

Cutaneous B-cell Lymphomas

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Cutaneous B-cell lymphomas

Primary cutaneous marginal zone B-cell lymphoma (pcMZL)

Primary cutaneous Follicle center lymphoma (pcFCL)

Primary cutaneous Diffuse large B-cell lymphoma, leg-type (pcDLBCL, leg)

Primary cutaneous Diffuse large B-cell lymphoma, other (pcDLBCL, other)

Clinical features and history

Cutaneous B-cell lymphomas usually present as one or more erythematous papules or nodules that may coalesce to form plaques. They are usually localized tumors effecting one cutaneous region and rarely ulcerate. There is some regional predilection for various sub-types of tumors; follicle center lymphoma more commonly arises on the scalp, marginal zone B-cell lymphomas usually occur on the trunk or extremities, and the more aggressive diffuse large B-cell lymphoma usually arises on the lower leg.

Histomorphology

In contrast to malignancies of T lymphocytes which frequently show epidermotropism, the tumor cells in cutaneous B-cell lymphomas spare the epidermis and are usually separated from it by a grenz zone of uninvolved dermis.

Immunophenotype

Some observers have proposed that a cutaneous lymphomas develop in the setting of a persistent inflammatory reaction or immune dysregulation. This hypothesis has been applied not only to T-cell proliferations in the setting of connective tissue disease, chronic actinic dermatitis (actinic reticuloid), and lymphomatoid drug eruptions, but also has been used to explain the development of cutaneous B-cell lymphomas in the setting of borrelia infection and tattoo. As with T-cell lymphomas, an aberrant B-cell immunophenotype supports the diagnosis of lymphoma, as may be seen in light chain restriction or co-expression of CD43 and CD20. Because the responder cell in cutaneous inflammatory processes is usually a T cell, most non-neoplastic cutaneous infiltrates are composed almost exclusively of T cells. Thus, when B cells comprise >75% of the dermal infiltrate a diagnosis of cutaneous B-cell lymphoma is favored. On the other hand, dense reactive T-cell infiltrates are frequently present in cutaneous lymphoma; in some cases of B-cell lymphoma the neoplastic B cells may represent only a minor component of the dermal lymphocytic infiltrate. An immunohistochemical panel including CD20, CD3, CD21, CD10, bcl-2, and bcl-6 is often useful in distinguishing follicle center lymphoma from marginal zone B-cell lymphoma.

Gene Rearrangements

The southern blot method of detecting T-cell receptor and immunoglobulin gene rearrangements may yield negative results if the tumor cells represent less than 5% of the sample. PCR based techniques are reported to be positive in most cases of cutaneous T-cell lymphoma but only 50% of cutaneous B-cell lymphomas. As with any diagnostic tool, the interpretation of the genetic results should be in the context of the clinical, histologic and immunophenotypic findings of the case.

Treatment and Prognosis

Patients with solitary or localized tumors are usually treated with excision and/or radiation therapy; solitary low-grade tumors may also be treated with injection of high dose steroids. Patients with multifocal or disseminated cutaneous lymphoma are usually treated with chemotherapy; single agent chemotherapy is given to patients with the more indolent tumors, multiagent chemotherapy is instituted for those with biologically aggressive lymphomas. In general, cutaneous lymphomas are more indolent than their nodal counterparts. Primary cutaneous B-cell lymphomas of marginal zone (pcMZL) and follicle center types (pcFCL) usually remain localized to the skin and are often cured by local therapy. Whereas primary cutaneous diffuse large B-cell lymphoma (pcDLBCL) of the leg is more often associated with eventual extracutaneous lymphoma. Even the pcDLBCL of the leg has a better disease free survival than does nodal diffuse large B-cell lymphoma (Table 1).

CLASSIFICATION OF PRIMARY CUTANEOUS LYMPHOMA

It is now widely recognized that there are many distinct B-cell and T-cell lymphomas that occur as primary tumors of the skin. In 1994 the Revised European-American Lymphoma Classification (REAL) scheme was published and shortly thereafter, the European Organization for Research and Treatment of Cancer (EORTC) Cutaneous Lymphoma Program Project Group published a classification scheme specifically for primary cutaneous lymphoma. One of the aims of the EORTC report was to define primary cutaneous tumors and draw attention to those lymphomas that have a clinical behavior that would not be predicted using classification schemes designed for nodal lymphomas. Since then, the WHO International Agency for Research and Cancer has published the Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues (Table 2). Additionally, but certainly not finally, a group of pathologist and dermatologist representatives of the WHO and have proposed the WHO/EORTC classification for cutaneous lymphomas (Willemze et al. Blood 2005).

An understanding of how the terms “primary” and “secondary” have been applied to cutaneous lymphomas is critical to understanding the classification schemes. Most observers use the term “secondary cutaneous lymphoma” to describe lymphomas that develop in the skin as a secondary manifestation of a lymphoma primarily arising at a site other than skin. The current most broadly accepted definition of primary cutaneous lymphoma is: lymphoma arising in the skin without evidence of extra-cutaneous lymphoma for six months following initial presentation and staging including bone marrow biopsy and radiological examination.

B-CELL LYMPHOMAS OF THE SKIN

Of all cutaneous lymphomas approximately 25% have been estimated to be of B-cell lineage. The estimated annual incidence of primary cutaneous B-cell lymphomas in Europe is 0.2/100,000 per year. The vast majority of these patients have cutaneous B-cell lymphomas of follicle center and marginal zone B-cell type, with a minor cohort of patients with large B-cell lymphomas. Other forms of cutaneous B-cell lymphoma represent rare but distinct clinical entities.

- Marginal zone B-cell lymphoma of (pcMZL)
- Follicle center lymphoma (pcFCL)
- Diffuse large B-cell lymphoma, leg-type (pcDLBCL, leg)
- Diffuse large B-cell lymphoma, other (pcDLBCL, other)

Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue

WHO-EORTC: Primary cutaneous marginal zone lymphoma B-cell lymphoma (pcMZL)

REAL: Extranodal marginal zone B-cell lymphoma (low grade B-cell lymphoma of MALT-type)

Primary cutaneous marginal zone lymphoma B-cell lymphoma (pcMZL) is defined as a neoplastic proliferation of small B cells including marginal zone (centrocyte-like) cells, monocytoid B cells and, in most cutaneous tumors, lymphoplasmacytoid cells and plasma cells. Primary cutaneous marginal zone lymphoma (pcMZL) shares features with extranodal lymphomas of Mucosa Associated Lymphoid Tissue (MALT). Primary cutaneous immunocytoma and cutaneous lymphoid hyperplasia with monotypic plasma cells are considered to be variants of marginal zone lymphoma.

- Epidemiology

Cutaneous MZL affects both men and women, with a median age of 50 years and a range of 24-77 years. pcMZL shows a predilection for the trunk and upper extremities. Because of the predominance of T-cell lymphomas in the skin, pcMZL are rare among all cutaneous lymphomas. MZL is estimated to comprise approximately 35% of primary cutaneous B-cell lymphomas, second only to follicular lymphoma.

- Etiology

The etiology of most pcMZL remains unclear. Several authors have proposed the existence of a skin associated lymphoid tissue (SALT) that with persistent antigenic stimulation may give rise to neoplastic proliferations of marginal zone B cells. Similar to the H. Pylori story for gastric MALToma, in Europe, *Borrelia burgdorferi* has been proposed as an etiological agent in the development of pcMZL. A few case reports even describe resolution of lesions following antibiotic therapy. Interestingly, no association between borrelia and pcMZL has been identified in reports from the United States and Asia. Other settings in which pcMZL have been described include tattoo, vaccination site, and insect bite (not related to tick borne illness).

- Clinical features

pcMZL usually presents as a solitary deep red or violaceous infiltrated nodule, usually on the upper arm or trunk. Occasionally tumors are multiple, or present as a confluent plaque of erythematous papules. Patients with pcMZL do not have B symptoms and have normal serum levels of LDH and β_2 microglobulins. A rare association of pcMZL is Waldenstrom macroglobulinemia with resulting hyperviscosity syndrome; serum protein electrophoresis is a reasonable part of the laboratory evaluation of patients with extranodal MZL.

- Morphology

The histologic features of pcMZL, as in other sites, include reactive germinal centers with a proliferation of marginal zone cells with sheets of interfollicular plasma cells, and surrounding reactive T lymphocytes, with or without lymphoepithelial lesions. The mid-dermal and occasionally subcutaneous proliferation of marginal zone B cells surround reactive germinal centers and occasionally fill the interfollicular dermis. The neoplastic B cells are centrocyte-like cells with small-cleaved nuclei and amphophilic cytoplasm. The foci with plasmacytic differentiation may contain plasma cells with intranuclear pseudo-inclusions of immunoglobulin, termed Dutcher bodies. Follicular colonization, e.g. the infiltration of reactive lymphoid follicles by neoplastic B cells, may be present. Invariably there is a reactive T-cell infiltrate admixed among the neoplastic B cells. The T-cell infiltrate may be sparse or extremely dense; in some cases the T cells out-number the neoplastic B cells.

Marginal zone lymphomas that arise at other sites characteristically display infiltration of glandular epithelium termed "lymphoepithelial lesions". This finding is less commonly observed in pcMZL and when present is observed in the epithelium of the hair follicles. The

epidermis is usually free of lymphocytes and is separated from the underlying dermal tumor by a grenz zone of uninvolved papillary dermis.

- Immunophenotype

In cases with plasmacytic differentiation, light chain restriction is identified in 70%. The plasma cells express CD138 and CD79a but not CD20. The neoplastic marginal zone cells usually have a CD20+, CD79a+, CD22+, CD5-, CD10-, CD23-, bcl-6- immunophenotype. Scattered rare large CD30+ activated T lymphocytes have also been reported in some cases of pcMZL.

Notably, the staining pattern when B and T cell stains are compared is deceptively benign with central zones of B cells and surrounding T cells. In cases with colonized follicles the bcl6⁻ bcl2+, CD10- neoplastic cells are observed admixed with bcl6+, bcl2+, CD10+ follicle center cells sometimes with splayed or dispersed CD21+ follicular dendritic cell meshworks.

- Genetics

Clonal rearrangement of immunoglobulin heavy chain genes has been detected using PCR based techniques in 70% of pcMZL. Bcl-2 protein expression is commonly observed in pcMZL. A proportion of pcMZL have displayed the presence of t(14:18)(q32;q21) involving the IGH gene on chromosome 14 and the MLT gene on chromosome 18.

- Clinical course

MZL is defined as a primary cutaneous tumor only when staging, including thoracoabdominal CT scan and bone marrow biopsy studies, has not revealed extracutaneous disease for 6 months after the diagnosis of the cutaneous lymphoma. pcMZL are usually clinically indolent, however, up to 30% of patients diagnosed with pcMZL will experience extracutaneous relapse, most commonly in other extranodal sites including breast, salivary glands and orbit. This clinical behavior is similar to marginal zone lymphoma reported at other sites and is associated with an excellent prognosis. Although rare, transformation to large cell lymphoma has been reported and may be lethal.

Patients with pcMZL have been effectively treated with election beam irradiation, radiotherapy, intralesional interferon alpha, chroambucil and/or local injection of steroids. Patients with disseminated disease receive more aggressive treatment including rituximab and combination chemotherapy.

- Differential Diagnosis

The differential diagnosis of pcMZL always includes cutaneous lymphoid hyperplasia (CLH) and primary cutaneous follicle center lymphoma (pcFCL). Cutaneous lymphoid hyperplasia (CLH) is a benign reactive proliferation in the skin that probably arises secondary to continued antigenic stimulation (e.g. arthropod bite, autoimmune disease, drugs, tattoos, or infectious agents). Synonyms for CLH include pseudolymphoma, lymphocytoma cutis, lymphadenosis benigna cutis, pseudolymphoma of Speigler-Fendt, and lymphadenoma granulosa. Because of overlap in the clinical presentation and histological features, it is likely that cutaneous low-grade B-cell lymphomas were diagnosed as CLH in past decades.

Clinically, CLH and pcMZL affect females more often than males, and present with single or multiple, slow-growing cutaneous nodules on the face, arms, or trunk. Both entities are characterized by a dermal lymphocytic infiltrate, a grenz zone, reactive follicles, and admixed inflammatory cells (Table 3). Marginal zone cells and confluent sheets or zones of plasma cells in the interfollicular regions and around the superficial vascular plexus support a diagnosis of pcMZL. In contrast, epidermal atrophy or hyperplasia, exocytosis, spongiosis, or hyperkeratosis, are seen in the majority of cases of CLH, and only rarely in pcMZL. The more common occurrence of epidermal changes in CLH may be the result of an ongoing local inflammatory response to external antigen. Recognition of pcMZL and the finding that reactive lymphoid

follicles are more commonly observed in pcMZL than CLH has led to a revision of the historical dictum that the presence of lymphoid follicles favors a benign diagnosis. In cases with inconspicuous follicles on hematoxylin-eosin stain, stains for bcl-2 and CD21 are useful in identifying focal non-staining areas and aggregates of follicular dendritic cells, respectively. The presence of a bottom-heavy infiltrate, although traditionally thought to favor a diagnosis of lymphoma is not diagnostic. A superficial dermal or "top-heavy" infiltrate may be observed in cutaneous B-cell lymphomas, whereas hypersensitivity reactions to injected antigens and lymphomatoid drug reactions may both show deep dermal, bottom-heavy, lymphoid infiltrates. While the presence of a grenz zone, eosinophils, or neutrophils, are not statistically significant distinguishing features, aggregates of eosinophils or abundant neutrophils with nuclear dust should lead one to carefully consider a diagnosis other than pcMZL.

PCR detects clonal rearrangement of immunoglobulin heavy chain genes in only 30 – 50% of B-cell lymphomas. More often, Immunohistochemistry demonstrates monotypic cytoplasmic expression of light chains by plasma cells in pcMZL. An infiltrate of $\geq 75\%$ B cells and co-expression of CD43 and CD20 also support a diagnosis of B-cell lymphoma.

In pcMZL the proliferation of marginal zone B cells may be minimal and inconspicuous; it is possible that the cases reported by others as reactive lymphoid hyperplasia with monotypic plasma cells represent cutaneous marginal zone lymphomas with inconspicuous marginal zone B cells.

There is also considerable overlap in the histological appearance of pcFCL and pcMZL. A predominantly nodular or follicular pattern is observed in most pcFCL, and the presence of diffuse areas is present in all pcMZL. However, pcFCL may be entirely diffuse or display diffuse areas, and the majority of pcMZL have at least a partially nodular pattern. A predominance of small cells with irregular, somewhat cleaved nuclei characterizes both tumors. Moreover, anti-CD21 immunostaining highlights follicular dendritic cell meshworks, indicating true follicular structures in both pcFCL and pcMZL.

A combination of immunostaining for bcl-6, CD10 and bcl-2, yields distinct patterns of staining in the follicular and extra-follicular regions of FL and MZL. Distinguishing neoplastic follicles of FL from reactive or colonized follicles of pcMZL may be difficult because bcl-6 and CD10 are expressed by both reactive and neoplastic follicles, and bcl-2 is not expressed in all neoplastic follicles of pcFCL. In cases of pcMZL with colonized follicles, bcl-6, CD10, bcl-2 and CD21 may allow the distinction of expanded or colonized meshworks of follicular dendritic cells from neoplastic follicles. The colonized follicles, which typically correspond to nodular areas on H&E sections, display tight, nodular aggregates of CD21+ follicular dendritic cells, similar to neoplastic follicles or reactive germinal centers, but contain distinct clusters of bcl-6-, bcl-2+ neoplastic B cells, in addition to clusters of bcl-6+, bcl-2- germinal center cells. The other pattern observed in pcMZL is that of expanded, colonized meshworks of follicular dendritic cells corresponding to areas that appear diffuse or only vaguely nodular on routine sections with only scattered bcl-6+ cells; most cells are bcl-6-. It remains unclear whether the bcl-6+ cells in the dispersed dendritic cell meshworks of pcMZL represent residual follicle center cells or blast transformation. Neoplastic follicles in pcFCL, on the other hand, contain a uniform population of neoplastic bcl-6+ cells, and in those cases expressing bcl-2, it is also uniformly expressed by cells within the follicles. In contrast to pcFCL, bcl-6+ and CD10+ cells are never seen in interfollicular and diffuse areas devoid of CD21+ cells in pcMZL.

Primary cutaneous follicle center lymphoma (pcFCL)

WHO/EORTC: Primary cutaneous follicle center lymphoma*

WHO Classification: Follicular lymphoma

REAL Classification: Follicle center lymphoma

* These tumors may have a follicular, follicular and diffuse, or diffuse growth pattern.

Primary cutaneous follicle center lymphoma (pcFCL) is likely the most common B-cell lymphoma to occur as a primary lymphoma of the skin. This tumor is characterized by the proliferation of a mixture of centrocytes and centroblasts often in a follicular pattern. Rarely, pcFCL displays diffuse areas or, even less commonly, an entirely diffuse pattern.

- Epidemiology

pcFCL is a tumor of adults with a median age of 65 years, affecting slightly more men than women. pcFCL are most commonly located in the head and neck region and occasionally present on the trunk, or other cutaneous site.

- Clinical features

Follicular lymphoma presents as solitary or grouped erythematous cutaneous papules, nodules or plaques. Tumors on the back may be associated with indurated plaques (so-called historically 'reticulohistiocytoma of the dorsum' or 'Crosti's lymphoma').

- Morphology

pcFCL is characterized by a mid-dermal and subcuticular admixed proliferation of centrocytes and centroblasts in either a follicular, follicular and diffuse, or diffuse pattern. Usually the centrocytes are more plentiful than the centroblasts and there is an admixed benign T-cell infiltrate of variable density. The centrocytes have small cleaved nuclei with inconspicuous nucleoli, or large cleaved nuclei with scant cytoplasm. Large centrocytes are generally more plentiful in diffuse pcFCL. Centroblasts have large round nuclei with peripherally located basophilic nucleoli and a rim with basophilic or amphophilic cytoplasm. Although centroblasts may be present they do not form confluent sheets in pcFCL.

This neoplasm often appears as expanded, irregularly shaped, lymphoid follicles in the dermis. Occasionally, the neoplastic cells appear to spill-out of the follicles and surround aggregates of benign small lymphocytes, termed "inside-out follicles" by some observers. Sclerosis, manifest as an increase in fibrous tissue within the tumor, may also be observed.

- Grading

Although grading is usually not reported with pcFCL, for comparison's sake, pcFCL is on a morphological continuum up to FL grade 3b and diffuse FL grade 3a. In this way, the cutaneous classification of pcFCL and pcDLBCL is site specific, in as much as a grade 3 follicular lymphoma would be termed large B-cell lymphoma in a lymph node.

- Immunophenotype

Immunohistochemical stains for kappa and lambda light chains reveal light chain restriction of the neoplastic centrocytes and centroblasts and a CD20+, CD79a+, CD10^{+/-}, CD5⁻, CD43⁻, bcl-6+ immunophenotype. Diffuse pcFCL more often have a CD10- immunophenotype. In contrast to nodal follicular lymphomas, which are almost all bcl-2+, fewer than 30% of pcFCL have been reported to express the bcl-2 protein. Because bcl-2 protein is normally present on most T cells and B cells, except for the B cells in reactive follicle centers, and because the neoplastic cells in pcFCL are often bcl-2 negative, a negative bcl-2 staining pattern of follicles with the remaining lymphocytes staining positively for bcl-2 does not allow for distinction between a reactive and neoplastic process in the skin. Staining for MUM-1/IRF4 is negative.

In reactive B cells, expression of the bcl-6 transcription factor and of the membrane metalloproteinase CD10 is restricted to germinal center cells. Among nodal small B-cell neoplasms, anti-bcl-6 and anti-CD10 have been shown to react exclusively with follicular lymphomas. The non-lymphoid CD21+, CD35+ follicular dendritic cells have elongated processes, and form nodular meshworks within germinal centers. In addition to their function in B-cell maturation following exposure to antigen, follicular dendritic cell meshworks are helpful in defining the presence of lymphoid follicles.

- Genetics

Primary cutaneous follicle center lymphomas have the gene expression profile of germinal center-like large B-cell lymphomas. pcFCL typically does not have the association of t(14;18) observed in nodal follicular lymphoma. Faint bcl-2 expression and/or the t(14;18) translocation has been reported in a minority of pcFCL. PCR techniques detect clonal rearrangement of immunoglobulin genes in only 50% of cases.

- Clinical course

PcFCL rarely spread to lymph nodes, spleen or bone marrow, unlike the majority of nodal follicular lymphoma. The estimated 5 year survival for patients with pcFCL is > 97%. Excision and radiation therapy is effective for localized lesions, disseminated disease may be treated with anthracycline-based chemotherapy. Systemic or intralesional rituximab may also be effective. Therapy is not linked to grade in contrast to extracutaneous follicular lymphoma. In tumors with a follicular growth pattern the presence or absence of bcl-2 protein is not associated with a difference in clinical presentation or behavior.

- Differential Diagnosis

From a histological viewpoint, when pcFCL has a prominently follicular architecture, the differential diagnosis includes pcMZL and cutaneous lymphoid hyperplasia. Whereas, when pcFCL has a diffuse pattern of growth the differential diagnosis includes pcDLBCL.

Both pcMZL and pcFCL are predominantly localized to the head, trunk or upper extremities both tend to be localized to the skin at diagnosis and to have a low risk of dissemination to lymph nodes or bone marrow.

pcFCL and pcMZL also have overlapping morphologic features. pcFCL typically has a partially follicular pattern. pcMZL typically contains reactive or colonized follicles, and thus B-cell follicles can be found in both lymphomas. Factors that create difficulties in distinguishing the neoplastic follicles in pcFCL from the reactive follicles in pcMZL include the lack of bcl-2 protein expression and BCL-2 gene rearrangement in the majority of pcFCL and the occasional presence follicular colonization in pcMZL.

Immunostaining for CD21, bcl-6, CD10 and bcl-2 often yields distinct patterns of staining in pcFCL and pcMZL. In both follicular and interfollicular/diffuse areas of pcFCL the neoplastic cells are bcl-6+, CD10+ and occasionally bcl-2+. In pcMZL, the neoplastic B cells are bcl-6-, CD10-, and bcl-2+. Three patterns of CD21+ follicles may be identified in pcMZL: 1. reactive germinal centers: uniformly bcl-6+, CD10+, bcl-2-; 2. colonized follicles: both bcl-6-, bcl-2+, CD20+ cells and bcl-6+, bcl-2- cells; 3. expanded or colonized follicular dendritic cell meshworks: bcl-6-, bcl-2+ B cells with rare residual bcl-6+, bcl-2- cells.

The presence of a CD21 follicular dendritic cell meshwork containing two immunophenotypically distinct populations of B cells (bcl6+, CD10+, CD5-, bcl-2+/- follicle center cells and bcl6-, CD10-, CD5-, bcl-2+ neoplastic marginal zone cells) supports the presence of colonized follicles in pcMZL. Whereas, expanded irregularly shaped aggregates of bcl-6+, CD10+ B cells are supportive of the diagnosis of follicular lymphoma.

In summary, the immunophenotype of pcFCL is distinct from that of pcMZL and consistent with a germinal center-derived tumor. Its unique clinical behavior may reflect a derivation from extranodal B-cell follicles rather than nodal lymphoid follicles in lymph nodes.

In addition to the difficulty in distinguishing pcFCL from pcMZL, there is also overlap in some features between follicle center lymphoma and large B-cell lymphoma (Table 4). For the purposes of this presentation, pcFCL is defined as a neoplastic proliferation of large and small centrocytes and centroblasts usually with a bcl-6+, CD10+ immunophenotype, supported by a meshwork of CD21+ follicular dendritic cells. Although usually displaying a follicular growth pattern, occasionally pcFCL may diffusely efface the dermis. A bcl-2⁻, MUM-1⁻ immunophenotype in diffuse cases supports the diagnosis of pcFCL. Tumors that are composed of a uniform proliferation of centroblasts are designated as large B-cell lymphoma and are discussed later. Notably this definition excludes diffuse large B-cell lymphoma whether occurring on the lower extremity or other cutaneous sites.

Primary cutaneous, diffuse large B-cell lymphoma of the leg

WHO/EORTC Classification (2004): Primary cutaneous diffuse large B-cell lymphoma, leg type.

WHO Classification: Large B-cell lymphoma

REAL Classification: Diffuse large B-cell lymphoma

Primary cutaneous diffuse large B-cell lymphoma (pcDLBCL) is defined morphologically as a dense, often diffuse, proliferation of confluent sheets of large transformed B cells resembling centroblasts and immunoblasts, with effacement of the dermis and the absence of lymphoid follicles (Table 5).

When presenting on the leg, these tumors are categorized as a distinct diagnostic entity (pcDLBCL, of the leg) because of the associated increased risk of recurrence and dissemination. Other defined variants of diffuse large B-cell lymphoma that occur in the skin include T-cell rich B-cell lymphoma, pcDLBCL of sites other than the leg (pcDLBCL, other), and intravascular B-cell lymphoma (pcDLBCL, intravascular).

- **Epidemiology**

Diffuse large B-cell lymphoma more commonly involves the lower extremities of women than men and occurs late in life with more than 80% of tumors occurring in patients older than 70 years.

- **Clinical features**

pcDLBCL of the leg presents as erythematous or violaceous nodules on one or both lower legs, often with ulceration. These tumors more often disseminate to non-cutaneous sites than pcDLBCL of non-leg type.

- **Morphology**

The dermis is diffusely infiltrated by a proliferation of mostly round, monomorphic large transformed B cells with prominent nucleoli and clumped chromatin, resembling centroblasts and immunoblasts. Epidermotropism is absent, however in ulcerated cases, the tumor cells may

extend to the dermal epidermal junction. Although the growth pattern is diffuse, some cases have an overall multi-nodular appearance at scanning magnification. There is variation in the proportion of centroblast-like and immunoblast-like cells in large B-cell lymphoma and recently the density of large B cells with round cell morphology has been reported to be of prognostic significance.

- Grading

B-cell lymphomas of the skin are characteristically not reported with a grade. For comparison's sake though, the pcDLBCL are comparable to diffuse grade 3b nodal LBCL.

- Immunophenotype

Monotypic surface immunoglobulin is identified along with a CD19+, CD20+, CD22+, CD79a+, bcl-2+/-, bcl6 +/-, CD10-/-, CD5-/-, CD138- immunophenotype. The intensity of bcl-2 stain may exceed that of the non-neoplastic T cells. The MIB-1/Ki-67+ fraction is high, ranging from 60 to 95%. Whether arising on the leg or other sites, these tumors have been demonstrated to occasionally express both bcl-6 and MUM1/IRF4 (multiple myeloma 1/ interferon regulatory factor 4) proteins. In this series the tumors did not have associated CD21+ follicular dendritic cells.

- Genetics

Immunoglobulin genes have detectable clonal rearrangements and t(14:18) is usually absent although bcl-2 protein expression is often strong. Translocation involving myc, bcl-6 and IgH genes have been reported.

- Clinical course

Irradiation is the most effective therapy for localized tumors, anthracycline-based chemotherapy is used to treat disseminated disease. pcDLBCL of the leg is the form of cutaneous B-cell lymphoma that is associated with the worst prognosis. In the following description of the clinical behavior reported for these tumors one should bear in mind that like other forms of cutaneous lymphoma, pcDLBCL has a more favorable overall prognosis than does large B-cell lymphoma arising in lymph nodes. Grange et al. reported the five-year disease-specific survival rate for DLBCL of the leg as 50% in 2001. An increased risk of recurrence and a reduced survival is associated with multiple tumors at presentation, location on the leg, and bcl-2 expression.

Primary cutaneous, diffuse large B-cell lymphoma, other type

WHO/EORTC Classification: Primary cutaneous diffuse large B-cell lymphoma, other.

WHO Classification: Large B-cell lymphoma

REAL Classification: Diffuse large B-cell lymphoma

Variants of pcDLBCL also include tumors composed of confluent sheets of large B cells with intense staining for bcl-2 protein occurring at sites other than the leg (pcDLBCL, other). In addition, tumors comprised purely of centroblasts or immunoblasts, which weakly express bcl-2 protein are included in this category (pcDLBCL, other). These rare cases of large B-cell lymphoma arising in the skin do not belong to the leg type group of DLBCL or the group of pcFCL.

Included in the group of diffuse large B-cell lymphoma, other is intravascular large B-cell lymphoma (pcDLBCL, intravascular). This tumor is characterized by a dermal intravascular accumulation of large neoplastic B cells that express monotypic immunoglobulin and pan-B-cell antigens (CD19+, CD20+, CD22+, CD79a+). The tumors appear as violaceous plaques on the trunk and lower extremities, and may disseminate to involve extracutaneous sites. CNS involvement is not infrequently observed and is associated with a poor outcome. Patients with

this disease have a poor prognosis with less than 50% survival at 5 years. Treatment is with combination chemotherapy.

Another rare histological variant of cutaneous diffuse large B-cell lymphoma is T-cell rich B-cell lymphoma. In these tumors there is a dominant reactive infiltrate of T cells with large neoplastic B cells comprising < 15% of infiltrate.

Table 1. General Features of Primary Cutaneous B-cell Lymphoma

Clinical	- significant similarity in cutaneous morphology between sub-types
Histological	- epidermotropism absent, minimal if any epidermal changes - grenz zone present - often with lymphoid follicles
Immunophenotype classification is linked to phenotype in most tumors	MZL: CD10 ⁺ , CD5 ⁻ , CD10 ⁻ , bcl-2 ⁺ , bcl-6 ⁻ FCL: CD20 ⁺ , CD5 ⁻ , CD10 ⁺ , bcl-2 ^{+/-} , bcl-6 ⁺ DLBCL, leg : CD20 ⁺ , CD5 ⁻ , CD10 ^{-/+} , bcl-2 ⁺ , bcl-6 ^{-/+}
Also helpful:	- CD21+ follicular architecture may be distinctive - Light chain restricted plasma cells in 70% of MZL - Co-expression of CD20 and CD43 favor CBCL - 75% B cells supports the diagnosis of CBCL
Gene rearrangements	Ig gene rearrangement detected in only 50% of CBCL False positives exceedingly rare
Treatment	Treatment most dependent on tumor location and number of lesions.

Table 2. WHO/EORTC schema for primary cutaneous follicle center lymphoma (pcFCL) and diffuse large B-cell lymphoma of the leg (pcDLBCL of the leg)

Diagnosis	pc FCL	pcDLBCL of the leg
Morphology	<p>Predominance of centrocytes that are often large, especially in diffuse lesions</p> <p>Centroblasts may be present, but not in confluent sheets</p> <p>Pattern may be follicular, follicular and diffuse, or diffuse (a continuum without distinct categories or grades)</p> <p>Sclerosis may be present</p>	<p>Predominance of large to medium sized B cells with round nuclei, prominent nucleoli, and coarse chromatic, cells may resemble centroblasts and immunoblasts</p> <p>Diffuse growth pattern</p> <p>Little stromal reaction, confluent destructive growth pattern</p>
Phenotype	<p>Bcl-2: -/+ Staining is weak, when present</p> <p>Bcl-6: +/-</p> <p>CD10: +/- Diffuse lesions more often CD10⁻</p> <p>MUM-1: -/+ usually negative</p>	<p>Bcl-2: ++ Staining is typically strong and in most neoplastic cells</p> <p>Bcl 6: +/-</p> <p>CD10: -/+ Usually negative</p> <p>MUM-1: +/- usually positive</p>
Clinical features	<p>Middle aged adults</p> <p>Most cases localized lesions on the head or trunk</p> <p>Tumor nodules, sometimes with satellite lesions</p> <p>Rarely multifocal lesions</p>	<p>More commonly in elderly, especially females</p> <p>Lesions localized on the leg, most often below the knee</p>

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