Refractory Cutaneous Lymphoid Hyperplasia Treated with Rituximab: A Case Report and Literature Review

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ABSTRACT:
Cutaneous lymphoid hyperplasia (CLH), recognized as reactive B-cell-rich lymphoid proliferations in the 5th edition of the World Health Organization Classification of Haematolymphoid Tumours, is a benign reactive inflammatory condition that clinically and histologically resembles cutaneous lymphoma and can present with a predominance of B-cells, T-cells, or a mixture of both. The majority of patients present with a single papule, nodule, or plaque. Nevertheless, numerous or extensive lesions can rarely develop. We report a case of CLH with multiple nodules and plaques on the face. The patient had a progressive refractory disease and showed poor response to numerous therapies, including topical, intralesional, and systemic corticosteroids, topical calcineurin inhibitors, doxycycline, isotretinoin, hydroxychloroquine, and methotrexate, but showed a great response to rituximab, a monoclonal antibody targeted against the CD20 antigen.
Key words: Cutaneous Lymphoid Hyperplasia, Reactive B-Cell-Rich Lymphoid Proliferations, Pseudolymphoma, Refractory, Rituximab

Introduction

Cutaneous lymphoid hyperplasia (CLH) is a benign, reactive condition that may have clinical and/or histological similarities to cutaneous lymphomas. In the 5th edition of the World Health Organization Classification of Haematolymphoid Tumours, CLH was categorized as reactive B-cell-rich lymphoid proliferations for the first time[1]. CLH is also known as pseudolymphoma, reactive lymphoid hyperplasia, lymphocytoma cutis, lymphadenosis benigna cutis, and Spiegler-Fendt sarcoid[2].

The majority of CLH patients present with a single papule, nodule, or plaque; multiple or disseminated lesions are uncommon. Some patients may have a history of known triggers, such as arthropod bites, infections, tattoos, medications, vaccinations, allergens, and neoplasms. However, a number of CLH patients have unknown causes. For patients with known causes, eradication or withdrawal of the etiology is the best course of action. Idiopathic cases have been successfully treated with antibiotics, intralesional and systemic corticosteroids, excision, and radiotherapy. Treatments with hydroxychloroquine (HCQ), methotrexate (MTX), rituximab, and dupilumab have been documented in rare cases[2-5]. We report a case of idiopathic CLH with progressive and extensive lesions on the face that were refractory to multiple treatment options but responded well to rituximab.

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Case report

A 46-year-old female presented to our dermatology clinic in 2014 with a 2-month history of a confluent itchy erythematous plaque on the cheeks and bridge of the nose (Figure 1A). She was initially diagnosed with rosacea, but she did not respond to therapy and developed some indurated, firm nodules after a few months (Figure 1B). A skin biopsy was performed on the cheek. The section revealed nodular lymphoid cell infiltration with germinal center formation, tingible body macrophages, and scattered plasma cells in the dermis. Direct immunofluorescence was negative. CLH was diagnosed. During her 6-year follow-up, the skin lesion worsened despite multiple treatment regimens, including oral doxycycline, isotretinoin, topical, intralesional, and systemic corticosteroids, topical pimecrolimus, pulsed-dye laser, chloroquine, HCQ, and MTX. She developed thicker erythematous indurated plaques and papulonodular eruptions on both cheeks, nose, forehead, and chin (Figure 1C). Mild pruritus was reported. The rebiopsy with immunohistochemical studies was performed on a nodule above the left upper lip. Similar histologic results to those from the first biopsy were seen in this section. Nodular lymphocytic infiltration with reactive germinal centers, which contain tingible body macrophages, scattered plasma cells, and a few eosinophils, were seen in the dermis. The mononuclear cells in the follicular area were positive for CD20, CD10, and BCL6 but negative for BCL2. CD21 highlighted the follicular meshwork. Ki67 staining revealed a high proliferative rate in the germinal centers. Kappa and Lambda light chain restrictions were not detected. CD3-positive T-cells with a mixture of CD4 and CD8-positive T-cells were observed in parafollicular areas (Figure 2).

The patient had no superficial lymphadenopathy, and the liver and spleen were not enlarged. A complete blood count, complete metabolic panel, and lactate dehydrogenase level were normal. An antinuclear antibody was negative. The computed tomography of the chest and abdomen was unremarkable. These investigations confirmed the diagnosis of CLH.

Due to the disease extent and the recalcitrant nature of CLH in this patient. Approximately 6 years after the first presentation, rituximab infusions were initiated at 1 gm (563.44 mg/m^2) for 2 doses, 2 weeks apart. The improvement was noticed within 1 month and significantly improved after 2 months of rituximab infusion (Figure 1D). No serious side effects were reported.

2 years later, the patient experienced recurrent disease (Figure 1E) and did not respond to HCQ, oral MTX, topical and intralesional corticosteroids, or topical tacrolimus. The second course of rituximab was administered with a favorable response (Figure 1F). At the time we reported this case, the patient was still in remission.

She was otherwise healthy, with no history of fever, night sweats, weight loss, or palpable abnormal mass. She denied history of tattooing, metal implantation, cosmetic injectables, or insect bites before the lesions occurred.

Discussion

CLH, or cutaneous pseudolymphoma, is a benign reactive inflammatory condition that may mimic cutaneous lymphoma clinically and histologically; it may show predominately B-cells, T-cells, or a mixture of both[3].

Although CLH is considered a reactive process and most cases are idiopathic, some patients might have a history of known stimuli, including foreign substances (e.g., tattoos, vaccination, allergen injections for immunotherapy, piercing), infections (e.g., Borrelia infection, herpes zoster, molluscum contagiosum, syphilis, HIV, scabies, leishmaniasis), drugs (e.g., anticonvulsants, antipsychotics, antihypertensives), and others (e.g., insect bites, leech therapy, photosensitivity, trauma)[2,6]. It is crucial to

identify the etiology of CLH because treating an underlying disease or eliminating identified stimuli may enhance treatment outcomes.

Typically, CLH appears gradually as a single erythematous papule, nodule, or plaque. It is more frequent in middle-aged females, and it preferentially affects the face (particularly the nose and cheeks), upper torso, and arms. Only 10-15% of patients present with more generalized or multifocal skin lesions[2].

Even though CLH is usually benign and indolent, its course can be extremely diverse, ranging from spontaneous regression to progression to lymphoma[7]. CLH with a severe or aggressive course is uncommon, but several studies show that CLH has the potential to transform into cutaneous B-cell lymphoma[6, 8].

CLH is a relatively rare disease without well-established standard guidelines for management. The diagnosis is based on a comprehensive evaluation of clinical presentation and behavior, routine histology, and/or immunophenotyping and molecular analyses. The necessity of a staging workup is controversial, but it should be reserved for patients with unusual clinical manifestations or aggressive CLH[6].

The principle of CLH therapy is to avoid or eliminate the triggers. However, a number of CLH patients are idiopathic. There are various treatment options with variable responses for idiopathic CLH. Topical or intralesional corticosteroids are most commonly used. Topical tacrolimus and imiquimod may be effective. Systemic therapy with MTX, antimalarials, antibiotics (amoxicillin, doxycycline, and cephalosporin), thalidomide, and dupilumab has been reported. Excision is preferred for a single small lesion. Cryotherapy, phototherapy, photodynamic therapy, and radiotherapy may be considered in certain circumstances. Combination treatments may be helpful, particularly for resistant cases[3, 5, 6].

Table 1 Literature review of cases of idiopathic cutaneous lymphoid hyperplasia treated effectively with rituximab.

Authors (year)	Location of lesion(s)	N	Age (year)/Sex	Route	Dose of rituximab	Efficacy	Recurrence	Additional treatment
Martin and Duvic[12] (2011)	Face	1	58/F	IL	Total dose of 10 mg/mL weekly for 18 wk	PR	2 mos	Topical tacrolimus
Matin et al.[13] (2019)	Face	3	A: 41/F B: 65/F C: 62/F	IL	A, C: 10 mg/lesion weekly for 18 wk B: 10 mg/lesion weekly for 6 wk	A, B: CR C: NR	C: 1 mo	None
Behrouz Sharif et al.[10] (2019)	Face and forearms	1	36/F	IV	500 mg weekly for 4 wk and 1 g 3 mos later	CR in 3 mos	None	None
Balode et al.[11] (2020)	Chin	1	46/F	IV	375 mg/m^2 weekly for 4 wk	CR	N/A	None
Besch-Stokes et al.[4] (2021)	Face	1	72/M	IV	375 mg/m^2 weekly for 4 wk	CR in 8 mos	N/A	MTX 20 mg/wk

Abbreviations: CR, complete response; F, female; IL, intralesional; IV, intravenous; M, male; MTX, methotrexate; mo, month; mos, months; N/A, not available; NR, no respond; PR, partial remission; wk, weeks

Our patient displayed an unusual presentation of CLH with a progressive disease despite various therapies, such as topical, intralesional and systemic corticosteroids, HCQ and MTX. In order to confirm the diagnosis and rule out overt cutaneous lymphoma, we

considered undertaking repeated biopsies with IHC investigations as well as a systemic staging workup. Even though the definitive diagnosis was benign CLH, the patient suffered from disfigurement from her facial lesions, which had an adverse impact on her social life. Rituximab was administered due to a significant B-cell infiltrate in her skin biopsies.

Rituximab is a monoclonal antibody that targets the CD20 marker on B-cells. It is FDA approved for various B- cell malignancies and autoimmune diseases, such as B-cell non-Hodgkin lymphoma, rheumatoid arthritis, and pemphigus vulgaris. Furthermore, it has been successfully used to treat primary cutaneous B-cell lymphoma. Numerous case reports have shown that intralesional or intravenous rituximab can treat CLH without serious side effects (Table 1). In 2007, the first report of successful treatment with intravenous rituximab in benign orbital pseudolymphomas was published[9]. Subsequently, numerous publications reported great results with intravenous rituximab therapy in CLH, with many cases achieving complete response[4, 10, 11]. In 2011, Martin and Duvic[12] demonstrated a favorable response to intralesional rituximab in a patient with recalcitrant CLH, and additional authors later confirmed this result[13]. The regimens of intralesional or intravenous rituximab injections may vary in different studies. Combination therapy with MTX has been documented[4].

Our case was treated with the rheumatoid arthritis protocol (1 g of rituximab intravenously on days 1 and 15), which is economical and has been used and well tolerated in pemphigus patients[14]. The lesions had significantly improved after 2 months. Subsequent rituximab therapy in the same regimen was given 2 years later due to relapse and also demonstrated a promising result. In terms of the biological effects, a study reported no significant difference in the complete response rate between the standard lymphoma protocol and the standard rheumatoid arthritis protocols in pemphigus, which is also a B-cell related disorder[15]. Nevertheless, the biological effects of these two treatment regimens continue to be a subject worthy of future exploration.

To the best of our knowledge, this is the first case report of resistant CLH being successfully treated with rituximab in a rheumatoid arthritis protocol.

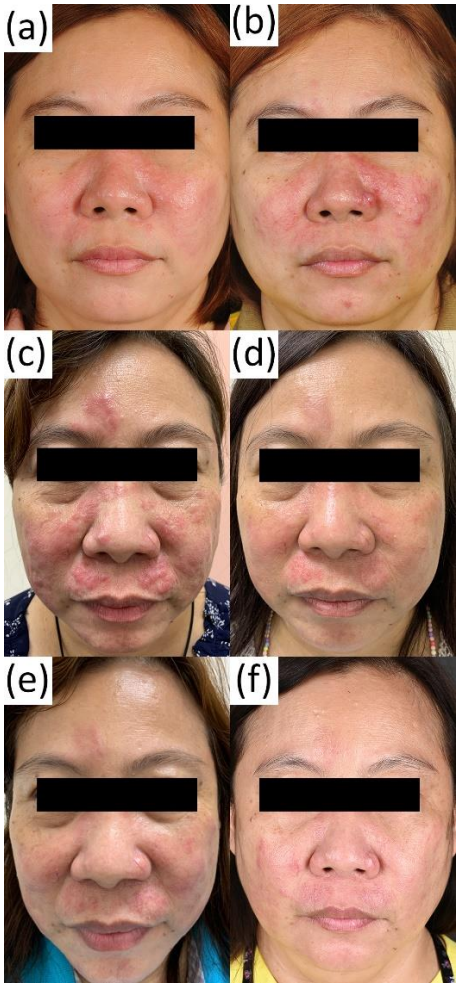

Figure 1 (A-C) Clinical manifestations of the case with cutaneous lymphoid hyperplasia before and (D) after treatment with first course of rituximab, and before (E) and after the second course of rituximab (F).

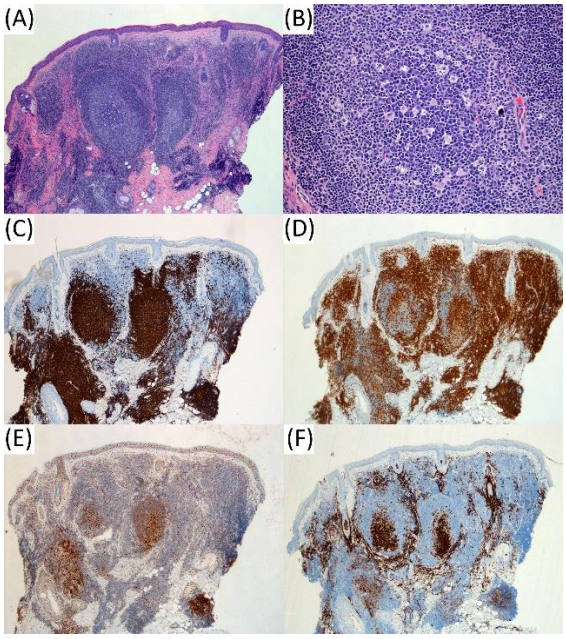

Figure 2. (A) Reactive lymphoid hyperplasia involving the dermis (hematoxylin–eosin [HE], original magnification ×40). (B) Tingible body macrophages in the lymphoid follicles (HE, ×100). (C) CD20-positive B-cells in lymphoid follicles (×40). (D) Predominant CD3-positive T-cells in interfollicular area (×40). (E) BCL6 positive in germinal centers (×40). (F) CD10 positive in germinal centers (×40).

References

1. Alaggio R, Amador C, Anagnostopoulos I, Attygalle AD, Araujo IBO, Berti E, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms. Leukemia 2022;36:1720-48.
2. Khalil S, Donthi D, Gru AA. Cutaneous reactive B-cell lymphoid proliferations. J Cutan Pathol 2022;49:898-916.
3. Miguel D, Peckruhn M, Elsner P. Treatment of Cutaneous Pseudolymphoma: A Systematic Review. Acta Derm Venereol 2018;98:310-7.
4. Besch-Stokes JG, Patel MH, Brumfiel CM, Costello CM, Rule W, Rosenthal A, et al. Cutaneous B cell pseudolymphoma treated with rituximab and methotrexate. Dermatol Online J 2021;27.
5. Joshi TP, Duvic M, Torres-Cabala CA, Tschen J. Treatment With Dupilumab for Refractory Cutaneous B-Cell Pseudolymphoma. JAMA Dermatol 2022;158:697-9.
6. Mitteldorf C, Kempf W. Cutaneous pseudolymphoma-A review on the spectrum and a proposal for a new classification. J Cutan Pathol 2020;47:76-97.
7. García-Rodiño S, Espasandín-Arias M, Suárez-Peñaranda JM, Rodríguez-Granados MT, Vázquez-Veiga H, Fernández-Redondo V. Persisting allergic patch test reaction to minoxidil manifested as cutaneous lymphoid hyperplasia. Contact Dermatitis 2015;72:413-6.
8. Singh N, Fagan KK, Patel RT, Grider DJ. Pseudolymphoma to Lymphoma: A Case of Chronic Reactive Lymphoid Hyperplasia Transforming to Primary Cutaneous Marginal Zone Lymphoma. Am J Dermatopathol 2023;45:250-3.
9. Witzig TE, Inwards DJ, Habermann TM, Dogan A, Kurtin PJ, Gross JB, Jr., et al. Treatment of benign orbital pseudolymphomas with the monoclonal anti-CD20 antibody rituximab. Mayo Clin Proc 2007;82:692-9.
10. Behrouz Sharif S, Neilagh A, Barenji M. Cutaneous Pseudolymphoma: A Brief Review and Report of a Case Treatment Using Rituximab. Annals of Pathology and Laboratory Medicine 2019;6.
11. Balode D, Beļajeva L, Ruesseler V, Quaas A, Lejniece S. Diagnostic Challenges and Treatment Options for Cutaneous T Cell Pseudolymphoma: A Case Study with Rituximab Treatment. Am J Case Rep 2020;21:e919616.
12. Martin SJ, Duvic M. Treatment of cutaneous lymphoid hyperplasia with the monoclonal anti-CD20 antibody rituximab. Clin Lymphoma Myeloma Leuk 2011;11:286-8.
13. Matin M, Asilian Mahabadi A, Poor S, Haftbaradaran E, Feily A. Treatment of Cutaneous Lymphoid Hyperplasia with Rituximab: A Case Report of 3 Patients. Dermatology Case Reports 2019;04.
14. Heelan K, Al-Mohammedi F, Smith MJ, Knowles S, Lansang P, Walsh S, et al. Durable remission of pemphigus with a fixed-dose rituximab protocol. JAMA Dermatol 2014;150:703-8.
15. Amber KT, Hertl M. An assessment of treatment history and its association with clinical outcomes and relapse in 155 pemphigus patients with response to a single cycle of rituximab. J Eur Acad Dermatol Venereol 2015;29:777-82.