Cutaneous-subcutaneous pseudolymphoma after specific immunotherapy with grass-rye pollen-allergen extract containing aluminium hydroxide

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Abstract

Allergen-specific immunotherapy is an important treatment procedure in IgE-mediated allergic diseases such as allergic rhinitis or insect toxin allergies. A reduction in the clinical reaction to the allergens to which the patient is known to be sensitized is intended by means of antigen-specific influence on the immune system. The allergen-specific immunotherapy can be applied by subcutaneous injections, and for selected allergens by means of sublingual application of the appropriate allergen. Occasionally, the injection of aluminium hydroxide-adsorbed sera induces a usually transient formation of granulomas. We are reporting on a rare case of cutaneous-subcutaneous pseudolymphoma in the injection area of both upper arms, probably induced by subcutaneous allergen-specific immunotherapy.

Key words: allergen-specific immunotherapy, pseudolymphoma, aluminium hydroxide.

In memoriam of Professor Dr. Dr. h. c. J. Hasik (Poznań) and dedicated to Professor Dr. Dr. h. c. K. Seige (Halle/Saale).

Introduction

"Semi-depot preparations" for use in subcutaneous allergen-specific immunotherapy (SCIT) are native or modified allergens coupled physically to a carrier substance such as aluminium hydroxide, tyrosine or calcium phosphate. The local onset of granulomas following injection of aluminium hydroxide-adsorbed sera or allergen extracts is a known side effect. Occasionally, the onset of these nodules and nodes is attributed to a superficial (intradermal) injection technique, but often, especially when localization is subcutaneous, to a foreign body reaction to aluminium hydroxide [1]. A possible contact sensitization to aluminium salts is also discussed, especially if the subcutaneous nodes persist [2, 3]. The induction of pseudolymphomas by allergen extracts containing aluminium hydroxide has been described thus far only in isolated cases.

Case report

A 24-year-old man developed pruriginous cutaneous-subcutaneous nodes at the injection sites on the extensor side of the upper arm 5 years after termination of a SCIT with grass-rye pollen allergen extracts containing aluminium hydroxide (Figs. 1-2). The SCIT had been conducted over 3 years without complications.

The histological findings in a tissue sample taken from the right upper arm revealed massive cell-rich infiltrate

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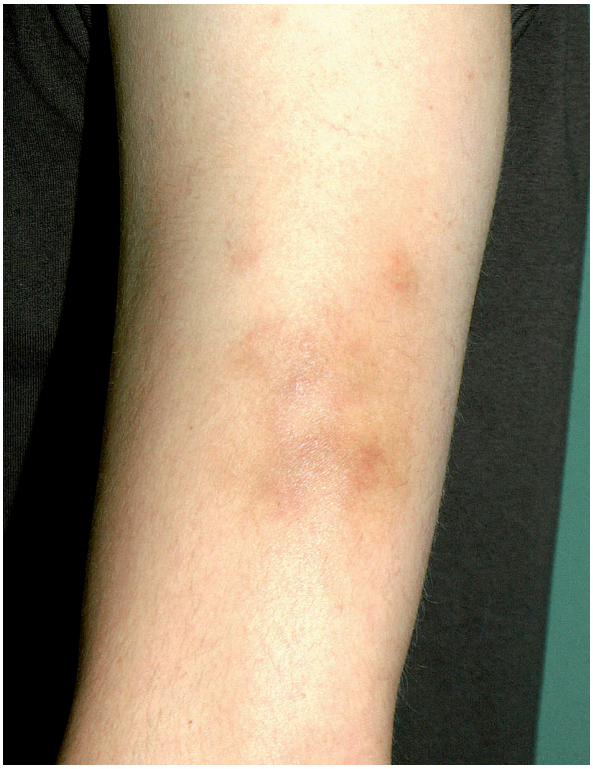

Fig. 1. Cutaneous-subcutaneous nodes at the injection sites on the extensor side of the left upper arm

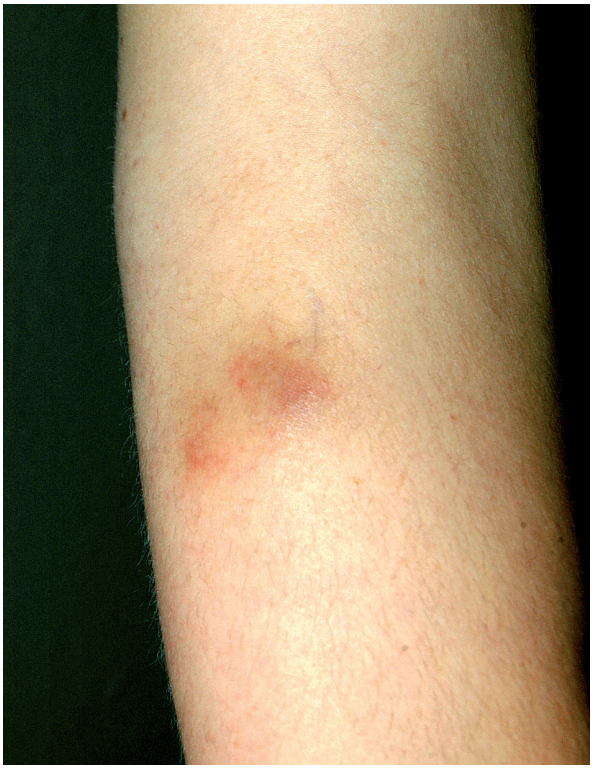

Fig. 2. Cutaneous-subcutaneous nodes at the injection sites on the extensor side of the right upper arm

zones with lymphocytes, plasma cells (infiltrate polymorphism) and pronounced marginal centres in the lower corium and neighbouring subcutis (Figs. 3A-B). Thus the general pattern of a reactive B-cell-accentuated pseudolymphoma was present, which could also be demonstrated in the immunohistochemical examination by means of proof of a so-called infiltrate polymorphism. Especially conspicuous was the detection of CD79-positive infiltrate cells (Fig. 4A), almost completely in the marginal centres and additionally in path-like patterns in the surrounding lymphocytic infiltrate. Moreover, in addition to a clear marking of CD4 positive cells, there was also a loose distribution (ca. 5%) of CD8-positive cells (Fig. 4B). There was no evidence of foreign-body granuloma.

Additional examinations

X-ray diffraction analysis of native and paraffin-fixed tissue (Bundesanstalt für Materialforschung und –prüfung, Berlin/Germany). No evidence of crystalline material. Clear classification with X-ray diffraction analysis was not possible.

Patch testing

Aluminium chloride 2% in Vaseline: negative (readings to 72 h).

Relevant laboratory parameters

Serology for *Borrelia* species and *Treponema pallidum*: both negative.

Therapy

Intralesional glucocorticosteroid injections were made. Regression of the lesions could only be achieved in part, so that excision or radiotherapeutic treatment of the nodes may have to be considered in the future.

Discussion

Allergen-specific immunotherapy (hyposensitization) as treatment of allergic diseases is an important and established therapeutic procedure these days, especially since, unlike with symptomatic therapeutic approaches, causal therapy of the underlying allergy is possible. The effect of aluminium as an adjuvant is not yet entirely understood. Recent articles, however, indicate that in addition to the production of proinflammatory cytokines such as IL-1β and IL-18 through macrophages via the release of endogenous danger signals (such as elevated uric acid values), and via activation of inflammatory dendritic cells, aluminium may potentiate the immune response [4, 5]. Local formation of granulomas after injection of aluminium hydroxide-adsorbed sera or allergen extracts is

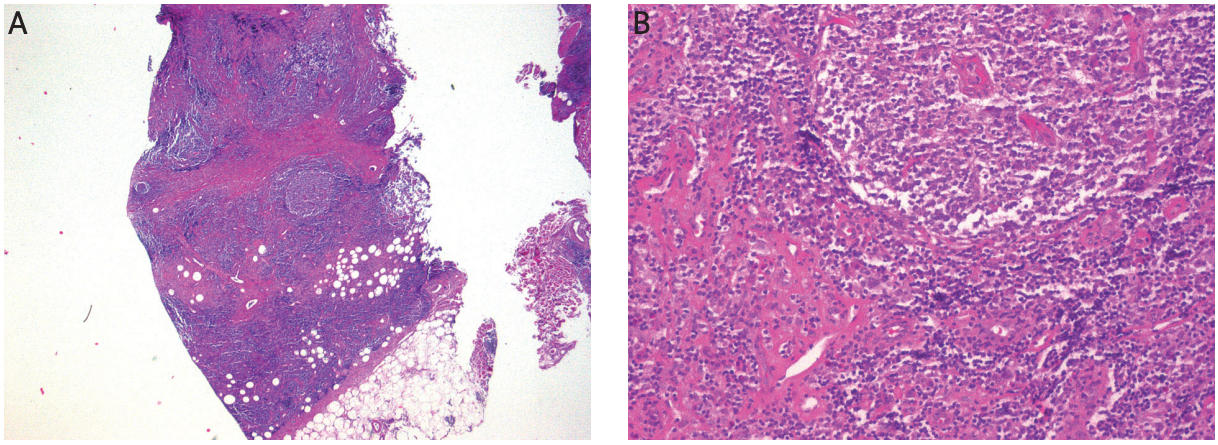

Fig. 3. A – Histology: cell-rich infiltrate zones with infiltrate polymorphism and pronounced marginal centres in the lower corium and neighbouring subcutis (overview), **B** – histology: cell-rich infiltrate zones with infiltrate polymorphism and pronounced marginal centres (detail)

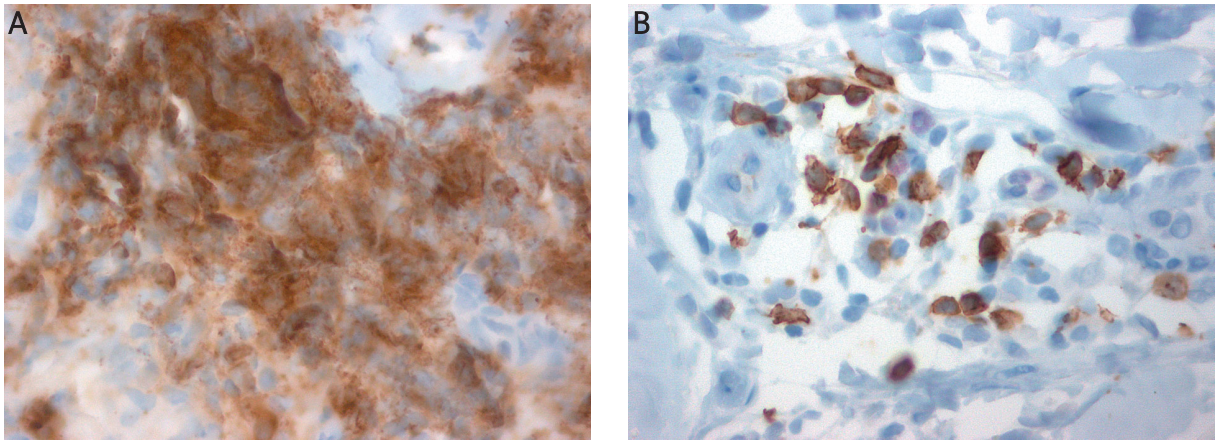

Fig. 4. A – Immunohistochemical examination: detection of CD79-positive infiltrate cells, **B** – immunohistochemical examination: loose distribution of CD8-positive cells

a known side effect. The pruriginous and occasionally painful nodes, which are usually localized subcutaneously, may persist for a number of years [1, 2]. By contrast, the occurrence of pseudolymphomas has only been rarely observed and was described for the first time in 1974 by Bernstein *et al.* [6]. These are benign, mostly subcutaneously located infiltrates consisting of B- and T-lymphocytes, often with formation of germinal centres [7, 8]. The lesions often do not arise until weeks or months after the injections [7]. In our case, there was a latency period of 5 years between termination of the subcutaneous specific immunotherapy and the development of the pseudolymphomatous changes. When pseudolymphomas occur, a connection with a *Borrelia* infection should be ruled out as far as possible. Cutaneous B-cell pseudolymphomas may also occasionally occur as a result of persistent insect bite reactions, colour tattooing, acupuncture, after trauma or even with no apparent cause [9, 10]. Aetiological factors for cutaneous T-cell pseudolymphomas, in addition to idiopathic forms, include drug reactions, allergic contact dermatitis, insect bites and actinic reticuloid [9]. Immunohistochemical differentiation from a follicular lymphoma or an extranodal marginal zone B-cell lymphoma is important [7, 9].

In the case presented here, it must be assumed that aluminium salt residuals in the skin, acting as continuous antigen stimulation, induced the subcutaneous infiltrates. The lack of proof of a type IV sensitization to aluminium chloride is not surprising, since genuine contact sensitizations to aluminium have only been rarely described [8].

We were unfortunately unable to prove aluminium salts by X-ray diffraction analysis. An attempt at ultrastructural proof by transmission electron microscopy might be helpful in this case. Intralesional steroid injections, complete excision or radiotherapy of the nodes are possible therapeutic measures. The application of hydroxychloroquine in one case did not produce a significant effect [8].

In summary, we wish to point out that in the event of subcutaneous nodes at the injection sites following subcutaneous specific immunotherapy with allergen extracts containing aluminium hydroxide, it is important to consider not only therapy-induced foreign body granulomas, but also pseudolymphomas as a rare differential diagnosis. Histological and immunohistochemical examinations are mandatory to avoid overlooking a malignant lymphoma.

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