive reactions were felt to be clinically relevant.[34] Isolated case reports have been published on ACD from triclosan exposure,[35-40] rarely presenting as antimicrobial suture use.[41-44] To our knowledge, such a case of CIED-related allergic contact dermatitis to triclosan-coated suture has not previously been published.

In addition to taking a detailed history and reviewing potential allergens, the standard approach for aiding in ACD diagnosis, is patch testing to the suspect culprit(s).[31] Standard screening patch tests include the American Contact Dermatitis Society (ACDS) Core Series (80 allergens) and the North American Contact Dermatitis Group (NACDG) Series (70 allergens) which contain the most common sensitizers that cause ACD.[32] Like patch testing guidelines, these screening series are continuously reviewed and updated. Given the removal of triclosan from consumer goods and low sensitizing potential, it was withdrawn from core patch allergen testing series in the most recent update by the ACDS.[45]Targeted and limited screening series may be performed, though require a high degree of clinical suspicion with potential to introduce delay in patient care.

Further complicating accurate and timely diagnosis is the imperfect science of patch test interpretation. A positive test result is merely a sign that sensitization to the tested material has occurred at some point and requires a physician's assessment of clinical relevance. This is best established by clinical improvement following a period of allergen avoidance.[46,47] Conversely, patch test reactions interpreted as morphologically negative or doubtful can sometimes be clinically relevant and important for the individual patient[48,49] and may need further work-up. Numerous factors contribute to false-negative patch tests, including inactive allergen or insufficient allergen concentration, poor allergen penetration, poor application technique, insufficient delay between application and interpretation, and concurrent chronic immunosuppression.[31,32]

When allergic contact dermatitis to a suture is suspected, placing a patch test with the suture material on the epidermis has low sensitivity. The interrupted dermal stitch test is a recognized technique to aid in the diagnosis of suspected ACD to a suture material[50-52], although further patch testing may be necessary to identify the specific culprit ingredient in the suture. Our case follows this pattern. While our patient's patch test to triclosan was negative, he had a robust reaction to in vivo placement of triclosan-coated polyglactin 910 (Vicryl Plus). Most other cases of suture allergy testing have performed interpretation around day five. It is noteworthy that our patient's test did not become positive until close to day 14. However, it is a well-known feature of type IV hypersensitivity reactions that they may occur several weeks after allergen exposure. Moreover, a hypersensitivity response to absorbable suture relates to the rate of suture hydrolysis, leading to a relative increase in allergen concentration as the surface area increases allowing greater exposure to antigen presenting cells in the dermis. Published Ethicon data reports an absorption rate between 56 to 70 days for Vicryl Plus suture.[53] Our patient followed this pattern, demonstrating a robust response to

suture material 6-8 weeks after each device system implantation. The test sites of other suture material, including uncoated polyglactin 910 (Vicryl), remained non-edematous and non-erythematous. These results also suggest possible allergic contact dermatitis to the combination of suture material and triclosan, but not to each ingredient independently. This phenomenon has been called "compound allergy"[54] and serves an alternative hypothesis for our patient's response to epidermal and intradermal testing.

While not performed in our case, pathology may supplement intradermal testing in the diagnosis of delayed hypersensitivity. Case reports published on surgical site pseudoinfections describe histologic findings of either a foreign body reaction including mixed inflammatory cell infiltrate, multinucleated giant cells and amorphous birefringent material or an allergic reaction comprised of a mixed population of lymphohistiocytes, granulocytes and eosinophils.[42,44,55-58] In contrast, an expected reaction involves minimal multicellular inflammatory infiltrate associated with suture filaments after 14 and 21 days.[56] While these findings are not specific to ACD, they serve as another clue in the clinical picture.

CONCLUSION

ACD to suture material should be considered in patients who present with early and delayed post-procedural induration and erythema, particularly in the setting of repeated culture-negative episodes. This report highlights the potential for triclosan, and specifically triclosan-coated sutures, to contribute to ACD. A single interrupted stitch test into the dermis improves the sensitivity of in vivo testing for suture hypersensitivity when conventional patch allergen testing proves negative. While this recognized entity remains an infrequent procedural complication, this is a treatable phenomenon which results in significant patient morbidity and increased costs to the healthcare system. Early consideration of ACD and engagement by a multi-disciplinary team including Infectious Disease and Allergy & Immunology leads to efficient diagnosis and improved patient outcomes.

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