Lamotrigine-Induced Cutaneous Pseudolymphoma

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PRACTICE **POINTS**

- Cutaneous pseudolymphomas are a heterogenous group of benign T-cell, B-cell, or mixed-cell lymphoproliferative processes that resemble cutaneous lymphomas clinically and/or histopathologically.
- Cutaneous pseudolymphomas have many causative factors, including medications, infections, tattoo ink, vaccinations, and insect bites.
- Lamotrigine is a potential inciting factor of cutaneous pseudolymphoma.

To the Editor:

An 8-year-old girl presented with new lesions on the scalp that were mildly painful to palpation and had been increasing in size and number over the last 2 months. Her medical history was remarkable for seizures, keratosis pilaris, and seborrheic dermatitis. The seizures had been well controlled on oxcarbazepine; however, she was switched to lamotrigine 6 months prior to presentation under the care of her neurologist. The patient was not taking other oral medications, and she denied any trauma/insect bites to the affected area or systemic symptoms such as fever, fatigue, weight loss, nausea, swollen lymph nodes, or night sweats. Physical examination revealed 3 well-circumscribed, pink, slightly scaly, indurated nodules on the frontal and vertex scalp (Figure 1). She reported pain on palpation of the lesions. Treatment with ketoconazole shampoo and high-potency topical corticosteroids was ineffective.

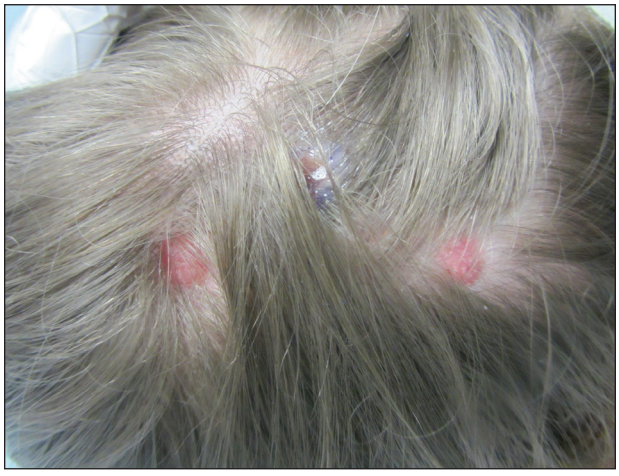

FIGURE 1. Lamotrigine-induced cutaneous pseudolymphoma presenting as 3 well-circumscribed, pink, slightly scaly nodules on the vertex scalp.

Over a period of 2 months after the initial presentation, the patient developed a total of 9 scalp lesions. Testing was performed 4 months after presentation of lesions. Bacterial and fungal cultures of the lesional skin of the scalp were negative. Two biopsies of lesions on the scalp were performed, the first of which showed a nonspecific lymphohistiocytic infiltrate. The second biopsy revealed a dense, nodular, atypical dermal lymphoid infiltrate composed primarily of round regular lymphocytes intermixed with some larger, more irregular lymphocytes and few scattered mitoses (Figure 2).

Immunohistochemical studies revealed small B-cell lymphoma 2–positive lymphocytes with a 2:1 mixture of $CD3^+$ T cells and $CD20^+CD79a^+$ B cells. The T cells expressed CD2, CD5, and CD43, and a subset showed a loss of CD7. The CD4:CD8 ratio was 10 to 1. No follicular dendritic networks were noted with CD21 and CD23. Rare, scattered, medium-sized

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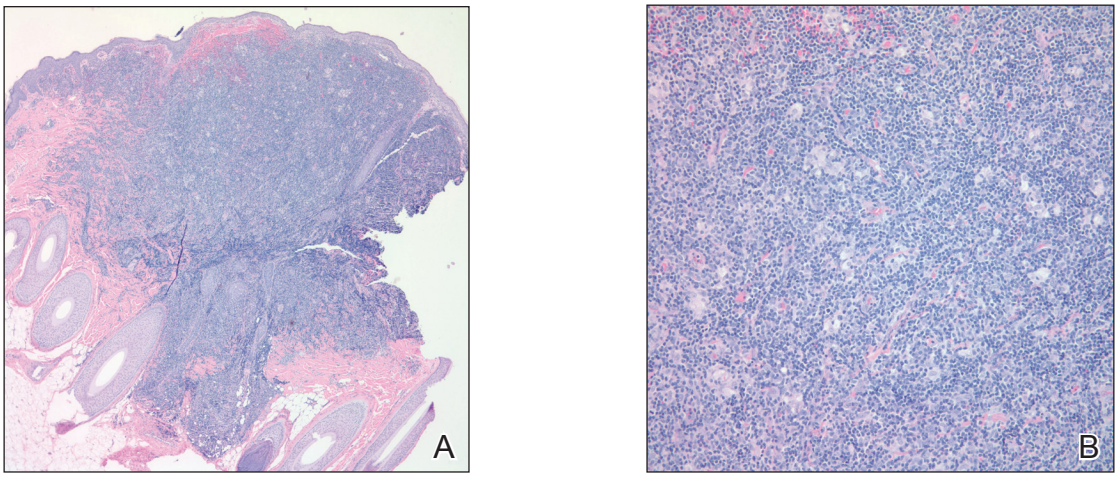

FIGURE 2. A, A punch biopsy of a lesion on the right lateral scalp showed an atypical dermal lymphoid infiltrate (H&E, original magnification ×4). B, A punch biopsy of a lesion on the right lateral crown of the scalp showed a closer view of the atypical dermal lymphoid infiltrate with a nodular proliferation of round regular lymphocytes intermixed with larger irregular lymphocytes and scattered mitoses (H&E, original magnification ×20).

CD30 cells were noted. Staining for CD10, B-cell lymphoma 6, anaplastic lymphoma kinase, Epstein-Barr virus–encoded RNA 1, IgD, and IgM were negative. The plasma cells had a κ/λ free light chain ratio of 2 to 1. Ki-67 was positive in 15% of lymphoid cells. Polymerase chain reaction analysis of T-cell receptor gene rearrangement revealed a peak at 228 bp in a predominantly polyclonal background. A thorough systemic workup including complete blood cell count, immunoglobulin assay, bone marrow transplant panel, comprehensive metabolic panel, lactate dehydrogenase test, inflammatory markers, and viral testing failed to reveal any evidence of underlying malignancy.

After conferring with the patient's neurologist, lamotrigine was discontinued. Within a few weeks of cessation, the scalp lesions resolved without recurrence at 9-month follow-up. In addition to the lack of clinical, histological, or immunohistochemical evidence of underlying malignancy, the temporal association of the development of lesions after starting lamotrigine and rapid resolution upon its discontinuation suggested a diagnosis of lamotrigine-induced cutaneous pseudolymphoma.

Cutaneous pseudolymphoma is a term used to describe a heterogenous group of benign reactive T-cell, B-cell, or mixed-cell lymphoproliferative processes that resemble cutaneous lymphomas clinically and/or histopathologically.[1] Historically, these types of proliferations have been classified under many alternative names that originally served to describe only B-cell–type proliferations. With advances in immunohistochemistry allowing for more specific cell marker identification, cutaneous pseudolymphomas often are found to contain a mixture of T-cell and B-cell populations, which also led to identifying and describing T-cell–type pseudolymphomas.[2]

The clinical appearance of cutaneous pseudolymphoma is variable, ranging from discrete nodules or papules to even confluent erythroderma in certain cases.[2] The high clinical variability further complicates diagnosis. Although our patient presented with 9 individual nodular lesions, this finding alone is not sufficient to have high suspicion for cutaneous pseudolymphoma without including a much broader differential diagnosis. In our case, the differential diagnosis also included cutaneous lymphoma, arthropod bite reaction, lymphomatoid papulosis, tumid lupus, follicular mucinosis, lymphocytic infiltrate of Jessner, and leukemia cutis.

The primary concern regarding diagnosis of cutaneous pseudolymphoma is the clinician's ability to effectively differentiate this entity from a true malignant lymphoma. Immunostaining has some value by identification of heterogeneous cell–type populations with a mixed T-cell and B-cell infiltrate that is more characteristic of a benign reactive process. Subsequent polymerase chain reaction analysis can detect the presence or absence of monoclonal T-cell receptor gene rearrangement or immunoglobulin heavy chain rearrangement.[3] If these monoclonal rearrangements are absent, a benign diagnosis is favored; however, these rearrangements also have been shown to exist in a case of cutaneous pseudolymphoma that earned the final diagnosis when removal of the offending agent led to spontaneous lesion regression, similar to our case.[4]

Many different entities have been described as causative factors for the development of cutaneous pseudolymphoma. Of those that have been considered causative, simple categories have emerged, including endogenous, exogenous, and iatrogenic causes. One potential endogenous etiology of cutaneous pseudolymphoma is IgG4-related disease.[5] A multitude of exogenous causes have been reported, including several cases of cutaneous pseudolymphoma developing in a prior tattoo site.[6] Viruses, specifically molluscum contagiosum, also have been implicated as exogenous causes, and a report of cutaneous

pseudolymphoma development at a prior site of herpes zoster lesions has been described.[7] Development of cutaneous pseudolymphoma in vaccination sites also has been reported,[8] as well as more obscure inciting events such as *Leishmania donovani* infection and medicinal leech therapy.[9]

A considerable number of reported cases of cutaneous pseudolymphoma have been attributed to drugs, including monoclonal antibodies,[10] herbal supplements,[11] and a multitude of other medications.[1] As a class, anticonvulsants are considered more likely to cause lymph node pseudolymphomas than strictly cutaneous pseudolymphomas[12]; however, many drugs in this class of medications have been described in the development of cutaneous pseudolymphoma.[3] A review of the literature by Ploysangam et al[1] revealed reports of the development of cutaneous pseudolymphomas after administration of phenytoin, carbamazepine, mephenytoin, trimethadione, phenobarbital, primidone, butabarbital, methsuximide, phensuximide, and valproic acid.

Our patient represents a rare case of strictly cutaneous pseudolymphoma caused by administration of lamotrigine. Our case demonstrated a clear temporal relation between the cessation of lamotrigine and rapid and spontaneous disappearance of cutaneous lesions. We found another case of pseudolymphoma in which lamotrigine was deemed causative, but only lymph node involvement was observed.[12]

Proper diagnosis of cutaneous pseudolymphoma is important not only with regard to the initial differentiation from true malignant lymphoma but in allowing for appropriate follow-up and vigilant surveillance. Cases of progression from cutaneous pseudolymphoma to true lymphoma have been reported.[1,2] It is recommended that watchful follow-up for these patients be carried out until at least 5 years after the diagnosis of cutaneous pseudolymphoma is made to rule out the possibility of malignant transformation, particularly in idiopathic cases.[13]

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