Primary cutaneous large B-cell lymphoma, leg type

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Primary cutaneous large B-cell lymphoma, leg type, is a rare and aggressive neoplasm as defined by the recently updated World Health Organization–European Organization for Research and Treatment of Cancer classification of cutaneous lymphomas. We present a case of a 74-year-old woman who presented with a cutaneous lesion on her forearm. Skin biopsy revealed pathology consistent with this entity. The patient was treated with systemic chemotherapy with rituximab combined with doxorubicin, cyclophosphamide, vincristine, and prednisone. Here, we review the available literature and summarize clinical features and management of this uncommon subtype of non-Hodgkin lymphoma.

CASE REPORT

A 74-year-old white woman was referred by her primary care physician for evaluation of a lesion on her right arm. She had a history of breast cancer, for which she underwent a unilateral mastectomy for breast cancer in 1992, and a second breast cancer on the opposite side in 1994 treated with mastectomy followed by chemotherapy with doxorubicin, cyclophosphamide, and 5-fluorouracil. On presentation, she was noted to have a hard, immobile, pea-sized nodule palpable just under the skin surface on the dorsum of her right forearm. She reported that the lesion had been present for approximately 1 month without significant change in size, color, or shape. She denied other symptoms including fever, chills, night sweats, or pruritus.

An excisional biopsy of the lesion revealed an infiltrate of monomorphic large cells in the dermis with vesicular chromatin, prominent nucleoli, and frequent mitoses *(Figure)*. Immunohistochemical evaluation revealed the abnormal cells to be CD20, BCL-2, BCL-6, and MUM-1 positive and CD10 negative, suggestive of a germinal center (B-cell) origin and with a high proliferative index (MIB-1 >90%) (Figure). The morphology and staining pattern were consistent with a diagnosis of primary cutaneous diffuse large B-cell lymphoma, leg type (PCLBLC, LT). Further staging evaluation, including bone marrow biopsy and computed tomographic imaging, was unremarkable.

The patient was subsequently started on systemic chemotherapy with rituximab combined with doxorubicin, cyclophosphamide, vincristine, and prednisone (R-CHOP) for three cycles, followed by replacement of doxorubicin with etoposide to avoid cardiac complications given her prior anthracycline

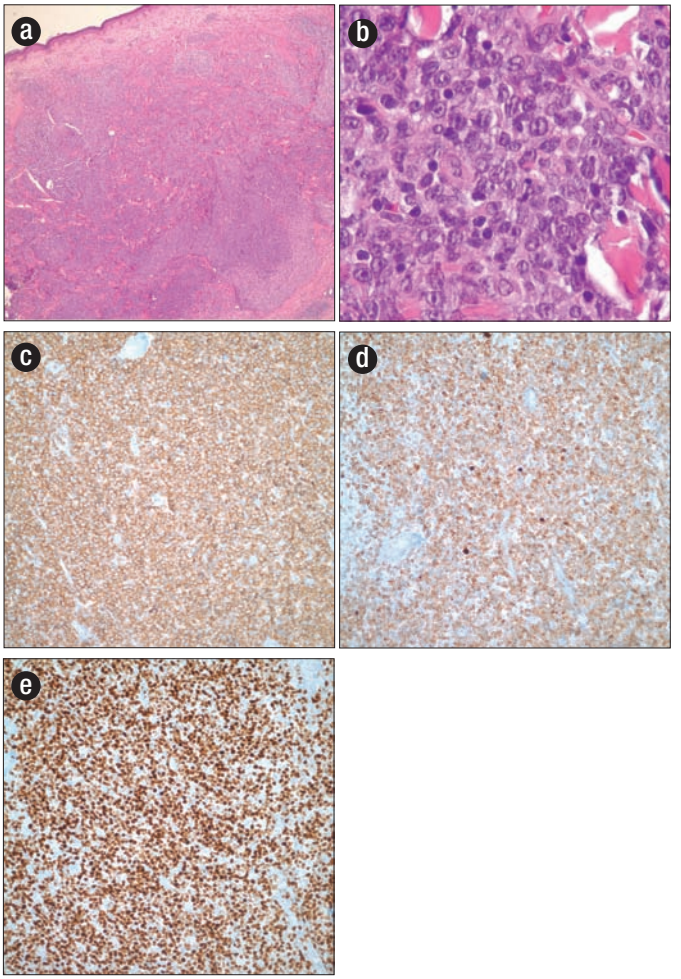

Figure 1. (a) Hematoxylin and eosin stain showing nodular infiltration of the superficial and deep dermis by primary cutaneous diffuse large B-cell lymphoma, leg type (low power). **(b)** Hematoxylin and eosin stain showing large monomorphic cells with a vesicular chromatin pattern, prominent nucleoli, and frequent mitoses (high power). **(c)** Immunohistochemical staining for CD20. **(d)** Immunohistochemical staining for Bcl-2. **(e)** Immunohistochemical staining for MIB-1.

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exposure during breast cancer treatment in 1994. She tolerated therapy well and remains free of disease approximately 1½ years after her lymphoma diagnosis.

DISCUSSION

Primary cutaneous B-cell lymphoma (PCBCL) belongs to a distinct group of B-cell lymphoproliferative disorders defined by its presentation in the skin, without evidence of extracutaneous spread at the time of diagnosis (1). Extranodal involvement occurs in approximately 25% of non-Hodgkin lymphomas, with the gastrointestinal tract being the most common site of extranodal involvement, followed by the skin (2). The annual incidence of cutaneous lymphomas is approximately 0.5 to 1 per 100,000 (1). While B-cell lymphomas account for the majority of nodal lymphomas, PCBCLs represent only 20% to 25% of all primary cutaneous lymphomas (3).

The new 2008 World Health Organization–European Organization for Research and Treatment of Cancer classification for cutaneous lymphomas identifies three main subtypes of PCBCLs: primary cutaneous marginal zone lymphoma (PCMZL), primary cutaneous follicular center lymphoma (PCFCL), and PCLBCL, LT. The consensus guidelines for the management of CBCL have been published only in the last 3 to 4 years (3).

The pathogenesis of PCBCL is unclear. There is some speculation that PCBCL may represent a lymphoproliferative response to antigenic stimuli in the cutis, a skin-associated lymphoid tissue–related B-cell lymphoma (a process similar to mucosa-associated lymphoid tissue lymphomas in the gastrointestinal tract) (4). In Europe, there is evidence linking *Borrelia burgdorferi* infection to the development of PCBCL (2). Jelic and colleagues reported borrelial serology in 12 of 22 (55%) PCBCL cases (5). Another study evaluating cases of PCBCL in an area with endemic borrelia infections in the Scottish Highlands found *B. burgdorferi*–specific DNA in 35% of cases using polymerase chain reaction, with a statistically significant positive association between *B. burgdorferi* and PCBCL (6). However, this association has not been readily demonstrated in US data. The relatively smaller frequency of PCBCL in the US (4.5% compared with 20% in Europe) may reflect geographic differences in the strains of *B. burgdorferi* (7). Molecular analysis of PCBCL supports the hypothesis of an antigen-driven germinal center origin based on findings of a characteristic pattern of somatic hypermutation and the presence of intraclonal diversity in B-cell immunoglobulin genes (8).

The subtype identified in our patient, PCLBCL, LT, represents approximately 20% of all PCBCLs and 4% of all cutaneous lymphomas (9, 10). It is more common in the elderly, with a median age in the mid 70s (11, 12). The male to female ratio ranges from 1:3 to 1:4 (10, 12, 13). Patients with PCLBCL, LT present with red to bluish nodules or tumors on one or both lower legs. Only about 10% to 15% of these patients are noted to develop lesions outside of the lower extremities, as was the case with our patient, who presented with a right arm nodule (10). Compared with other subtypes of PCBCLs (PCMZL and PCFCL), these tumors are more aggressive with worse outcomes, as they frequently disseminate to lymph nodes and visceral organs (3).

Staging of PCBCL includes a complete history and physical examination, and laboratory studies include a complete blood count, comprehensive serum chemistries, serum protein electrophoresis, and serum lactate dehydrogenase, along with radiographic imaging with computed tomographic or positron emission tomography scans to evaluate for extracutaneous disease. Bone marrow aspiration and biopsy should be performed routinely for initial staging of PCLBCL, LT, though it is optional with indolent cutaneous B-cell lymphomas (14).

Definitive diagnosis is based on the combination of morphologic, histologic, immunohistochemical, and genotypic analyses of preferably an excisional biopsy specimen (3). Pathology reveals diffuse nonepidermotropic infiltrates made up of a monotonous population of large noncleaved B cells usually extending into the subcutaneous tissue. There is generally a paucity of reactive or inflammatory cells (2, 12). The neoplastic cells express B-cell markers (CD12, CD20, CD22, CD79a) and also often express surface immunoglobulin (3, 15). They are strongly positive for bcl-2; however, unlike PCFCL, the t(14;18) which often leads to bcl-2 overexpression is not seen in PCLBCL, LT (2, 16). Bcl-6, MUM-1, and FOXP1 are usually positively expressed, while CD10 and CD138 are negative (3, 12, 17). Similar to its systemic counterpart, diffuse large B-cell lymphoma, but unlike PCFCL, fluorescent in situ hybridization studies reveal that 80% of PCLBCL, LT cases have breakpoints in at least one loci involving *IGH, MYC, BCL6,* or *MALT1* genes (2). Inactivation of the *CDKN2A* gene by deletion of chromosome 9p21.3 has been reported in 67% of PCLBCL, LT cases and is associated with an inferior prognosis (18). A recent paper investigating the expression of polycomb-group genes in primary nodal and cutaneous large B-cell lymphomas found that unlike primary nodal large B-cell lymphoma, PCLBCL, LT lacked *BMI-1* oncogene expression (which plays a role in regulation of p16 cell cycle inhibitor). The *HPH1* gene was also noted to be rare in PCLBCL of the head and trunk, while it was abundant in the leg primaries, supporting "leg-type" as a distinct entity (2, 19).

As previously mentioned, PCLBCL, LT has an inferior prognosis compared with PCFCL and PCMZL. Disease-related 5-year survivals for PCLBCL, LT range from 36% to 55% compared with over 95% for the other subtypes of primary cutaneous lymphomas (3, 11, 12). In an analysis of 60 patients with PCLBCL, LT, Grange and colleagues showed that patients with skin lesions on the leg had a statistically significantly worse prognosis compared with patients having nonleg lesions, with 3-year disease-specific survival rates of 43% vs. 77%, respectively (P = 0.02). Age over 75 and multiple lesions were also noted to be poor prognostic factors (11). Other factors contributing to the poor prognosis of PCLBCL, LT include a higher incidence of multiple relapses, shorter time to progression, and more frequent extracutaneous spread (20).

Given the rarity of PCLBCL, LT, prospective randomized therapeutic trials are lacking. Current patterns of care are based on retrospective and anecdotal evaluations. While

watch-and-wait strategies are often employed with the other subtypes, aggressive systemic therapy with combination chemotherapy with or without involved-field radiation therapy remains the recommended approach for PCLBCL, LT. Radiation therapy alone is much less effective in PCLBCL, LT than in other CBCLs, with higher rates of relapse and frequent distant metastases (21, 22). A recent review of literature revealed that of 32 patients with PCLBCL, LT who received multiagent chemotherapy (without rituximab), the complete response rate was 81% and the relapse rate, 58% (3). A more recent study of 12 patients treated with R-CHOP demonstrated a complete response in 92% of patients (11/12) with only one relapse (11). Current treatment guidelines recommend that in the absence of an available clinical trial, these patients should be treated similar to patients with limited-stage diffuse large B-cell lymphoma given their similar clinical behaviors. Alternative therapy with systemic single-agent rituximab may be appropriate in elderly patients unable to tolerate multiagent chemotherapy; however, long-term data are lacking (23, 24).

Trials of experimental therapies utilizing autologous transplantation combined with rituximab, gene therapy, immunotherapy with interleukin 2, and radioimmunotherapy are ongoing for patients with relapsed or refractory disease. However, most data are currently extrapolated from positive responses seen in patients with nodal B-cell non-Hodgkin lymphomas (25).

In summary, PCLBCL, LT has only recently been recognized as a distinct clinical subtype of PCBCL based on its unique clinical features, morphology, immunophenotype, and molecular characteristics. Given its aggressive nature and the lack of large trials, PCLBCL, LT is treated similar to diffuse large B-cell lymphoma. However, relapse rates remain >50% with frequent extracutaneous dissemination. On presentation, patients should be referred for enrollment in a clinical trial, when one is available. Otherwise, treatment with multiagent chemotherapy with or without involved-field radiation therapy is most appropriate.

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Avocations

"Water drops." Photo © Rolando M. Solis, MD. Dr. Solis is an interventional cardiologist on the medical staff of Baylor Medical Center at Garland.