

Persistent Subcutaneous Nodules in Children Hyposensitized with Aluminium-Containing Allergen Extracts

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A follow-up study of 202 children who had received hyposensitization with aluminium-containing allergens showed that 1-3 years after cessation of hyposensitization 13 children still had severely pruriginous treatment-resistant subcutaneous nodules in their forearms. Because of their long persistence the nodules of six children were studied in detail. Histologically, the nodules showed infiltration with lymphocytes (forming germinal centres), macrophages, plasma cells, mast cells and a few eosinophils. In five patients aluminium crystals were found scattered between the cells and, in addition, the phagosomes of the macrophages contained aluminium. Patch tests for aluminium were positive in four of the six patients. It is concluded that persisting nodules during hyposensitization with aluminium-containing allergens may indicate development of aluminium hypersensitivity, and if this is confirmed hyposensitization should be discontinued.

Key words: aluminium-hypersensitivity; hyposensitization; persistent subcutaneous nodules.

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Treatment of IgE-mediated allergies by means of specific hyposensitization is becoming increasingly widespread. The most commonly used extracts are aluminium-containing antigen solutions. A known side effect of these solutions is in about one third of the patients is the development of palpable nodules after the acute local reaction has subsided (7, 12). The cellular composition of the cutaneous infiltrates forming the nodules has been examined in detail by Baumgarten (1). Normally, the nodules are transient in nature and to our knowledge have never persisted for more than 6 months after the completion of hyposensitization.

After we had seen a patient with severely pruriginous, treatment-resistant cutaneous nodules, which had persisted for more than 12 months after cessation of hyposensitization, we decided to estimate the frequency of this

unpleasant side effect, and to study the nodules in greater detail.

PATIENTS AND METHODS

The study comprised 202 children aged 6-15 years (mean age 10.5 years) who, after evaluation at the Children's Allergy Clinic, had received hyposensitization therapy with various aluminium-containing allergen extracts from their general practitioner for an average of 3 years. All the injections had been given subcutaneously on the patients' forearms. Thirteen (4%) of the children complained of severe itching of the forearms for more than 1 year (range 1-3 years) after cessation of hyposensitization. None of the 13 children suffered from atopic dermatitis. In most of the 13 children persisting, pruriginous nodules had developed

Table 1

Patient No.	1	2	3	4	5	6
Allergen used	Mi	T	T	T + M	T	T
Itching with allergen contact	-	-	+	-	-	+
Years since last hyposensitization	2½	1½	3	1	1	1
Aluminium deposits in the skin	+	-	+	+	(+)	+
Positive patch test to A1C1	pos	pos +	pos +	neg	neg	pos +

In patient No. 2 Alpyral® was used, in the others Alutard®.

Mi: Mite; T: Timothy; M: Mould.

(+): No typical cellular reaction.

pos +: Tested twice.

on the forearms during the course of treatment. In addition, some patients had experienced aggravation of pruritus in contralateral nodules at the time of hyposensitization and exacerbation of the symptoms on environmental exposure to the antigen for which they received hyposensitization therapy.

Of the 202 children studied, 179 had received hyposensitization with Alutard® and 23 with Alpyral®. One of the 13 children with nodules had been treated with Alpyral, the remaining with Alutard.

The parents of six of the 13 children gave their informed consent for their child to have a nodule removed for histological examination.

The biopsies were divided into two parts. One part was frozen in liquid nitrogen and stored at -80°C, the other was fixed in formalin and processed for routine histological examination. Paraffin sections were stained with hematoxylin and eosin, van Gieson, methylgreen-pyronin and Giemsa. Mast cells and neutrophils were visualized by naphtol-ASD-chloroacetate esterase reaction (11), and aluminium was demonstrated by the method described by Irwin (4).

Paraffin and cryostat sections were also stained by the two-layer immunoperoxidase method (8) for IgG, IgA, IgM, IgD and IgE heavy chains. The antibodies used were all purchased from DAKO, Copenhagen, Denmark. Sections were also stained by the immunoperoxidase method for timothy grass (*Phleum pratense*) antigen in a patient hyposensitized with

this allergen using a rabbit anti-timothy grass antibody purchased from Allergologisk Laboratorium, Copenhagen, Denmark. In one case small specimens were taken from the paraffin block and re-embedded in Epon for electron microscopical examination.

All six patients, none of whom had active eczema at the time, were patch-tested with 2% aluminium chloride in water applied on filter paper discs occluded with Finn-Chambers® and fixed with Scan-pore® tape. The tests were read after 48 and 72 h. Positive tests were repeated at a later date, with and without Finn-Chambers. For control purposes, 25 children between the ages of 5 and 15 years with atopic dermatitis who had not been desensitized were patch-tested by the same method.

During a 3-year period, 251 patients with other dematoses were patch-tested routinely with metal screening agents which included the above aluminium patch test.

RESULTS

Some clinical details of the six patients are presented in Table 1. All had received immunotherapy with Al-containing allergen extracts. None suffered from atopic dermatitis. Itching on environmental exposure to the allergen in question was observed in two.

The nodules varied in size from 0.3 to 2 cm, and in number from 3 to 20. Most of the nodules were firm, dark red or brown and with excoriations.

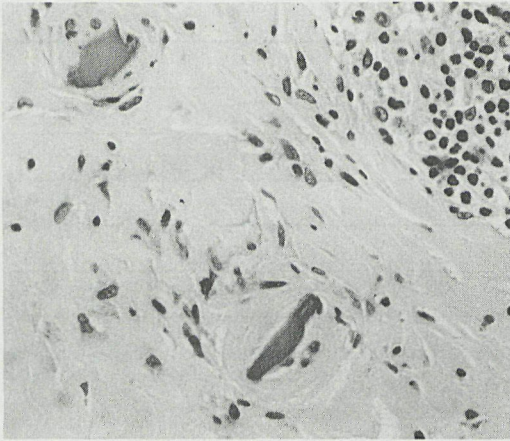


Fig. 1. Arrows indicate crystal-like structures embedded in collagen and surrounded by a few macrophages. Hematoxylin-eosin.

Four of the six patients (Table 1) had positive patch tests to aluminium. Two had intense itching at the patch test site for 2 weeks after the test. A follicular reaction was seen in patient No. 1. All the positive tests remained positive for at least a week. The aluminium patch tests were repeated in patients 2, 3 and 6 and were also positive the second time, both with and without Finn-Chambers. Patient No. 3 experienced increased itching of the nodules on the forearms after both patch tests. Because of severe discomfort the first time, patient No. 1 did not want to have the patch test repeated.

None of the children who were patch-tested for control purposes had positive reactions, neither were there positive reactions among the other 251 control patients.

Histologically, the nodules of four of the patients (Nos. 1, 3, 4 and 6, Table 1) were located to the subcutaneous tissue. Apart from focal acanthoses and non-specific perivascular lymphocytic infiltration in the dermis, the epidermis and dermis showed no changes in these patients. The subcutaneous tissue showed nodular cellular infiltrates separated by bands of collagen. The composition of the cellular infiltrates varied from patient to patient, and from one area to another in the same patient, but for all of them it was dominated by lymphocytes and macrophages. The lympho-

cytes were seen either diffusely or in nodules forming germinal centres. The macrophages had an abundant, heavily granulated cytoplasm. Mast cells, plasma cells and a few eosinophils were scattered between lymphocytes and macrophages. In the subcutaneous tissue of all four patients crystal-like structures (Fig. 1) 20–30 μ wide and up to 100 μ long were seen in the collagen or surrounded by groups of macrophages. These structures stained pale eosinophilic or amphophilic with hematoxylin eosin, and stained positive for aluminium. The macrophage cytoplasm stained negative for aluminium by the histochemical method. The Epon-embedded tissue contained a few of these crystal-like structures together with groups of macrophages (Fig. 2a and b). Both the crystal-like structures and the macrophage phagosomes contained aluminium as revealed by X-ray microanalysis (Fig. 3a and b).

In patient No. 2 focal fibrous thickening, without cellular infiltration or deposition of crystal-like structures was found in the dermis. In patient No. 5 a well-circumscribed collagen nodule with a central fibrinoid necrosis was found in the junction area between the dermis and subcutaneous tissue. The collagen was almost acellular, but contained a few macrophages and a few crystal-like structures which stained positive for aluminium, but no other cellular elements.

The immunoperoxidase-stained section showed, in the section stained for immunoglobulins, that the plasma cell component was dominated by IgG-producing cells with scattered IgA- and IgM-positive cells and very few IgE-positive cells. In both paraffin embedded material and fresh frozen material the mast cells stained positive for IgE. No timothy grass antigen could be demonstrated in the tissue. The dermatologist and the pathologist made their observations without knowledge of each other's findings.

DISCUSSION

Cutaneous infiltrates following injections of Al-containing allergen extracts are not uncommon (5, 9), and similar lesions have been reported in

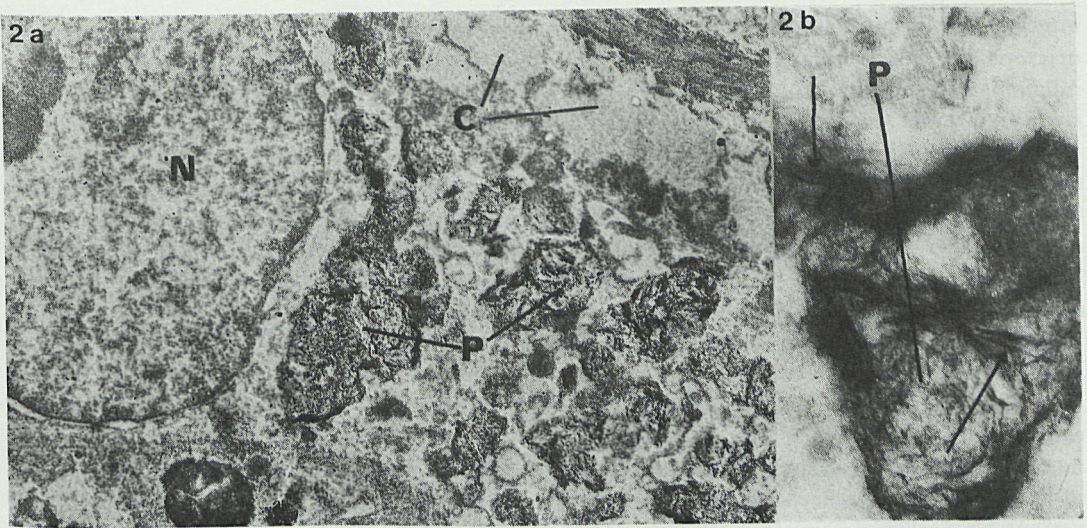


Fig. 2a, b. Part of a macrophage with phagocytosed material. N denotes the nucleus and P phagosomes containing electron dense needle-shaped material (arrows) which gave a strong aluminium signal. Extracellular collagen is marked C. Magnification: Fig. 2a 10,500 $\times$, Fig. 2b 64,000 $\times$.

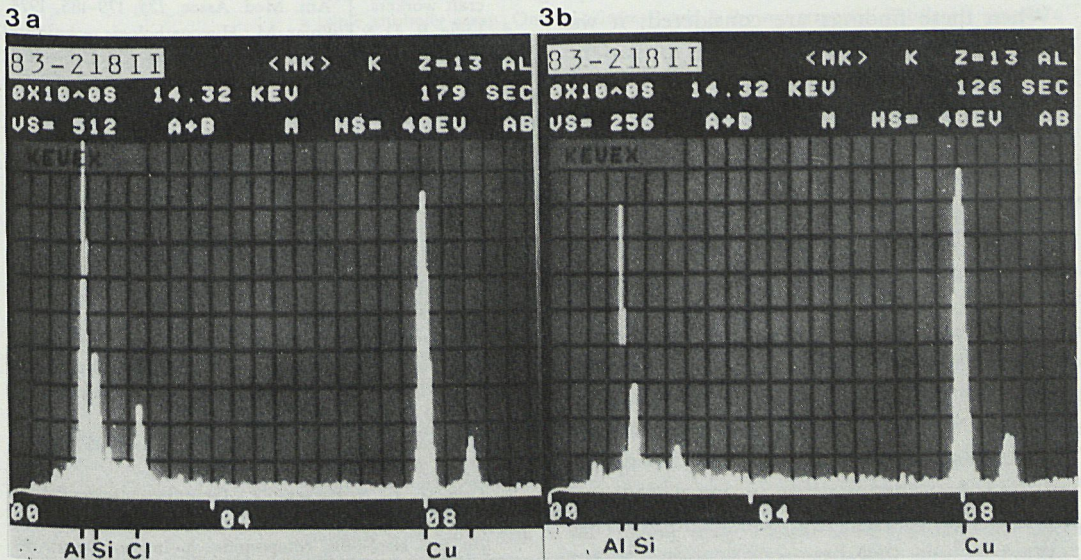


Fig. 3a, b. X-ray microanalysis spectra from a macrophage phagosome (Fig. 3a) and nucleus (Fig. 3b) showing the K-peaks for the elements present. The aluminium K-peak of the phagosomes is absent over the nucleus. Silicon, chloride and copper peaks originate from the X-ray detector, the Epon embedding medium, and the copper grid, respectively.

patients immunized with Al-containing diphtheria/tetanus vaccines (6). The cellular composition of the nodules resembled that of an immediate immunological reaction as described by Baumgarten (1). However, these earlier described cutaneous infiltrates all vanished after a few weeks or months (mean 4 weeks). In

contrast, the nodules of our patients persisted for 1-3 years after cessation of hyposensitization therapy and we were not able to demonstrate persisting antigen in the nodules. On the other hand, the majority of the nodules contained crystal-like structures showing a positive histochemical reaction to aluminium, and alumi-

um content was found in the phagosomes of the macrophages. These findings, together with the inflammatory infiltrates, suggest hypersensitivity towards aluminium in these patients.

Contact sensitivity to aluminium is rare. Clemmensen & Knudsen (2) described a patient who was hyposensitized with an aluminium-absorbed allergen. This patient, who did not have a previous history of skin problems, developed eczema during hyposensitization, and patch tests with various aluminium salts showed a strong positive reaction. None of the 53 adults, and nine children who served as controls, had positive patch tests to aluminium, nor were positive aluminium patch tests found in 10 patients who had been hyposensitized with various aluminium-precipitated allergens. Hall (3) did not find any with contact sensitivity to aluminium among 202 workers in factories contaminated with aluminium dust.

When these findings are considered, it was highly unexpected that four of our six patients had a positive patch test to aluminiumchloride and not to any other metal. Aluminium hypersensitivity was found not only in the patients with intense infiltration of the subcutaneous tissue with inflammatory cells, but also in the patient with acellular fibrosis in whom no aluminium deposits were seen. The lack of aluminium deposits in this patient may have been due to an unrepresentative biopsy. On the other hand, a typical clinical and histological reaction with aluminium deposits was seen in the patient without aluminium hypersensitivity. The fibrosis in the junction between the dermis and the subcutaneous tissue in one patient was probably due to false injection technique (10).

We conclude that hyposensitization therapy with Al-containing allergen extracts may represent a potential risk for the development of persisting aluminium-containing pruriginous nodules at the injection sites, and that the appearance of such nodules may be associated with aluminium hypersensitivity. In all the children studied this was a very unpleasant and disturbing event which seemed resistant to all kinds of treatment, perhaps because the aluminium was constantly present. In the present patients, as well as in other children on

hyposensitization therapy (unpublished results), we have observed that pruriginous nodules, which develop after injection with Al-containing allergen extracts and persist for more than 6 weeks, may indicate that the patient is developing hypersensitivity to aluminium. In such cases, we recommend testing for hypersensitivity, and if the test is positive discontinuation of hyposensitization with the aluminium-containing extract.

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