
Cutaneous B-cell Lymphoma at the Injection Site of Airborne Allergen Immunotherapy: Progression to Cutaneous Metastasis

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Injection site reactions in subcutaneous immunotherapy (SCIT) with airborne allergens are common, with up to 86% of patients experiencing this adverse effect [1].

Delayed local reactions are often self-limiting, although they can sometimes be persistent owing to granulomatous foreign body reactions or, rarely, to cutaneous pseudolymphoma (CPL)

In 1974, Bernstein et al [2] reported 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].

Given that aluminum hydroxide was present as an adjuvant in most cases [3,4,6], it is thought to have a causal role. However, cases in which this adjuvant was not present have been described [7].

CPL affecting vaccine injection sites tends to have a benign course and rarely progresses to lymphoma [8,9]. The reported causes were influenza and anthrax vaccines, and one of the patients died [8].

We present the case of a patient who developed CPL at the injection site of a hyposensitizing extract of pollens with aluminum hydroxide that progressed to 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 hyposensitizing depot pollen extract for 4 years. The extract contained aluminum hydroxide as an adjuvant. The patient did not present any local or systemic adverse reactions, and her seasonal respiratory symptoms improved.

Four years after the end of the hyposensitizing treatment, she presented itchy, papulonodular lesions on the external aspect of both arms, exactly in the areas where the vaccine was injected. Aluminum hydroxide-induced granulomas were suspected, and treatment with topical corticosteroids was



Figure. Lesions on the left arm.

indicated. Three years later, the lesions had increased in size and the itching had become more intense. Several confluent and infiltrated plaques with erythematous and lichenified surfaces were located on the deltoid area of both arms (Figure).

An allergology work-up with patch tests was carried out with the standard series of the Spanish Research Group on Contact Dermatitis and Skin Allergy. The tests included aluminum hydroxide and the extract involved. All results were negative.

Skin biopsies revealed a nodular lymphocytic infiltrate with reactive germinal centers. The tumor cells were predominantly negative for bcl-2 (ie, compatible with CPL). Initiation of treatment with intralesional corticosteroid injections led to a partial response.

Three years after the diagnosis of CPL, the patient developed new erythematous-edematous lesions along the frontal hairline (Supplementary figure 1). She did not report any accompanying general symptoms

The biopsy of the new lesion and of the lesions on both arms showed a deep lymphocytic infiltrate that formed follicles with a compact center and no polarization. The immunohistochemical study revealed expression of CD20 and bcl-6 and restriction of κ light chains (Supplementary figures 2 and 3). Histology findings and the immunophenotype were consistent with CBFCL, both in the scalp lesion and in the lesions on the external face of both arms. The genetic study with polymerase chain reaction revealed a polyclonal rearrangement.

The analytical study included a complete blood count, erythrocyte sedimentation rate, kidney and liver function, total proteins, protein panel, serum immunoglobulins, β_2 -globulins, antinuclear antibodies, cytomegalovirus, HIV, and hepatitis A, B, and C. Normal findings were reported for *Borrelia burgdorferi* IgG, tumor markers, and blood immunophenotype.

A full-body PET-CT scan, bone marrow aspiration, and bone biopsy were then performed, ruling out tumor extension.

The patient received a weekly dose of rituximab for 5 weeks, followed by systemic corticosteroids starting at 60 mg/d in a step-down regimen.

One year later, owing to the persistence of the lesions, the patient received 12 intralesional interferon α infiltrations in the scalp and arms and 18 sessions of radiotherapy in the arms. Her condition improved. A skin biopsy performed once treatment was complete revealed no evidence of neoplastic infiltration.

The patient has experienced no recurrences after an 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. The lymphoma spread to distant cutaneous sites, thus necessitating systemic treatment and radiotherapy to achieve remission. Given that the lesion on the scalp appeared years after those on the arms and outside the injection site, we consider it to be a skin metastasis from the initial lesions. The lesion did not respond to rituximab, and the patient required interferon α and radiotherapy before her disease went into 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 in 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% of cases progress to extracutaneous involvement. It is characterized by solitary or grouped nodules, tumors, and plaques, which are 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 antigen stimulation in the skin, infection by the spirochete *B burgdorferi*, and by components of tattoos [10]. To date, there have been very few cases caused by influenza [8] or anthrax [9] vaccines.

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

We cannot be sure whether aluminum hydroxide or other components of the vaccine triggered the malignant transformation of the skin lesion in the present case.

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 cutaneous lymphoma and initiate early and appropriate treatment.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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