

Cutaneous Pseudolymphoma Appearing Two Decades After Immunotherapy for Allergic Asthma

Dear Editor:

Cutaneous pseudolymphoma (CPL) is histologically defined by benign reactive lymphoid proliferations simulating cutaneous lymphomas.¹ We report herein two cases of disseminated and delayed CPL due to aluminum-containing allergen immunotherapy indicated for allergic asthma.

The first patient was a 62-year-old woman who reported the appearance, 20 years earlier, of erythematous nodules on both arms, corresponding to sites of hypersensitizing allergen injections received to treat asthma. The skin biopsy, then performed, was consistent with the diagnosis of cutaneous pseudolymphoma. The lesions resolved spontaneously after discontinuation of hyposensitization vaccines. She presented to our department with pruritic erythematous plaques on the cheeks of one-year duration (Figure 1A). Physical examination revealed bilateral infiltrated plaques on both cheeks of 6 cm and 2 cm. Dermoscopy showed pink-orange background color with perifollicular and follicular whitish spots (Figure 1E). Histopathological examination showed dense and nodular lymphoid infiltrate in the dermis with small size lymphocytes and eosinophils (Figure 1F and 1G). Immunohistochemical study revealed CD20-positive cells admixed with CD3-positive cells (Figure 1H, 1I). The diagnosis of recurrent cutaneous pseudolymphoma was established based on clinicopathological correlation. The patient received monthly intralesional corticosteroid injections, using a ¼ dilution of betamethasone dipropionate 5 mg/mL with a 0.9% saline solution. Both clinical and dermoscopic remission was obtained (Figure 1B).

The second patient was a 55-year-old female patient with a past medical history of allergic rhinitis and allergic asthma treated with hypersensitizing airborne allergen vaccines. Twenty-two years later, she presented with four firm and itchy nodules on the abdomen and the umbilic (Figure 1C). Histopathological

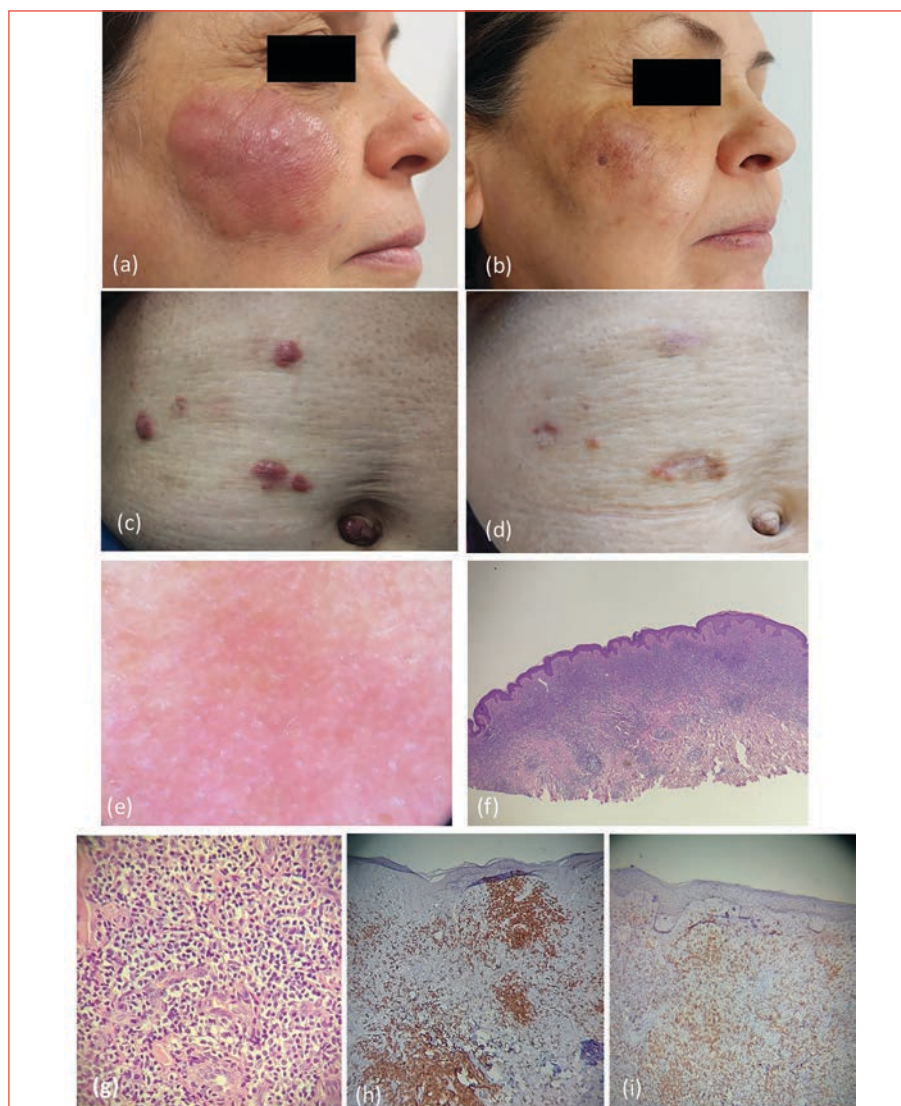


FIGURE 1. Clinical, histopathological, and dermoscopic aspects of cutaneous pseudolymphoma. A) A 6-cm wide, erythematous, infiltrated plaque on the right cheek of the first patient; B) Improvement of the lesion after 10 months of intralesional corticosteroid injections. C) Nodular lesions on the abdomen and the umbilicus of the second patient; D) Improvement of cutaneous lesions after a three-month treatment. E) Dermoscopy of the infiltrated plaque of the first patient showing pink salmon background with structureless orange areas. F) Histopathological examination of the right cheek infiltrated plaque showing dense lymphoid infiltrate of the dermis (HE x40). G) The infiltrate was composed of small-to-medium-sized lymphocytes admixed with eosinophils (HE x400). H) Immunohistochemical staining for CD20; (I) Immunohistochemical staining for CD3

examination showed similar dense dermal infiltration of small to medium-sized lymphocytes supporting the diagnosis of cutaneous pseudolymphoma. The patient was started on corticosteroid intralesional injections with good response (Figure 1D).

Multiple causes of CPL have been identified

including infections, drugs, and foreign agents.¹ However, only a few cases of CPL associated with allergen injections for hyposensitization have been described (Table 1).²⁻⁶ CPL is reported to appear after a delay of 1 to 4 years (Table 1). One possible hypothesis is that continuous chronic antigenic stimulation can induce

TABLE 1. Reported cases of cutaneous pseudolymphomas induced by hyposensitizing airborne allergen vaccines.

DEMOGRAPHICS	BERNSTEIN H ET AL ²	GOERDT S ET AL ³	GERLINI G ET AL ⁴		KINDEM S ET AL ⁵	MORENO LOZANO L ET AL ⁶
Age/Sex	27/F	24/F	30/F	47/F	4 cases. Age and sex were not mentioned	42/F
Vaccine	Antigens derived from house dust and bacteria and antigens derived from pollens and molds	Six injections of Novo-Helisen Depot (allergen extracted from various pollen species, epithelia, or dust mites)	Specific immune therapy	Specific immune therapy	Hyposensitization vaccines (against dust mites)	Depot pollen hyposensitizing extract
Latency	1 year	Few weeks	Not mentioned	Not mentioned	Not mentioned	4 years
Presentation	Multiple erythematous nodules and plaques on arm at sites of injections	Multiple red to brown subcutaneous nodules on external side of both arms (injection sites)	Erythematous-cyanotic plaques and nodules on external side of both arms (injection sites) and on the left buttock and the left thigh.	Pigmented infiltrated and itching plaques on external side of both arms (injection sites) and on the thighs, buttocks, and lower back.	Multiple subcutaneous nodules on external side of both arms (injection sites) 1 case: neck, face, and forehead	Itchy papulonodular and infiltrated lesions on external side of both arms (injection sites) Then of the scalp
Histologic findings	Dense infiltrate of lymphoreticular cells arranged in aggregations that resemble germinal centers within which there were polychrome bodies (nuclear dust) and numerous mitotic figures.	Dense perivascular and periadnexal lymphoid infiltrates with formation of a lymphoid follicle showing germinal center and mantle zone.	Nodular and diffuse lymphohistiocytic infiltrate in the superficial and mid dermis, with the presence of numerous typical reactive lymphoid follicles	Nodular and diffuse lymphohistiocytic infiltrate composed by T and B cells, organized in typical lymphoid follicles with germinal centres in the mid and deep dermis.	Pseudolymphoma B pattern: granulomatous reaction + enlarged histiocytes with granular cytoplasm	Nodular lymphocytic infiltrate with reactive germinal centers
Immunohistochemical findings	Data regarding immunohistochemical findings were not described.	L26 (CD20; pan-B cell marker) UCHL-1 (CD45RO; memory T-cell marker)	The reactive follicles were mostly CD20+, although they occasionally harboured scattered CD3+ T-lymphocytes. The interfollicular areas were rich in T-lymphocytes, with isolated or small groups of B cells and CD68+ histiocytes. The reactive germinal centers were BCL-2 negative, contrasting with the positive cells in the mantles and interfollicular areas.		Data regarding immunohistochemical findings were not described.	CD20 + BCL-6 + BCL-2 -
Treatment	None	Treatment was not specified	Treatment was not specified.	Local radiotherapy + Intralesional corticosteroids	Treatment was not specified	Corticosteroid intralesional injections
Outcome	Spontaneous resolution of some lesions	Data regarding immunohistochemical findings were not described	Data regarding the outcome were not described	No improvement	Data regarding the outcome were not described	Partial response. Transformation into a primary cutaneous B-cell follicular center lymphoma

activation of antigen-specific B cell clones and lead to disseminated lesions.⁴ In our patient, CPL developed several years after the culprit allergen immunotherapy. Furthermore, the occurrence of CPL lesions, far from the injection sites, has been previously reported in only two cases.^{4,5}

The main differential diagnosis is primary cutaneous B cell lymphoma (PCBCL). The possible occurrence of vaccine-induced PCBCL and the risk of progression of vaccine-induced CPL into PCBCL, make the diagnosis even more challenging.⁶ Histologically, it is difficult to differentiate PCBCL from CPL. Dense mixed infiltrate arising from the papillary dermis with prominent germinal centers and prominent vasculature are characteristic of pseudolymphomas.² The detection of B-cell clonality favors the diagnosis of PCBCL, but clonal B-cell proliferation was also described in nodular CPL.¹ Thus, the diagnosis is based on careful clinical, histopathological, and immunohistochemical correlation. In our patients, histopathological findings and benign clinical course were consistent with the diagnosis of CPL. Intralesional corticosteroid injections showed good efficacy and safety.

With regard,

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FUNDING. No funding was provided for this study

DISCLOSURES. The authors report no conflicts of interest relevant to the content of this article.

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REFERENCES

1. Mitteldorf C, Kempf W. Cutaneous pseudolymphoma—A review on the spectrum and a proposal for a new classification. *J Cutan Pathol.* 2020;47(1):76–97.
2. Bernstein H, Shupack J, Ackerman AB. Cutaneous Pseudolymphoma Resulting From Antigen Injections. *Arch Dermatol.* 1974; 110:756–757.
3. Goerdts S, Spieker T, Wölffer LU, et al. Multiple cutaneous B-cell pseudolymphomas after allergen injections. *J Am Acad Dermatol.* 1996;34(6):1072–1074.
4. Gerlini G, Mori M, Massi D, et al. Specific immune therapy-related cutaneous B-cell pseudolymphoma with following dissemination. *J Eur Acad Dermatol Venereol.* 2003;17:208–212.
5. Kindem S, Llombart B, Llorca D, et al. Subcutaneous nodules in patients with hyposensitization to aluminium-containing vaccination. *J Am Acad Dermatol.* 2012;66(4):AB82.
6. Moreno Lozano L, Sánchez Caminero M, García Arpa M, et al. Cutaneous B-cell lymphoma at the injection site of airborne allergen immunotherapy followed by cutaneous metastasis. *J Invest Allergy Clin Immunol.* 2021;32(4). **JCAD**