

Cutaneous B-cell lymphoma at the injection site of airborne allergen immunotherapy followed by cutaneous metastasis

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Local reactions at the injection site of subcutaneous immunotherapy (SCIT) with airborne allergens are common and as many as 86% of patients receiving SCIT may suffer this type of adverse effect [1].

Delayed local reactions are often self-limited but sometimes can be persistent due to granulomatous foreign body reactions or, rarely, to cutaneous pseudolymphoma (CPL)

Bernstein [2] reported in 1974 the first case of CPL induced by a hyposensitizing vaccine against mites and bacteria. Since then, several cases of B-cell CPL have been published with tetanus, meningoencephalitis and hepatitis vaccines [3,4] and hyposensitizing extracts [5,6].

In most cases, aluminum hydroxide was present as an adjuvant [3,4,6], for which it has been suggested that it could have a causal role. However, there are cases in which this adjuvant was not present [7]

Most CPL developed at the injection site of the vaccines tend to have a benign course, but, very rarely, they have evolved to lymphomas [8,9]; the causes were flu and anthrax vaccines and one of the patients had a fatal outcome [8].

We present the case of a patient who developed a CPL at the injection site of a hyposensitizing extract of pollens with aluminum hydroxide that evolved into a primary cutaneous B-cell follicular center lymphoma (CBFCL)

A 42-year-old woman diagnosed with rhinoconjunctivitis and asthma due to pollen allergy was treated with monthly injections of a depot pollen hyposensitizing extract for

four years. The extract contained aluminum hydroxide as adjuvant. The patient did not present any local or systemic adverse reactions and her respiratory seasonal symptoms improved.

Four years after the end of the hyposensitizing treatment, she presented itchy, papulonodular lesions on the external side of both arms, exactly in the areas where the vaccine was injected. Aluminum hydroxide granulomas were suspected and treatment with topical corticosteroids was indicated. Three years later the lesions had increased in size and the itching was more intense. Several confluent and infiltrated plaques were located on the deltoid area of both arms with erythematous and lichenified surfaces (Fig 1)

An allergological work-up with patch tests was carried out with the battery of the Spanish Research Group on Contact Dermatitis and Skin Allergy, with aluminum hydroxide and the extract involved. All tests were negative.

Skin biopsies showed a nodular lymphocytic infiltrate with reactive germinal centers. The tumor cells are predominantly negative for bcl-2, compatible with CPL. Treatment was started with corticosteroid intralesional injections, with a partial response.

Three years after the diagnosis of CPL the patient manifested new erythematous-edematous lesions in the interparietal area and in the scalp root, with local alopecia (Supplementary figure 1). She did not report any type of accompanying general symptoms

The biopsy of the new lesion and of the lesions in both arms showed a deep lymphocytic infiltrate that formed follicles, with a compact center, without polarization. The immunohistochemical study showed expression of CD20, bcl-6 and restriction of Kappa light chains (Supplementary figures 2 and 3). The histology and immunophenotype were consistent with a CBFCL, both in the scalp lesion and in the lesions on the external face of both arms. The genetic study with PCR showed a polyclonal rearrangement

The analytical study that included hemogram, sedimentation rate, kidney and liver function, total proteins, proteinogram, serum Immunoglobulins, beta2-globulins, ANAs, CMV, HIV, A, B and C Hepatitis A, B. Burgdorferi IgG, tumor markers and blood immunophenotype were normal.

A full-body PET-CT, bone marrow aspiration and bone biopsy were then performed, ruling out tumor extension. Rituximab treatment was prescribed, 5 doses at weekly

intervals followed by systemic corticosteroids starting at 60 mg / day in a step-down regimen.

One year later, due to the persistence of the lesions, she received 12 intralesional Interferon alpha infiltrations in the scalp and arms and 18 sessions of radiotherapy in the arms, with improvement. After finishing the treatment, a skin biopsy was performed with no evidence of neoplastic infiltration.

The patient had no recurrences after a 11-year follow-up period.

We present the first case of primary cutaneous B-cell lymphoma at the injection site of a hyposensitizing airborne allergen vaccine, with distant cutaneous spread, which required systemic treatment and radiotherapy for remission. The lesion on the scalp appeared years after those on the arms and outside the injection site of the vaccine, so we consider it to be a skin metastasis from the initial lesions. The patient did not respond to Rituximab and, Interferon alpha, along with radiotherapy, were needed for remission.

CBFCL is a malignant B-cell neoplasm that originates in the skin, with no evidence of extracutaneous involvement at the time of diagnosis. It is composed of neoplastic cells of the center of the follicle. Tumor cells express B cell antigens (CD20 and CD79a) and germinal center markers, most often bcl-6. The prognosis for CBFCL is excellent, and only 10% progress towards extracutaneous involvement. It is characterized by solitary or grouped nodules, tumors or plaques, usually located on the head or trunk. There are no clearly defined risk factors for the development of this disease and there is no identifiable inheritance trend. It has been associated with chronic antigenic stimulation at the skin level, in relation to infection by the spirochete *Borrelia Burgdorferi* or by components of tattoos [10], having so far only few reported cases caused by influenza [8] or anthrax [9] vaccines.

The pathogenesis of such reactions is unclear. The antigenic stimulus of the virus, bacillus or the components of the hyposensitizing extracts or vaccines could trigger aberrant inflammatory responses that could finally provoke the blast transformation of lymphocytes, although the circumstances that finally direct the inflammatory response toward malignancy remains unknown.

We cannot be sure whether aluminum hydroxide or other components of the vaccine were the triggers for the malignant transformation of the skin lesion in our patient.

We conclude that in the event of a persistent local reaction at the injection site of a hyposensitizing vaccine, a biopsy of the lesions should be performed to rule out the appearance of cutaneous lymphoma in order to establish an early and adequate treatment.

The study has not been founded

The authors declare no conflicts of interest.

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Figure 1. Left arm lesions.

