Vasculitis during immunotherapy treatment in a patient with allergy to *Cupressus arizonica*

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ABSTRACT

Allergen immunotherapy dates back to 1911 and has been used successfully to treat large numbers of patients throughout the last century.

Case report: a 66-year-old woman presented with symptoms of allergic rhinitis and asthma due to sensitization to *Cupressus arizonica*. Specific immunotherapy was prescribed as a continuous 2-year treatment with a depot preparation of standarized and characterized allergen extracts of *Cupressus arizonica* pollen. Forty-eight hours after one maintenance dose of 0.8 cc, the patient presented palpable violaceous purpuric lesions and pruritus on both legs. We performed skin prick and intradermal tests with *Cupressus arizonica*. Twenty-four hours later, the 1/1 dilution intradermal skin test was positive. Biopsy showed leukocytoclastic vasculitis.

Conclusions: A middle-aged woman experienced cutaneous non-necrotizing vasculitis after 2 years of maintenance immunotherapy. The interval between injections and the first appearance of cutaneous lesions suggests a type III hypersensitivity immune reaction. Skin biopsy of the positive intradermal test also supports this hypothesis.

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INTRODUCTION

Allergen immunotherapy dates back to 1911 and has been used succesfully to treat large numbers of patients through out last century. Studies of the efficacy of this treatment abound, but studies about long-term safety of immunotherapy (except for immediate reactions) are exceptional[1].

Although it is generally accepted that immunotherapy is not associated with significant long-term adverse effects, the question of immune complex disease caused by allergic injections is still unsolved[1].

Systemic vasculitis or a polyarteritis nodosa-like clinical presentation, are an unusual associations with immunotherapy[2,3].

CASE REPORT

A 66-year-old white woman was first observed with symptoms of allergic rhinitis and asthma from January to February for 3 years. She was in all respects a healthy woman. Physical examination was normal. Skin prick tests with a series of commercially available inhalant allergens (grass, weeds and tree pollens, house dust mites, molds, cat and dog dander) were positive for *Cupressus arizónica* pollen. A positive histamine (histamine chloride 10 mg/ml) and a negative control were used. Serum level of specific Ig E for *Cupressus arizónica* and *Cupressus sempervirens* were measured by CAP (Pharmacia, Uppsala, Sweden), according to the manufacturer's instructions The results were expressed in KU/l with

the following results: *Cupressus arizónica* 0.94 KU/l and *Cupressus sempervirens* 1.26 KU/l.

Specific immunotherapy was prescribed as a continuous 2-year treatment with a depot preparation of standarized and characterized allergen extracts of *Cupressus arizónica* pollen (Pangramin depot, Lab. ALK-Abelló, Horlsholm, Denmark).

The patient received the buildup doses weekly during 3 months and continued with the maintenance therapy monthly for 2 years without any problem. 48 hours after one maintenance dose of 0'8 cc, 1000 STU/mL (19475 STU accumulated), the patient presented palpable violaceous purpuric lesions and pruritus on both legs. She did not present any other sympton. The lesions disappeared in 3 days without treatment. A similar episode occurred after the following maintenance dose one month later.

Immunotherapy was stopped because of this convincing association. Nevertheless we decided to perform the vasculitis study. The following laboratory studies were carried out: complete blood cell count, sedimentation rate, blood urea, glucose, lipids, liver functions tests (ALT, AST, alkalin phosphatase, albumine and bilirubin levels), and urianalysis with normal results. Prothrombin time and partial thromboplastin time were also normal. Serum Ig G, Ig E, Ig A, Ig M and serum protein electrophoresis were within normal range. Tests for rheumatoid arthritis and antinuclear antibody were twice negative. Rapid plasma reagin, antistreptolysin titer and C-reactive protein were also negative. C3, C4 and total hemolytic complement were within normal range. Finally, serological studies for viral hepatitis (A, B and C) and cryoglobulins were negative.

Six months later, we performed skin prick and intradermal tests: 1/1, 1/10 and 1/100 dilution with *Cupressus arizónica* (ALK-Abelló, Horlsholm, Denmark) with negative result. 24 hours after, 1/1 dilution intradermal skin test was positive. The same 1/1 dilution intradermal skin test performed in 10 control subjects, 5 atopic (allergic to *Cupressus arizónica*) and 5 non atopic, was negative. The biopsy of this positive skin test showed leucocitoklastic vasculitis.

DISCUSSION

Hypersensitivity vasculitis are clinical syndromes characterized by inflammation of small vessels (arteriolae, capillaries and venules). It can affect any organ, but the dermic affection is the most frequent[4].

Identification of an etiologic agent for the majority of vasculitis disorders cannot be made[2]. There are evidence about the relation with different infectious agents (hepatitis B and C, human immunodeficiency virus and streptococcus) and several drugs (penicillin, amphetamines, allopurinol)[5,6].

Phanuphak and Kohler[3] suggested the possible relation between vasculitis and immunotherapy treatment. They reported six patients with polyarteritis nodosa associated with immunotherapy. Five of these patients had evidence of circulating immunocomplexes that included cryoglobulinemia, increased C1q binding or complement comsumption. A causal role for hyposensitization in the development of systemic arteritis was suggested.

The pathogenic mechanism responsible for this complication during the course of immunotherapy remain to be elucidated[2]. In our patient, the laboratory studies were all normal. The time delayed between injections and the first appearance of cutaneous lesions (48 hours) points to a type III hypersensitivity immune reaction. Skin biopsy of the positive intradermal test also supports this hypothesis. Taylor[1] did not find laboratory alterations either.

On the other hand, Branco-Ferreira et al[7] reported a similar case, but they found decreased C4 and elevated levels of circulating immune complexes with normalization of both values after clinical resolution.

There was also a report of pericarditis associated with immunotherapy with positive rechallenge and avoidance tests, in which an immunologic mechanism was clearly suspected, although not demonstrated[8].

In summary, a middle-aged woman experienced a cutaneous nonnecrotizing vasculitis after 2 years of immunotherapy manteinance. The rash subsided without any treatment in 3 days. The same episode repeated with the next 2 doses.

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