Reverse koebnerization of primary cutaneous follicle center lymphoma following skin biopsy

Bohmyi Choi, BSc,[a] Marcus G. Tan, MD,[b] Melinda J. Gooderham, MD, MSc,[c] and Jennifer Beecker, MD, FRCPC, CCFP-EM, DABD[a,b,d]
Ottawa and Kingston, Canada

Key words: case report; primary cutaneous B-cell lymphoma; primary cutaneous follicle center lymphoma; reverse Koebner phenomenon; reverse koebnerization; skin biopsy.

INTRODUCTION

Primary cutaneous follicle center lymphoma (PCFCL) is the most common form of cutaneous B-cell lymphoma and makes up 55% to 60% of all primary cutaneous B-cell lymphomas.[1] The prognosis for PCFCL is excellent, and the 5-year survival rate is >95%. However, recurrences can be common, and therefore, safe and effective treatments that can be repeated are desirable.[1] Patients commonly present with grouped pink papulonodules, with the scalp and forehead as favored locations.[1] The limited number of patients with PCFCL makes it difficult to study its pathogenesis, which remains largely unknown. A minority of primary cutaneous B-cell lymphoma cases originating in Austria and Scotland have been associated with endemic *Borrelia* species infection.[2]

Koebnerization, and reverse koebnerization, are 2 phenomena that are also poorly understood.[3] The Koebner phenomenon describes the appearance of new lesions on previously unaffected sites following local trauma, and has been reported in various dermatological conditions, including lichen planus, psoriasis, and vitiligo.[3] Reverse koebnerization, however, is a significantly rarer event that describes the improvement or resolution of lesions locally following trauma.[3] This report describes 3 instances of the reverse Koebner phenomenon in 2 individuals with PCFCL, induced by punch biopsies.

Abbreviations used:

CT: computed tomography
PCFCL: primary cutaneous follicle center lymphoma

CASE REPORT

A 59-year-old man presented with a 5-month history of multiple asymptomatic, violaceous nodules and telangiectasia on the right frontal aspect of the scalp (Fig 1). He described 2 months of intermittent non-drenching night sweats, but denied fevers, chills, or weight loss. He was otherwise healthy and not on any medication. Four years previously, he had a 4-mm asymptomatic nodule at the same site. A skin biopsy then showed an atypical $CD20^+$ B-cell proliferation and rare $CD68^+$ histiocytes. One month following the biopsy, the nodule resolved spontaneously. His skin disease had been in remission for 4 years. When he presented again with new lesions at the same site, a punch biopsy demonstrated a nodular, deep dermal lymphocytic proliferation with a significant population of larger, atypical cells but no tingible body macrophages nor evidence of polarization. The CD4:CD8 ratio was within normal limits. Immunohistochemical staining showed $CD10^+$, $CD20^+$, $CD21^+$, $BCL2^+$, $BCL6^+$, and $MUM1^-$ B lymphocytes. Ki67 was ~40%. Because of the presence of rare $CD68^+$ histiocytes and $BCL2^+$

From the Faculty of Medicine, University of Ottawa, Ottawa,[a] the Division of Dermatology, University of Ottawa, and The Ottawa Hospital, Ottawa,[b] the Department of Medicine, Queen's University, Kingston,[c] and The Ottawa Hospital Research Institute, Ottawa.[d]
Authors Choi and Tan are cofirst authors.
Funding sources: None.
IRB approval status: Not applicable.
Correspondence to: Jennifer Beecker, MD, FRCPC, CCFP-EM, DABD, The Ottawa Hospital - Civic Campus, 4th Floor, 737 Parkdale Avenue, Ottawa, Ontario K1Y 1J8, Canada. E-mail: jbeecker@toh.ca.
JAAD Case Reports 2021;16:149-51.
2352-5126

https://doi.org/10.1016/j.jdcr.2021.08.029

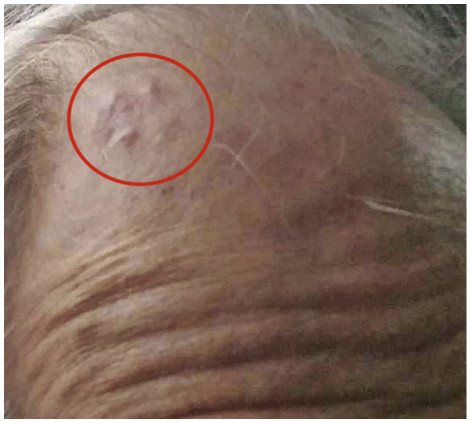

Fig 1. Multiple, asymptomatic, firm violaceous nodules on the right frontal aspect of the scalp that had been present for 4-5 months.

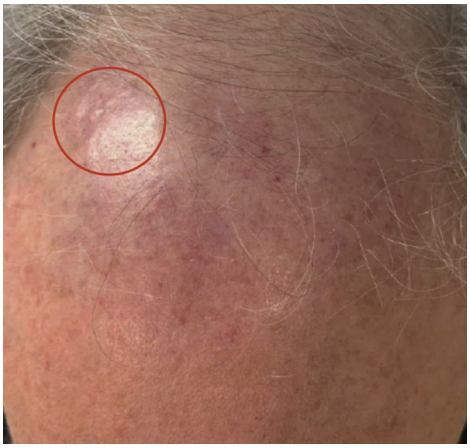

Fig 2. Resolution of nodules. Photograph taken 4 weeks following punch biopsy.

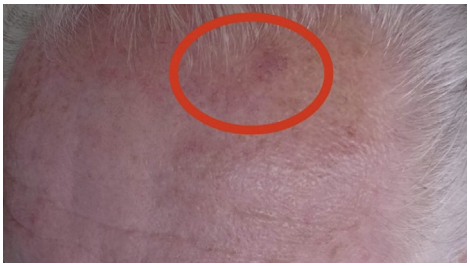

Fig 3. A 2-cm violaceous plaque with telangiectasia on the left frontal aspect of the scalp that had been present for 2 years, reportedly developing after an insect bite.

B cells, pseudolymphoma was also considered. However, the predominant lymphocytic infiltrate, alongside the absence of eosinophils, plasma cells, or tingible body macrophages, favored a diagnosis of PCFCL. Although PCFCL is classically associated with negativity for BCL2, $BCL2^+$ PCFCLs are possible and have not been found to have any worse prognosis.[4] Furthermore, although $BCL2^+$ often implies secondary cutaneous follicle center lymphoma, cases of $BCL2^+$ PCFCL are not uncommon either.[5] Physical examination revealed no cervical, axillary, or inguinal lymphadenopathy nor hepatomegaly. His complete blood count, lactate dehydrogenase, creatinine, liver transaminases, flow cytometry, urinalysis, and computed tomography (CT) scan of his head, neck, chest, abdomen, and pelvis were unremarkable. At 1-month follow-up, all cutaneous nodules had resolved again following biopsy (Fig 2). He was referred to hematology and it was verified that his lymphoma was skin-limited.

The second case is a 77-year-old man presenting with a 2-year history of a 2-cm pale, violaceous plaque with telangiectasia on the left frontal aspect of the scalp, which reportedly developed after an insect bite (Fig 3). It improved with topical steroids but never resolved. He has a history of type 2 diabetes, gastroesophageal reflux, hypothyroidism, migraines, and deep vein thrombosis following orthopedic surgery. His medications included levothyroxine, pantoprazole, empagliflozin, warfarin, metformin, and gabapentin. He had no other cutaneous lesions, weight loss, or systemic complaints, but reported non-drenching night sweats 2-3 times per week. A punch biopsy revealed a dense lymphocytic infiltrate throughout the dermis, separated from the epidermis by a grenz zone. The infiltrate predominantly involved centrocytes admixed with some centroblasts with irregularly shaped lymphoid follicles. The CD4:CD8 ratio was within normal limits. Immunohistochemical stains revealed $CD20^+$, $CD79a^+$, $BCL2^+$, $BCL6^+$, variable $CD23^+$, $CD5^-$, $CD10^-$, $CD30^-$, $CD56^-$, cyclin $D1^-$ and $MUM1^-$ B lymphocytes. Ki67 was ~10%. A diagnosis of pseudolymphoma was considered, given the history of possible arthropod assault. However, the biopsy showed a predominantly lymphocytic infiltrate, and lacked eosinophils, plasma cells, or tingible body macrophages. When he returned for suture removal after 2 weeks, the plaque had resolved (Fig 4). He was referred to hematology for further workup. A staging CT revealed 3 small lymph nodes (size, 1.2-1.4 cm) in the paratracheal and hilar region that were perceived to be inflammatory, and a follow-up CT scan will be done after 3 months. He is monitored by hematology with the diagnosis of PCFCL.

DISCUSSION

Although reverse koebnerization in PCFCL has not been formally reported in the dermatology

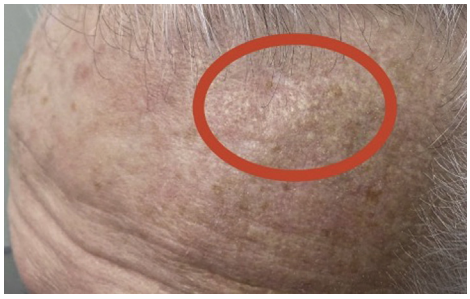

Fig 4. Resolution of plaque following punch biopsy.

literature, it appears to be a phenomenon clinically recognized by clinicians from both dermatology and hematology disciplines (Dr C. Faught, MD, Hematologist, email communication, April 18, 2020). Reverse koebnerization, although rare, has been reported in dermatologic conditions such as granuloma annulare, leukocytoclastic vasculitis, and bullous pemphigoid, which can be induced by a skin biopsy, tattooing, or tight clothing.[6-8] The infrequent and diversified nature of this phenomenon causes difficulties in elucidating a plausible mechanism.

The current hypothesis suggests that alteration of the immunologic microenvironment at the site of trauma is an important factor in this phenomenon.[6] For reverse koebnerization in leukocytoclastic vasculitis and bullous pemphigoid, it has been hypothesized that trauma prevented immune complexes from depositing in adequate concentrations within the area of trauma, leading to the resolution of lesions.[7,9]

The recurrence of PCFCL in our first case in the same anatomical site aligns with the concept of *locus minoris resistentiae*, describing a body site that is more susceptible to the onset of disease than the rest of the body due to a localized immune dysregulation.[10] Skin biopsies in both cases likely triggered local inflammatory responses to clear the malignant lymphocytes, which is similar to the reverse koebnerization seen in granuloma annulare.[9]

Reverse koebnerization is a rare phenomenon, which seems to result from changes in the local immunological microenvironment. More research is needed to gain a deeper understanding of the underlying physiological process. Knowledge of reverse koebnerization is clinically useful, as skin biopsy may become an inadvertent therapeutic option for local skin disease in PCFCL, as has been observed in granuloma annulare.[8] Recurrence and "retreatment" with biopsy may be needed. Years of remission, as experienced by our patient, would likely be considered an acceptable response.

Conflicts of interest

None disclosed.

REFERENCES

1. Vitiello P, Sica A, Ronchi A, Caccavale S, Franco R, Argenziano G. Primary cutaneous B-cell lymphomas: an update. *Front Oncol*. 2020;10:651.
2. Goodlad JR, Davidson MM, Hollowood K, et al. Primary cutaneous B-cell lymphoma and *Borrelia burgdorferi* infection in patients from the Highlands of Scotland. *Am J Surg Pathol*. 2000;24(9):1279-1285.
3. AlHargan A, AlKhawajah M, AlAjlan M, AlHumidi A, AlTuwaijri R. Reverse Koebner phenomenon induced by the Mantoux test in erythrodermic psoriasis: a case report and literature review. *JAAD Case Rep*. 2018;4(6):586-589.
4. Pileri A, Agostinelli C, Bertuzzi C, et al. BCL-2 expression in primary cutaneous follicle center B-cell lymphoma and its prognostic role. *Front Oncol*. 2020;10:662.
5. Kim BK, Surti U, Pandya A, Cohen J, Rabkin MS, Swerdlow SH. Clinicopathologic, immunophenotypic, and molecular cytogenetic fluorescence *in situ* hybridization analysis of primary and secondary cutaneous follicular lymphomas. *Am J Surg Pathol*. 2005;29(1):69-82.
6. Chen CA, Mikailov A, Faulkner-Jones B, Wu PA. Leukocytoclastic vasculitis sparing a tattoo with halo effect. *JAAD Case Rep*. 2015;1(5):269-271.
7. Mohapatra L, Samal K, Mohanty P, Dash S. Reverse Koebner phenomenon in bullous pemphigoid - a case report. *Indian Dermatol Online J*. 2019;10(6):692-694.
8. Naveen KN, Pai VV, Athanikar SB, Gupta G, Parshwanath HA. Remote reverse Koebner phenomenon in generalized granuloma annulare. *Indian Dermatol Online J*. 2014;5(2):219-221.
9. Yadav S, De D, Kanwar AJ. Reverse Koebner phenomenon in leukocytoclastic vasculitis. *Indian J Dermatol*. 2011;56(5):598-599.
10. Ruocco V, Ruocco E, Piccolo V, Brunetti G, Guerrera LP, Wolf R. The immunocompromised district in dermatology: a unifying pathogenic view of the regional immune dysregulation. *Clin Dermatol*. 2014;32(5):569-576.