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An unusual case of itchy subcutaneous nodules secondary to aluminium allergy from vaccination

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Dear Sir,

A 2-year 7-month-old Chinese girl presented with a 1-year history of bilateral subcutaneous nodules on her anterior thighs, at the site of intramuscularly administered 5-in-1 combination vaccine (containing diphtheria, pertussis, tetanus, polio and *Haemophilus influenzae* type B) and measles-mumps-rubella (MMR) vaccine at 18 months of age. She had previously also received the 5-in-1 combination vaccines at 3, 4 and 5 months of age. Over the past year, the nodules remained constant in size, and were intensely pruritic, with resultant persistent scratching leading to overlying hypertrichosis and hyperpigmentation. Apart from mild atopic dermatitis, she was otherwise healthy, and her growth and development were within normal parameters. On examination, there were indurated, non-tender subcutaneous nodules measuring about 1 cm in diameter on each thigh. There was also overlying hypertrichosis and hyperpigmentation (Fig. 1). There was no attachment to overlying skin or deeper structures.

Fig. 1 Hyperpigmented patch with hypertrichosis on the left lateral thigh.

A patch test showed a positive reaction to aluminium hydroxide 10% pet (Fig. 2), with negative reactions to other allergens on the paediatric standard series, most notably nickel and chromium. She was diagnosed with itchy subcutaneous nodules from delayed hypersensitivity reaction to aluminium in 5-in-1 vaccines. The patient was treated with regular emollients and topical betamethasone valerate 0.025% cream.

Fig. 2 Patch test showing positive reaction to aluminium (arrow).

Delayed-type hypersensitivity reaction to aluminium-containing vaccines is an uncommon but known complication of intramuscularly-administered vaccines in children, with most reports and case series from Scandinavia and Australia.[1-3] Our case is the first reported case from Singapore. Aluminium is a common vaccine adjuvant and is incorporated as an aluminium salt, especially aluminium hydroxide, in vaccines. It is found in almost all inactivated vaccines, and acts to improve the host's immunologic response to the vaccine.[4] The most commonly implicated vaccines include Infanrix-Hexa (combined diphtheria, tetanus, acellular pertussis [DTPa], hepatitis

B, inactivated poliovirus, *Haemophilus influenzae* type b), Infanrix-IPV (combined DTPa, inactivated poliovirus), DTaP (combined diphtheria, tetanus, acellular pertussis) and Prevnar (pneumococcal polysaccharide conjugate). Interestingly, the onset of symptoms can be preceded by other vaccines, particularly the MMR vaccine, which do not typically contain aluminium but can act as a triggering factor.[1]

There is usually a long delay between vaccination and onset of symptoms, with a median of 3 months. The median age of onset is 15 months and the time from onset to diagnosis can range from between 8 months to 2 years.[1-3] There is usually intense itching at the vaccination site that can lead to localised eczema, hypertrichosis and dyspigmentation. Worsening of symptoms can occur during intercurrent illnesses. Biopsy of a nodule typically shows granuloma formation with aluminium crystals demonstrated by staining or atomic absorption spectrometry.[5] Positive patch test to aluminium may be observed in 77-95% of patients.[1,2] Patch testing to aluminium chloride hexahydrate 2% has been reported to be more sensitive than patch testing to metallic aluminium.[6] A proportion of children with these subcutaneous nodules and positive patch test to aluminium have been reported to develop symptoms of allergic contact dermatitis to aluminium-containing deodorants, sunscreens, cosmetics, lotions, creams, and buttons.[1] Contact allergy to aluminium has been reported to disappear with time, with up to 77% of them having negative results when retested 5-7 years after the initial patch test.[7]

Symptoms have been reported to resolve spontaneously after a few years, with a median duration of 3–4 years. Treatments is mainly expectant and supportive adjuncts include topical corticosteroids and oral antihistamines. Intralesional corticosteroid injections and surgical excision have also been described but may be difficult in young children. Currently, there is no consensus on whether the occurrence of these nodules warrants withholding subsequent immunizations with

aluminium-containing vaccines.[1-3] The use of vaccines with lower aluminium content, delaying further vaccinations, as well as deep intramuscular injections have been suggested to reduce the risk of inducing further reactions.[1-3] A detailed discussion with parents of these options should be undertaken, in view that subsequent vaccinations may result in similar or more severe delayed-type hypersensitivity reaction.

Our case is the first reported case of itchy subcutaneous nodules caused by aluminium-containing vaccine in Singapore. Health care providers, especially family physicians, community paediatricians and dermatologists should be aware of this uncommon complication of vaccines in children.

Yours sincerely,

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REFERENCES

1. Bergfors E, Trollfors B. Sixty-four children with persistent itching nodules and contact allergy to aluminium after vaccination with aluminium-adsorbed vaccines--prognosis and outcome after booster vaccination. Eur J Pediatr 2013; 172:171-7.
2. Bergfors E, Hermansson G, Nyström Kronander U, et al. How common are long-lasting, intensely itching vaccination granulomas and contact allergy to aluminium induced by currently used pediatric vaccines? A prospective cohort study. Eur J Pediatr 2014; 173:1297-307.

3. Silcock R, Crawford NW, Selvaraj G, et al. Subcutaneous nodules following immunization in children; in Victoria, Australia from 2007 to 2016. Vaccine 2020; 38:3169-77.
4. Jefferson T, Rudin M, Di Pietrantonj C. Adverse events after immunisation with aluminium-containing DTP vaccines: systematic review of the evidence. Lancet Infect Dis 2004; 4:84-90.
5. Chong H, Brady K, Metze D, Calonje E. Persistent nodules at injection sites (aluminium granuloma)--clinicopathological study of 14 cases with a diverse range of histological reaction patterns. Histopathology 2006; 48:182-8.
6. Gente Lidholm A, Inerot A, Gillstedt M, Bergfors E, Trollfors B. Comparison of reactivity to a metallic disc and 2% aluminium salt in 366 children, and reproducibility over time for 241 young adults with childhood vaccine-related aluminium contact allergy. Contact Dermatitis 2018; 79:26-30.
7. Gente Lidholm A, Bergfors E, Inerot A, et al. Unexpected loss of contact allergy to aluminium induced by vaccine. Contact Dermatitis 2013; 68:286-92.