

Distal digital vasculitis induced by specific immunotherapy

A 43-YEAR-OLD white woman, a dressmaker, had had moderate/severe perennial allergic rhinoconjunctivitis for 3 years without associated asthma. She presented monosensitization to house-dust mite (HDM), documented by skin prick tests and specific IgE (RAST), without other allergic sensitizations. Because nasal steroid plus oral antihistamine daily therapy led only to insufficient clinical improvement, she was given desensitization therapy. Besides her perennial allergic rhinoconjunctivitis, the patient had also had mild arterial hypertension, well controlled with diet and nifedipine 10 mg b.i.d., for 5 years. Immunotherapy with a standardized, aluminum-adsorbed allergenic extract of *Dermatophagoides pteronyssinus* was administered weekly with a twofold increase between injections, while maintaining daily therapy with nasal steroids and oral antihistamines.

At 6-8 h after the second dose (0.2 ml) of the more concentrated vial (100 U/ml, corresponding to 250 AUR (activity unit by RAST)/ml, the patient noticed the appearance of violaceous erythema confined to the distal areas of the fingers of both hands, accompanied by local cutaneous hyperesthesia. No other part of her body was involved, and the complaints disappeared completely in 4 or 5 days, without treatment. The patient did not seek medical assistance and completely disregarded this episode. Ten days later, she was given the next immunotherapy injection (0.4 ml). After 4 h, the patient reported the appearance of a cutaneous reaction similar to the one previously described but much more intense (Fig. 1). When she sought assistance (24 h after the immunotherapy injection), she presented violaceous digital erythema, affecting mainly the distal areas of the three first fingers of both hands with a symmetric appearance. The affected areas were warm and painful, with cutaneous hyperesthesia and diminished tactile perception, causing total professional incapacity. Immunotherapy was immediately discontinued, and therapy with pentoxifylline 400 mg t.i.d. was instituted, leading to slow but gradual improvement and complete resolution without sequelae

after 3 weeks. She refused to allow cutaneous biopsy during or after the active phase of the lesions. There was no other cutaneous or mucosal involvement. Ophthalmologic examination did not reveal any signs of retinal vasculitis or other significant alterations.

We performed a laboratory work-up on the first day after the appearance of the lesions and after 2 months, when the patient was already asymptomatic. Search for autoantibodies, including cryoglobulins, was always negative. Urinalysis did not show any alterations, and all other analytic values were normal with the exception of slightly depressed C4 levels (12 mg/dl; reference values 13-75 mg/dl) and increased circulating immune complexes (7.6 µg/ml; reference values <5 µg/ml), both returning to normal values 2 months later. The patient also presented an elevated level of specific IgG to *D. pteronyssinus* (72%), which is not usually seen in the early stages of specific immunotherapy (SIT).

■ Even without histopathologic confirmation, the clinical picture observed was undoubtedly that of nonnecrotizing digital vasculitis. The temporal relation with the SIT injections is strongly suggestive of a causal relation, supported by a positive

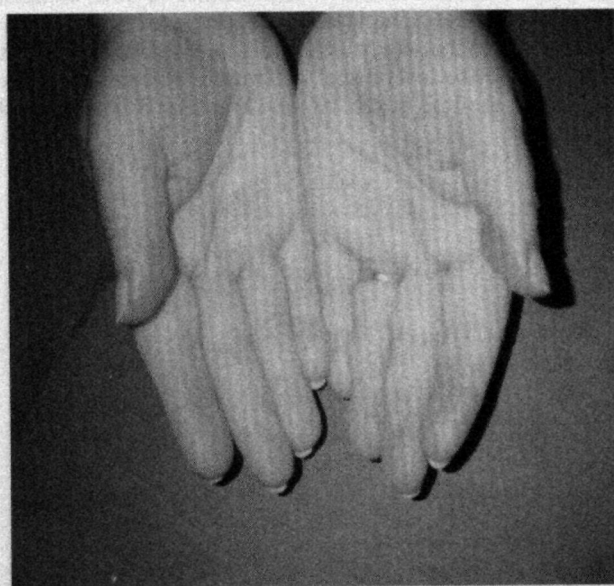


FIGURE 1 Distal digital erythema 24 h after immunotherapy injection.

rechallenge and also by the absence of further clinical episodes with the interruption of SIT. The time delay between injections and the first appearance of cutaneous lesions – 4–6 h – points to a type III hypersensitivity immune reaction. This hypothesis is consistent with decreased C4 and elevated levels of circulating immune complexes (IC), with normalization of both values after clinical resolution. The high level of specific IgG, not usually seen so early in the course of SIT, could provide an important antibody source for IC generation.

Vasculitic lesions developed exclusively in the fingers, sparing other small-vessel territories such as the toes or retina.

Vasculitis was not severe, since the patient recovered and did not develop digital necrosis, as is frequently seen in severe digital vasculitis. We did not find evidence of systemic involvement, but it is possible that equally mild vasculitic lesions developed in other organs, without clinical expression and undetectable without biopsy. Finally, the patient's profession – dressmaker – which involves repeated microtrauma of the fingers, particularly in the distal areas of the first three fingers, could have played a role in the appearance of the clinical lesions.

Although rarely described, there have been recent reports of cases of vasculitis consistent with an IC process associated with SIT (1, 2). There was also a report of pericarditis associated with SIT, with positive rechallenge and avoidance tests, in which an immunologic mechanism was clearly suspected, although not demonstrated (3).

It is the common view that SIT does not induce significant long-term adverse effects. Nevertheless, long-term side-effects are far less well studied than immediate ones. In particular, IC disease induced by SIT remains controversial. Furthermore, administration of specific immune complexes, formed in autologous antibody excess and containing *D. pteronyssinus* as antigen, has been reported to be successful as desensitization therapy (4), a fact which adds to the controversy on the beneficial or deleterious role of IC-containing allergens. Regarding IC generation during SIT, some authors have found no evidence

of it (5–9), while others have published data showing such generation (10–13). However, in one of these reports (11), circulating IC levels were also increased during natural allergen exposure, and in another (13), IC formation during SIT was considered to play a regulatory role, its presence being associated with clinical improvement (13).

Despite the controversy, it is our view that this case corroborates the hypothesis that SIT has, although probably in only a few patients, the potential of inducing generation of IC and disease.

Key words: adverse effects; specific immunotherapy; vasculitis.

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*We report two episodes
of symmetric distal
digital vasculitis,
associated with
injections of aluminum-
adsorbed*

*Dermatophagoides
pteronyssinus
allergenic extract.*

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