

Case report

Recurrent pericarditis: a rare complication of allergen immunotherapy

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We report on a 29-year-old woman suffering from hay fever due to grass and olive tree pollens. She developed recurrent pericarditis during her first course of immunotherapy with an alum-adsorbed pollen extract. A causal relationship was established between the allergen injections and the acute pericarditis episodes on two consecutive occasions, which presented with blood eosinophilia. Blood cultures and serological tests for microorganisms were negative. There were no signs of autoimmune disease or systemic vasculitis. To the best of our knowledge, allergen immunotherapy-induced pericarditis has not been previously reported.

Key words: immunotherapy; pericarditis; pollen; side-effects; allergen extracts.

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In most instances, correctly performed specific allergen immunotherapy is a safe and effective therapeutic modality of various IgE-mediated allergic diseases. However, immunotherapy is a potentially dangerous treatment since the margin between optimal therapeutic doses and concentrations that produce unacceptable side-effects is narrow (3).

Local reactions (wheals, erythema, swelling) at the site of injection are almost inevitable and usually are not a contraindication to further treatment. There may also be immediate systemic reactions, including anaphylaxis and life-threatening exacerbations of asthma (16). Systemic reactions, such as rhinitis, worsening of asthma, generalized urticaria, or even anaphylaxis, have been observed in 0.1% of subjects treated (18). Another study reported one death for every 750 000 injections (4). Although it is generally accepted that immunotherapy is not associated with significant long-term adverse effects or immune complex disorders (8, 9), there have been anecdotal reports of the development of serum sickness (6, 17) and connective tissue diseases (12, 15).

Case report

A 29-year-old woman was admitted in December because of a fever of 39°C, malaise, dyspnea, orthopnea and a continuous retrosternal chest pain radiating to the left shoulder and aggravated by

coughing and deep inspiration. The patient was a previously healthy, non-smoking Caucasian with no past history of heart or respiratory diseases, with the exception of hay fever. She had had allergic rhinoconjunctivitis symptoms in springtime during the last 2 years. These symptoms could not be controlled with the oral, non-sedating antihistamines and nasal corticosteroids that she refused to use on a regular basis. The results of skin prick testing, performed with a battery of common inhalants (Bencard, Worthing, UK), and the RAST levels are shown in Table 1. Her allergologist prescribed immunotherapy with an aqueous, aluminum-adsorbed grass pollen (80%) and olive tree pollen (20%) extract without pyridine (Allergovac depot, Aristegui Lab., Bilbao, Spain). The potency of this extract was expressed in biological units (10 000 EBU [equivalent biological units] = 1 SPT = concentration of the extract producing a wheal = histamine phosphate 10 mg/ml) and was characterized by IEF, SDS-PAGE and CIE.

Twenty-four hours before admission she had received the third subcutaneous injection (0.8 ml, vial I, concentration 100 EBU/ml) of the grass and olive tree pollen extract. The extract was administered weekly, and she was receiving no other drugs. Later, after specific questioning she mentioned having malaise and febricula the day after receiving the second allergy injection, but had not sought medical advice.

Table 1. Results of allergological tests

	Skin prick tests (mm)	RAST (PRU/ml)
<i>Lolium perenne</i>	5	13.5
<i>Phleum pratense</i>	6	30
<i>Olea europaea</i>	10	11
Histamine phosphate (10 mg/ml)	6	
Saline	0	

Local or other systemic reactions had not been observed during the treatment.

At the time of admission, physical examination disclosed a pericardial friction rub, tachycardia and fever of 38.5°C. Neither cutaneous nor articular involvement was present. Chest radiograph showed heart enlargement, and echocardiography revealed pericardial effusion. Electrocardiogram showed diffuse ST-segment elevation and upright T waves. Laboratory examination showed an erythrocyte sedimentation rate of 63 mm in the first hour, hemoglobin 13.4 g/dl, and white count cell 8120/mm³ with 500 eosinophils/mm³. The blood cultures were negative, as were serological tests for viruses (influenza A and B, adenovirus, enteroviruses, Epstein-Barr, hepatitis B), bacteria (*Brucella*, *Salmonella*, *Mycobacterium tuberculosis*), *Chlamydia* and *Mycoplasma pneumoniae*. Antistreptolysin titre was normal. Evidence of connective tissue disorders was not found, the rheumatoid factor was negative, and anti-nuclear and anti-heart muscle antibodies were absent. Complement concentration was normal. The blood proteinogram showed an increase in alpha-1 and alpha-2 fractions. Total serum IgE level was 561 IU/ml. Concentration of other serum immunoglobulins was normal. Blood urea, bilirubin, glucose, lipids, and results of liver function tests and urinalysis were also normal. At that time no relationship was suspected with the allergen immunotherapy, and a diagnosis of acute benign idiopathic pericarditis was made. Treatment with aspirin 500 mg q.i.d. for 3 weeks resulted in clinical improvement and disappearance of the pericardial effusion and eosinophilia, as well as normalization of the erythrocyte sedimentation rate, electrocardiogram, and chest radiograph.

One month later the patient restarted allergen immunotherapy with a new allergen extract vial (0.1 ml, vial II, concentration 1000 EBU/ml). Twenty-four hours after this dose was given, she complained of mild dyspnea and febricula which lasted 48 h, but no local reaction was observed. Nevertheless, a week later the patient received the same allergen dose (0.1 ml, vial II), without consulting her allergologist, and within 24 h she had to be readmitted because of acute pericarditis with a clinical picture

similar to that on the previous admission. This time a clear-cut relationship with the allergen immunotherapy was recognized and immunotherapy was stopped. Toxic and microbiological contamination of the allergen extract was discounted and we checked that the same allergen batch had been administered to several patients without ill effect. At 1-year follow-up she has had no new episodes of pericarditis since the immunotherapy was stopped.

Discussion

We consider that in our patient there is a clear relationship between the allergen injections and the development of acute pericarditis on at least two consecutive occasions, presenting with blood eosinophilia. The absence of typical anaphylactic symptoms during these episodes is noteworthy, as well as the nonrecurrence of pericarditis since cessation of immunotherapy. On the other hand, there were no signs of autoimmune disease or systemic vasculitis and the patient was not taking other drugs.

We know of no previous reports of pericarditis as an adverse reaction to immunotherapy. However, drug-induced acute pericarditis is not uncommon, usually manifesting with hypereosinophilia and probably caused by a hypersensitivity reaction (2, 13). Recurrent pericarditis has also been reported as a rare complication of influenza vaccination, the mechanism of which is unknown (14). Moreover, allergic pollen-induced myocarditis has been described (10), and hypersensitivity myocarditis is now recognized as a clinical entity that can be produced by drugs (7).

In all cases in which pericarditis has been related to an antigen challenge (vaccines, drugs, haptens), one may suspect that an immunological reaction is involved, although the exact nature of the pericarditis remains obscure. There are several causes of pericarditis presumably related to hypersensitivity and/or autoimmunity (Table 2) (2); however, the underlying immunopathologic mechanisms can vary considerably (11). When an external agent is implicated, a

Table 2. Causes of pericarditis presumably associated with hypersensitivity and/or autoimmunity

Rheumatic fever
Collagen vascular disease
systemic lupus erythematosus
rheumatoid arthritis
scleroderma
polyarteritis nodosa
Wegener's granulomatosis
Drug-induced
procainamide, hydralazine, reserpine, methyl dopa, isoniazid, phenylbutazone,
penicillin, cromolyn, others
Postcardiac injury
postmyocardial infarction (Dressler's syndrome)
postpericardiotomy

hypersensitivity mechanism can be suspected if the reaction is not dose-dependent and it can occur at any time during treatment. A toxic reaction is dose-dependent, and its effects usually progressing despite discontinuation of the causative agent.

Microbiological contamination of the extract was thoroughly checked for and discounted; it was, in any case, unlikely, as extract production under sterile conditions is strictly controlled by the pharmaceutical company, and there was no local swelling at the injection site. The allergen extract was stored at 4°C by the patient and denaturation was not suspected.

Another aspect to analyze is the eventual toxic effect of aluminum hydroxide in the extract, since aluminum has been recognized as a potentially toxic agent (1). However, aluminum-containing allergen solutions are the most commonly used extracts in Europe (5) and the concentration of serum aluminum is not raised in patients treated with these extracts (19). The only remarkable side-effect with aluminum-containing allergens is the presence of transient subcutaneous nodules and, occasionally, persistent nodules that could indicate a delayed-type hypersensitivity to aluminum salts (5). As our patient had neither immediate nor late local reactions, this type of hypersensitivity seems unlikely, unless an organ-specific reaction had occurred.

In conclusion, we feel it reasonable to consider that pollen immunotherapy was responsible for the pericarditis episodes. A hypersensitivity reaction to antigen/s in the extract and/or neoantigens formed in the pericardium might have occurred but we cannot rule out other possible mechanisms, and the true nature of the reaction remains unknown.

In spite of the basic safety of allergen immunotherapy, allergologists and clinicians should be aware of its inherent risks and of the necessity of correct safety monitoring in order to avoid them. Specific allergen immunotherapy-induced pericarditis should be considered to be a rare but potentially life-threatening complication of this therapy.

References

1. ARIEFF AI, COOPER JD, ARMSTRONG D, LAZAROWITZ VC. Dementia, renal failure, and brain aluminium. *Ann Intern Med* 1979; 90: 741-7.
2. BRAUNWALD E. Acute pericarditis. In: BRAUNWALD E, ed. *Heart disease*. Philadelphia: W.B. Saunders, 1988: 1487-534.
3. DREBORG S, MOSBECH H, WEEKE B. Immunotherapy (hyposensitization) and bronchial asthma. In: KAY AB, ed. *Baillière's clinical immunology and allergy (The allergic basis of asthma)*. London: Baillière Tindall, 1988: 245-58.
4. FRANKLAND AW. Anaphylactic reaction to desensitization. *Br Med J* 1980; 281: 1429.
5. FROST L, JOHANSEN P, PEDERSEN S, et al. Persistent subcutaneous nodules in children hyposensitized with aluminium-containing allergen extracts. *Allergy* 1985; 40: 368-72.
6. KAAD PH, OSTERGAARD PA. The hazard of mould hyposensitization in children with asthma. *Clin Allergy* 1982; 12: 317-20.
7. KOUNIS NG, ZAVRAS GM, SOUFRAS GD, KITROU MP. Hypersensitivity myocarditis. *Ann Allergy* 1989; 62: 71-4.
8. LEVINSON AI, SUMMERS RJ, LAWLEY TJ, et al. Evaluation of the adverse effects of long-term hyposensitization. *J Allergy Clin Immunol* 1978; 62: 109-14.
9. NEGRINI AC, TROISE C, VOLTOLINI S, et al. Long-term hyposensitization and adverse immunological responses. A laboratory evaluation. *Ann Allergy* 1985; 54: 534-7.
10. PEREDKOVA EV, KULIKOVA AT, POROSHINA IUA. Allergicheskii pyl'tsevoi miokardit. *Ter Arkh* 1986; 58: 56-8.
11. PERSELLIN ST, RAMÍREZ G, MOATAMED F. Immunopathology of rheumatic pericarditis. *Arthritis Rheum* 1982; 25: 1054-8.
12. PHANUPHAK P, KOHLER PF. Onset of polyarteritis nodosa during allergic hyposensitization treatment. *Am J Med* 1980; 68: 479-85.
13. SCHOENWETTER AH, SILBER EN. Penicillin hypersensitivity, acute pericarditis and eosinophilia. *JAMA* 1965; 191: 136.
14. STREIFER J, SHLOMO D, GARTY M, ROSENFELD J. Recurrent pericarditis: a rare complication of influenza vaccination. *Br Med J* 1981; 283: 526-7.
15. TAYLOR RJ. Hypersensitivity vasculitis occurring in a patient receiving immunotherapy. *J Allergy Clin Immunol* 1991; 87: 889-90.
16. THOMPSON RA, BOUSQUET J, COHEN S, et al. Current status of allergen immunotherapy (WHO/IUIS Working Group Report). *Lancet* 1989; i: 259-61.
17. UMETSU DT, HAHN JS, PEREZ-ATAYDE AR, GEHA RS. Serum sickness triggered by anaphylaxis. A complication of immunotherapy. *J Allergy Clin Immunol* 1985; 76: 713-18.
18. VERVLOET D, KHARIRALLAH E, ARNAUD A, CHARPIN J. A prospective national study of the safety of immunotherapy. *Clin Allergy* 1980; 10: 59-64.
19. VIND JOELT S, MALLING HJ, GERNER SVENDSEN U, et al. Serum aluminium in hyposensitized allergics. *Allergy* 1985; 40: 487-90.

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