

Case report

Aluminium-induced granulomas after inaccurate intradermal hyposensitization injections of aluminium-adsorbed depot preparations

Background: The development of persistent subcutaneous nodules at the injection sites of aluminium-adsorbed hyposensitization solutions is rare. These nodules have been interpreted as a delayed, granulomatous hypersensitivity reaction to aluminium. We report for the first time a case of persistent intradermal granulomas that developed at the sites of inaccurate intradermal, instead of subcutaneous, hyposensitization injections.

Methods: An intradermal nodule was excised and processed for histopathology, scanning electron microscopy, and X-ray microanalysis. Intradermal and patch tests with aluminium hydroxide were performed.

Results: Histologically, the nodule presented a pattern of granulomatous inflammatory reaction surrounding foci of necrotic tissue. Scanning electron microscopy and X-ray microanalysis revealed deposits of aluminium within the granulomas. Patch tests with aluminium hydroxide were negative, and intradermal tests caused persistent intradermal granulomas. Subsequent hyposensitization therapy in our department with the usual subcutaneous injections of aluminium-adsorbed allergen extracts was well tolerated by the patient.

Conclusions: Local toxic effects of aluminium may be crucial in the development of persistent intradermal injection-site granulomas. Such intradermal nodules may develop even if the subcutaneous route is well tolerated. We conclude that inaccurate intradermal injections of aluminium-containing solutions have to be strictly avoided.

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Key words: aluminium hydroxide granulomas; hyposensitization; injection-site granulomas; intradermal tests; patch tests; side-effects; X-ray microanalysis.

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Accepted for publication 23 March 2000

Aluminium-containing hyposensitization solutions are widely used, as the aluminium adjuvant is thought to prolong the period of activity of the antigen, thus increasing the immunologic response (1). With these vaccines, transient subcutaneous nodules have been observed in 20–30% of patients at the injection site after the acute local reaction has subsided (2–4). The palpable subcutaneous nodules usually resolve within a few weeks (2). A foreign-body reaction to aluminium hydroxide and an immunologic interaction with the administered antigen have been postulated to explain the appearance of these transient injection-site nodules (4). However, 0.5–6% of hyposensitized patients develop persistent subcutaneous nodules at the injection site (2, 5–7). These nodules are usually painful and pruritic and may last for up to several years (2, 6–7). The persistent subcutaneous nodules have been attributed either to a foreign-body reaction to aluminium hydroxide (7, 8) or, more frequently, to a delayed hypersensitivity reaction to aluminium hydroxide

(2, 7, 9). For the first time, we describe the development of intradermal aluminium-induced granulomas at the injection sites after inaccurate intradermal, instead of subcutaneous, hyposensitization injections.

Case report

A 59-year-old woman with a 2-year history of multiple persistent intracutaneous nodules on both forearms was first seen in our department. The nodules had developed over the preceding 2 years at the sites of inaccurate intradermal injections of aluminium-containing hyposensitization solutions (ALK-Depot SQ 802, Scherax, Hamburg, Germany, containing selectively purified major allergens of wasp venom [*Vespula* spp.] adsorbed to aluminium hydroxide [4 mg/ml]). The lesions had never been painful or itching. We could ascertain that the intradermal injections were repeatedly given over 2 years in an out-of-town outpatient department, although multiple nodules had developed at the



Figure 1. Dorsal aspect of forearms. Multiple reddish, indurated, intradermal nodules at previous intradermal injection sites.

injection sites. The intradermal nodules developed after the inaccurate hyposensitization injections with a delay of approximately 1 week. The injections were given on the lower forearms, and not on the upper arms, which are normally used for hyposensitization injections.

On examination, the patient was found to have multiple reddish, indurated, intradermal nodules at the previous injection sites on the forearms (Fig. 1). The size of the nodules ranged from 1 to 2 cm in diameter.

After test applications of aluminium hydroxide, which are described below, subsequent wasp-venom immunotherapy in our department, with the usual subcutaneous injections of aluminium-adsorbed allergen extracts (ALK-Depot SQ 802, Scherax, Hamburg, Germany) given on the upper arms, was well tolerated by the patient without development of persistent nodules in the injection sites. In our department, subcutaneous injections of 1.0 ml ALK-Depot SQ 802 containing wasp venom (concentration 100 µg/ml) were initially done weekly and later monthly over a period of 1 year without development of persistent nodules during this time. Before we started the hyposensitization therapy, we performed prick and intradermal tests with a pure wasp-venom solution (without aluminium) to confirm wasp-venom allergy. Both prick and intradermal tests with wasp-venom solution showed a positive reaction after 20 min, confirming wasp-venom allergy, but granulomas did not develop.

Material and methods

An intradermal nodule on the lower part of the patient's right arm was excised and fixed in formalin. One-half of the nodule was processed for histopathology by standard techniques and stained with haematoxylin-eosin (HE), a combined periodic acid-Schiff (PAS)-Alcian blue stain, Ziehl-Neelsen, Gram, and Giemsa. The other half of the nodule was processed for scanning electron microscopy and EDAX microanalysis (energy

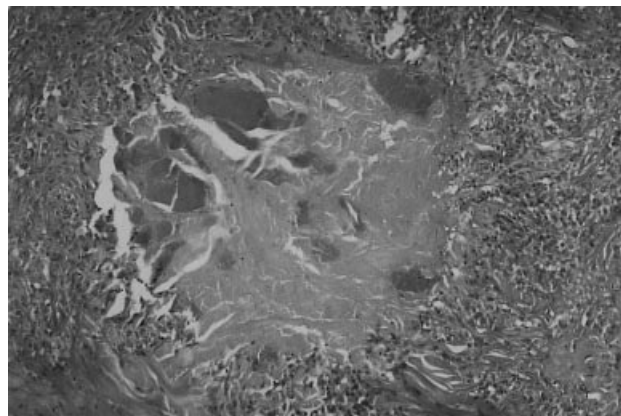


Figure 2. Granuloamorphous necrotic foci surrounded by palisaded histiocytes with granular, PAS-positive cytoplasm (Alcian blue-PAS, × 10).

dispersive analysis of X-rays). Intradermal and patch tests were performed after informed consent by the patient with a sterile aluminium hydroxide aqueous solution without wasp venom at a 0.5% dilution for intradermal testing and a 10% dilution for patch testing, respectively (Scherax, Hamburg, Germany). Intradermal tests were done on the volar aspect of the forearm, with histamine (10 mg/ml) and normal saline as positive and negative control, respectively. Reactions were read after 20 min, 24 h, 48 h, and 72 h. Intradermal testing of a healthy control person with aluminium hydroxide was also done. Both the patient and the control person were followed up for 1 year to detect the development of granulomas at injection sites. Patch tests were done with large Finn chambers with a diameter of 12 mm. A volume of 70 µl of the patch test preparation was applied. Patch tests were performed twice. First, the patches remained only 24 h on the back before removal to show a toxic/irritative reaction. This patch test was read at 24, 48, 72, and 96 h. Later, after exclusion of a toxic/irritative test reaction, a second patch test was done with occlusion for 48 h. These reactions were read at 48, 72, and 96 h.

Results

Histologically, the reticular dermis contained basophilic granuloamorphous necrotic foci staining positively with PAS, intermingled with fragments of collagen fibres (Fig. 2). Surrounding these necrotic foci, zones of palisaded histiocytes containing granular PAS-positive material were found, some of them with an epithelioid appearance. These granulomas were surrounded by some nodular aggregations of lymphocytes and a mixed inflammatory infiltrate consisting of abundant eosinophils, lymphocytes, histiocytes with mostly granular cytoplasm, neutrophils, plasma cells, a few multinucleated giant cells, and some collections of epithelioid cells. Special stains (PAS-Alcian blue, Ziehl-Neelsen,

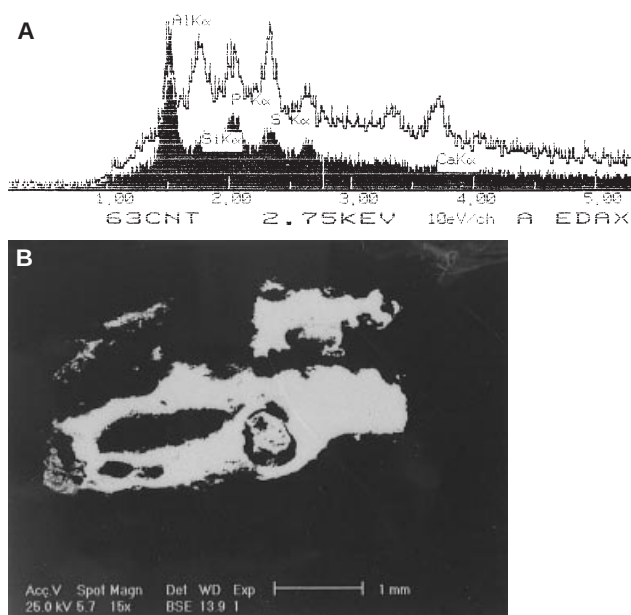


Figure 3. A) X-ray microanalysis establishing presence of aluminium (Al-1.46 keV). B) Image of aluminium by scanning electron microscopy. Diffuse distribution of deposits in reticular dermis (BSE image).

Gram, and Giemsa) did not reveal any organism. The subcutaneous tissue was not affected. Scanning electron microscopy with back-scattered electron detector (BSE) showed a diffuse distribution of deposits throughout the dermis (Fig. 3B). These deposits were confirmed as aluminium by EDAX. Spot analysis over the positive intradermal regions showed a prominent peak at 1.46 keV representing the K_{α} peak of aluminium (Fig. 3A).

Intradermal tests with aluminium hydroxide were negative at 20 min, but showed a local reaction (erythematous infiltration with a diameter of 5 mm) at 24, 48, and 72 h. Intradermal testing of a healthy control person with aluminium hydroxide was negative at 20 min, but showed a local reaction with a diameter of 6 mm at 24, 48, and 72 h. Both the patient and the control person developed a small persistent intradermal nodule at the injection site after the acute local reaction had subsided. These intradermal nodules persisted during a follow-up period of 1 year (patient) and 18 months (control person). After the follow-up period, we excised the intradermal nodule of the control person. Histologically, there was a histiocytic formation of an intradermal granuloma similar to the patient's granulomas. Both patch tests of the patient, with occlusion times of 24 and 48 h, respectively, showed a negative reaction to aluminium hydroxide at 24, 48, 72, and 96 h.

Discussion

Transient nodules frequently occur at vaccination or

hyposensitization injection sites, and disappear spontaneously after a few weeks (2, 7, 10). In contrast, persistent subcutaneous granulomas at injection sites rarely follow vaccine or hyposensitization injections (2, 6, 7, 11). Persistent subcutaneous nodules have been reported to develop after injection of diphtheria-tetanus-pertussis, hepatitis B, influenza, smallpox, and poliomyelitis vaccines, and after hyposensitization therapy with allergen extracts (2, 6, 7, 10–14). These reactions are different from those in our patient, because they are typically located subcutaneously. In contrast, our patient presented with persistent intradermal nodules due to inaccurate intradermal injections of hyposensitization solutions. To our knowledge, this peculiar constellation has not been reported before.

In previous studies, aluminium crystals have been demonstrated within subcutaneous injection-site granulomas by histochemistry (9, 10, 15), electron microscopy (10, 16), X-ray microanalysis (1, 10, 14–16), and atomic absorption spectrophotometry (10, 14). Therefore, it is generally accepted that aluminium is the causative agent. In our patient, the intradermal granulomas also contained aluminium, as shown by electron microscopy and X-ray microanalysis. Thus, we also support a causative role of aluminium in the development of intradermal granulomas in our patient. However, the pathogenesis of aluminium hydroxide granulomas is still a matter of discussion. A foreign-body reaction to aluminium hydroxide has been suggested, as some injection-site granulomas were shown to be composed of histiocytes and giant cells with central necrosis, lacking a significant inflammatory infiltrate (6–8). This appearance of a foreign-body granuloma with a predominant histiocyte response has been interpreted as a nonallergic, possibly direct toxic effect of aluminium (7–14). In contrast, other injection-site granulomas were defined histologically as immunogenic granulomas (17) presenting a distinct lymphocytic infiltrate with some nodular lymphoid aggregation and abundant eosinophils in addition to a granulomatous reaction (7, 10, 14, 17). This pattern suggests a delayed granulomatous hypersensitivity reaction secondary to persistence of the antigen (7, 14, 16, 18). Further evidence of aluminium allergy has been offered by various studies of patients with injection-site granulomas showing positive patch tests with aluminium (5, 7, 11, 13). Moreover, positive reactions to aluminium have been found in intradermal tests (17, 19). As aluminium has a low sensitization potential, a delayed hypersensitivity reaction to this metal is uncommon, despite its wide distribution in drugs and cosmetics, and its extensive industrial use (2, 20, 21). A typical route of sensitization appears to be the injection of aluminium-adsorbed vaccines (2, 5, 12), whereas topical applications of aluminium, as in antiperspirants, or occupational exposure to aluminium dust does not seem to be strongly sensitizing (5, 22).

Our findings suggest that a toxic local reaction to aluminium with formation of necrosis was crucial in the pathogenesis of the intradermal granulomas of our patient. Histologically, the nodules corresponded to granulomas surrounding necrotic foci with features of a so-called granular cell reaction (23, 24), which is occasionally found at sites of trauma (24, 25). While this histologic pattern supports a nonallergic pathogenesis, the presence of focally dense lymphocytic infiltrates with abundant eosinophils and plasma cells may be interpreted as a superimposed immune response. In addition, collections of epithelioid histiocytes were found within the granulomas. Granulomas consisting of epithelioid cells have been interpreted as granulomatous allergic reactions (26).

In contrast, patch tests to aluminium hydroxide were negative in our patient. Thus, aluminium allergy could not be confirmed in our patient. The delayed local reaction that was revealed in the intradermal testing may be interpreted as a nonallergic reaction, possibly due to a local toxic effect of injected aluminium, as a similar reaction was found in intradermal tests of a healthy control person. The delay may be due to local toxic necrosis followed by nonallergic reactive granuloma formation. After the local reaction had subsided, both the patient and the control person developed a small persistent intradermal nodule at the injection site of the aluminium solution. The intradermal nodule of the control person was excised, and it showed, histologically, an intradermal granuloma formation similar to the patient's granulomas. In contrast, prick and intradermal testing of the patient with a pure wasp-venom solution (without aluminium) did not cause development of granulomas. In summary, the intradermal injection of aluminium caused development of

granulomas, whereas the intradermal injection of wasp venom did not. Thus, a causative, possibly toxic role of aluminium in the development of intradermal granulomas is supported by these findings. Although a superimposed effect of the wasp venom cannot be totally excluded in the granuloma formation, wasp venom appears not to be necessary for this formation.

Interestingly, our patient tolerated very well subsequent immunotherapy with the usual subcutaneous injections of aluminium-adsorbed allergen extracts without development of persistent nodules at the injection sites. This observation provides further evidence that the development of the intradermal nodules may be due to a nonallergic foreign-body reaction to aluminium hydroxide, and not to aluminium allergy. The tight reticular dermis may enhance the local toxic effect of injected aluminium, whereas injections into the loose subcutaneous tissue are likely to be less toxic.

It may be concluded that local toxic effects of aluminium with consecutive dermal necrosis were probably crucial in the development of intradermal injection-site granulomas in our patient. However, a superimposed immune response is suggested by the histopathologic findings, especially with regard to the abundant eosinophils and nodular aggregations of lymphocytes and epithelioid cells. This is in agreement with a recently proposed hypothesis for the pathogenesis of subcutaneous injection-site granulomas (7).

Of course, intradermal injections of allergen extracts containing aluminium have never been recommended. The findings presented herein show very clearly that such injections have to be strictly avoided, and emphasize the necessity of competent performance of immunotherapy.

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