CASE REPORT

A child with a long-standing, intensely itching subcutaneous nodule on a thigh: an uncommon (?) reaction to commonly used vaccines

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Received 23 October 2012

Revised 28 November 2012

Accepted 6 December 2012

SUMMARY

A 2-year-old girl presented with an intensely itching subcutaneous nodule on the front of a thigh. The nodule persisted for 10 months until it was excised. Subsequent investigation for malignancy and systemic disease showed no pathological findings. The diagnosis, persistent itching vaccination granuloma, was revealed by hazard almost 2 years after the onset of symptoms. Persistent itching subcutaneous nodules at the injection site for aluminium containing vaccines (mostly diphtheria-tetanus-pertussis combination vaccines for primary immunisation of infants) may appear with a long delay after the vaccination (months), cause prolonged itching (years) and are often associated with contact allergy to aluminium. The condition is poorly recognised in Health Care which may lead to prolonged symptoms and unnecessary investigations.

BACKGROUND

We describe a local vaccine reaction that is probably not as uncommon as previously thought, may be troublesome for a small child, alarming to the parents and at worst lead to unnecessary investigations including surgery—but is easy to recognise and diagnose once you have become aware of it.

CASE PRESENTATION

In the summer of 2008, a 2-year-old girl in Sweden got an intensely itching subcutaneous nodule on the front of her left thigh. The nodule grew larger during the autumn, the overlying skin became bluish discoloured and the itching continued, though temporarily reduced during treatment with a topical weak steroid. There was no fluctuation, suppuration, tenderness or other signs of infection. An attempt of treatment with flucloxacillin was of no benefit. In January, 2009, during an acute bacterial bronchitis, the pruritus increased and a new itching induration appeared also on the front of her right thigh. Ultrasound investigation revealed “a subcutaneous mass of undecided nature” measuring 14×16 mm frontally in the left thigh. As a soft tissue malignancy could not be ruled out, the nodule was excised in general anaesthesia in April, 9 months after the appearance. At this time, her parents were really worried.

The histopathological examination of the excised nodule, including light microscopy and immunohistochemistry, showed fibrosing panniculitis with eosinophils. There were no signs of lymphoma or malignancy (figures 1 and 2). So-called eosinophilic

panniculitis, a non-specific tissue reaction associated with a wide variety of conditions including systemic diseases, parasitic infestations, arthropod-induced reactions, infections, atopy and local injections, was mentioned. Clinical-pathological correlation was requested, especially regarding exotic exposure and local injection.

The investigation went on in the paediatric department of the hospital in order to exclude systemic disease. Blood count, differential leucocyte count, sedimentation rate, C reactive protein, serum IgE, electrophoresis and immunoelectrophoresis with subclasses all showed normal values. Blood tests for liver diseases and thyroid function tests were normal. The girl felt well and appeared healthy apart from a mild atypical eczema. The investigation was terminated in September 2009.

In April 2010, the nature of the girl's itching nodule was revealed by hazard when a baby cousin of hers, living in the same county, was invited to a prospective study on vaccination granulomas induced by aluminium (Al) containing vaccines. The enquiry had the title “Do you have a child that itches on the front of a thigh?” The mother of the girl heard about the study and was informed of the typical symptoms and signs of *persistent itching vaccination granulomas*, all of which she now could recognise in her daughter's history.

INVESTIGATIONS

The *history* and *local findings* are crucial in the diagnosis of persistent itching vaccination granulomas. In typical cases, a child aged 1–3 years is observed itching on the front or lateral side of one or both thighs where one or a couple of 2–15 mm subcutaneous firm rounded untender nodules or flat infiltrates can be felt. The intense itching may be very troublesome to the child and frustrating to the family.^{1 2} Increased hair growth, pigment alterations, bluish discolouration and localised eczema may be seen in the itching area.^{1–3} Intensified itching and swelling of the nodules are often reported when the child has a cold or another infection.^{1 2} The course is protracted,^{1 2 4} in average 4–5 years, but, eventually, the nodules disappear and the itching wanes.¹

The *vaccination record* must be checked. The site of the itching subcutaneous nodule shall correspond with the injection site for an Al containing vaccine (mostly a diphtheria-tetanus-pertussis (DTP) combination vaccine). The delay between vaccination and onset of symptoms is often

To cite: Bergfors E, Lundmark K, Nyström Kronander U. *BMJ Case Reports* Published Online First: [please include Day Month Year] doi:10.1136/bcr-2012-007779

Figure 1 (A) Biopsy of subcutaneous fat with well-circumscribed area of fibrosis and heavy inflammatory infiltrate with diffuse and follicular pattern. (B) The infiltrate is composed of macrophages, lymphocytes and eosinophils. There is no cellular atypia. (C) Areas of fibrosis contain eosinophils. (D) The reactive lymphoid follicle. A-D H&E stain, Bar=100 μm.

remarkably long (months or even years).^{1 2 5} The onset may be preceded by an acute infection or by another vaccination without Al content, for example, measles, mumps and rubella (MMR) or inactivated polio virus.^{1 2}

A total of 77–95% of children with vaccine induced itching granulomas are contact allergic to Al.^{1 2 6} An *epicutaneous (patch) test* with metallic Al (an empty Finn Chamber) and Al chloride hexahydrate 2% in petrolatum is recommended in

Figure 2 Infiltrate contains numerous T lymphocytes (A), B lymphocytes, forming reactive follicles (B) and macrophages (C). Proliferative activity is confined mainly to the reactive follicles (D). Immunoperoxidase stains for CD3 (A), CD20 (B), CD68 (C) and Ki67 (D). Bar=100 μm. Arrow points to area with fibrosis, the line encircles reactive follicle.

order to determine if the child has become sensitised or not. A positive patch test confirms the diagnosis vaccination granuloma induced by an Al adsorbed vaccine. On the contrary, the diagnosis is not excluded by a negative test.

DIFFERENTIAL DIAGNOSIS

Other local vaccine reactions are easy to distinguish from the Al-induced itching nodules.

The very common warm red swelling that may occur at the injection site of all vaccines and in all ages may be itching for a while, but appears soon after vaccination (a day or two) and seldom lasts for more than a week. Asymptomatic hard little nodules are often found accidentally at vaccination sites in infants but never itch. An aseptic abscess can also appear months after vaccination but does not itch and has another course with fluctuation and sometimes rupture. Local patches of itching atopic or nummular eczema may, of course, also appear in vaccination areas but are often multiple and seldom fixed to one single location, and lack underlying subcutaneous nodules or infiltrates.

TREATMENT

The subcutaneous nodule will sooner or later resolve spontaneously and needs no treatment but can be excised if it causes very severe itching. Symptomatic treatment with topical steroids group I–III may diminish the pruritus temporarily but parents are often reluctant to use prolonged cortisone treatment. Local cover with a hydrocolloid dressing (Comfeel, Duoderm) protects the sore skin from scratching, seems to have a soothing effect and can be used for a long time.

OUTCOME AND FOLLOW-UP

According to the vaccination record, the girl had received three doses of Al adsorbed DTaP-polio-*Haemophilus influenzae* type b (Hib) vaccine (Pentavac, Sanofi Pasteur MSD) alternating in both thighs at 3, 5 and 12 months. The injections were given intramuscularly in the front of the thighs corresponding to the itching areas. The histopathological findings were consistent with persistent itching vaccination granuloma.

In September 2010, the girl was epicutaneously tested with positive reactions to both Al chloride and metallic Al (figure 3) which, more than 2 years after the onset of symptoms, confirmed the diagnosis. She had no more itching on the left thigh after excision of the nodule. The itching on the right thigh has continued in periods, especially when she has a common cold, and so far lasted for 4 years. The prognosis of the aluminium allergy is unknown. Her next vaccination with an Al containing vaccine, a booster dose of DTP-polio, is planned at the age of 5 years, but will probably be postponed because her parents do not want risk of a new itching nodule.

DISCUSSION

Persistent subcutaneous nodules with intense and long-lasting itching at the injection site of Al adsorbed vaccines (vaccination granulomas, Al granulomas) have been described since the 1970s^{7 8} but were considered to be rare until 2003, when itching nodules at the vaccination site were described in 645 out of about 76 000 children (0.8%) who received Danish DT/P vaccines in a clinical trial in Sweden¹ and later also after currently used DTP-polio-Hib vaccines for primary vaccination of infants (Infanrix and Pentavac).^{2 6} Histopathological examination of the nodules shows granuloma formations in which Al crystals can be demonstrated by staining or atomic absorption spectrometry.^{5 8}

Figure 3 Positive patch test reactions to aluminium chloride hexahydrate 2% in petrolatum (superior) and metallic aluminium (an empty Finn Chamber) (inferior).

Figure 4 The girl's condition, according to herself, 3 years after the excision. Note scar on the front of her left thigh.

Al salts (Al hydroxide and Al phosphate) are used as adjuvants in all vaccines against diphtheria, tetanus and pertussis alone or in combination with polio and Hib vaccines. Also, vaccines against tick-borne encephalitis (TBE), human papilloma virus, and hepatitis A and B are adsorbed to Al. Persistent itching nodules/Al granulomas/ and contact allergy to Al are reported after all these vaccines except TBE.^{1-3 6 9 10}

Contact allergy to Al, which is otherwise considered to be very rare,^{4 11} has been reported in occasional patients with vaccine-induced itching nodules since the 1980s^{3 4 9} and in a high frequency in three studies in Sweden.^{1 2 6} Injection-site itching nodules and contact allergy to Al are also reported in patients injected with Al containing allergen extracts in immuno-specific immunotherapy.^{11 12}

Both persistent itching subcutaneous nodules (vaccination granulomas) and contact allergy to aluminium induced by Al containing vaccines seem to be more common than earlier thought as shown in Sweden in a vaccine trial¹ and following a national investigation.^{2 6} This may of course reflect the active search for adverse events in the trial and our personal interest in the conditions, but it cannot be excluded that aluminium adjuvants (mostly Al hydroxide) in modern vaccines are more reactive than in older vaccines. Strikingly, there have been no reports of itching nodules after the Al phosphate containing DT vaccine that was given in four doses to approximately 1 700 000 children in Sweden from 1979 to 1996.¹

The risk of vaccination granulomas and Al allergy is probably lower when the vaccine is injected intramuscularly rather than subcutaneously. Injecting children is, however, a delicate art and some amount of vaccine might be deposited more superficially than intended during an intramuscular injection. This might explain why an intramuscular injection can cause a subcutaneous nodule as shown in this and several other cases.⁶

An important question is whether children with vaccine-induced itching granulomas and Al allergy can be vaccinated in the future with Al containing vaccines. The main principle is that the risk for new itching granulomas must never withhold vaccination of a child at substantial risk for vaccine preventable diseases. In clinical practice, additional vaccination with Al adsorbed vaccines can be performed without problems when the symptoms of the original itching nodule have ceased. In a recently published follow-up study, only two children of 25 had new itching nodules with mild symptoms after DTP-polio booster vaccination 4–7 years after the primary vaccination.⁶ In children with pronounced and protracted pruritus, the scheduled doses of Al containing vaccines can be postponed for a year or two waiting for the symptoms to subside. The Al allergy is a delayed hypersensitivity type IV, without increased risk for systemic reactions and does not contraindicate future vaccination with Al adsorbed vaccines. Aluminium-free vaccines, like MMR, can be given without restrictions.

Unfortunately, vaccination granulomas are not commonly recognised in health-care which is demonstrated by this case where a small child had to undergo unnecessary treatment with a broad spectrum antibiotic, unnecessary surgery in general anaesthesia, unnecessary investigation with ultrasound and extensive blood sampling—not to tell the anxiety of her parents—before the diagnosis was set by hazard 2 years after the onset of symptoms. Vaccination granulomas mistaken for tumours have also been described by other authors.¹³

Neither persistent itching nodules nor Al hypersensitivity are stated as adverse events in product descriptions for any of the modern DTP combination vaccines which, along with the long

interval between the onset of symptoms and the vaccination, may contribute to poor knowledge of the condition.

The child described in this report was vaccinated according to Swedish routine in the front of her thighs. Persistent itching nodules may of course appear in all ages and at any injection site for Al-containing vaccines.

Certain dermatological products, for example, antiperspirants, lotions, sun protectors, ear drops, Al acetate-based antiseptics and pigments used in tattooing may contain Al. The use of antiperspirants may therefore be impossible in individuals sensitised to aluminium,¹¹ and intradermal deposition of Al containing pigment in a tattoo might lead to severe agony.¹⁴

Al adjuvants are also used in allergen extracts used for allergen-specific immunotherapy (hyposensitisation).^{11 12} Individuals with Al allergy and a history of itching nodules should be aware of this so that Al free allergen extracts can be considered in case they will need this treatment later in life.

Although persistent itching vaccination granulomas may cause great discomfort to a child and frustration to the parents, and we wish that Al salts were replaced by other adjuvants, the condition is benign and self-limiting and, in our opinion, no cause to refrain from vaccination. Recognising adverse events is, however, important to maintain confidence in recommended vaccination programmes.

PATIENT'S PERSPECTIVE

'The lump was itching very much and was troublesome for her during a long time. No one could tell us what it was. We got divergent information. It has been a huggermugger. Now it is a relief to get an answer and good if we can be to any help.' - The girl's mother. The girl now feels well (figure 4).

Learning points

- ▶ Intensely itching subcutaneous nodules (granulomas) may appear at the injection site for aluminium containing vaccines and persist for many years.
- ▶ The nodules appear remarkably long time after vaccination (months or even years).
- ▶ Most patients with vaccine-induced itching nodules have become contact allergic to aluminium.
- ▶ Vaccine-induced itching nodules are mostly seen in small children after DTP vaccination.
- ▶ Aluminum is present in all vaccines against diphtheria-tetanus-pertussis, hepatitis B, human papilloma virus infection and tick-borne encephalitis and in some vaccines against hepatitis A and pneumococcal and meningococcal infections.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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