Diagnosis and Management of Cutaneous B-cell Lymphoma

Lauren C. Pinter-Brown, MD

KEYWORDS

• Cutaneous B-cell lymphoma • Marginal zone lymphoma
• Primary cutaneous follicle center lymphoma • DLBCL, leg type • Primary cutaneous lymphoma

KEY POINTS

- A primary cutaneous B-cell lymphoma (CBCL) by definition is one in which the lymphoma involves no other tissue but skin at the time of diagnosis.
- Primary cutaneous follicle center lymphoma and diffuse large B-cell lymphoma, leg type, are unique clinicopathologic entities, not to be confused with nodal counterparts with similar names.
- The diagnosis of CBCL requires a 4-mm to 6-mm punch biopsy or incisional or excisional biopsy that includes the reticular dermis and subcutaneous fat.
- Along with histologic differences, the common CBCLs present on different parts of the body in different age groups.
- The treatment approach may vary widely between observation, local therapy, or systemic therapy depending on the histology and extent and area of skin involvement. Histology of the lesion determines prognosis.

INTRODUCTION

The skin is the second most common extranodal site involved by non-Hodgkin lymphomas (NHLs) after the gastrointestinal tract. By definition, the designation of a lymphoma as primary to the skin implies that there is no extracutaneous disease discovered at diagnosis. As such, the cutaneous B-cell lymphomas (CBCLs) make up 25% to 30% of all primary cutaneous lymphomas, with cutaneous T-cell lymphomas (CTCLs) being the more common subtype.[1]

Although the clinical presentation of CBCLs compared with CTCLs is more uniform, clinicopathologic correlation is still important and, in the absence of features clearly suggesting a benign diagnosis, the evaluation of nonepidermotrophic or dermal lymphoid cutaneous infiltrate such as seen in these cancers requires assessment of multiple parameters, including a good clinical history and physical examination.

The 3 most common histologic types of primary cutaneous lymphomas as designated in the World Health Organization (WHO) 2008 Classification of Tumors of Haematopoietic and Lymphoid Tissues are primary cutaneous follicle center lymphoma (PCFCL), extranodal marginal zone lymphoma (MZL) of mucosa-associated lymphoid tissue (MALT; previously called primary cutaneous MZL [PCMZL]), and primary cutaneous diffuse large B-cell lymphoma (PCDLBCL), leg type. The first and last of these are recognized as unique entities in the WHO 2008 classification.[2] Although they carry names and have some histologic similarities with nodal counterparts, there remain differences not only in presentation and histology but also in

The author has done consulting for Celgene, Pharmacyclics.
Department of Internal Medicine, Division of Hematology-Oncology, Geffen School of Medicine, University of California, Los Angeles, 2020 Santa Monica Suite 600, Santa Monica, CA 90404, USA
E-mail address: lpinterbrown@mednet.ucla.edu

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natural history, treatment, and outlook. PCMZL, however, is discussed within the general category of extranodal MZLs, which are frequently found in extranodal sites such as skin or stomach. Although both PCFCL and PCMZL are considered slow-growing or indolent diseases with an excellent outlook, PCDLBCL, leg type, is a more aggressive entity with behavior more similar to its nodal counterpart.

DIAGNOSIS AND STAGING

The diagnosis of a CBCL first requires a biopsy of these mostly papular or tumoral erythematous to violaceous skin lesions. To this end, a 4-mm to 6-mm punch biopsy or excisional or incisional biopsy that includes the reticular dermis and fat should be obtained.

After the diagnosis is confirmed, staging procedures in addition to history and physical examination should be performed to evaluate for extracutaneous disease and anticipate treatment. Groups such as the National Comprehensive Cancer Network (NCCN)[3] have suggested performance of complete blood count (CBC) with differential, a comprehensive chemistry panel, and lactate dehydrogenase level. If a lymphocytosis or immature cells are seen in the CBC, peripheral blood flow cytometry should be ordered to evaluate for a monotypic lymphoid population, which may signify blood involvement by the lymphoma. In the case of PCMZL, both a serum protein electrophoresis and quantitative immunoglobulins should be sent to evaluate for a paraprotein given the increased incidence of this finding in this specific entity. Serologic testing for hepatitis B and C, especially if systemic therapies such as rituximab, systemic steroids, or other immunomodulatory agents are being considered, and testing for *Borrelia burgdorferi* serologies should be considered. Although an association between *B burgdorferi* infection and CBCL has been made in several European countries, such a relationship has not been shown in North American patients and the strength of this association may relate in part to geographic diversity.[4]

In addition to laboratory testing, PET/computed tomography (CT) scanning or CT scanning with contrast of the chest, abdomen, and pelvis should be performed at diagnosis, but not routinely in follow-up unless clinical or laboratory parameters are concerning for extracutaneous progression. Bone marrow examination should be performed if the diagnosis is PCDLBCL, leg type, and considered if the diagnosis is PCFCL.

Although a TNM (tumor, node, metastasis) classification for cutaneous lymphomas other than MF/SS has been proposed,[5] unlike the larger group of NHLs, the histology of these diseases remains the main determinant of a patient's outcome. However, the TNM classification can be used effectively for the documentation of anatomic location and extent of disease involvement.[6]

The histology of primary cutaneous lymphomas is discussed in depth elsewhere in this issue, the clinical presentation and treatment of the 3 most common forms of CBCLs are discussed here separately. Other uncommon CBCLs, such as intravascular large B-cell lymphoma, a subtype of diffuse large B-cell lymphoma (DLBCL) that may present primarily in skin, and cutaneous immunodeficiency-associated lymphoproliferative diseases such as Epstein-Barr virus (EBV)–positive mucocutaneous ulcer are briefly discussed.

PRIMARY CUTANEOUS FOLLICLE CENTER LYMPHOMA

The most common type of primary CBCL, PCFCL, represents 60% of all cases. The median age of patients is 51 years, with a slight male predominance (1.5:1).[7,8] Lesions are firm, erythematous to violaceous nodules or plaques with a smooth skin surface; ulcerations are rarely observed. These lesions characteristically present as solitary or localized skin lesions on the scalp, head and neck, or trunk. Only 5% present on the leg and 15% are multifocal.[7,8]

In contrast with its nodal counterpart, follicular lymphoma, PCFCL does not necessarily have CD10 staining by immunohistochemistry, and may have negative or faint staining with bcl-2. When present, these positive stains raise suspicion for secondary rather than primary skin involvement. Surface immunoglobulin (Ig) G is usually negative in PCFCL, in contrast with follicular lymphoma. In addition, PCFCL is not graded as nodal follicular lymphoma in terms of number or proportion of large cells noted.[2]

Although the rate of cutaneous relapse with PCFCL reaches 30%, the condition has an excellent prognosis, with a 5-year survival of greater than 95%. Although some patients experience spontaneous regression, approximately 10% experience extracutaneous dissemination.[7,8]

EXTRANODAL MARGINAL ZONE LYMPHOMA OF MUCOSA-ASSOCIATED LYMPHOID TISSUE

Primary cutaneous MALT lymphomas are described in the WHO classification of 2008 as part of the general group of extranodal MZLs of MALT in which there is often a role described for a chronic antigenic stimulus to lymphomagenesis. Approximately 11% of MALT lymphomas involve