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Cutaneous B-cell lymphomas: 2021 update on diagnosis, risk-stratification, and management

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Disease overview: Approximately one-fourth of primary cutaneous lymphomas are B-cell derived and are generally classified into 3 distinct subgroups: primary cutaneous follicle center lymphoma (PCFCL), primary cutaneous marginal zone lymphoma (PCMZL), and primary cutaneous diffuse large B-cell lymphoma, leg type (PCDLBCL, LT).

Diagnosis: Diagnosis and disease classification is based on histopathologic review and immunohistochemical staining of an appropriate skin biopsy. Pathologic review and an appropriate staging evaluation are necessary to distinguish primary cutaneous B-cell lymphomas from systemic B-cell lymphomas with secondary skin involvement.

Risk-stratification: Disease histopathology remains the most important prognostic determinant in primary cutaneous B-cell lymphomas. Both PCFCL and PCMZL are indolent lymphomas that infrequently disseminate to extracutaneous sites and are associated with 5-year survival rates that exceed 95%. In contrast, PCDLBCL, LT is an aggressive lymphoma with an inferior prognosis.

Risk-adapted therapy: PCFCL and PCMZL patients with solitary or relatively few skin lesions may be effectively managed with local radiation therapy. While single-agent rituximab may be employed for patients with more widespread skin involvement, multiagent chemotherapy is rarely appropriate. In contrast, management of patients with PCDLBCL, LT is comparable to the management of

patients with systemic DLBCL.

Disease Overview

Primary cutaneous lymphomas are a heterogeneous group of extranodal non-Hodgkin lymphomas, approximately 25% of which are B-cell derived and are classified into 3 major entities in the 2018 World Health Organization (WHO)-European Organization for Research and Treatment of Cancer (EORTC) joint classification: primary cutaneous follicle-center lymphoma (PCFCL), primary cutaneous diffuse large B-cell lymphoma, leg type (PCDLBCL, LT), and primary cutaneous marginal zone lymphoma (PCMZL) (1). The incidence of cutaneous B-cell lymphomas (CBCL) has been increasing and is currently ≈4 per million persons, based on Surveillance, Epidemiology, and End Results (SEER) registry data, with the highest incidence rates being reported among males, non-Hispanic whites, and adults over the age of 50 (2, 3).

Diagnosis

Diagnosis and classification of a CBCL requires an incisional, excisional or 4-6 mm punch biopsy which includes reticular dermis and subcutaneous fat for morphologic and immunohistochemical analysis, and an appropriate staging evaluation to exclude systemic disease (4). The use of appropriate immunohistochemical stains (e.g. CD5, cyclin D1) may also aid in distinguishing CBCL from secondary skin involvement by a systemic lymphoma.

PCFCL. PCFCL commonly present as a solitary purple to pink colored papule (often biopsied to rule out a non-melanoma skin cancer) or as multiple papules, plaques or tumors with a rim of peripheral erythema occurring on the forehead, neck and upper back in middle-aged adults. While grouped lesions may be observed, multifocal disease is less common, as are less common presentations, including rhinophyma and scarring alopecia with tumid pink plaques. Dermoscopy may help differentiate these cutaneous lymphomas from more common non-melanoma skin cancers (5). Histopathologically, PCFCL are characterized by a follicular, diffuse, or mixed growth pattern comprised of large centrocytes and variable centroblasts derived from germinal-center B-cells (6-8). In contrast to systemic follicular lymphomas, the majority of PCFCL do not harbor the t(14;18) translocation involving the bcl-2 locus, and do not strongly express bcl-2 by immunohistochemistry, although expression may be observed in a minority of cases (9-12). Strong expression of bcl-2 and CD10 may suggest secondary cutaneous involvement by follicular lymphoma. PCFCLs express bcl-6, variably express CD10, and are MUM-1/IRF-4, FOXP1 and IgM negative, consistent with their origin from germinal-center B cells.

PCDLBCL, LT. , PCDLBCL, leg type commonly affects elderly women and presents with rapidly progressive red brown to blue tumors involving either one or both lower legs (12, 13). Tumors may be ulcerated, and larger tumors

may be surrounded by smaller satellite lesions. Less common presentations include verrucous and multicolored nodules. Approximately 10-15% of cases may involve other cutaneous sites apart from the lower legs, and extracutaneous dissemination is common (12). These lymphomas are characterized by diffuse sheets of centroblasts and immunoblasts that spare the epidermis, but frequently extend deep into the dermis and subcutaneous tissue. In contrast to PCFCL, lymphoma cells highly express bcl-2, likely due to gene amplification (14, 15), as t(14;18) is not observed in PCDLBCL, LT. Dual expression of both bcl-2 and c-myc is common, and is associated with inferior overall survival compared with the minority of PCDLBCL, LT that do not express c-myc (15). C-myc translocations (and "double hits") are rare among PCDLBCL, LT (15). Most cases are MUM-1/IRF-4, FOXP1, IgM and bcl-6 positive, CD10 negative, and have a gene expression profile resembling activated B cells (8). Perhaps not surprisingly, the genetic landscape observed in PCDLBCL, LT is similar to that observed in activated B-cell-type diffuse large B-cell lymphoma (ABC-DLBCL), with NF-κB-activating mutations being observed in *CD79B*, *CARD11*, and *MYD88* (16-19). Of these, somatic MYD88 L265P mutations appear most common with a prevalence of ≈75% (15, 17-19). Loss of *CDKN2A* has also been identified in a large number of DLBCL-LT patients (20). Despite the use of somatically hypermutated immunoglobulin heavy-chain variable (IGHV) regions, Staphylococcal

superantigen binding sites within the IGHV are preserved, thus implicating superantigen-dependent B-cell receptor signaling in disease pathogenesis (21).

PCMZL. Patients with PCMZL frequently present with solitary asymptomatic pink papule on the trunk, arm and head and neck area, or as red brown multifocal papules, plaques or nodules involving the trunk and arms. While an association with *Borrelia burgdorferi* has been observed in Europe, a similar association has not been observed in cases from the United States (22-25). PCMZL are composed of a variably mixed infiltrate of small, “centrocyte-like” marginal zone B cells, monocytoid B-cells, lymphoplasmacytic cells, plasma cells, cells resembling centroblasts and immunoblasts, and reactive T cells. Marginal zone B cells characteristically express bcl-2 and may express CD43, but lack bcl-6, CD10, CD5 and CD23 expression. Recently, two groups of PCMZL have been identified (1, 26-28). The majority of PCMZL express class-switched immunoglobulin and show an indolent course; some have recommended that this type of PCMZL should be considered a lymphoproliferative disorder to reflect its clinical and histopathologic overlap with atypical reactive B-cell infiltrates (pseudo B-cell lymphomas). A second group expresses IgM and shows a behavior similar to extracutaneous extranodal marginal zone lymphomas, with frequent recurrences and extracutaneous spread.

Risk-stratification

The International Society for Cutaneous Lymphomas (ISCL) and EORTC recently proposed staging recommendations for cutaneous lymphomas other than mycosis fungoides and Sezary syndrome (4). Staging should include a history, physical examination, and imaging (either CT, PET, or increasingly PET/CT) of the chest, abdomen, pelvis, and neck (in cases with involvement of the head or neck). A bone marrow biopsy and aspirate should be performed in cases of PCDLBCL, LT. The joint ISCL/EORTC does not endorse routine bone marrow examination in cases of PCFCL or PCMZL, although approximately 10% of patients with follicle center lymphomas have bone marrow involvement and in most of these patients, the bone marrow is the only site of extracutaneous disease (29). Bone marrow involvement was associated with significantly inferior disease-specific survival. While the TNM staging classification describes the extent of disease, staging in CBCL is of limited prognostic value, as the disease histopathology is the major determinant in risk-stratification. This is highlighted by a population-based study which identified histopathology and the site of skin involvement as important prognostic factors (30). In contrast, the International Extranodal Lymphoma Study Group identified 3 independent prognostic factors (i.e. elevated LDH, >2 skin lesions, and nodular lesions) among patients with PCFCL and PCMZL. These factors were combined to form the cutaneous

lymphoma international prognostic index (CLIPI). The absence of any adverse prognostic factor was associated with a 5-year progression-free survival of 91%. In contrast, the presence of 2 or 3 adverse prognostic factors was associated with a 5-year progression-free survival of 48%. As the vast majority of relapses were confined to the skin, the CLIPI was unable to risk-stratify patients by overall survival. The presence of multiple skin lesions was associated with inferior disease-free survival in a European series (31), but was not associated with disease-free survival in a large North American series (32). The most important factor for risk-stratification among the cutaneous B-cell lymphomas remains the histopathologic classification. Indolent CBCL (PCFCL and PCMZL) are associated with 5-year disease-specific survival ≥95% (6, 32), though PCMZL with IgM expression have been associated with a more aggressive course. Differences in growth pattern, the density of centroblasts, and cytogenetic findings do not appear to provide meaningful prognostic information in PCFCL. Although numbers are limited, some authors have found that PCFCL occurring on the leg have a worse prognosis and are more likely to have an immunophenotype that overlaps with DLBCL-LT (12, 33) These authors suggest that consideration should be given to systemic chemotherapy in such patients. In contrast, PCDLBCL, LT is associated with a 5-year disease-specific survival of approximately 50%, and dual bcl-2 and c-myc expression (6, 15, 17, 34) and loss

of *CDKN2A* are associated with inferior survival (20). The presence of a somatic $MYD88^{L265P}$ mutation is also associated with inferior disease-specific and overall survival (17). In contrast to patients presenting with only a single tumor, involvement of multiple sites, on one or both legs, is associated with a significantly inferior disease-specific survival (35).

Treatment

As no randomized controlled trials are available, treatment recommendations for CBCL are largely based on small retrospective studies and institutional experience. The EORTC and ISCL have published consensus treatment recommendations that are consistent with NCCN guidelines (36). In most cases, optimal patient management requires a multidisciplinary approach, including dermatology, medical oncology and radiation oncology.

PCFCL. For patients with solitary lesions, low-dose radiation therapy is safe and highly affective, with a complete remission rate approaching 100%. Radiation does not appear inferior to multiagent chemotherapy among patients with multiple lesions that can be included in multiple radiation fields (37). In a large North American series, the rate of local control for indolent CBCL with radiation alone was 98% (32). In the same series, a local recurrence requiring radiation therapy was observed in 25% of patients who had undergone surgical excision alone. Reserving radiation until disease recurrence did not appear to

compromise disease-specific or overall survival (32). Therefore, complete excision alone, deferring radiation until disease recurrence, is also reasonable. Intralesional [e.g. corticosteroids or rituximab (38)] or topical therapies including corticosteroids, nitrogen mustard and bexarotene may also be considered (39, 40). While radiation therapy is generally recommended for patients with a solitary lesion, radiation therapy or observation (i.e. “watch and wait”) are reasonable options for those patients with multiple lesions. Rarely, patients with PCFCL may show a locally aggressive course (41, 42) and some have suggested the possibility of transformation to DLBCL (43, 44), suggesting that “watch and wait” patients require close clinical follow-up. Patients with more extensive skin involvement are effectively managed with single-agent rituximab (36). Approximately one-third of patients may relapse following either radiation or single-agent rituximab, but relapses are usually confined to the skin and are approached in a manner similar to that described for the initial management of PCFCL.

PCMZL. Patients with PCMZL are approached in a manner analogous to that described in the initial management of PCFCL. Radiation therapy or surgical excision are associated with high response rates for patients with a single or few lesions (36). Those with more widespread skin involvement may be observed. Once symptomatic, culprit lesions may be irradiated or surgically excised (45). As

for PCFCL, single-agent rituximab may be utilized in patients with symptomatic, widespread skin lesions. An initial trial of antibiotics for those with *B. burgdorferi*-associated PCMZL has been recommended (46), but is less relevant for North American patients.

PCDLBCL, LT. As previously noted, the natural history of PCDLBCL, LT more closely resembles that of systemic DLBCL. Therefore, R-CHOP (with or without radiation therapy) is utilized in these patients. While few reports are available in the literature, the use of R-CHOP in these patients is associated with disease-free survival rates rivaling those reported for patients with high-risk systemic DLBCL (12, 13, 32, 36). Most patients present with disease confined to the leg(s) and are managed like patients with limited stage systemic DLBCL with R-CHOP and involved field radiation therapy. The management of relapsed disease is comparable to that for relapsed systemic ABC-DLBCL [e.g. lenalidomide (47), ibrutinib (48)]. In a small phase II study (n=19), the 6-month overall response rate with single-agent lenalidomide in relapsed/refractory PCDLBCL, LT was 26%, but was significantly higher in patients without the $MYD88^{L265P}$ mutation (49).

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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