

# Widespread cutaneous eruption after aluminum-containing vaccination: A case report and review of current literature

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## Abstract

Aluminum salts are adjuvants found in many vaccines. Although rare, patients have reported cutaneous reactions to aluminum salts including persistent pruritic subcutaneous nodules at the injection site. We report the case of an 11-year-old male who at the age of 5 years developed a generalized pruritic cutaneous eruption after receiving the aluminum-containing Quadracel<sup>®</sup> vaccination. Patch testing at that time was positive to aluminum salts and again on repeat patch testing 6 years later. Our case highlights a delayed systemic cutaneous reaction to a vaccine containing aluminum salts. We review cutaneous allergic reactions to vaccines containing aluminum salts and vaccination advice for patients with aluminum contact allergy.

## KEYWORDS

allergy, aluminum, patch testing, vaccination

## 1 | INTRODUCTION

Aluminum salts were introduced in vaccines as an adjuvant to enhance the immunogenicity and generate immunological memory.<sup>1</sup> They have been found in many vaccines including *Hemophilus influenzae* type b, pneumococcus conjugates, hepatitis A, hepatitis B, and diphtheria-tetanus-acellular pertussis (DTaP) vaccines.<sup>1</sup> Reported cutaneous reactions to aluminum salts include persistent pruritic subcutaneous nodules at the injection site. A Swedish study reported a prevalence of positive patch test reactions of 77%-95% among children with persistent skin reactions following a vaccination.<sup>2</sup> We report the case of a 11-year-old male who developed a widespread pruritic cutaneous eruption after receiving the aluminum-containing Quadracel<sup>®</sup> (Sanofi Pasteur) vaccination. He was patch tested on two occasions following this generalized eruption and found to be positive to aluminum chloride. This represents a rare case of a generalized delayed systemic cutaneous reaction to a vaccine containing aluminum salts.

## 2 | CASE REPORT

A 5-year-old male patient who had a past medical history of mild eczema as an infant developed a diffuse erythematous papular

eruption 2 weeks after receiving the Quadracel<sup>®</sup> vaccination, an adsorbed vaccine containing diphtheria and tetanus toxoids and acellular pertussis vaccine combined with inactivated poliomyelitis vaccine (Sanofi Pasteur). He had initially developed a red itchy "bump" at the vaccination site within 24-48 hours of administration. He then developed a pruritic red papular eruption 2 weeks following his vaccination, beginning on his face before spreading to the rest of his body, with accentuation on his forearms and hands. He had no systemic symptoms. He was treated with multiple courses of oral prednisone and topical corticosteroids. The rash lasted 4-5 months before finally resolving. He was subsequently seen by a dermatologist who then patch tested him on the back using aluminum Finn chambers<sup>®</sup> and on the arm with aluminum chloride hexahydrate 2% in petrolatum within a plastic IQ chamber<sup>®</sup>. He developed a severe red pruritic eruption around every aluminum Finn chamber<sup>®</sup>, and a 3+ strong patch test reaction to the aluminum chloride hexahydrate, resulting in early removal of the patch testing plates.

He was retested at the age of 11 years to selected aluminum salts (aluminum chloride hexahydrate 2% pet, aluminum hydroxide 10% pet) in plastic chambers, an empty Finn chamber<sup>®</sup>, 2% aqueous formaldehyde, neomycin 20% in petrolatum, and thimerosal 0.1% in petrolatum. This was done at the family's request to see whether his allergic contact sensitization was still present in order to guide

selection of future immunizations. At 96 hours, he had strong positive 3+ reactions (ie, spreading bullae) to aluminum chloride hexahydrate, aluminum hydroxide and to the aluminum Finn chamber®.

### 3 | DISCUSSION

Aluminum salts are used in vaccines against diphtheria, tetanus and pertussis (DTP), hepatitis A, human papillomavirus, and tick-borne encephalitis, as well as some conjugated vaccines against pneumococcal and meningococcal infections.<sup>3</sup> Aluminum salts, such as aluminum hydroxide and aluminum phosphate, have been used as adjuvants in vaccines since the 1920s.<sup>2</sup> Contact allergy related to aluminum-containing vaccination is rare. Cutaneous eruptions described in the literature include pruriginous subcutaneous nodules, hypertrichosis, eczema, sterile abscesses, Wells syndrome, and contact dermatitis.<sup>4-6</sup> One study reported the appearance of vaccination-induced subcutaneous granulomas with a median duration of 18-49 months.<sup>2</sup> Some of the aluminum salt reactions are due to type IV hypersensitivity.<sup>6-8</sup> The pathogenesis of this reaction is thought to be due to improper placement of the vaccine in the dermis or subcutis, rather than intramuscularly.<sup>9-11</sup>

It is unclear why some aluminum-containing vaccinations have led to a higher incidence of cutaneous eruptions. The physicochemical properties of aluminum may play a role in inducing cutaneous eruptions.<sup>12</sup> No cutaneous reactions were reported in the 1980s to mid-1990s in a Swedish population that received vaccinations containing aluminum phosphate.<sup>2</sup> However, this changed in the 1990s when many patients developed postvaccination injection-site granulomas following a new acellular aluminum hydroxide-adsorbed pertussis vaccine.<sup>2</sup> From 2000 to 2014, there were three large Swedish studies investigating vaccination-induced aluminum contact allergy.<sup>3</sup> Of 601 children who developed persistent pruritic postvaccination granulomas, 475 (79%) were patch test-positive to aluminum.<sup>3</sup> Interestingly, subsequent follow-up of these patients found that the contact allergy to aluminum acquired in childhood seemed to weaken or resolve with time as demonstrated by the pertussis trials by Gente Lidholm et al.<sup>3,13,14</sup> Of the 241 children with a known aluminum allergy, only 55 (23%) were positive when retested 5 to 9 years following the initial patch test.<sup>3,13,14</sup> In this study, the disappearance of aluminum patch test reactivity and of aluminum-related cutaneous patch test reactions (eg, pruritic subcutaneous nodules and granulomas) was correlated with increasing age and time from first vaccination.<sup>13</sup> Our patient continued to have a positive aluminum patch test, making future immunization recommendations challenging.

Our case may represent a systemic cutaneous reaction or systemic contact dermatitis to aluminum salts. Systemic allergic contact dermatitis has been described following administration of both formaldehyde and thimerosal-containing vaccines.<sup>15,16</sup> Most reported aluminum-adsorbed vaccine skin reactions (eg, itchy subcutaneous nodules at the injection site) occur months to years after the vaccination.<sup>3</sup> Our patient's generalized eruption was delayed by only

1-2 weeks. This may be due to a type IV hypersensitivity reaction developing secondary to exposure to the exogenous antigen at the site of injection or due to systemic absorption. Aluminum has been found in toothpaste, antiperspirants, tattoos, eardrops, cosmetic skincare products, and some sunscreens, but the bioavailability of different aluminum compounds is not well investigated.<sup>17</sup> Interestingly, Veien et al<sup>18</sup> reported two patients who may have had a systemically aggravated contact dermatitis at previous vaccination sites caused by a small amount of aluminum oxide in toothpaste. It was postulated that aluminum was systemically absorbed by the gastrointestinal tract. Some children have developed nodules at the former injection site during the patch test, potentially suggesting a systemic allergy.<sup>3</sup>

Patients who develop a cutaneous reaction following an aluminum-containing vaccination should be patch tested. A Swedish study verified contact allergy to aluminum in 77%-95% of the children with vaccination granulomas.<sup>2</sup> Recommendations for preparations used for patch testing to aluminum salts have been recently proposed. One recent review recommends using aluminum chloride hexahydrate 2% in petrolatum for patch testing in children.<sup>3</sup> This appears to be sufficient to demonstrate aluminum contact allergy in children; the 10% preparation can cause unwanted strong patch test reactions.<sup>3</sup> There are no studies investigating the recommended concentration of aluminum hydroxide for patch testing. Another review noted that the diagnosis of an aluminum allergy would have been missed in 10 of 601 cases tested with aluminum chloride hexahydrate 2% in petrolatum if the patients were not also patch tested with aluminum Finn chambers®.<sup>3,14</sup> One case report suggested testing patients with aluminum chloride hexahydrate 10% in petrolatum if a false negative to 2% is suspected.<sup>19</sup> Hedberg et al<sup>17</sup> found that the amount of aluminum released from Finn chambers® corresponds to a skin dose of 0.03% to 0.5% of aluminum chloride hexahydrate applied in plastic chambers. In one study of 37 children who were patch tested, aluminum allergy was found in 8 patients with 10% aluminum chloride hexahydrate and in only three patients with 2% aluminum chloride hexahydrate.<sup>20</sup> There currently is no consensus as to which aluminum compound, vehicle, and concentration should be the gold standard for patch testing.<sup>13</sup>

Vaccination advice in patients with a contact allergy to aluminum is challenging. In one case report, a 3-year-old patient who developed subcutaneous nodules following an aluminum-based vaccine continued to receive her standard immunizations without modifications and did not have a recurrence of the granulomas.<sup>6</sup> Physicians must provide constructive management strategies if an aluminum allergy is detected. This may include substituting vaccines from the standard schedule that do not contain aluminum. If a vaccine does not have an aluminum-free alternative, then a risk/benefit discussion is important weighing the risk of the reaction against the risk of exposure and the consequences of a vaccine-preventable disease.<sup>7</sup> Physicians may consult local health guidelines for appropriate vaccination substitutions. One can refer to the Canadian immunization guidelines found at <https://www.canada.ca/en/public-health/services/publications/healthy-living/canadian-immunization-guide-part-1-key-immunization-information/page-15-contents-immun>

izing-agents-available-use-canada.html that detail the specific vaccines that contain aluminum salts. Adjuvant system 04 (AS04) is an aluminum salt identified in Cervarix® vaccine noted in these Canadian immunization guidelines. In Canada, all hepatitis A, hepatitis B, HPV, and DTaP vaccines contain aluminum. There are alternative aluminum-free vaccines for *Haemophilus influenzae* type b, meningococcal, mumps, pneumococcus, rabies, rotavirus, smallpox, typhoid, varicella, yellow fever, and zoster (see link above).

Physicians in the United States can consult the Centers for Disease Control and Prevention website found at <https://www.cdc.gov/vaccinesafety/concerns/adjuvants.html>. Currently, in the United States, all DTaP, HPV, and hepatitis A vaccines contain aluminum. Alternative, aluminum-free vaccines for hepatitis B, cholera, enterotoxigenic *Escherichia coli*, meningococcal, pneumococcal, influenza, measles, mumps, rubella, rabies, rotavirus, smallpox, polio, varicella, yellow fever, zoster, and typhoid in the United States are available.

Our case highlights the importance of identifying and considering a delayed systemic aluminum contact hypersensitivity reaction in patients following the administration of a vaccine. Vaccination advice for children with a proven sensitization to aluminum must be evaluated on a case-by-case basis, but can include repeat patch testing in the future and offering alternative aluminum-free vaccines. Future studies may consider the role of immunosuppressant medications given prophylactically at the time of immunization.

#### DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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