We report a case of histologically confirmed primary cutaneous diffuse large B-cell lymphoma, leg type (PCDLBCL-LT) that subsequently underwent spontaneous regression in the absence of systemic treatment. The case showed an atypical lymphoid infiltrate that was CD20+ and MUM-1+ and CD10−. A subsequent biopsy of the spontaneously regressed lesion showed fibrosis associated with a lymphocytic infiltrate comprising reactive T cells. PCDLBCL-LT is a cutaneous B-cell lymphoma with a poor prognosis, which is usually treated with chemotherapy. We describe a case of clinical and histologic spontaneous regression in a patient with PCDLBCL-LT who had a negative systemic workup but a recurrence over a year after his initial presentation. (J Am Acad Dermatol 2018;8:305-9.)

Key words: B cell; lymphoma; primary cutaneous diffuse large B-cell lymphoma; leg type; regression.

INTRODUCTION

Primary cutaneous B-cell lymphoma is a lymphoma confined to the skin, with no evidence of extracutaneous disease. The 4 major subtypes of cutaneous B-cell lymphoma include primary cutaneous follicle center lymphoma (PCFCL), primary cutaneous marginal zone lymphoma (PCMZL), primary cutaneous diffuse large B-cell lymphoma, leg type (PCDLBCL-LT), and primary cutaneous diffuse large B-cell lymphoma, other (PCDLBCL-other).1,2 PCDLBCL-LT is an aggressive subtype of primary cutaneous B-cell lymphoma that presents at a median age of 76 with a slight female predominance. Diagnosis relies on clinical and histologic features and a characteristic MUM-1 immunophenotype.

PCDLBCL-LT most commonly presents as red-to-purple nodules of the lower extremities. Extracutaneous spread typically occurs to regional lymph nodes and bone marrow with the central nervous system being the most common location of visceral involvement.3,4

CASE REPORT

A 79-year-old white man presented with a plaque on his left leg that was present for 1 week. Physical examination found a 20- × 12-cm irregular, rectangular-shaped, erythematous, reticulated plaque on his left anterior shin with prominent follicular accentuation (Fig 1).

Biopsy found an atypical lymphoid infiltrate in the upper dermis composed of cells with scant cytoplasm and large round-to-oval nuclei with prominent nucleoli, numerous mitotic figures, and apoptotic bodies. The atypical cells were positive with CD20, MUM-1, Bcl-2 and Bcl-6 stains. A CD3 stain showed a minor component of small, round T lymphocytes. Systemic workup was negative, and the findings were compatible with a PCDLBCL-LT.
Approximately 1 month later, significant improvement of the lesion was seen in the absence of any systemic therapy. The plaque spontaneously resolved, and a punch biopsy of the area found a superficial and deep perivascular inflammatory infiltrate comprised of mature lymphocytes. The atypical, pleomorphic lymphoid infiltrate seen in the previous biopsy was not identified. Immunohistochemistry showed significant CD3+ T cells with a minority of CD20+ B cells. These histologic findings were consistent with spontaneous regression of the patient’s PCDLBCL-LT.

A computed tomography scan of the head, chest, abdomen, and pelvis were negative for lymphoma and lymphadenopathy. A bone marrow aspirate and biopsy of the right iliac bone was negative for malignancy. The oncology department recommended 4 cycles of rituximab, cyclophosphamide, doxorubicin, oncovin/vincristine and prednisone (R-CHOP) therapy followed by local radiation. The patient declined treatment and remained disease free for more than a year but ultimately presented more than a year later with a new plaque confirmed as a recurrence of his PCDLBCL-LT.

DISCUSSION

Four subtypes of cutaneous B-cell lymphoma currently recognized include PCFCL, PCMZL, PCDLBCL-LT, and PCDLBCL-other. These subtypes are based on histologic morphology and immunohistochemistry (Table I).8-11 PCDLBCL-LT accounts for 2.6% of primary cutaneous non-Hodgkin lymphomas with a female/male ratio of 1:6.3,7 PCDLBCL-LT occurs on the lower extremities, trunk, head/neck, and upper extremities in 66.6%, 7.8%, 2%, and 2% of cases, respectively, with the remaining 21.6% of cases being disseminated.

Histopathologic evaluation is the primary method used in the diagnosis of PCDLBCL-LT. Biopsy results show diffuse monotonous large B cells separated from the epidermis by a Grenz zone and numerous mitotic figures (Fig 2, A). The atypical lymphoid cells
are enlarged and have distinct nuclei (Fig 2, B). There is paucity of T cells. PCDLBCL-LT stains positive for B-cell markers CD19, CD20, and CD22 and oncogenes Bcl-2 and MUM-1 (Fig 2, C and D). Bcl-2 and MUM-1 help differentiate PCDLBCL-LT from the less-aggressive counterpart, PCFCL. However, up to 10% of PCDLBCL-LT lack the presence of Bcl-2 or MUM-1 staining, and careful clinicopathologic correlation is required for definitive diagnosis. Currently, no staining pattern has been found to be indicative of prognosis in these patients. Pseudolymphoma and T-cell rich B-cell lymphoma should also be considered in the differential. The Bcl-2 positivity and the low density of reactive T cells in our case make T-cell rich B-cell lymphoma less likely, and the cytological features and clonality would rule out pseudolymphoma.

Genetics may provide a way to stratify a patient’s prognosis. Genetic analysis has found that PCDLBCL-LT does not express the BMI-1 oncogene. BMI-1 expression encodes the p-16 cell cycle inhibitor, which is frequently found in other forms of large B-cell lymphoma. PCDLBCL-LT typically demonstrates the presence of polycomb-group gene complexes containing human polycomb-group gene protein HPFH1 and inactivation of CDKN2A gene. Lack of HPFH1 and active CDKN2A is often found in more favorable presentations of PCDLBCL-LT. Further genetic analysis in those who have spontaneous regression of different types of diffuse large B-cell lymphoma may lead to the identification of associated genetic profiles and allow for better prognostic reporting.

Regression of primary cutaneous lymphoma is rare and is most often reported in CD30+ anaplastic large cell lymphoma and very rarely in primary cutaneous T-cell–rich B-cell lymphoma. Regression of PCDLBCL-LT without treatment is extremely rare with only 2 cases reported during a literature review. In the only reported case of

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**Table I. The histology, genetics, and immunophenotyping of the 4 types of cutaneous diffuse large B-cell lymphoma**

|                           | Histologic morphology1,5 | Genetics2,6 | Immunophenotyping2,5,6 |
|---------------------------|--------------------------|------------|------------------------|
| PCDLBCL-LT               | Immunoblasts and centroblasts within a sheet of moderate- to-large sized B cells (Fig 2). Frequent mitotic figures and typically few T cells. | • Absence of t(14;18) | • Bcl-2, Bcl-6, FOXP1, MUM-1/IRF-4+ |
|                           |                          | • Inactivation of p15 and p16 tumor suppression genes | • CD20, CD79a+ |
|                           |                          | • 18q, 7p, 6q chromosomal imbalances | • CD10 (-) |
|                           |                          | • Translocations of myc, Bcl-6, and IgH genes | • Monotypic sIg or cIg+ |
|                           |                          | • CDKN2A (9p21.3) and CDKN2B gene deletions |  |
|                           |                          | • Bcl-2 and MLT amplification |  |
| PCFCL                     | Nodular or diffuse infiltrate with the presence of centrocytes, specifically large multilobated centrocytes, and few centroblasts with many T cells | • Rare t(14;18) | • Bcl-6+ follicular cells surrounded by CD21+ and CD35+ dendritic cells |
|                           |                          | • Clonal Ig rearrangement | • CD20+, CD45RA+, and CD79a+ |
|                           |                          | • Somatic hypermutation of heavy and light chains | • CD10+ in follicular pattern negative are in diffuse pattern |
|                           |                          |  | • Bcl-2- and MUM-1/IRF4-  |
| PCMZL                     | Presence of germinal centers with a nodular and diffuse infiltrate pattern composed of marginal zone B cells, lymphoplasmacytoid, plasma, and centroblastlike and immunoblastlike cells. | • Reports of t(14;18)(q32;q21) and t(3;14)(p14.1;q32) | • CD20, CD79a, CD43+ |
|                           |                          | • Chromosomes 14, 18, and 3 involving IGH, MLT, and FOXP1 genes, respectively | • CD5, CD10- |
|                           |                          |  | • Bcl-2-, Bcl-6-  |
|                           |                          |  | • MUM-1/IRF4-+, CD138+ (Note: Marginal zone B cell-specific staining profile) |
| PCDLBCL-other             | Variable malignant B-cell arrangement not consistent with the other type of cutaneous diffuse large B-cell lymphoma | • Variable | • Variable profile not consistent with other subtypes |

FOXP1, Forkhead box P1 protein. FOXP1 is part of the FOX transcription factor family; IGH, immunoglobulin heavy-chain; MLT, mucosa-associated lymphoid tissue lymphoma translocation gene.
spontaneous regression of PCDLBCL-LT with biopsy of the regressed lesion, histology findings showed a significant dermal T-cell infiltrate as seen in our case. Spontaneous regression of lymphomas have been reported in the presence of T-cell infiltration, suggesting that an inadequate T-cell immune response may play an important role in the disease pathogenesis and progression.

PCDLBCL-LT carries a poor prognosis with reported 5-year survival rates of approximately 45%. Current treatment consensus recommends a polychemotherapeutic regimen of R-CHOP with possible radiation therapy. R-CHOP treatment recommendations are based on systemic diffuse large B-cell lymphoma treatment studies due to limited PCDLBCL-LT research. R-CHOP therapy has been found to improve 5-year survival rates but still carries a poor prognosis. Therapeutic options for patients that cannot receive R-CHOP therapy include radioimmunotherapy and external beam radiation.

CONCLUSION
It is important to keep PCDLBCL-LT high on the differential for violaceous, indurated, nodules on the lower extremities. A delay in therapy for PCDLBCL-LT can significantly affect prognosis. PCDLBCL-LT should be promptly identified and treated aggressively with close collaboration between multiple specialties including dermatology, oncology, hematology, and internal medicine. We report an unusual case of PCDLBCL-LT with spontaneous regression after a completely negative systemic workup and a later relapse. Identification of and treatment protocols for this spontaneously regressing variant will require further studies.

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