Cutaneous Lymphoid Hyperplasia: A Case Report and Brief Review of the Literature

CPT Jeffrey N. Lackey, MC, USA; CPT Yang Xia, MC, USA; CPT Sunghun Cho, MC, USA; Leonard C. Sperling, MD

GOAL

To understand cutaneous lymphoid hyperplasia (CLH) to better manage patients with the condition

OBJECTIVES

Upon completion of this activity, dermatologists and general practitioners should be able to:

1. Discuss the etiology of CLH.
2. Describe the histologic presentation of CLH.
3. Identify treatment options for CLH.

CME Test on page 462.

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Cutaneous lymphoid hyperplasia (CLH) is considered a benign lymphoid reactive process that results from various antigenic stimuli and may have potential for progression to overt lymphoma. CLH lesions may closely resemble lymphoma both clinically and histologically. We present a case of a 54-year-old woman who spontaneously developed lesions of unknown cause consistent with CLH. We also review the literature and discuss the etiology, clinical features, diagnosis, and management of CLH.

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From Dermatology Services, Walter Reed Army Medical Center, Washington, DC. Dr. Lackey is an intern, Drs. Xia and Cho are dermatology residents, and Dr. Sperling is a staff dermatologist and dermatopathologist.

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Case Report

An otherwise healthy 54-year-old woman presented with a 6-month history of multiple asymptomatic papules on her nose. The patient's past medical history included hypertension and hyperlipidemia. Her medications included atenolol, hydrochlorothiazide, and gemfibrozil. She denied prior infection suggestive of *Borrelia* species or molluscum contagiosum. Results of a physical examination revealed 4 firm,

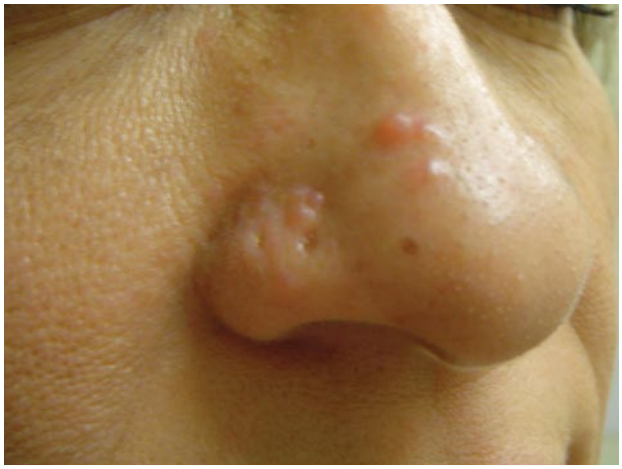

Figure 1. Characteristic skin-colored to pink, well-circumscribed papules on the right nasal ala.

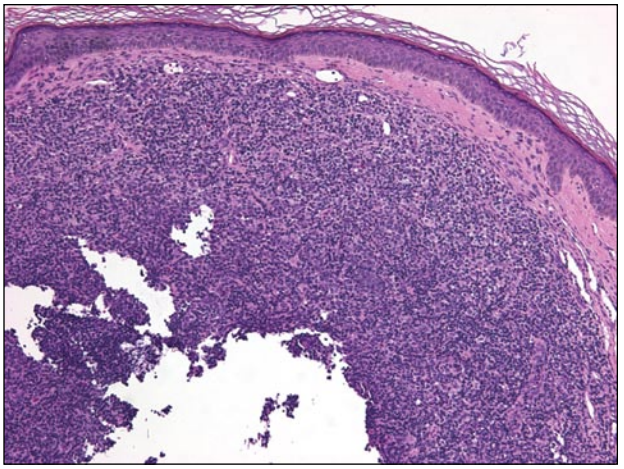

Figure 2. Diffuse basophilic infiltrate in the dermis (H&E, original magnification ×4).

skin-colored to pink, dome-shaped papules on the right nasal ala (Figure 1) and dorsum. A shave biopsy of a lesion on the right nasal ala was performed. Results of a routine histologic evaluation revealed a diffuse basophilic infiltrate in the dermis (Figure 2). The infiltrate consisted of polyclonal B and T cells (Figure 3). The B cells were $CD20^+$ and T cells were $CD4^+$ and $CD8^+$. In addition, there was a mixed expression of κ and λ chains within the infiltrate. The patient was diagnosed with cutaneous lymphoid hyperplasia (CLH).

For cosmetic reasons, numerous treatment modalities were attempted. The lesions initially were treated with a variety of topical steroids and immunomodulators, with minimal success. In addition, cryotherapy and intralesional steroids were used, with some short-lived response. However, the treated lesions never completely regressed and returned to their pretreatment size within 10 to 14 days after therapy. The lesions did respond well to shave removal, but the patient's personal fear of needles prevented her from continuing this treatment option. She subsequently was lost to follow-up.

Comment

The term *cutaneous lymphoid hyperplasia* was coined by Caro and Helwig[1] in 1969. The disease also has been called lymphadenosis benigna cutis, Spiegler-Fendt pseudolymphoma, lymphocytoma cutis, and cutaneous lymphoplasia.[2] Although the pathogenesis of CLH remains unknown and most cases are idiopathic, certain drugs and long-term antigenic stimulation are implicated in many cases.[3] Anticonvulsant medications (ie, phenytoin, phenobarbital, carbamazepine, sodium valproate) appear to be the most common pharmaceutical agents to cause CLH. Losartan, gemcitabine, bromocriptine, fluoxetine, amitriptyline, and injected silicone also have been associated with this disease.[4-8] Rarely, infectious agents such as *Borrelia* species and molluscum contagiosum have been linked with CLH.[9-11] Additionally, CLH has occurred following exposure to various foreign antigens, including tattoos, trauma, body piercing jewelry, cobalt, leeches, and arthropod bites and stings.[9,12-14] Appearance of multiple lesions has been reported following injection of allergen for hyposensitization.[15,16] May et al[3] described CLH localized to the site of influenza vaccination.

CLH is seen in both adults and pediatric patients and is 2 to 3 times more likely to occur in females.[9] Morphologically, CLH appears as clusters of firm pink-colored to plum-colored papules, plaques, nodules, or tumors that occur on any skin surface but most commonly on the face. Although patients usually are asymptomatic, many seek treatment for cosmesis. CLH can be associated with regional lymphadenopathy, though most cases are not associated with other physical findings. The clinical differential diagnosis includes cutaneous lymphomas.[10,17]

On histologic examination, lesions of CLH may display multiple lymphoid follicles and dense superficial to deep infiltration of mostly mature lymphocytes.[2,9] Lymphocytes often are admixed with histiocytes and occasional eosinophils and plasma cells.[1] Germinal centers with tingible body macrophages often are apparent.[9,10,18] Because these features also may be seen in lymphomas, determination of polyclonality by immunophenotyping with either polymerase chain reaction or other techniques is helpful in the evaluation of CLH. Lesions of CLH may consist of an infiltrate that mostly consists of mixed $CD4^+$ and $CD8^+$ T lymphocytes in the periphery, with B lymphocytes predominating within germinal centers. Mixed expression of κ and

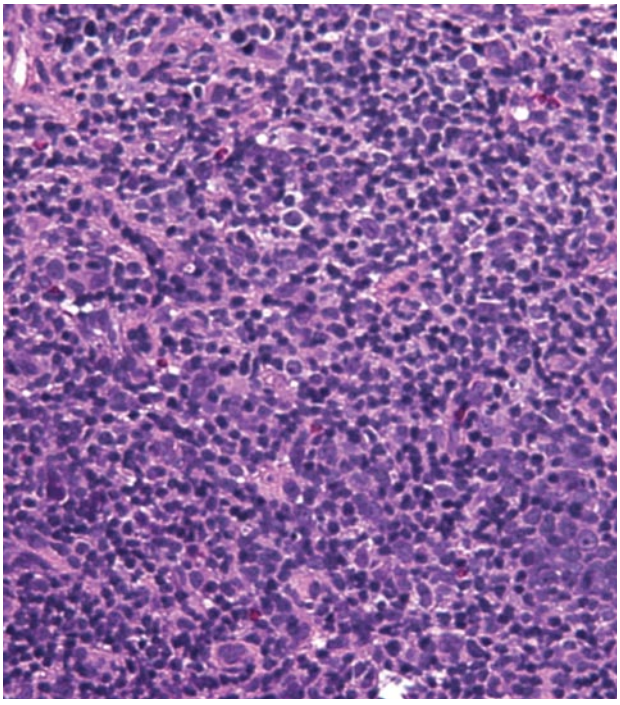

Figure 3. Polyclonal B and T cells in the dermis (H&E, original magnification ×10).

λ chains also has been suggested as a marker for CLH because most lymphomas demonstrate restricted expression of κ or λ chains.[3,10] Despite the general rule of polyclonality with CLH and monoclonality with lymphomas, there have been reports of CLH in the presence of a monoclonal lymphocyte population and clinically malignant cutaneous B-cell lymphomas without evidence of monoclonality.[9,19]

Although the characteristic lymphocytic proliferation appears to be reactive and polyclonal, the literature suggests that some cases of CLH have the potential to become malignant.[9,20] A study by Nihal et al[9] identified several cases of CLH that harbored monoclonal B-cell populations that eventually progressed to overt lymphomas. During follow-up of these patients, polymerase chain reaction analysis of their lymphomas revealed malignant lymphocytes from the same cell lineage noted in the original CLH lesion. Although the molecular pathogenesis of B-cell proliferations in CLH is poorly understood, recent literature has shown that a B-cell chemoattractant, BCA-1 (B-cell attracting chemokine 1), and its receptor, CXCR5 (chemokine receptor 5), are expressed by lymphocytes in moderate quantities in lesions of CLH.[20] The same lesions also have shown expression of BCA-1 on dendritic cells within lymphoid follicles. Low-grade and high-grade B-cell lymphomas also express both BCA-1 and its receptor, but expression is restricted to neoplastic B cells.[20] Neither BCA-1 nor CXCR5 are expressed in healthy skin.

Lesions of CLH often regress spontaneously, though some cases become chronic and others recur locally.[19] Rarely, some lesions progress to cutaneous lymphoma. However, it is uncertain if this represents true progression of a benign lesion along a continuum leading to lymphoma or a failure to diagnose a lesion that was malignant from the start.[2,9,21]

For CLH that results from known stimuli, the first step in treatment is removal of the causative agent. Antibiotic therapy has been effective in cases related to infective causes.[10,18] Reported therapies for persistent or idiopathic cases include topical or intralesional corticosteroids, cryosurgery, local radiation, excision, interferon alfa, and laser ablation.[19,22,23] Good response to thalidomide has been documented in one small study.[24]

Conclusion

CLH is a benign lymphoid proliferation resulting from various antigenic stimuli and may have the potential for progression to overt lymphoma. Lesions may closely resemble lymphoma both clinically and histologically, highlighting the importance of immunophenotyping in establishing a diagnosis. Treatment of this benign disease entity needs to be individualized for each patient. Although there are numerous treatment options for CLH, none are consistently effective.

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