VACCINATION GRANULOMA WITH CONFIRMED ALUMINUM ALLERGY: TWO CASES AND A LITERATURE REVIEW

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Case reports. *Case 1*. A healthy, full-term, 2-year-old little girl presented with her parents to our pediatric dermatology clinic with recurrent localized inflammation on the right thigh, which began around six months of age. Each episode was characterized by pruritus, leading to scratching, followed by erythema and swelling, and was frequently complicated by secondary bacterial superinfection. Previous topical treatments, initiated due to suspicion of a subcutaneous abscess, included topical hydrocortisone butyrate and fusidic acid. Systemic treatment with flucloxacillin led to temporary improvement but not complete resolution. Notably, each flare-up was preceded by a viral or bacterial infection.

On clinical examination, a mildly erythematous macule was observed on the right thigh. Palpation revealed a subtle subcutaneous nodule (Fig. 1). There were no remaining signs of active infection.

An ultrasound performed during the initial exacerbation revealed an ill-defined area of increased echogenicity within the subcutaneous fat at the site of induration, indicative of edema. Additionally, several small, partially communicating hypoechoic components were noted, extending over a total length of approximately 1.7 cm (Fig. 2). Color Doppler imaging showed moderate localized hyperemia.

A follow-up ultrasound performed one month later showed a persistent but slightly reduced inflammatory reaction in the anterior region of the right thigh. Furthermore, a minimal reduction in the volume of the branching and lobulated hypoechoic collections was noted. These findings were consistent with a chronic granulomatous inflammatory process.

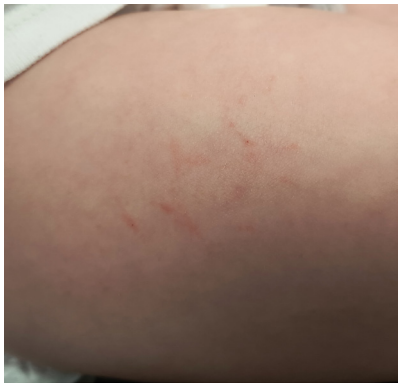

Fig. 1

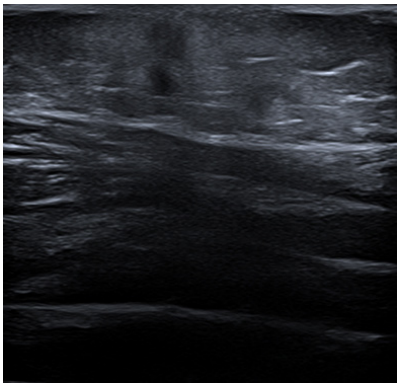

Fig. 2

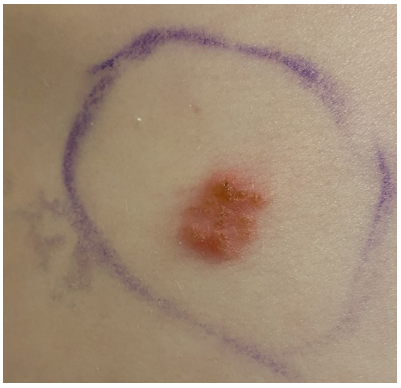

Fig. 3

Figs 1, 2, 3: Vaccination granuloma in Case 1: erythema of the right thigh (Fig. 1); ultrasound shows ill-defined hyperechoic areas and several small, partially communicating hypoechoic components within the subcutaneous tissue. Fig. 3 shows a positive patch test to aluminum on day 4.

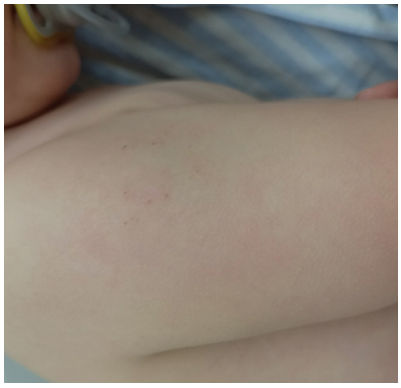

Fig. 4

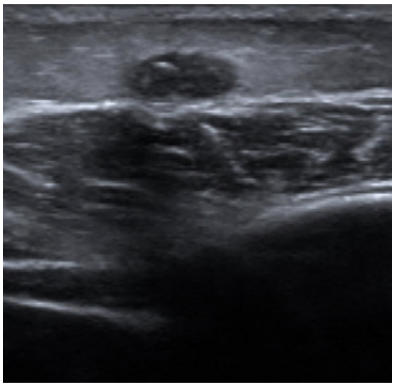

Fig. 5

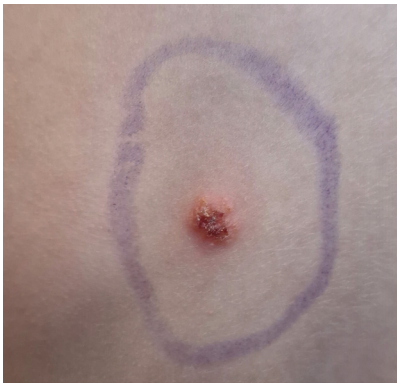

Fig. 6

Figs. 4, 5, 6: Mild eczematous reaction on the right arm in Case 2 (Fig. 4); ultrasound (Fig. 5) shows a dermo-hypodermal hypoechoic area within the palpable plaque beneath the eczema. Fig. 6 shows a positive patch test to aluminum.

Following a review of her medical history, our patient had been vaccinated against diphtheria, tetanus, pertussis, and polio (DTP-IPV vaccine) and *Haemophilus influenzae* type b (Hib) in her right thigh at 2, 3, 5, and 13 months of age.

A diagnosis of vaccination granuloma was suspected, and patch testing was performed using an IQ patch test chamber® (Chemotechnique Diagnostics, Vellinge, Sweden) secured with Mefix® (Mölnlycke Health Care, Gothenburg, Sweden). Aluminum (III) chloride hexahydrate 2% in petrolatum (Chemotechnique Diagnostics) was applied to the upper back. Patch test readings were performed according to the guidelines of the European Society of Contact Dermatitis (ESCD) on day (D) 2 and D4. The test was positive at D2 (+) and strongly positive at D4 (3+), confirming a contact allergy to aluminum (Fig. 3).

Case 2. A second case involves a 2-year-old boy who presented to our pediatric dermatology clinic with recurrent firm subcutaneous nodules located on the right arm and, to a lesser extent, on the right thigh over the past year. The nodules were first noted following the application of a moisturizing cream. According to the mother, excoriation marks had been observed over the lesions one year prior. Otherwise, the nodules remained asymptomatic. The general practitioner initially suspected they were lipomas.

Upon physical examination, two firm, palpable subcutaneous plaques were identified—one on the right arm (Fig. 4) and another, smaller one, on the right thigh.

An ultrasound examination demonstrated a tubular hypoechoic area within the subcutaneous adipose tissue extending up to the dermis, with no detectable internal Doppler signal. In addition, a less well-defined, irregular hypoechoic area measuring approximately 5 × 5 × 5 mm was observed in the subcutaneous fat, which also reached the dermis. There appeared to be an extension toward deeper tissues, with a component measuring up to 7 mm beneath the muscle fascia. No internal Doppler signal was detected. The overall clinical impression favored a post-inflammatory process or sequela (Fig. 5).

Upon further inquiry, the child was found to have been vaccinated with a hexavalent vaccine (Hexyon®; Sanofi, Machelen, Belgium) against diphtheria, tetanus, pertussis, polio, *Haemophilus influenzae* type b, and hepatitis B at 2, 4, 6, and 16 months of age.

Epicutaneous patch testing was performed according to the same procedure as in our first case, using aluminum chloride hexahydrate 2% in petrolatum (Chemotechnique Diagnostics). The test yielded a clearly positive reaction at D2 (1+) and a strongly positive reaction at D4 (2+) (Fig. 6).

Consequently, a diagnosis of vaccination granuloma in the context of a confirmed contact allergy to aluminum was established in both cases.

Discussion. Aluminum-containing vaccines – including those for diphtheria, tetanus, pertussis, hepatitis A and B, human papillomavirus, pneumococcus, meningococcus, and tick-borne encephalitis – are widely used and generally considered safe. However, in a small subset of individuals (approximately 1%), particularly children, subcutaneous or intramuscular administration of aluminum-adjuvanted vaccines can result in the delayed onset of pruritic granulomas at the injection site (1). These granulomas typically present as small, pruritic nodules that emerge weeks to months after vaccination during early childhood. The risk of developing pruritic nodules increases proportionally with the number of vaccine doses administered. Additional manifestations include localized eczematous skin changes, hypertrichosis, and discoloration of the overlying skin, as well as exacerbation of symptoms during intercurrent infections (1). In both of our cases, localized eczematous changes were observed, as well as symptom exacerbation during intercurrent infections.

Granuloma formation is believed to be associated with sensitization to aluminum-containing vaccines, which can result in allergic contact dermatitis upon re-exposure. A contact sensitization to aluminum is seen in 77% to 95% of children presenting with granulomas (2). Sensitization has also been reported following cutaneous exposure to other aluminum-containing products, such as sunscreens, antiperspirants, topical medications, and even metallic aluminum. Interestingly, although isolated cases have been described in both children and adults, most reported vaccination granulomas occur in pediatric populations (3).

From an immunological perspective, aluminum is deliberately added to many vaccines as an adjuvant to enhance the immune response by stimulating the innate immune system. However, a large Danish nationwide cohort study demonstrated that both the type and dosage of the aluminum adjuvant significantly influence the risk of granuloma formation, reinforcing the importance of adjuvant formulation in vaccine safety. Nearly all granulomas in that study were associated with a confirmed aluminum contact allergy. Moreover, aluminum hydroxide adjuvant appears to confer a higher risk than aluminum phosphate (4).

Hoffmann et al. investigated a potential link between vaccination granulomas and atopic predisposition. Their case-control study revealed a significantly higher risk of granuloma formation in children with a diagnosis of atopic dermatitis (AD), while no significant associations were found with asthma or allergic rhinitis. This finding suggests that impaired skin barrier function in AD may facilitate aluminum sensitization via transcutaneous or percutaneous exposure (5).

For diagnostic purposes, patch testing with aluminum chloride hexahydrate 2% in petrolatum has been shown to be more sensitive than testing with metallic aluminum in the form of an empty metallic Finn Chamber® (SmartPractice®, Phoenix, Arizona). This method may therefore be more effective for identifying individuals with an aluminum contact allergy, particularly when evaluating persistent vaccination-site reactions in children (6).

In most cases, aluminum-induced granulomas are benign and self-limiting. They can appear between 2 weeks and 13 months after vaccination and persist for an average of 4.6 years. This finding was confirmed in a French study where 77% of children tested negative for aluminum after 5 years (7). Another long-term clinical study showed that children whose granulomas had completely disappeared did not experience any further recurrences when given aluminum-containing vaccines. Conversely, children whose granulomas were still present may have an increased risk of developing new granulomas. In the latter scenario, the severity of symptoms must be assessed on a case-by-case basis and weighed against the consequences of postponing vaccination (1). This finding was supported by Lidholm et al., who observed that contact allergy to aluminum may diminish over time, as indicated by decreasing patch test reactivity in sensitized individuals (8). It is therefore established that there are no absolute contraindications to further aluminum-adsorbed vaccinations. However, it is recommended to inject the vaccine deeper and preferably at a different anatomical site from where the previous granuloma occurred (9).

In both of our cases described above, itchy nodules were observed within a year after vaccination with an aluminum-containing vaccine. The granulomas appeared to fluctuate, causing concern among the parents. In the first case, the granuloma was misdiagnosed as cellulitis, whereas in the second case it was misdiagnosed as a lipoma, highlighting that aluminum granulomas remain poorly recognized among healthcare providers. Ultrasound imaging allowed for the visualization of the granulomas, but definitive diagnostic confirmation was achieved through a positive epicutaneous patch test for aluminum chloride hexahydrate. This underscores the clinical importance of patch testing.

Conclusion. The present case series is reported to alert clinicians to consider the diagnosis of vaccination granuloma and to demonstrate the causal role of aluminum through patch testing.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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