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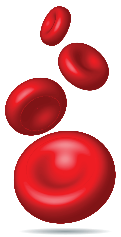
CME Information: Cutaneous B-cell lymphomas: 2015 update on diagnosis, risk-stratification, and management



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ANNUAL CLINICAL UPDATES IN HEMATOLOGICAL MALIGNANCIES
AJH Educational Material

Cutaneous B-cell lymphomas: 2015 update on diagnosis, risk-stratification, and management

Ryan A. Wilcox*

Disease overview: Approximately one-fourth of cutaneous lymphomas are B-cell derived and are generally classified into three 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 histologic 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 histology remains the most important prognostic determinant. 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 affectively 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.
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Disease Overview

Primary cutaneous lymphomas are a heterogenous group of extranodal non-Hodgkin lymphomas, approximately 25% of which are B-cell derived and are classified into three major entities in the 2008 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 3.1 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].

Diagnosis

Diagnosis and classification of a CBCL requires an excisional or punch biopsy for careful morphologic and immunohistochemical analysis, and an appropriate staging evaluation to exclude systemic disease [3]. 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 are commonly solitary plaques or tumors involving the trunk, particularly the head or scalp. While grouped lesions may be observed, multifocal disease is less common. Histologically, PCFCL are characterized by a follicular, diffuse, or mixed growth pattern comprised of large centrocytes derived from germinal center B cells [1,4,5]. 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 weak expression may be observed in a minority of cases [6–8]. These CBCL express bcl-6, variably express CD10, and are MUM-1/IRF-4 negative, consistent with their origin from germinal center B cells.

PCDLBCL, LT

In contrast to PCFCL, which is an indolent CBCL largely involving the head and trunk commonly affecting middle-aged adults, PCDLBCL, leg type commonly affects elderly females and presents with rapidly progressive tumors involving the lower legs [9,10]. Approximately 10% of cases may involve other cutaneous sites apart from the lower legs, and extracutaneous dissemination is common [10]. These lymphomas are

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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 [11], as t(14;18) is not observed in PCDLBCL, LT. Most cases are MUM-1/IRF-4 and bcl-6 positive, CD10 negative, and have a gene expression profile resembling activated B cells [5]. 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 [12,13]. Of these, somatic MYD88 L265P mutations appear most common, with a prevalence of 59% in the largest series [13].

PCMZL

Patients with PCMZL frequently present with multifocal patches, 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 [14–17]. PCMZL are composed of a mixed infiltrate of small, marginal zone B cells, lymphoplasmacytic cells, plasma cells, and reactive T cells. Marginal zone B cells characteristically express bcl-2, but lack bcl-6 or CD10 expression.

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 [3]. Staging should include a history, physical examination, appropriate laboratory studies (including lactate dehydrogenase), 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. While the joint ISCL/EORTC does not endorse routine bone marrow examination in cases of PCFCL or PCMZL, approximately 10% of patients with PCFCL have bone marrow involvement [18]. Furthermore, bone marrow involvement was associated with significantly inferior disease-specific survival. Therefore, in the opinion of this author, bone marrow examination is justified in cases of PCFCL. While the TNM staging classification describes the extent of disease, staging in CBCL is of limited prognostic value, as the disease histology is the major determinant in risk-stratification. This is highlighted by a population-based study which identified histology and the site of skin involvement as important prognostic factors [19]. In contrast, the International Extranodal Lymphoma Study Group identified three 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 two or three 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 [20], but was not associated with disease-free survival in a large North American series [21]. The most important factor for risk-stratification among the CBCLs remains the histologic classification. Indolent CBCL (PCFCL and PCMZL) are associated with 5-year disease-specific survival ≥95% [1,21]. Differences in growth pattern, the density of centroblasts, and cytogenetic findings do not appear to provide meaningful prognostic information. Bcl-2 expression among PCFCL with a diffuse large B-cell histology may be a notable exception [22]. In contrast, PCDLBCL, LT is associated with a 5-year disease-specific survival of approximately 50% and with cytogenetic changes, including translocations involving c-myc, that confer a poor prognosis among systemic DLBCLs [1,13,23]. The presence of a somatic MYD88 L265P mutation is also associated with inferior disease-specific and overall survival [13]. 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 [24].

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 [25]. In most cases, optimal patient management requires a multidisciplinary approach, including dermatology, medical oncology, and radiation oncology.

PCFCL

For patients with solitary lesions, 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 [26]. In a large North American series, the rate of local control for indolent CBCL with radiation alone was 98% [21]. 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 [21]. Therefore, complete excision alone, deferring radiation until disease recurrence, may be reasonable. 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. Patients with more extensive skin involvement are effectively managed with single-agent rituximab [25]. Multiagent chemotherapy (e.g., R-CHOP) is rarely required in the management of PCFCL. 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 is associated with a similarly high response rate for patients with a single or few lesions [25]. Those with more widespread skin involvement may be observed. Once symptomatic, culprit lesion may be irradiated (or surgically excised). 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 [27], 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 [9,10,21,25]. 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 [28]).

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