Case Report of Subcutaneous Nodules and Sterile Abscesses Due to Delayed Type Hypersensitivity to Aluminum-Containing Vaccines

Christine T. Lauren, MD, a, b Donald V. Belsito, MD, a Kimberly D. Morel, MD, a, b Philip LaRussa, MD b

Departments of aDermatology, and bPediatrics, Columbia University Medical Center, New York, New York

Dr Lauren drafted the initial manuscript and critically reviewed the manuscript; Drs Morel, Belsito, and LaRussa critically reviewed the manuscript; and all authors approved the final manuscript as submitted.

DOI: 10.1542/peds.2014-1690
Accepted for publication Jun 16, 2016

Address correspondence to Christine T. Lauren, MD, Departments of Dermatology and Pediatrics, Columbia University Medical Center, 161 Fort Washington Ave, 12th Floor New York, NY 10032. E-mail: cat35@cumc.columbia.edu

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).
Copyright © 2016 by the American Academy of Pediatrics

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

POTENTIAL CONFLICTS OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

FUNDING: This work was supported in part by the Clinical Immunization Safety Assessment Network through a subcontract with America’s Health Insurance Plans under contract 200-2002-00732 and in part by contract U50 CU220700 from the Centers for Disease Control and Prevention.

Although anaphylaxis is recognized as a rare side effect of vaccination with rates of 0.0001 to 0.002% or less, 1, 2 delayed type hypersensitivity (DTH) reactions are less well known, with reported frequencies of 0.35% to 1.18%. 3 We present a case of persistent subcutaneous nodules and sterile abscesses due to DTH to aluminum to increase awareness of this reaction and resources for vaccine safety expert consultation.

PATIENT PRESENTATION

A 7-month-old healthy boy presented with a 3-month history of subcutaneous nodules at sites of previous immunizations. Vaccinations at 2 months of age (Prevnar 13 [pneumococcal 13-valent conjugate vaccine], ActHib [Haemophilus influenzae b conjugate vaccine], and Pediarix [diphtheria-tetanus-acellular pertussis [DTaP]-hepatitis B [hep B]-inactivated polio vaccine [IPV]) at 3 months of age occurred without incident. At 4 months of age, he received second doses of Prevnar 13 and Haemophilus influenzae b vaccine (PedvaxHIB) in the right and left thighs, respectively. Within 3 to 5 days, his mother reported a right thigh nodule and an erythematous left thigh nodule. At 5 months of age, he received Pediarix in his left arm and 3 to 5 days later, developed erythema and swelling that persisted for 5 weeks. Culture-negative purulent material was drained after incision, suggesting a sterile abscess. Violaceous subcutaneous nodules were still present at all 3 sites when the child was seen at 7 months of age (Fig 1). He had no history of hives, respiratory distress, mucosal swelling, or fever. Ultrasound examination of these nodules demonstrated teardrop-shaped echogenic areas extending from the skin to the subcutis, the largest measuring 1.1 cm in diameter (Fig 2).

Aluminum was the only component common to the vaccinations that
resulted in nodule formation (Table 1). Patch testing was performed by using empty Finn chambers (SmartPractice, Phoenix, AZ) on Scanpor tape (Actavis Norway) applied to the back for 48 hours. Readings at 48 and 96 hours demonstrated 1+ and 2+ reactions, respectively (Fig 2).

The history and clinical findings supported our impression of DTH to aluminum. Subsequent vaccination with IPOL (aluminum-free IPV) was well-tolerated. The patient’s case was reviewed by the Centers for Disease Control and Prevention (CDC)-funded Clinical Immunization Safety Assessment (CISA) Network, which provides expert consultation on the evaluation, management, and assessment of causality of adverse events after licensed vaccines. The review concurred with the diagnosis of aluminum hypersensitivity and assisted with the development of a vaccination plan to minimize subsequent aluminum exposure. The recommendation was that future vaccinations be aluminum-free when available (eg, H. influenzae b: ActHib, inactivated trivalent polio: IPol, and trivalent influenza: Fluzone). Although aluminum-free alternatives were not available for subsequent DTaP, conjugate pneumococcal, and Hep B immunizations, the benefits of vaccination were felt to outweigh the potential of an adverse reaction. It was recommended that pneumococcal and DTaP vaccinations were first priorities, with the stipulation that topical steroid preparations could be used to mitigate the severity of the expected reactions. Live viral vaccines (measles-mumps-rubella, Varicella) do not contain aluminum and should be given according to the recommended schedule. Hepatitis A vaccine (aluminum-containing) was deferred until higher priority vaccinations were completed.

Subsequent vaccinations included a third Prevnar 13 (aluminum-containing) in the right deltoid and influenza (aluminum-free) in the left deltoid at 12 months of age. He then inadvertently received an aluminum-containing PedvaxHIB vaccine in his right deltoid at 13 months. Two weeks later, redness was noted on the skin of the right arm with a palpable 2.5 × 1.8 cm subcutaneous nodule (Fig 4) at the site of his Prevnar 13 and PedvaxHIB vaccinations. Topical steroids under occlusion resulted in subsequent improvement. Six weeks later, the nodule spontaneously drained purulent material, followed by resolution. At the time of manuscript preparation, measles-mumps-rubella, Varicella, IPV, and influenza vaccines, all of which are aluminum-free, were received without incident.

### DISCUSSION

Aluminum hypersensitivity, a DTH reaction, is a rare, underrecognized entity. Local erythema and induration are more common after aluminum-containing vaccines compared with aluminum-free vaccines. Although mild vaccination site reactions are most commonly reported, persistence of erythema, sterile abscess, or subcutaneous nodules weeks to months after vaccination can also occur. Lesions and severe pruritus may develop within days to months after vaccination, may last for years, and may be recalcitrant to treatment. Cutaneous changes include dermatitis, hyperpigmentation, lichenification, and hypertrichosis. It is not clear how many cases of sterile abscesses are secondary to DTH, but the association with this reaction pattern and aluminum has been reported. Nonencapsulated granulomatous infiltrates in subcutaneous nodules and sterile abscesses have been described with evidence of aluminum within macrophages.
There are various aluminum formulations, including: hydroxyphosphate sulfate, hydroxide, phosphate, or potassium sulfate. Aluminum-hydroxide has become more widely used and has been implicated in the increased incidence of DTH reactions. Our patient received immunizations containing the hydroxide and phosphate forms.

Improper placement of vaccine in the dermis or subcutis, as opposed to intramuscularly, has been proposed as a trigger for development of aluminum hypersensitivity. Epidermal Langerhans cells have been implicated in the pathogenesis of this reaction. In some reports, the rate of hypersensitivity reaction decreased by adjusting the route of administration to intramuscular injection. In our case, ultrasonography showed a tract from the skin surface, suggesting deposition of vaccine along the path of the injection to the subcutaneous space, which may have allowed priming of antigen presenting cells.

Treatment of symptomatic nodules may be ineffective. Topical steroids may be unsuccessful given the depth of the reaction pattern. Occlusion may increase the potency of the topical steroid and limit scratching; hydrocolloid dressings alone have also been reported with variable effect. Intradermal steroids and topical capsaicin have been used with varying success; side effects include atrophy and absorption. The effect of these treatments on the immune response is not clear.

Patch testing to evaluate allergen-induced eruptions has been described. Plastic or aluminum wells (Finn chambers) containing small amounts of suspected allergens are placed on the skin and left undisturbed for 48 hours or longer. Skin eruptions present at 72 to 96 hours after application are graded on a severity scale of 1+ to 3+ and signify a DTH to the suspected allergen.

Testing with the Finn chamber preparation for patch testing. Previous studies suggested that the higher concentration of aluminum in this preparation results in more positive test results. Other studies used diluted aluminum chloride. Given our patient’s positive reaction to the empty Finn chamber, we did not proceed to testing with the standard preparation, however many reports test both chamber and reagent simultaneously to limit the number of potential office visits.

As with other DTH reactions, recurrence can be anticipated with repeat exposure. Patch testing and intercurrent illness have been reported to result in progression or recurrence of previous subcutaneous nodules. Symptoms include increasing pruritus, enlargement of existing nodules or development of new nodules. In our patient, reexposure to aluminum-containing vaccines resulted in a similar reaction at the injection site, but without flare of previous nodules in the remaining extremities.

Delayed reaction to aluminum has been previously classified as an irritant reaction rather than the more fitting immunologically mediated DTH reaction. DTH may manifest days to weeks after the inciting agent. Sensitization after initial exposure is

---

**FIGURE 3**
Patch testing to empty aluminum Finn Chambers revealed a 2+ papulovesicular reaction with accentuation at the margin along the point of maximal contact with the chamber rim. Finn chamber, inset.

**FIGURE 4**
Site of re-exposure to aluminum containing vaccine when the patient was 15 months of age. Pen markings outline the border of the palpable subepidermal nodule.

Intramuscular injection of aluminum, a common adjuvant in inactivated vaccines and in allergen immunotherapy leaves a “depot” of antigen, prolonging exposure to antigen presenting cells and improving host immunologic response. Common vaccinations given within the first year of life, including DTaP, Pediarix, hepatitis A, Hep B, pneumococcal conjugate (Prevnar), and some H. influenzae b vaccines contain aluminum. Live virus vaccines are aluminum-free, as are some inactivated vaccines, including meningococcal, seasonal influenza, IPV, and certain H. influenzae b vaccines. Other excipients and preservatives used in the immunization manufacturing process have also been reported to cause DTH reactions. The package insert should be reviewed because ingredients may change. A list of excipients can be found at http://www.cdc.gov/vaccines/pubs/pinkbook/downloads/appendices/B/excipient-table-2.pdf

---

DTH reaction. DTH may manifest days to weeks after the inciting agent. Sensitization after initial exposure is
necessary for development of a DTH. Our patient’s initial vaccinations at age 2 and 3 months likely sensitized him to aluminum with a resultant hypersensitivity reaction on reexposure at age 4, 5, 12, and 13 months. Aluminum has been reported to be responsible for 77% to 85% of all DTH to vaccinations.\(^3\),\(^1\),\(^5\) Other reported ingredients include polysorbate,\(^32\) thimerosal,\(^33,\)\(^34\) phenoxyethanol,\(^35\) formaldehyde,\(^36\) and polymyxin B.\(^37\) Although neomycin and others are known causes of DTH, there have been no reports of vaccine DTH to date.

Although severe vaccine-associated allergic reactions are a contraindication to reexposure,\(^38\) there are no reports of life threatening reactions to aluminum-containing vaccines in a sensitized patient. Alternative preparations that do not contain, or contain less of, the suspected allergen should always be selected when available. For immunizations without an aluminum-free alternative, a risk/benefit discussion on a case-by-case basis is important, because the risk of reaction should be weighed against the risk of exposure and potential consequences of vaccine-preventable disease(s). Consultation with a pediatric allergist-immunologist or infectious disease specialist with vaccine expertise is suggested. The CDC-funded CISA network\(^2\) was able to provide the necessary vaccine safety expertise in this case. US healthcare providers with a vaccine safety question about a specific patient residing in the United States can contact CISA at CISAeval@cdc.gov to request a case evaluation; this service is free of charge, but not all cases are accepted. Any unexpected or clinically significant suspected immunization reaction should be reported to the Vaccine Adverse Event Reporting System (http://vaers.hhs.gov/index\(^{39}\)) to allow for proper signal detection of this reaction within the US population. Additional information regarding vaccines and vaccine safety may be found at http://www.cdc.gov/vaccinesafety/index.html.\(^40\)

ACKNOWLEDGMENTS

The CISA Hypersensitivity Working Group members were: Jane Gidudu, MD, (CDC), Neal Halsey, MD, and Robert Wood, MD (Johns Hopkins University), Cornelia Dekker, MD, (Stanford University), Nicola Klein, MD, PhD, and Roger Baxter, MD, (Kaiser Permanente of Northern California), Kathryn Edwards, MD (Vanderbilt University), Renata Engler, MD, (Walter Read Army Medical Center), Melvin Berger, MD, PhD (Case Western Reserve University) and Steven Dreskin, MD, PhD (University of Colorado Denver).

ABBREVIATIONS

CDC: Centers for Disease Control and Prevention
CISA: Clinical Immunization Safety Assessment
DTaP: diphtheria-tetanus-acellular pertussis
DTH: delayed type hypersensitivity
IPV: inactivated polio vaccine

REFERENCES

10. Jefferson T, Rudin M, Di Pietrantonj C. Adverse events after immunisation with aluminium-containing DTP.


17. Frederiksen MS, Tofte H. Immunisation with aluminium-containing vaccine of a child with itching nodule following previous vaccination. Vaccine. 2004;23(1):1–2


26. Thierry-Carstensen B, Stellfeld M. Itching nodules and hypersensitivity to aluminium after the use of adsorbed vaccines from SSI. Vaccine. 2004;22(15-16):1845


Case Report of Subcutaneous Nodules and Sterile Abscesses Due to Delayed Type Hypersensitivity to Aluminum-Containing Vaccines
Christine T. Lauren, Donald V. Belsito, Kimberly D. Morel and Philip LaRussa
Pediatrics 2016;138; DOI: 10.1542/peds.2014-1690 originally published online September 27, 2016;

Updated Information & Services
including high resolution figures, can be found at:
http://pediatrics.aappublications.org/content/138/4/e20141690

References
This article cites 32 articles, 1 of which you can access for free at:
http://pediatrics.aappublications.org/content/138/4/e20141690#BIBL

Subspecialty Collections
This article, along with others on similar topics, appears in the following collection(s):
Dermatology
http://www.aappublications.org/cgi/collection/dermatology_sub
Infectious Disease
http://www.aappublications.org/cgi/collection/infectious_diseases_sub
Vaccine/Immunization
http://www.aappublications.org/cgi/collection/vaccine:immunization_sub

Permissions & Licensing
Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
http://www.aappublications.org/site/misc/Permissions.xhtml

Reprints
Information about ordering reprints can be found online:
http://www.aappublications.org/site/misc/reprints.xhtml

American Academy of Pediatrics
DEDICATED TO THE HEALTH OF ALL CHILDREN®
Case Report of Subcutaneous Nodules and Sterile Abscesses Due to Delayed Type Hypersensitivity to Aluminum-Containing Vaccines
Christine T. Lauren, Donald V. Belsito, Kimberly D. Morel and Philip LaRussa
Pediatrics 2016;138;
DOI: 10.1542/peds.2014-1690 originally published online September 27, 2016;

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://pediatrics.aappublications.org/content/138/4/e20141690