

Case report

Foreign-body reaction due to incorrect injections of allergen extracts containing aluminum hydroxide gel

Réactions à corps étranger à la suite de l'injection d'extraits allergéniques contenant de l'hydroxyde d'alumine

Okan Gülbahar *, Gunseli Ozturk, Ali Can Kazandi, Ali Kokuludag

Department of Internal Medicine, Division of Clinical Immunology and Allergy, Ege University Faculty of Medicine, 35100 Bornova-Izmir, Turkey

Received 24 January 2005; accepted 9 February 2005

Available online 11 March 2005

Abstract

Background. – Subcutaneous allergen immunotherapy is considered as effective and safe in allergic patients. Although mild local cutaneous reactions occur frequently, the development of persistent nodules at the injection site is a rare event. We describe a case with unusual persistent nodular reactions at the sites of previous immunizations incorrectly performed via the intradermal route.

Case. – A 42-year-old female presented with multiple persistent lesions on both forearms that appeared after allergen immunotherapy. Immunotherapy with an aluminum hydroxide-adsorbed mite extract had been started 3 years earlier. Prescription of immunotherapy and injections of the extract were performed in a rural private medical facility, under the supervision of a physician with no special allergy training; injections had been given erroneously intradermally rather than subcutaneously. Physical examination revealed multiple reddish, indurated cutaneous nodules at the injection sites. The diagnosis of a foreign-body granulomatous reaction was confirmed by histological examination of the lesions.

Conclusions. – Intradermal injections of aluminum hydroxide-containing allergen extracts should be strictly avoided. This case emphasizes published international recommendations according to which specific allergen immunotherapy should be prescribed only by allergy specialists in order to avoid unsuitable indications and methods that can sometimes result in serious side effects.

© 2005 Elsevier SAS. All rights reserved.

Résumé

Introduction. – L'immunothérapie spécifique est considérée comme une thérapie efficace et sûre chez les patients allergiques. Bien que des réactions cutanées locales, sans gravité, se produisent fréquemment, le développement de nodules persistants au site d'injection est un événement rare. Nous décrivons un cas insolite de nodules persistants s'étant développés sur les sites d'injections effectuées par la voie intradermique.

Le cas. – Il s'est agi d'une femme de 42 ans présentant des lésions persistantes multiples sur ses deux avant-bras, apparues depuis la mise en route d'une immunothérapie spécifique. L'immunothérapie, avec un extrait d'acariens adsorbé sur hydroxyde d'aluminium, avait été débutée 3 ans auparavant, à l'instigation d'un médecin sans compétence particulière en allergologie, dans un cabinet privé, en milieu rural. Les injections d'immunothérapie ont été effectuées par la voie intradermique, et non par la voie sous-cutanée. L'examen clinique a révélé de nombreux nodules cutanés rougeâtres et indurés, sur les sites d'injection de l'extrait allergénique. Le diagnostic de réaction granulomateuse, du type réaction à corps étranger, a été confirmé par l'examen histologique des lésions.

Conclusion. – Les injections d'extraits allergéniques contenant de l'hydroxyde d'aluminium doivent être effectuées par voie sous-cutanée stricte. Ce cas confirme aussi les recommandations internationales, selon lesquelles l'immunothérapie spécifique ne devrait être prescrite et supervisée que par des médecins spécialistes, dans le but d'éviter des indications et des pratiques inadaptées, voire néfastes.

© 2005 Elsevier SAS. All rights reserved.

* Corresponding author.

E-mail addresses: ogulbahar@yahoo.com; gulbahar@med.ege.edu.tr (O. Gülbahar).

Keywords: Allergen immunotherapy; Adverse effects; Aluminum hydroxide; Foreign-body reaction; Granulomas

Mots clés : Hydroxyde d'aluminium ; Réaction à corps étranger ; Granulome ; Immunothérapie spécifique ; Effets secondaires

1. Introduction

Allergen immunotherapy is indicated in patients with allergic rhinitis [1] and bronchial asthma [2], and anaphylactic reactions to hymenoptera venoms [3]. It is generally considered as a very effective and safe therapy. Mild local cutaneous reactions occur frequently at the site of injection, but the development of persistent nodules that cause pain and itching at the injection site is a rare event [4]. These lesions have been mainly attributed to a hypersensitivity reaction to aluminum hydroxide, which is used as an adsorbing agent in many vaccines and allergenic extracts [5]. We describe a case of unusual persistent nodular reactions at the sites of previous injections of an allergenic extract inaccurately performed by the intradermal route.

1.1. Case report

A 42-year-old female patient presented with multiple persistent lesions of her both forearms (Fig. 1).

She had perennial rhinoconjunctivitis since her childhood and asthma for 10 years. She had started immunotherapy 3 years ago with a *Dermatophagoides farinae* (*D. far*) and *Dermatophagoides pteronyssinus* (*D. pter*) purified major allergens containing extract adsorbed on aluminum hydroxide (ALK, Copenhagen, Denmark), after mite sensitivity had been determined by skin prick tests (SPT) in a rural private medical facility with no special training in the field of allergy. Erroneously, injections of the extract were performed by the intradermal route rather than the subcutaneous one. The nodules developed just after the initiation of the immunotherapy. The patient reported that injections of the extract induced immediate local reddish and indurated reactions (5–10 cm in diameter) with itching and sensation of burning. Then, the



Fig. 1. Multiple reddish, indurated, cutaneous nodules at immunotherapy injection sites.

nodules developed within a week. Although multiple nodules had developed, the patient was continuously given irregularly intradermal injections of the extract over 3 years. She also reported that immunotherapy did not alleviate her symptoms. She had no history of familial atopy.

Physical examination revealed multiple reddish, (some of them with hyperpigmentation of the overlying skin) indurated nodular lesions at the previous injection sites located on her both forearms. The lesions were asymmetrical, circular, erythematous nodules. The size of the nodules ranged from 0.5 to 2 cm in diameter.

2. Methods

An intradermal nodule on the volar side of the patient's right arm was excised and fixed in formalin. The nodule was stained with haematoxylin-eosin (HE).

Skin prick tests (SPT) were performed with commercially available *D. pter* and *D. far* reagents (Stallergenes, Antony Cedex, France). Histamine phosphate (10 mg/ml) and glycerinated saline were the positive and the negative controls respectively. The SPT was regarded as positive if there was a wheel at least 3 mm larger than the negative control. *D. pter* and *D. far* serum specific IgE (Pharmacia CAP system, Uppsala, Sweden) were measured according to the manufacturer's instructions.

3. Results

Histopathological examination of the specimen showed a normal epidermis. Multifocal granulomatous infiltrates were seen in the deep dermis. The infiltrate was predominantly composed of diffuse histiocytes with mostly granular cytoplasm, multinucleated giant cells, and few lymphocytes. The subcutaneous tissue was not affected. The diagnosis of foreign-body granulomatous reaction was confirmed by histological evaluation of the lesions (Fig. 2). SPT with mites, as well as *D. pter* and *D. far*-specific IgE, were negative. The patient was advised to take medical therapy for her perennial rhinitis and asthma and to stop immunotherapy.

4. Discussion

In this case report, we describe a patient who developed multiple itching nodules following inaccurately performed specific immunotherapy for her asthma and rhinitis with house dust mite allergens adsorbed on aluminum hydroxide. The lesions were persistent and lasted for several years. Histopathological findings were those of a foreign-body reaction.

Specific hyposensitization with aluminum-adsorbed vaccines is frequently used in the treatment of IgE-mediated aller-

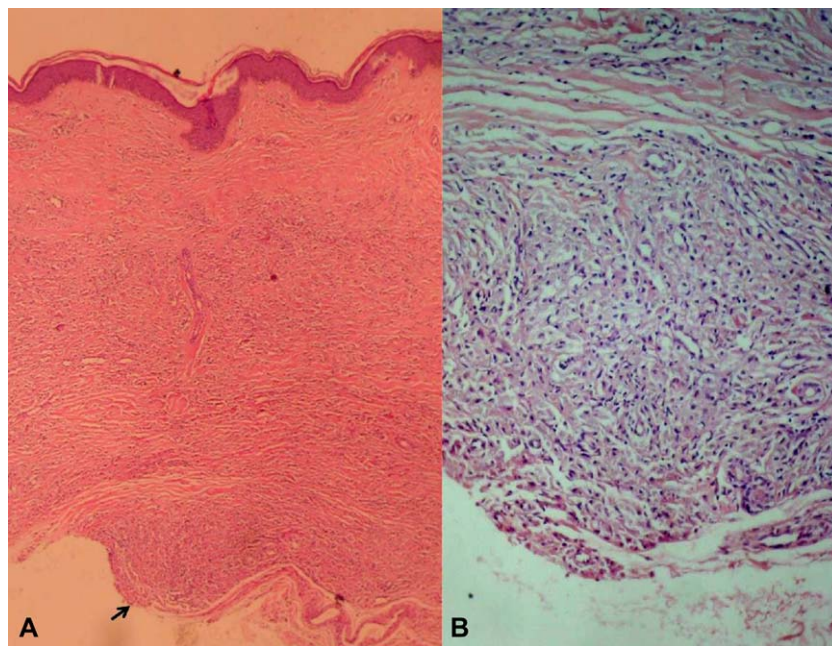


Fig. 2. A. HE $\times 40$. Epidermis was intact. There was a fibrosis in superficial dermis. Multifocal granulomatous infiltrates with eosinophilic crystalline material were seen in the deep dermis. The subcutaneous tissue was not affected. B. HE $\times 400$. The infiltrate was predominantly composed of diffuse histiocytic cells with mostly granular cytoplasm, multinucleated giant cells, and few lymphocytes.

gies. Mild local cutaneous reactions occur frequently at the site of injection, but persistent lesions are less common [4]. Recently, Vogelbruch et al. [6], reported a case of persistent intradermal granulomas that developed at the sites of inaccurate intradermal, instead of subcutaneous, hyposensitization injections. Subsequent subcutaneous injections of the aluminum-adsorbed allergen extract were well tolerated by the patient, without development of persistent nodules at the injection sites. As our patient did not benefit from immunotherapy, and as SPT and serum specific IgE were negative, we decided to stop immunotherapy. For this reason we do not know whether subsequent doses of subcutaneously performed injections would have been tolerated.

The pathogenesis of aluminum hydroxide granulomas may be explained by two nonexclusive mechanisms based on histopathological features. The foreign-body granuloma is histologically characterized by diffuse histiocytic cells, and giant cells with central necrosis, lacking a significant inflammatory infiltrate. This appearance of a foreign-body granuloma with a predominant histiocytic response has been interpreted as a non-allergic, possibly direct toxic effect of aluminum [7]. In some cases, there is a superimposed unifocal or multifocal unencapsulated granulomatous reaction with an infiltrate composed of nodular aggregations of lymphocytes with lymphoid follicles, large histiocytic cells, abundant eosinophils, and some plasma cells. This immunogenic granulomas pattern suggests a delayed hypersensitivity granulomatous type reaction to aluminum [5]. Although not consistently positive, patch test to aluminum compounds can be used to confirm the histopathological diagnosis of delayed granulomatous hypersensitivity reaction [5]. In the case presented herein, the histological infiltrate was predominantly composed of dif-

fuse histiocytic cells and multinucleated giant cells with only few lymphocytes around, suggesting a foreign-body granulomas reaction rather than delayed hypersensitivity reaction. As a consequence patch-tests with aluminum salts have not been performed in our case.

The decision-making process leading to indication of specific immunotherapy and choice of allergen extract necessitates a huge background knowledge. It is evident that a prescription should be given only by a physician with special training in the field of allergy. The International Consensus [8] and the GINA [9] guidelines specify that immunotherapy should be prescribed by specialists to prevent inappropriate immunotherapy. Our patient's persistent lesions were caused by intradermal injections, instead of the subcutaneous route recommended by the guidelines. Moreover, the indication of the immunotherapy, the choice of the allergen extract, and the injections of the extract were performed by a physician without training in allergy. Thus, we would like to emphasize once again the necessity of competent performance of immunotherapy.

References

- [1] Ross RN, Nelson HS, Finegold I. Effectiveness of specific immunotherapy in the treatment of allergic rhinitis: an analysis of randomized, prospective, single- or double-blind, placebo-controlled studies. *Clin Ther* 2000;22:342–50.
- [2] Ross RN, Nelson HS, Finegold I. Effectiveness of specific immunotherapy in the treatment of asthma: a meta-analysis of prospective, randomized, double-blind, placebo-controlled studies. *Clin Ther* 2000;22:329–41.
- [3] Allergen immunotherapy: therapeutic vaccine for allergic diseases: Geneva; January 27–29, 1997. *Allergy* 1998;53(Suppl):1–42.

- [4] Frost L, Johansen P, Pedersen S, Veien N, Aabel Østergaard P, Nielsen MH. Persistent subcutaneous nodules in children hyposensitized with aluminium-containing allergen extracts. *Allergy* 1985;40: 368–72.
- [5] Garcia-Patos V, Pujol RM, Alomar A, Cistero A, Curell R, Fernandez-Figueras MT, et al. Persistent subcutaneous nodules in patients hyposensitized with aluminum-containing allergen extracts. *Arch Dermatol* 1995;131(12):1421–4.
- [6] Vogelbruch M, Nuss B, Korner M, Kapp A, Kiehl P. Aluminium-induced granulomas after inaccurate intradermal hyposensitization injections of aluminium-adsorbed depot preparations. *Allergy* 2000; 55:883–7.
- [7] Turk JL, Parker D. Granuloma formation in normal guinea pigs injected intradermally with aluminium and zirconium compounds. *J Invest Dermatol* 1977;68:336–40.
- [8] US Department of Health and Human Services: Public Health Service. National Institutes of Health. International consensus report on diagnosis and management of asthma. NIH Publication 92-3091, June 1992.
- [9] National Institutes of Health, National Heart, Lung, and Blood Institute: Global Initiative for Asthma: global strategy for asthma management and prevention. NHLBI/WHO workshop report, March 1993, NIH Publication 95-3659, January 1995.