Spectrum of Primary Cutaneous B-Cell Lymphomas

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When diagnosing and approaching the treatment of primary cutaneous B-cell lymphoma (PCBCL) proper classification is extremely important. In 2005, the World Health Organization (WHO) and the European Organization for Research and Treatment of Cancer (EORTC) collaborated to define the classifications of cutaneous lymphomas, including PCBCL. Since then, many studies and reclassifications have been performed to support these classifications. This review article draws from these publications to display a clinically supported understanding of the spectrum of cutaneous B-cell lymphomas.

Primary cutaneous B-cell lymphoma (PCBCL) is a heterogeneous group of neoplasms that present solely on the skin with no evidence of extracutaneous involvement at the time of diagnosis or initial staging evaluation.[1,2] Unlike some cutaneous lymphomas that are present only on the skin (ie, mycosis fungoides [MF]), PCBCL histologically mirrors the morphology of its non-Hodgkin lymphoma (NHL) counterpart found in the germinal center of the lymph nodes.[3] In fact, 6% to 10% of patients with systemic NHL develop secondary cutaneous disease at some point.[4] Although PCBCL is structurally similar to its counterpart in the lymph nodes, the clinical behavior, immunophenotypic profile, and prognosis are very different, which suggests that they represent distinct entities.[5] Therefore, understanding the spectrum of PCBCL is extremely important when diagnosing and approaching treatment.

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EPIDEMIOLOGY

Although B-cell lymphomas comprise 90% of systemic lymphomas, they are considered a minority when compared to T-cell lymphomas in regard to presentation on the skin.[6] Cutaneous T-cell lymphoma (CTCL) accounts for 71% of primary cutaneous lymphomas. Therefore, PCBCL accounts for the remaining 29%.[7]

Primary cutaneous B-cell lymphoma occurs mainly in white individuals. Non-Hispanic white individuals with PCBCL have the highest incidence rate of 3.5 per 1,000,000 person-years, followed by Hispanic white, Asian/Pacific Islander, and black individuals (2.8, 1.9, and 1.5/1,000,000 person-years, respectively). Cutaneous T-cell lymphoma shows a reverse trend with black individuals having the highest incidence rate of 10.0 per 1,000,000 person-years. Sex distribution reveals males are consistently more affected than females. In contrast to the classic "bathing suit" lesion distribution of cutaneous T-cell lymphoma, the head and neck are the most common sites for PCBCL followed by the trunk.[7]

DIAGNOSIS

By definition, PCBCLs are diagnosed as a primary malignancy when no systemic involvement exists at the time of diagnosis and up to 6 months after. A suspected lesion

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must be confirmed by adequate histologic and immunohistochemical studies. Therefore, a representative biopsy specimen, preferably excisional, is necessary for making the diagnosis.[8] Besides considering the morphology of the neoplastic B-cell population and the growth pattern of the malignant infiltrate, immunohistochemical studies are required to make a definite diagnosis.[8] Flow cytometry cannot be considered a substitute for immunohistochemical studies even though successful application has been reported in diagnosing PCBCL.[9] Diagnosing difficulties exist in the challenges to obtain a sufficient viable single-cell suspension. This is due to cutaneous B-cell vulnerability, lack of architectural information, and the need for additional fresh tissue material.[8,9] The demonstration of gene rearrangements may be useful in the diagnosis of PCBCL but results should always be considered in conjunction with clinical, histologic, and immunohistochemical data.[8,10-13] Clinical features are considered the most important markers for therapeutic planning.[2]

STAGING

The most widely used staging structure for systemic lymphomas is the Ann Arbor staging system but it has numerous shortcomings when staging extranodal lymphomas. Therefore, cutaneous lymphoma staging has had its own modified TNM + blood staging system for the past 30 years. Although helpful for the most common primary cutaneous lymphomas, MF/Sézary syndrome, the TNM staging classifications and descriptions of other cutaneous lymphomas were questioned. A proposal was made in 2007 by the International Society for Cutaneous Lymphomas (ISCL) and the European Organization for Research and Treatment of Cancer (EORTC) for a TNM staging system for patients with non–MF/Sézary syndrome primary cutaneous lymphomas.[14] The goals of the staging system were to offer a basis for management, predict prognosis, and compare therapy results. The TNM staging system has been regarded as a means to document only the extent of disease and not one to be used as a prognostic guide.[2,14]

Proper staging evaluation for PCBCL, as directed by the ISCL-EORTC, should begin with taking a complete medical history, physical examination, and review of symptoms.[8,14] Laboratory studies include a complete blood cell count with differential and complete metabolic profile, including lactate dehydrogenase levels; and in selected cases serum electrophoresis, flow cytometry, or both, on peripheral blood to exclude a monoclonal gammopathy. Computed tomography imaging of the chest, abdomen, and pelvis should be performed with area-appropriate studies, especially of the head and neck when lesions specify.[8,14] According to the ISCL-EORTC guidelines, bone marrow biopsy is indicated for primary cutaneous diffuse large B-cell lymphoma (PCDLBCL), leg type, but it is optional for indolent primary cutaneous marginal zone B-cell lymphoma (PCMZL) and primary cutaneous follicle center lymphoma (PCFCL).[8] A recent study indicates bone marrow biopsy is essential for PCFCL as well, but a consensus has not been drawn and clinicians are advised to follow the standard of care for their regional practice.[8,15]

CLASSIFICATION

Classification for PCBCLs has been a process. In a report published in 2005 the World Health Organization (WHO) and EORTC united on the histologic and immunophenotypic diagnosis of PCBCL.[16] Prior to this publication the separate systems lacked organ-specific classifications and did not sufficiently differentiate between some similar subgroups of PCBCL with different prognoses and treatments. Thus, an indolent form of PCBCL may have been classified as aggressive and treated unnecessarily with systemic chemotherapy.[17,18]

Primary cutaneous B-cell lymphomas are classified into the following 3 categories: PCMZL; PCFCL; and PCDLBCL, leg type; the latter containing 2 subclasses, primary cutaneous diffuse large B cell lymphoma, other (PCDLBCL, other) and intravascular large B cell lymphoma (IVLBCL)(Table 1).[14,16]

PRIMARY CUTANEOUS MARGINAL ZONE B-CELL LYMPHOMA

Marginal zone B-cell lymphomas (MZLs), both nodal and extranodal, originate from the outermost portion of the B-cell follicle. The spleen, lymph nodes, and mucosal lymphoid tissues are regarded as the anatomical sites where MZLs arise because of high exposure to antigens.[19] The WHO-EORTC classification of PCMZL also includes cases previously designated as primary cutaneous immunocytoma (Waldenström macroglobulinemia), follicular lymphoid hyperplasia with monotypic plasma cells, and extramedullary plasmacytoma of the skin.[16]

Most studies regarding PCMZL support an indolent disease course with prolonged survival.[1,16,20] It is the least common PCBCL.[8] Primary cutaneous marginal zone B-cell lymphoma traditionally is localized on the trunk and extremities but a recent study showed the head and neck as more common presentation sites.[1,7] In contrast to PCFCL, PCMZL appears as multiple deep-seated nodular lesions on clinical evaluation that tend to recur but rarely disseminate to extracutaneous sites.[21] Spontaneous resolution of PCMZL lesions can occur and secondary anetoderma has been observed.[22,23]

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Histopathologic examination demonstrates nodular to diffuse infiltrates with sparing of the epidermis. Clonal proliferation of small B lymphocytes, including marginal zone (centrocytelike) cells, lymphoplasmacytoid cells, and plasma cells is observed.[24] The plasma cells often are located at the periphery of the infiltrates and in the superficial dermis. The diffuse cellular infiltrate can be a distinguishing feature from the typical nodular pattern of PCFCL.[16] Immunophenotype studies can help to distinguish among these often overlapping classes. Primary cutaneous marginal zone B-cell lymphoma cells express CD19, CD20, CD22, CD79a, and bcl-2 but are negative for CD5, CD10, CD23, cyclin D1, and bcl-6.[3,25]

Primary cutaneous marginal zone B-cell lymphoma is considered part of the broad group of extranodal MZLs that commonly involve mucosal sites, particularly mucosa-associated lymphoid tissue (MALT) lymphomas.[16] Emerging information shows that characteristics delineate the differences between these similar forms of MZL. The main distinctions between MALT and PCMZL relate to etiology. Mucosa-associated lymphoid tissue lymphomas have a strong association between lymphomagenesis and chronic inflammation/antigenic stimulation.[19,26,27] Primary cutaneous marginal zone lymphoma only has minor ties to infection. *Borrelia burgdorferi* infection has been associated with a small portion of PCMZL cases in endemic areas of Europe, but has not been reported in the United States or Asia.[28,29] Many cases cannot be differentiated from pseudolymphoma.[30] Most cases of PCMZL exhibit a cytokine/chemokine profile of T_H2^+/CXCR3$^-$ whereas rare forms of PCMZL linked with *B burgdorferi* exhibit T_H1^+/CXCR3$^+$ (similar to the profile of MALT lymphoma).[31] Despite this rare exception, PCMZL is believed to recognize different antigens than MALT lymphomas and thus develop in response to a uniquely different inflammatory environment.[19]

PRIMARY CUTANEOUS DIFFUSE LARGE B-CELL LYMPHOMA, LEG TYPE

Primary cutaneous diffuse large B-cell lymphoma, leg type, typically occurs in elderly female patients, has a localized distribution, often is resistant to therapy, and frequently recurs after radiotherapy.[32] This pattern of recurrence in the therapy field rarely is exhibited in other classic forms of PCBCL.[33]

Although it most commonly presents on the legs, PCDLBCL, leg type, is not exclusive to this anatomical location.[16,34] Many cases involve multiple and non–lower extremity sites suggesting that anatomic site alone is not sufficient for classification.[35] Prior to the combined 2005 WHO-EORTC definition, confusion existed because of overlapping definitions for PCDLBCL, leg type, and PCFCL.[36,37] Previous designations were made between cleaved vs round cell morphology and nonleg vs leg lesion distribution.[38-41] This method of definition led to a high intraobserver variation in classification.[17] Primary cutaneous diffuse large B-cell lymphoma, leg type, has been defined more specifically as confluent sheets of medium to large B cells with round nuclei resembling centroblasts, immunoblasts, or both.[16] Primary cutaneous diffuse large B-cell lymphoma, leg type, typically demonstrates strong bcl-2 expression and positive staining for MUM1 and FOXP1 transcription factors.[3,34,35,42]

Bcl-2 expression has been labeled as the strongest predicting factor of death from lymphoma.[3,43,44] Therefore, PCDLBCL, leg type, has the poorest prognosis of all PCBCLs. Recent studies show a 5-year survival rate of 41% to 53%.[7,35,45] Presentation on the leg, regardless of the type of PCBCL, has been proven to have a worse prognosis than if the lesion presented at other locations.[32] Primary cutaneous diffuse large B-cell lymphoma with only a single leg lesion has been shown to be much more favorable than a multiple-lesion course.[34,44] Overall, PCDLBCL, leg type, has a lower complete response rate, higher incidence of multiple relapses, shorter time to progression, and more frequent extracutaneous metastases.[44]

An epidemiologic study of this subtype has revealed some unique findings among Asian and Pacific Islanders. Although white individuals have the highest incidence rates in the other subtypes of PCBCL, Asian and Pacific Islanders have a higher incidence rate with PCDLBCL, leg type.[7] Another study of Japanese individuals also reported PCDLBCL, leg type, as the most frequent PCBCL affecting Asian and Pacific Islanders.[46] Genetic susceptibility in etiology also is exhibited among Asian individuals born in the United States.[47]

PRIMARY CUTANEOUS DIFFUSE LARGE B-CELL LYMPHOMA, OTHER

Primary cutaneous diffuse large B-cell lymphoma, other, is defined by the WHO-EORTC classification as rare cases of typically T-cell and histiocyte-rich large B-cell lymphomas with anaplastic and plasmablastic subtypes. More commonly found on the head and trunk, these lymphomas have similarities to both PCFCL and PCMZL and present as a skin manifestation of systemic lymphoma.[16] The primary cutaneous form has a more favorable prognosis than its nodal counterpart.[48] A recent large study also confirmed a favorable overall 5-year relative survival rate of 81% for PCDLBCL, other.[7] Cases that lack bcl-2 expression have been controversially included in the PCDBLCL, other, classification. These cases exhibit the confluent, large, round B-cell morphology of PCDLBCL, leg type, and a poor

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TABLE 1

WHO-EORTC Classification of Primary Cutaneous B-Cell Lymphomas

	PCMZL	PCDLBCL, leg type	PCDLBCL, other	IVLBCL	PCFCL
Morphology	Small B lymphocytes, including marginal zone (centrocytelike) cells, lymphoplasmacytoid cells, and plasma cells (located at periphery)	Confluent sheets of medium to large B cells with round nuclei resembling centroblasts, immunoblasts, or both Prominent nucleoli and coarse chromatin	Subtypes: Anaplastic Plasmablastic T cell and histiocyte rich	Large B cells within dilated vessels of the dermis and subcutis	Large-cleaved follicular centrocytes and non-cleaved follicular centroblasts Centroblasticlike large B cells may be present, but not in confluent sheets
Growth pattern	Diffuse	Diffuse	Various	In vascular lumens but rarely infiltrates parenchyma	Follicular Follicular/diffuse Diffuse
Phenotype	bcl-2$^+$, bcl-6$^-$ CD19$^+$, CD20$^+$, CD22$^+$, CD79a$^+$ CD5$^-$, CD10$^-$, CD23$^-$, and cyclin D1$^-$ T_H2^+/CXCR3$^-$	bcl-2^{++}, bcl-6$^{+/-}$ CD10$^-$ MUM1$^+$, FOXP1$^+$	bcl-2$^-$ B cells: CD20$^+$, CD79a$^+$ T cells: CD45RO$^+$, CD3$^+$	bcl-2$^{+/-}$ CD20$^+$, CD45$^+$ HLA-DR$^+$	bcl-2$^{+/-}$, bcl-6$^+$ CD10$^{+/-}$ MUM1/IRF4$^-$
5-year survival rate	>95%	41%–53%	81%	50%	93%–95%
Presentation	Sixth decade	Eighth decade, more common in females			Sixth decade
Location	Trunk, extremities, head, and neck	Legs (90%), most often below the knee	Head, trunk, or extremities	Vessels of CNS and skin	Head, neck, or trunk (90%)
Clinical features	Multiple deep-seated nodular lesions Spontaneous resolution and secondary anetoderma can occur	Rapid growing red or bluish-red nodules	Like an exaggerated T-cell infiltrate in association with other forms of PCBCL	Violaceous papules or nodules Intravascular thrombotic disorders with livedo reticularis or panniculitis-like lesions	Tumor surrounded by less-infiltrated erythematous plaques

Abbreviations: WHO, World Health Organization; EORTC, European Organization for Research and Treatment of Cancer; PCMZL, primary cutaneous marginal zone B-cell lymphoma; PCDLBCL, primary cutaneous diffuse large B-cell lymphoma; IVLBCL, intravascular large B-cell lymphoma; PCFCL, primary cutaneous follicle center lymphoma; IFR4, interferon regulatory factor 4; CNS, central nervous system; PCBCL, primary cutaneous B cell lymphoma.

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prognosis and therefore are argued to be included in PCDLBCL, leg type.[34] Further official definition may be needed.

INTRAVASCULAR LARGE B-CELL LYMPHOMA

Intravascular lymphoma is an uncommon, very aggressive, extranodal NHL that classically involves both the skin and central nervous system.[49] Most cases are of B-cell origin and rarely of T-cell phenotype.[50] Large malignant B cells proliferate within the lumens of capillaries, arterioles, venules, and small arteries but rarely infiltrate the parenchyma. Vascular occlusion is responsible for the clinical signs and symptoms, in which skin lesions can resemble classic lymphoma with violaceous papules and nodules or can present as intravascular thrombotic disorders with livedo reticularis or panniculitislike lesions.[51] Central nervous system involvement displays symptoms ranging from generalized confusion or dementia to facial motor and sensory deficits.[49,51]

Diagnosis is made easily by performing a skin biopsy, and even biopsy specimens of healthy-appearing skin can be diagnostic. On histologic evaluation, IVLBCLs demonstrate dilated vessels of the dermis and subcutis filled with the large B-cell proliferations.[16] Venules, capillaries, and arterioles often are occluded and focal extravascular accumulations may be seen. Cutaneous IVLBCL without multiple-organ involvement presents with limited clinical symptoms, an indolent course, and a good therapeutic response.[52] Some argue that the prognosis is similar to multiorgan IVLBCL.[41] The estimated 5-year survival rate of classic multiorgan IVLBCL is 50%.[53]

PRIMARY CUTANEOUS FOLLICLE CENTER LYMPHOMA

The most common PCBCL is considered to be PCFCL, which accounts for approximately 40% to 57% of cases despite a recent large cohort study demonstrating it to be second to PCDLBCL, leg type, at 30% of cases.[8,17,44] The lesions of PCFCL generally present clinically on the head, neck, and trunk as tumors surrounded by less-infiltrated erythematous plaques. The infiltrate consists of cleaved follicular centrocytes and noncleaved follicular centroblasts with a follicular, follicular and diffuse, or diffuse growth pattern.[54] When PCFCL with a diffuse growth pattern is present, it may be confused with PCDBLCL, leg type. The key PCFCL-defining cells are centrocytes, whereas in PCDLBCL, leg type, there are distinctive confluent sheets of centroblastlike large B cells with rounded nuclei.[16,32] A prominent stromal component also is present in PCFCL.[16]

The histology of PCFCL is variable because of the age and growth rate of the skin lesion used as a biopsy specimen. Primary cutaneous follicle center lymphoma lesions, as with other indolent PCBCLs, can undergo morphologic changes over time.[55] For example, early lesions initially present with small numbers of B cells in the background of a larger T-lymphocyte population, which may be misleading. This variation, as well as the absence of clinical symptoms can ascribe to the difficulties of diagnosing PCFCL, where multiple years can precede a definitive diagnosis.[55] Thus, the diagnosis of lymphoma should never be excluded because of the inability to verify morphology. Location can affect diagnosis as well. Scalp lesions have been shown to provide a quicker diagnosis because of a more frequent, clear-cut follicular growth pattern.[54]

Markers of PCFCL B-cell maturation stage are CD20 and CD79a antigens. CD10 is observed more commonly in cases with follicular, not diffuse, growth pattern.[54] Unlike its nodal counterpart and most cases of PCDLBCL, leg type, PCFCL does not express bcl-2 protein.[54,56] Staining for MUM1/IRF4 is negative, further differentiating PCFCL from the commonly MUM1-positive PCDLBCL, leg type.[56] Nevertheless, controversies over antigen expression in the definition of PCBCL, particularly PCFCL, remain and are part of an ongoing debate.[57]

Regardless of growth pattern (follicular, follicular and diffuse, or diffuse) PCFCL has a very favorable prognosis.[7,16,44] When the WHO-EORTC definitions were applied in trials, many studies found participants with diffuse PCFCL who were previously classified and treated as having PCDLBCL, leg type. Therefore, some participants with a 5-year survival rate of 93% to 95% may have been diagnosed and treated as though they had an aggressive form of PCBCL.[7,16]

SUMMARY

In the years since the WHO-EORTC combined classification of PCBCL was published, many studies verifying and supporting the current classifications have been produced.[16] Most single-center and multiple-center reclassification trials found diagnosis and treatment to be more accurate by applying the most recent WHO-EORTC classification system.[1,17,19,20,24,35,44] Despite the continuing debate,[58] effective classification, prognosis, and treatment can be achieved by understanding the spectrum of PCBCLs through the current clinically proven definitions.

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