Small lymphocytic lymphoma presenting as chronic diffuse lip swelling

Jennifer E Yeh1,2 MD PhD, Mayra E Lorenzo2 MD PhD, Cecilia Larocca3 MD, David C Fisher4 MD, Ruth K Foreman5 MD PhD

Affiliations: 1Department of Dermatology, Stanford University School of Medicine, Palo Alto, California, USA, 2Department of Dermatology, Massachusetts General Hospital, Boston, Massachusetts, USA, 3Department of Dermatology, Dana-Farber Cancer Institute, Boston, Massachusetts, USA, 4Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, Massachusetts, USA, 5Department of Pathology, Massachusetts General Hospital, Boston, Massachusetts, USA

Corresponding Author: Ruth K Foreman MD PhD, 55 Fruit Street, Boston, MA 02114, Tel: 617-726-8490; Email: rkforeman@partners.org; Jennifer Yeh MD PhD, 450 Broadway Street, Pavilion C, 2nd floor, Redwood City, CA 94063, Tel: 650-723-6316, Email: jeyeh@stanford.edu

Abstract
Although rare, small lymphocytic lymphoma can present as chronic lip swelling and papules, thus mimicking the features of orofacial granulomatosis, a chronic inflammatory disorder characterized by subepithelial noncaseating granulomas, or papular mucinosis, characterized by localized dermal mucin deposition of mucin. When assessing lip swelling, one must carefully consider the clinical clues and have a low threshold to perform a diagnostic tissue biopsy, preventing delays in treatment or progression of the lymphoma.

Keywords: chronic, lip swelling, lymphocytic leukemia, small

Introduction
Oral symptoms including lip swelling, pain, and paresthesia are rare manifestations of low-grade lymphoma, most commonly marginal zone lymphoma. In this case we review a patient with chronic lip swelling who was ultimately found to have small lymphocytic lymphoma, highlighting the importance of inspecting for subtle clinical clues (presence of papules), maintaining a broad differential diagnosis, and performing a diagnostic biopsy so that appropriate treatment can be initiated.

Case Synopsis
A 54-year-old previously healthy man presented with diffuse swelling of his upper and lower lip vermilion with overlying papules of two years’ duration. He was an avid skier and hockey player and had initially attributed his lip swelling to a wool allergy. He had received multiple prednisone tapers with waning efficacy. He underwent allergy and screening inhalant testing, which were both negative. Given mild lip scaling, he received

Figure 1. Clinical presentation with diffuse rubbery soft swelling of the upper and lower lips and overlying papules.
desonide 0.05% ointment, clotrimazole cream, and tacrolimus 0.03% ointment for presumed perioral dermatitis and cutaneous candidiasis with minimal improvement. Given persistent lip papules concerning for atypical HSV, valacyclovir 1000mg twice daily for 10 days was added.

He was referred to dermatology clinic, at which time he endorsed lip sensitivity with a tingling sensation, noting minimal improvement since adding valacyclovir. He denied prior episodes of lip swelling, papules, or injection of foreign material. Skin examination revealed diffuse rubbery soft swelling of the upper and lower lips, with a rim of 3-5mm smooth pink papules with fine overlying telangiectasias on the upper vermilion lip border without scaling, fissuring, vesicles, or erosions (Figure 1). Cervical lymphadenopathy was absent. A 2mm punch biopsy was performed from a papule on the upper vermilion lip and showed a dense superficial and deep dermal lymphocytic inflammatory infiltrate without epidermal involvement (Figure 2A). The infiltrate was composed of uniformly small cells with scant cytoplasm that grew in sheets and clusters (Figure 2A, B).

Immunohistochemistry revealed that the lymphocytic infiltrate showed positive staining for CD20 (Figure 2C), CD5 (Figure 2D), and CD23 (Figure 2E). Peripheral blood flow cytometry showed a small population of monotypic B cells. Taken together, the findings were consistent with a diagnosis of chronic lymphocytic leukemia/small lymphocytic lymphoma, National Comprehensive Cancer Network (NCCN) small lymphocytic lymphoma/localized (Lugano Stage I). Lymph node involvement was assessed based on physical examination and PET/CT imaging. Complete blood count was normal and staging CT scans were negative. He was treated with betamethasone ointment with no response. He then received brachytherapy (2000cGy delivered in 8 fractions of 250cGy over 15 days) with complete resolution of oral changes and symptoms.

On dermatology follow-up 6 months later, he had developed firm, slightly tender swelling of the upper and lower lips. Skin examination revealed a few skin-
colored waxy <1mm monomorphic papules on the vermilion border of the upper central lip concerning for subtle signs of cutaneous recurrence for which he was prescribed topical imiquimod 5% cream five times weekly for two weeks. At follow-up several months later, he was in remission with no evidence of recurrence and only mild dysesthesia in the area treated with radiation and imiquimod.

Case Discussion
Small lymphocytic lymphoma and chronic lymphocytic leukemia are considered different manifestations of the same disease, with small lymphocytic lymphoma involving abnormal lymphocytes primarily in the lymph nodes and chronic lymphocytic leukemia involving abnormal lymphocytes predominantly in the blood. Small lymphocytic lymphoma/chronic lymphocytic leukemia constitutes approximately 7% of newly diagnosed non-Hodgkin lymphoma (NHL) cases [1]. Chronic lymphocytic leukemia is more commonly diagnosed in men and the elderly, with a median age at diagnosis of 70 years. Although some chronic lymphocytic leukemia patients have indolent disease with prolonged survival, others have more aggressive diseases with poor outcomes [2]. For localized small lymphocytic lymphoma (Stage I), as in this patient, locoregional radiation therapy is appropriate for induction therapy [1]. Oral manifestations of lymphoma are rare, comprising only 3% of all lymphomas in the general population [3]. The main clinical manifestations are lip swelling, pain, and paresthesia. A retrospective review of 23 cases of non-Hodgkin lymphoma of the lips showed that most cases presented on the lower lip, involved the lip salivary glands, and were associated with extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue [4].

Small lymphocytic lymphoma presenting as chronic lip swelling can clinically mimic the features of orofacial granulomatosis (OFG), a chronic inflammatory disorder characterized by subepithelial noncaseating granulomas [5]. Therefore, when assessing lip swelling, one must carefully consider the clinical clues, such as papules, and have a low threshold to biopsy to make the diagnosis. Lymphoma of the lips should be suspected even in the absence of systemic symptoms. Prompt diagnosis is critical to prevent delays in appropriate treatment or potential progression of the lymphoma.

Orofacial granulomatosis, also termed granulomatous cheilitis, oral granulomatosis, and cheilitis granulomatosa, is an uncommon disorder characterized by persistent enlargement of the soft tissues of the lip, oral mucosa, and perioral region [6]. Orofacial granulomatosis may be the first manifestation of a systemic condition such as Melkersson-Rosenthal syndrome, which involves orofacial edema, a fissured tongue, and facial nerve palsy. Orofacial granulomatosis is a diagnosis of exclusion and other granulomatous disorders such as inflammatory bowel disease, sarcoidosis, leprosy, and tuberculosis must be ruled out before making the diagnosis. The pathogenesis of orofacial granulomatosis is not fully understood, with proposed triggers including infection, hereditary factors, and allergy. On histopathology, orofacial granulomatosis shows non-necrotizing granulomas with multinucleated giant cells, a perivascular mononuclear infiltrate, often with edema. Management options include topical, intralesional, or systemic corticosteroids. In addition, pulse-dose oral azithromycin, low phenolic acid diet, and in some severe cases, surgical procedures such as reduction cheiloplasty have been beneficial [6-8].

Papular mucinosis or lichen myxedematosus can present with localized areas of discrete firm waxy papules and is characterized by dermal deposition of mucin [9]. Histopathology shows abundant mucin deposition between collagen bundles, fibroblast proliferation, and fibrosis. It is important to distinguish papular mucinosis from scleromyxedema, which has areas of woody indurated skin and can be associated with systemic symptoms and monoclonal gammopathy.

The differential diagnosis for diffuse lip swelling also includes angioedema, lip augmentation dermal filler reaction, and rosacea lymphedema or Morbihan disease. Angioedema presents as localized
subcutaneous or submucosal swelling, most commonly of the lips, tongue, and face with associated pain and warmth. Angioedema is typically transient, with the onset of swelling within minutes-to-hours and spontaneous resolution within 24 hours. Triggers for angioedema include medications (common culprits include angiotensin-converting enzyme inhibitors) and foods, though many cases are idiopathic [10]. Dermal fillers have distinct histopathologic patterns, for instance basophilic lakes for hyaluronic acid and clear bubbly spaces mimicking lipoblasts for silicone [11]. Morbihan disease, also known as rosacea lymphedema, is characterized by chronic and persistent erythematous solid facial edema and while refractory, has been reported to respond to tetracyclines and oral isotretinoin [12,13].

**Conclusion**

We herein describe a patient with two years of diffuse lip swelling, subtle papules, and paresthesia as the primary manifestation of small lymphocytic lymphoma. Although rare, small lymphocytic lymphoma can involve the skin and clinically mimic more common causes of lip swelling. Given the importance of early diagnosis of this entity, we highlight the clinical clues that raise the suspicion for cutaneous small lymphocytic lymphoma and add it as an important entity to include in the differential diagnosis for patients who present with chronic lip swelling.

**Potential conflicts of interest**

The authors declare no conflicts of interest.

**References**