Primary cutaneous epidermotropic marginal zone B-cell lymphoma treated with total skin electron beam therapy

Blake W. Boudreaux, MD,[a] Meera H. Patel, BS,[b] Caitlin M. Brumfiel, MS,[b] Jake Besch-Stokes, BS,[c] David J. DiCaudo, MD,[b] Fiona Craig, MD,[d] Allison C. Rosenthal, DO,[e] William G. Rule, MD,[f] Mark R. Pittelkow, MD,[b] and Aaron R. Mangold, MD[b]
Orange Park, Florida and Scottsdale, Arizona

Key words: B-cell lymphoma; cutaneous B-cell lymphoma; cutaneous marginal zone lymphoma; CXCR3; epidermotropic marginal zone B-cell lymphoma; IgG; IgM; marginal zone lymphoma; total skin electron beam therapy.

INTRODUCTION

Epidermotropism, the infiltration of lymphocytes into the epidermis, is a distinguishing histopathologic feature of cutaneous T-cell lymphomas (CTCLs). It is a rare finding in cutaneous B-cell lymphomas (CBCLs) and may be associated with more aggressive disease.[1] Fewer than 10 cases of epidermotropic primary cutaneous marginal zone lymphoma (PCMZL) have been reported in the literature.[2] Here, we present a case of epidermotropic PCMZL successfully treated with total skin electron beam therapy (TSEBT).

Abbreviations used:

CBCL:	cutaneous B-cell lymphoma
CTCL:	cutaneous T-cell lymphoma
IgM:	immunoglobulin M
MZL:	marginal zone lymphoma
PCMZL:	primary cutaneous marginal zone lymphoma
TSEBT:	total skin electron beam therapy

CASE REPORT

An 80-year-old man presented with sudden onset of asymptomatic rash on the trunk of 1 month's duration. Examination revealed multiple bright red, indurated, nummular plaques with a slight overlying scale on the back, chest, and abdomen (Fig 1). Prior treatment included high-potency topical corticosteroids without improvement. He denied B symptoms.

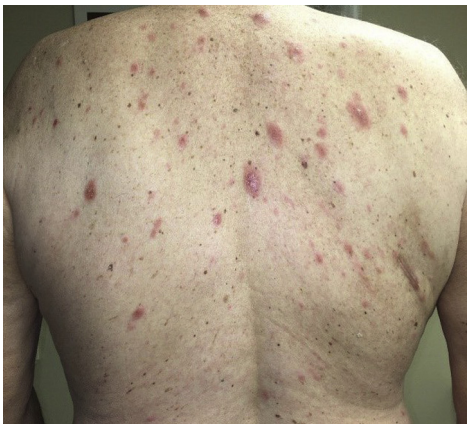

Fig 1. Clinical presentation before treatment (June 18, 2018). Multiple, bright red, indurated, nummular plaques with a slight overlying scale were observed.

Biopsies of the upper portions of the back and right flank lesions revealed an atypical lymphocytic infiltrate in a band-like distribution in the papillary dermis with involvement around vessels, follicles, and eccrine ducts with marked involvement of the epidermis. The atypical B lymphocytes were hyperchromatic and mildly enlarged. The atypical lymphocytes were $CD20^{+}$, $Bcl\text{-}2^{+}$, $CD3^{-}$, $CD4^{-}$, $CD5^{-}$, $CD7^{-}$, $CD10^{-}$, $CD21^{-}$, MUM-1^{-}, $Bcl\text{-}6^{-}$, and Cyclin $D1^{-}$ (Fig 2). Immunophenotypic findings confirmed B cell lineage and supported the diagnosis of

From the Department of Graduate Medical Education, Orange Park Medical Center[a]; and Department of Dermatology,[b] Alix School of Medicine,[c] Department of Pathology,[d] Division Hematology-Oncology, Department of Medicine,[e] and Department of Radiation Oncology, Mayo Clinic Arizona, Scottsdale.[f]

Funding sources: None.
IRB approval status: Not applicable.

Correspondence to: Aaron R. Mangold, MD, Department of Dermatology, Mayo Clinic Arizona, 13400 East Shea Blvd, Scottsdale, AZ 85259. E-mail: mangold.aaron@mayo.edu.

JAAD Case Reports 2021;15:15-8.
2352-5126

https://doi.org/10.1016/j.jdcr.2021.06.027

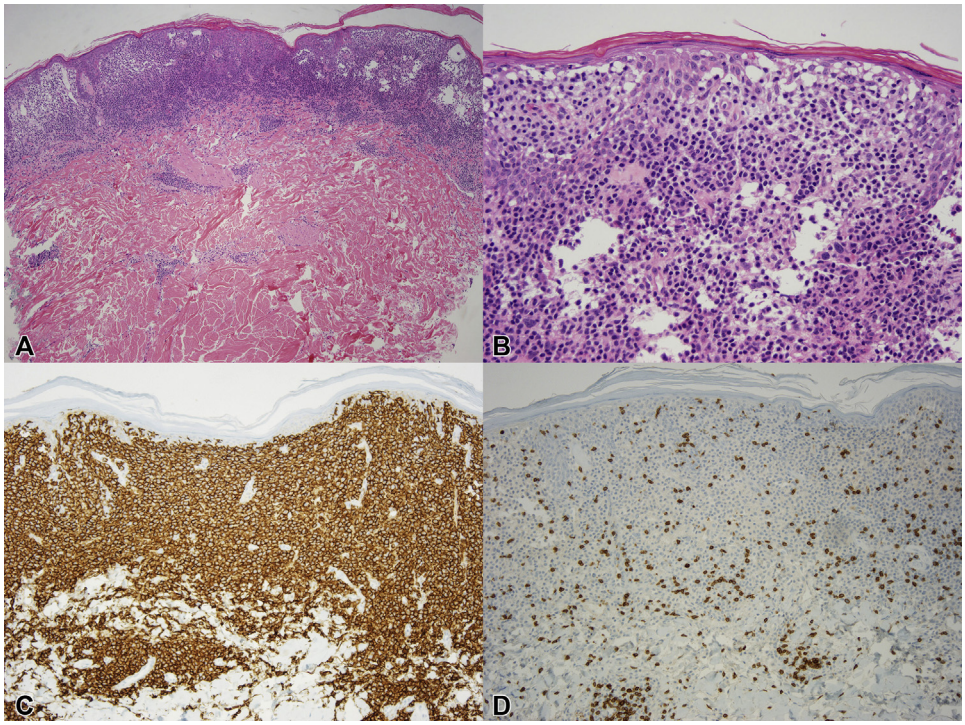

Fig 2. Skin biopsy from the right flank. Dense, band-like epidermotropic infiltrate of $CD20^+$ B cells with a few scattered $CD3^+$ T cells. (**A** and **B**, Hematoxylin-eosin stain; **C**, CD20 stain; **D**, CD3 stain; original magnifications: **A**, ×40; **B**, ×200; **C**, ×100; **D**, ×100.)

marginal zone lymphoma (MZL). Approximately 10% to 20% of lymphocytes were Ki-67^+. No κ/λ light chain restriction was detected. Both specimens demonstrated identical clonal immunoglobulin gene rearrangements with no T-cell receptor gene rearrangement. They exhibited robust expression of cytoplasmic immunoglobulin M (IgM), whereas IgG staining was weak (Fig 3). Histopathologic, immunophenotypic, and molecular findings were diagnostic of IgM^+ cutaneous MZL with epidermotropism.

Complete blood cell count, serum protein electrophoresis, serum free light chains, and quantitative immunoglobulins were unremarkable. Positron emission tomography/computed tomography of the whole body revealed subtle uptake localized to the skin without systemic involvement. Bone marrow biopsy was negative for lymphoma. Given his lack of systemic disease but widespread cutaneous involvement, the patient elected to undergo TSEBT. He received 2 fractions of 4 Gy separated by 1 week, for a total of 8 Gy, a hypofractionated regimen utilized in CTCL.[3] He demonstrated an excellent therapeutic response, and aside from some residual hyperpigmentation, the lesions completely resolved 2 months following the treatment (Fig 4).

Approximately 1 year later, several similar lesions developed on the patient's right arm. Biopsy confirmed recurrence of epidermotropic cutaneous MZL. Computed tomography of the chest, abdomen, and pelvis incidentally revealed a renal mass that was later resected and found to be a papillary renal cell carcinoma. The recurrent lesions on his arm responded well to high-potency topical corticosteroids.

DISCUSSION

CBCL is less common than CTCL. PCMZL, a subtype of CBCL, comprises just 9% of cutaneous lymphoma diagnoses.[1] It affects men more commonly than women, with a mean age of 49 years at the time of diagnosis. PCMZL frequently presents as a solitary red or violaceous tumor or plaque on the trunk; however, approximately half of the patients have multiple lesions, which may be localized or multifocal.[4] PCMZL has a 5-year disease-specific survival rate approaching 100%.[1] Most cases have a complete response to the initial therapy; however, relapse is common. Seventy-seven percent of patients with multifocal disease experience relapse with a median disease-free survival of 1.1 years.[4] Extracutaneous spread occurs in 1.7% to 4.0% of PCMZL cases overall; however, patients exhibiting

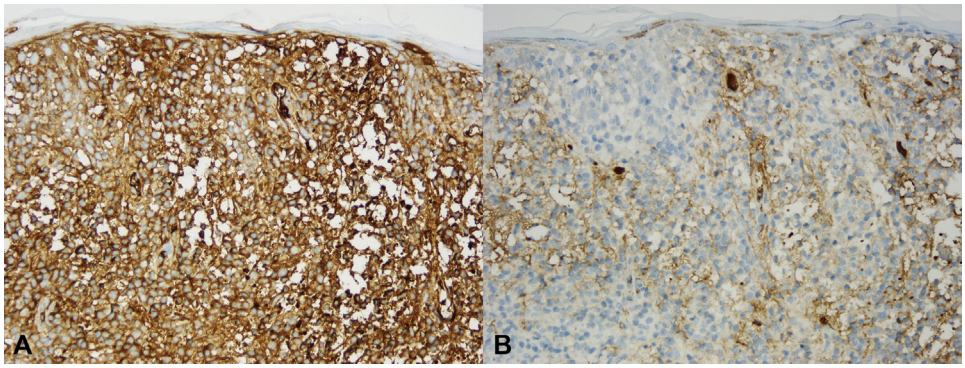

Fig 3. Immunoglobulin isotype expression. The epidermotropic B cells express cytoplasmic immunoglobulin M. IgG expression is weak. (**A**, Immunoglobulin M stain; **B**, IgG stain; original magnifications: **A**, ×200; **B**, ×200.)

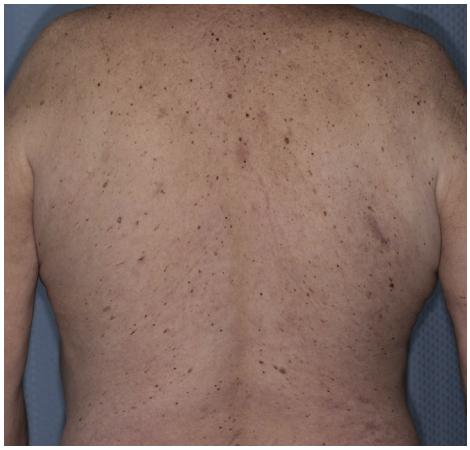

Fig 4. Clinical presentation after treatment (January 18, 2019). The resolution of primary cutaneous marginal zone lymphoma lesions with residual hyperpigmentation was observed.

epidermotropism appear to have a higher likelihood of concurrent or subsequent development of extracutaneous disease.[5,6] In a series, 5 of the 7 cases of epidermotropic MZL developed extracutaneous involvement; 1 case was lost to follow-up, and the last case remained disease-free.[5] Although data describing associations between PCMZL and other malignancies are lacking, a review of 137 PCMZL cases found that 9 patients had a history of cancer. Most were hematologic malignancies, and none were renal cell carcinoma.[4]

Histopathologically, PCMZL is characterized by nodular to diffuse infiltrate of atypical marginal zone B cells (small lymphoid cells with irregular nuclei and abundant, pale cytoplasm), reactive T cells, and plasma cells involving the dermis and subcutis. The infiltrate often grows around benign lymphoid follicles and may extend into germinal centers (follicular colonization). An overlying grenz zone is characteristically present, sparing the epidermis. The neoplastic cells stain $CD20^+$ and $Bcl\text{-}2^+$. Monoclonal restriction of κ/λ light chains is observed in approximately 75% of cases.[6,7] PCMZL is subdivided into 2 types: the more common class-switched (IgG, IgA, and immunoglobulin E) variant and the less common IgM variant. In the class-switched variety, the lymphocytic infiltrate is dominated by reactive T cells with interspersed neoplastic B cells and extracutaneous involvement is uncommon. By contrast, IgM-only PCMZL has a predominantly B cell infiltrate and is more likely to present with involvement of bone marrow, spleen, and mucosa-associated lymphoid tissue.[1,6]

Epidermotropic PCMZL expresses CXCR3, a receptor for interferon gamma–induced chemokines that is thought to play a role in the migration of malignant B cells to mucosa-associated lymphoid tissue.[1,5,6] Typically, IgM^+ PCMZL expresses CXCR3, whereas class-switched PCMZL does not, which is in accordance with their respective propensity for extracutaneous involvement.[1,6] CXCR3 and CXCR4 positivity occurs in the early phases of CTCL and is lost in advanced disease.[5] Taken together, CXCR3 expression may play a role in the unusual epidermotropic and extracutaneous spread of neoplastic B lymphocytes in these cases.[1,6]

Among the reported cases of epidermotropic MZL, various therapeutic strategies include systemic chemotherapy, rituximab, subcutaneous interferon alfa with psoralen plus ultraviolet A phototherapy, and ultraviolet B phototherapy.[5,8] These strategies have led to the resolution of disease, although 1 patient experienced systemic recurrence that subsequently responded to chemotherapy.[6,8] TSEBT involves irradiation of the entire skin surface and spares deeper tissues. Radiotherapy is extremely effective in treating mycosis fungoides and localized T1 and T2 CBCL.[4,9] Traditional dosing for localized

T1 and T2 PCMZL is 24 to 30 Gy. Low-dose TSEBT regimens for mycosis fungoides range from 8 to 12 Gy.[9] Palliative doses, most often 2 Gy × 2, are used in select cases with higher rates of relapse and retreatment within the first year.[10] As noted above, our patient was treated with a hypofractionated regimen (4 Gy × 2) and had an excellent response, although he did experience recurrent lesions on his arm 1 year following the treatment, which responded to topical corticosteroids.

Conflicts of interest

None disclosed.

REFERENCES

1. Willemze R, Cerroni L, Kempf W, et al. The 2018 update of the WHO-EORTC classification for primary cutaneous lymphomas. *Blood*. 2019;133(16):1703-1714. https://doi.org/10.1182/blood-2018-11-881268
2. Kheterpal MK, Dai J, Geller S, et al. Role of imaging in low-grade cutaneous B-cell lymphoma presenting in the skin. *J Am Acad Dermatol*. 2019;81(4):970-976. https://doi.org/10.1016/j.jaad.2019.01.037
3. Jeans EB, Hu YH, Stish BJ, et al. Low-dose hypofractionated total skin electron beam therapy for adult cutaneous T-cell lymphoma. *Pract Radiat Oncol*. 2020;10(6):e529-e537. https://doi.org/10.1016/j.prro.2020.08.001
4. Servitje O, Muniesa C, Benavente Y, et al. Primary cutaneous marginal zone B-cell lymphoma: response to treatment and disease-free survival in a series of 137 patients. *J Am Acad Dermatol*. 2013;69(3):357-365. https://doi.org/10.1016/j.jaad.2013.04.047
5. Magro CM, Momtahen S, Lee BA, Swanson DL, Pavlovic MD. Epidermotropic B-cell lymphoma: A unique subset of CXCR3-positive marginal zone lymphoma. *Am J Dermatopathol*. 2016;38(2):105-112. https://doi.org/10.1097/DAD.0000000000000401
6. Swerdlow SH. Cutaneous marginal zone lymphomas. *Semin Diagn Pathol*. 2017;34(1):76-84. https://doi.org/10.1053/j.semdp.2016.11.007
7. Suárez AL, Pulitzer M, Horwitz S, Moskowitz A, Querfeld C, Myskowski PL. Primary cutaneous B-cell lymphomas: part I. Clinical features, diagnosis, and classification. *J Am Acad Dermatol*. 2013;69(3):329.e1-329.e13 [quiz: 341-342]. https://doi.org/10.1016/j.jaad.2013.06.012
8. Magro CM, Davis TL, Kurtzman DJB. Epidermotropic marginal zone lymphoma: an uncommon cutaneous B-cell lymphoma responsive to rituximab. *JAAD Case Rep*. 2017;3(6):474-476. https://doi.org/10.1097/DAD.0000000000000401
9. Specht L, Dabaja B, Illidge T, Wilson LD, Hoppe RT, International Lymphoma Radiation Oncology Group. Modern radiation therapy for primary cutaneous lymphomas: field and dose guidelines from the International Lymphoma Radiation Oncology Group. *Int J Radiat Oncol Biol Phys*. 2015;92(1):32-39. https://doi.org/10.1016/j.ijrobp.2015.01.008
10. Neelis KJ, Schimmel EC, Vermeer MH, Senff NJ, Willemze R, Noordijk EM. Low-dose palliative radiotherapy for cutaneous B- and T-cell lymphomas. *Int J Radiat Oncol Biol Phys*. 2009;74(1):154-158. https://doi.org/10.1016/j.ijrobp.2008.06.1918