Primary Cutaneous B-Cell Lymphomas

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19.1 Introduction and Epidemiology

Cutaneous lymphomas (CL) are a heterogeneous group of neoplasias that are characterized by an accumulation of mononuclear, mostly lymphocytic cells in the skin (Burg et al. 2006). Cutaneous lymphomas are the second most prevalent extranodal non-Hodgkin lymphomas (after gastrointestinal), representing approximately 19 % of extranodal non-Hodgkin lymphomas. Primary cutaneous B-cell lymphomas represent less than one third of cutaneous lymphomas (Willemze et al. 2005; Bradford et al. 2009). Distinguishing between low-grade CBCL and reactive B-cell pseudolymphomas can be quite difficult; even clonality studies cannot with certainty separate the two entities (Dummer et al. 2008).

The World Health Organization-European Organization for Research and Treatment of Cancer (WHO-EORTC) has categorized primary cutaneous B-cell lymphomas to three

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main subtypes: primary cutaneous follicle center lymphoma(PCFCL), primary cutaneous marginal zone lymphoma(PCMZL), and primary cutaneous diffuse large B-cell lymphoma (DLBCL) ("leg type" and "others") (Willemze et al. 2005). The relevance to distinguish these subtypes is in the different treatment options as well as different prognosis (Dummer et al. 2007). MZL and PCFCL are characterized as indolent disease with 99–95 % 5-year survival in comparison to DLBCL, leg type that has a more aggressive nature and less than a 50 % 5-year survival (Senff et al. 2007). The diagnosis of primary cutaneous B-cell lymphoma is only established when the complete staging is negative after the initial clinical and histopathological diagnosis.

19.2 Staging

The Ann Arbor system, first introduced as a staging system for Hodgkin disease in 1971, is the most widely used staging system for lymphoma. However, the Ann Arbor system has limited prognostic value when evaluating patients with extranodal lymphomas such as the cutaneous lymphomas (Rosenberg 1977). Therefore, in 2007, the International Society for Cutaneous Lymphoma and European Organization of Research and Treatment of Cancer (ISCL/EORTC) proposed anatomical classification of primary cutaneous lymphoma other than Mycosis fungoides (MF) and Sézary syndrome (SS) for documentation of disease extent and not necessarily as a prognostic guide (Table 19.1, Kim et al. 2007). ISCL/EORTC recommends complete staging at the time of initial diagnosis including a thorough history and physical exam; laboratory studies including complete blood count, comprehensive blood chemistry, and lactate dehydrogenase(LDH) level; and obtaining appropriate images (CT or PET-CT) of at least the chest, abdomen, and pelvis. Bone marrow biopsy is not needed in indolent CBCL (i.e., PCMZL) but is required in clinically intermediate to aggressive cutaneous B-cell lymphoma (Kim et al. 2007).

Table 19.1 ISCL/EORTC proposal on TNM classification of cutaneous lymphoma other than MF/SS (Kim et al. 2007)

T
T1: Solitary skin involvement
T1a: A solitary lesion <5 cm diameter
T1b: A solitary >5 cm diameter
T2: Regional skin involvement: multiple lesions limited to one body region or two contiguous body regions*
T2a: All-disease encompassing in a <15-cm-diameter circular area
T2b: All-disease encompassing in a >15- and <30-cm-diameter circular area
T2c: All-disease encompassing in a >30-cm-diameter circular area
T3: Generalized skin involvement
T3a: Multiple lesions involving two noncontiguous body regions
T3b: Multiple lesions involving >3 body regions
N
N0: No clinical or pathologic lymph node involvement
N1: Involvement of one peripheral lymph node region† that drains an area of current or prior skin involvement
N2: Involvement of two or more peripheral lymph node regions† or involvement of any lymph node region that does not drain an area of current or prior skin involvement
N3: Involvement of central lymph nodes
M
M0: No evidence of extracutaneous non-lymph node disease
M1: Extracutaneous non-lymph node disease present

*Definition of body regions (see Fig. 19.1): Head and neck: inferior border—superior border of clavicles, T1 spinous process. Chest: superior border—superior border of clavicles; inferior border—inferior margin of rib cage; lateral borders—midaxillary lines, glenohumeral joints (inclusive of axillae). Abdomen/genital: superior border—inferior margin of rib cage; inferior border—inguinal folds, anterior perineum; lateral borders—mid-axillary lines. Upper back: superior border—T1 spinous process; inferior border—inferior margin of rib cage; lateral borders—mid-axillary lines. Lower back/buttocks: superior border—inferior margin of rib cage; inferior border—inferior gluteal fold, anterior perineum (inclusive of perineum); lateral borders—midaxillary lines. Each upper arm: superior borders—glenohumeral joints (exclusive of axillae); inferior borders—ulnar/radial-humeral (elbow) joint. Each lower arm/hand: superior borders—ulnar/radial-humeral (elbow) joint. Each upper leg (thigh): superior borders—inguinal folds, inferior gluteal folds; inferior borders—mid-patellae, midpopliteal fossae. Each lower leg/foot: superior borders—mid-patellae, mid-popliteal fossae

†Definition of lymph node regions is consistent with the Ann Arbor system: Peripheral sites: antecubital, cervical, supraclavicular, axillary, inguinal-femoral, and popliteal. Central sites: mediastinal, pulmonary hilar, paraortic, iliac

19.3 Definitions and Clinical Features

19.3.1 Primary Cutaneous Marginal Zone Lymphomas (PCMZL)

Primary cutaneous marginal zone lymphomas of MALT type (PCMZL), previously known as primary cutaneous immunocytomas, comprises 24 % of all primary cutaneous B-cell lymphomas (Senff et al. 2007). They present as single or multiple lesions, with multifocal lesions being more common (72 %) (Hoefnagel et al. 2005a). MZL affects most commonly adults between third and fifth decade of life with a male to female ratio of 2.1. MZL presents as red to violaceous infiltrated cutaneous and subcutaneous plaques or multifocal nodules with a diameter of less than 2 cm (Golling et al. 2008). Over half of patients (55 %) have lesions on the trunk with upper and lower extremities being involved in 37 and 27 % of patients, respectively. The head and neck are involved in 14 % of patients. The tumors display slow growth and usually do not ulcerate. Biopsies should be deep in order to reflect the extent of the infiltrate. In Europe there have been cases of CMZL associated with Borrelia burgdorferi infection (Hoefnagel et al. 2005a; Aberer et al. 2011). An association of primary cutaneous MALT lymphomas with infectious etiologies (similar to *H. pylori* and gastric MALT lymphomas) has been postulated for many years, and *Borrelia burgdorferi* has been suggested and found in a fraction of cases in some series; however, recent reports are contradictory (Cerroni et al. 1997; Goodlad et al. 2000a; Ponzoni et al. 2011; Wood et al. 2001). Although still debatable, it has been suggested that MZL is associated with chronic inflammatory process or infections (Zendri et al. 2005; May et al. 2005). *H pylori* infection is often found in MALT lymphomas of the gastric mucosa and intestine, and remission has been induced by treatment of the underlying infection. This may also hold true for a subset of patients with cutaneous B-cell lymphomas (Bogle et al. 2005).

19.3.2 Primary Cutaneous Follicle Center Lymphoma (PCFCL)

PCFCL is the most common type of primary cutaneous B-cell lymphomas, making up 57 % of cases in a recent large review. The median age at diagnosis is 58 years with a male/female ratio of 1.8 (Senff et al. 2007). It presents as an erythematous papule, plaque, or nodule most commonly located on the trunk or head/neck. Lesions may be single or multiple but are localized when multiple. It is only rarely seen on the upper (2.3 % of patients) or lower (6.4 % of patients) extremities. The latter is at times difficult to differentiate from DLBCL, LT.

19.3.3 Primary Cutaneous Diffuse Large B-Cell Lymphoma, Leg Type (PCDLBL-LT)

PCDLBCL-LT comprises approximately 20 % of primary cutaneous B-cell lymphomas and has several distinctive clinical features. Compared to the above two types, this lymphoma occurs in an older population (median age 78 years) and has a striking female predominance (M:F ratio of 0.5). As the name implies, it presents most commonly (88 % of patients) on the lower extremity. However, it can occur at other sites including the head/neck, trunk, and upper extremities in 5–12 % of patients (Willemze et al. 2005; Senff et al. 2007). Clinically it presents as a nodule, either singly or as multiple regional lesions. Multifocal disease is seen in 20 % of cases. Uncharacteristic to other cutaneous lymphomas, PCDLBCL-LT will often disseminate to nodal and visceral site, which likely portends a transition in its already aggressive behavior (Grange et al. 2007; Vermeer et al. 1996).

19.4 Pathology

PCMZL manifests as a mid-dermal lymphoid infiltrate that can extend into the superficial dermis and deep dermis/subcutis. As in other marginal zone lymphomas, reactive germinal centers are usually

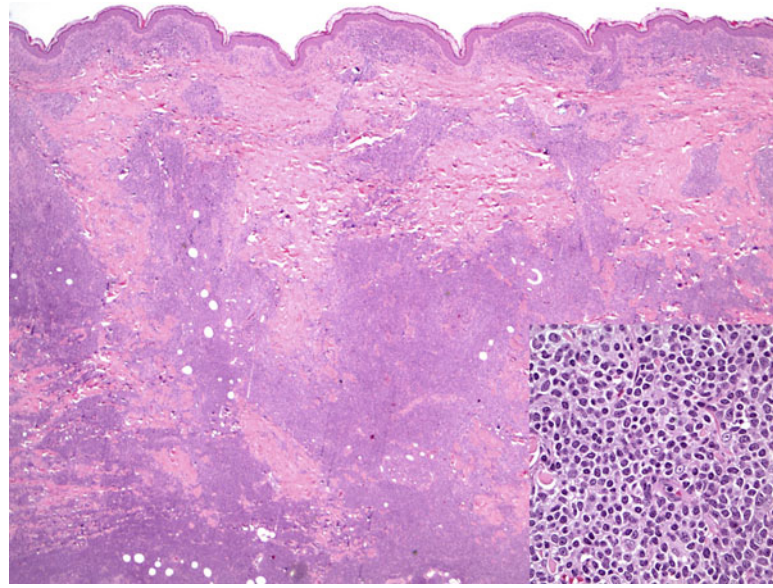

Fig. 19.1 Primary cutaneous marginal zone lymphoma. A dense lymphoid infiltrate is seen (hematoxylin and eosin, H&E, 20×). The inset shows the cytologic features of marginal zone cells (H&E 400×)

present but may become colonized and eventually obliterated. The cells are small with condensed chromatin, slight nuclear irregularities, and moderate-to-abundant amounts of pale cytoplasm. These marginal zone cells are often centered on the residual lymphoid follicles and expand into the surrounding dermis (Fig. 19.1). Admixed plasma cells may be present. These can represent plasmacytic differentiation of the lymphoma or an inflammatory component. Dutcher bodies, if present, would favor the former and investigation of the plasma cell component by immunohistochemistry or in situ hybridization for kappa and lambda immunoglobulin light chain expression is advisable. Although lymphoepithelial lesions (destructive infiltration of epithelium by clusters of lymphoma cells) are common in MALT-type lymphomas at sites such as stomach or salivary glands, they are not frequently seen in PCMZLs. When present they are usually seen in hair follicle epithelium. Some cases may have an extensive reactive, nonneoplastic lymphoid infiltrate and may be the type composed of class-switched PCMZL (Edinger et al. 2010). An eosinophilic infiltrate has been described in cases originating in Asia (Takino et al. 2008).

PCFCL has a heterogeneous appearance. The common features are a dense dermal lymphoid infiltrate of follicle center cells (varying proportions centrocytes and centroblasts). The architecture may be follicular, follicular and diffuse, or completely diffuse. Follicles may have attenuated or absent mantle zones, are not polarized, and lack tingible body macrophages. In diffuse examples that are composed of predominantly centroblastic cells, the histopathology may be that of a diffuse large B-cell lymphoma in other sites; however, the appropriate diagnosis given the anatomic site is still PCFCL (Fig. 19.2) (Cerroni and Kerl 2001a, b; Goodlad et al. 2002; Mirza et al. 2002). Thus, this lymphoma is defined more by the type of cells (follicle center cells) rather than architecture.

PCDLBL-LT shows a diffuse architecture and is entirely composed of large immunoblastic or centroblastic cells with round nuclear contours and variably prominent nucleoli (Fig. 19.3) (Vermeer et al. 1996). The dominant round cell morphology contrasts with PCFCL. Mitotic figures are easily found and characteristically there are few infiltrating small reactive lymphocytes.

19.5 Immunophenotype

The immunophenotype of PCMZL is CD19+, CD20+, CD5−, and CD10− with monotypic immunoglobulin light chains often demonstrable in paraffin sections (Fig. 19.4). The cells are often class switched (IgG, IgA, IgE), unlike other

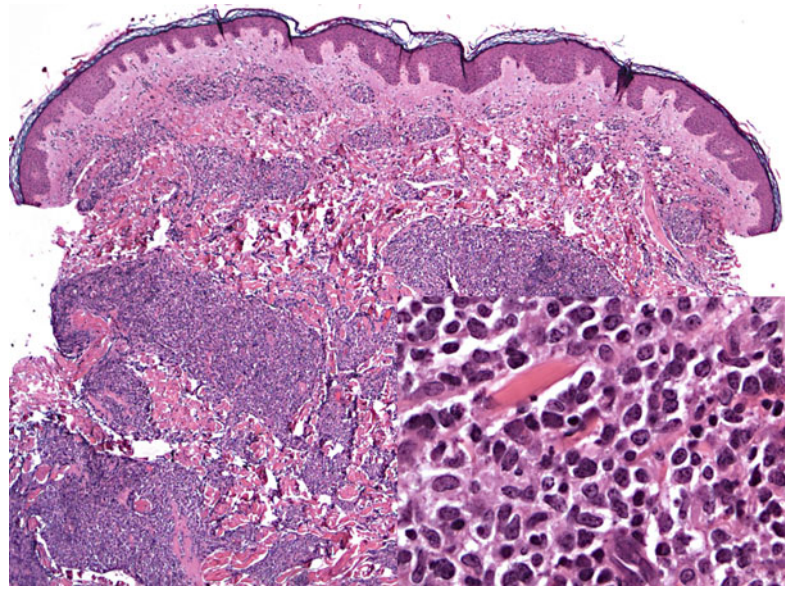

Fig. 19.2 Primary cutaneous follicle center lymphoma. A dense dermal lymphoid infiltrate is present (Fig. 19.2, H&E 400×) and is composed of follicle center-type cells (*Inset*, H&E 400×)

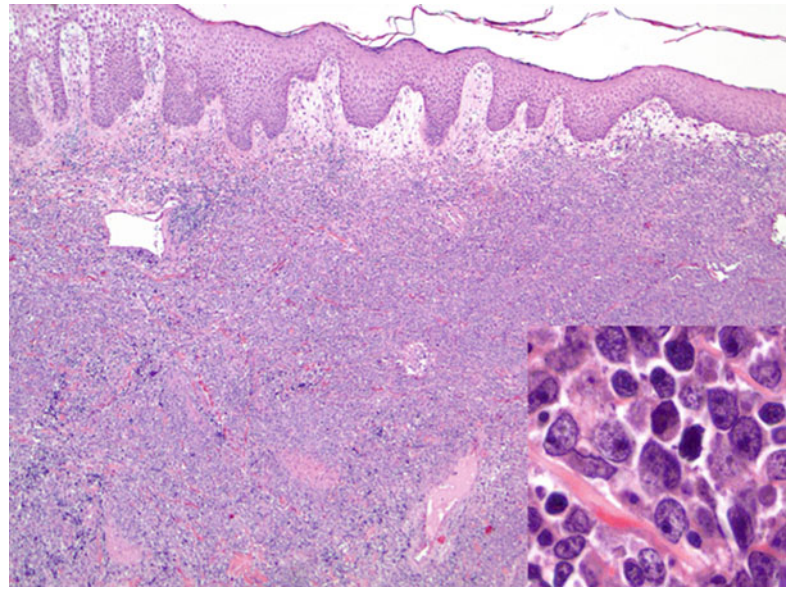

Fig. 19.3 Diffuse large B-cell lymphoma, leg type. A dense dermal lymphoid infiltrate is present and is composed of monotonous round large cells

types of extranodal marginal zone B-cell lymphomas. BCL2 is expressed in most cases (Edinger et al. 2010; Servitje et al. 2002; Cho-Vega et al. 2006). The characteristic presence of reactive follicles can be highlighted by a CD21 stain that marks follicular dendritic cells.

PCFCL expresses pan-B-cell markers CD19 and CD20 but also coexpresses BCL6. Other germinal center B-cell markers are also often expressed including CD10 and HGAL (Xie et al. 2008). Unlike nodal follicular lymphoma, in which BCL2 expression is a hallmark that reflects a t(14;18)(q32;q21), PCFCL is characteristically negative for BCL2 (Fig. 19.5). However, in examples that are follicular, especially when predominantly small cleaved cells, BCL2 is expressed in approximately 40 % of cases (Mirza et al. 2002; Xie et al. 2008).

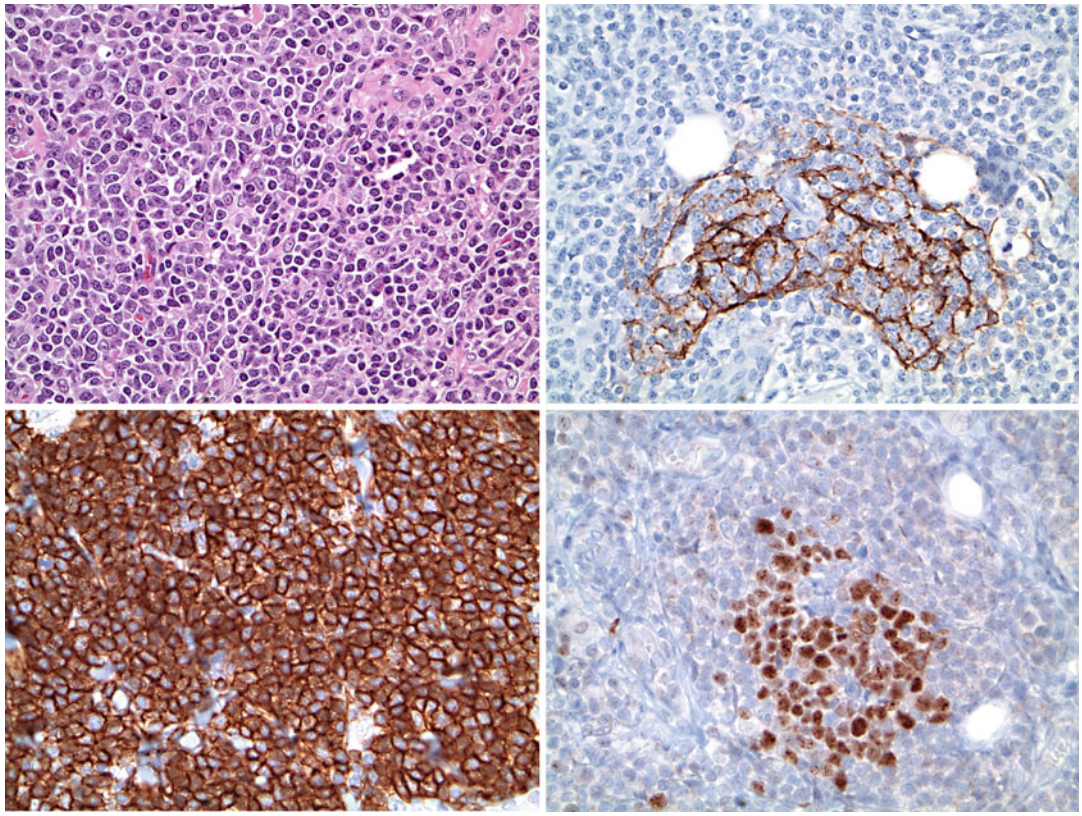

Fig. 19.4 Primary cutaneous marginal zone lymphoma. The *upper left panel* shows a remnant germinal center (*upper left*) with clusters of centroblastic cells. The marginal zone component extends into the surrounding dermis. A CD21 stain (*upper right*) showed one of many remnant follicular dendritic cell network. CD20 is expressed (*lower left*) and a BCL6 stain (*lower left*) shows that residual germinal center B cells are present but undergoing colonization by the neoplastic cells

PCDLBL-LT also expresses CD19 and CD20. Unlike PCFCL, expression of BCL2 is the rule and the post-germinal center B-cell maker MUM1 is usually expressed. BCL6 is expressed by most cases, but CD10 is not (Fig. 19.6) (Xie et al. 2008; Geelen et al. 1998; Grange et al. 2004; Hoefnagel et al. 2003; Sundram et al. 2005).

19.6 Molecular Genetics

Application of modern PCR-based methods for determining monoclonality in formalin-fixed tissue has greatly increased our ability to diagnose cutaneous lymphomas. At least 85 % of cases demonstrate monoclonality(Morales et al. 2008). However, since monoclonality can be seen rarely in reactive processes, interpretation in the context of histopathologic and immunophenotypic findings is essential (Morales et al. 2008; Fujiwara et al. 2013; Nihal et al. 2000). t(11;18)(q21;q21) involving *API2-MALT1* and t(3;14)(p14;q32) involving *FOXP1* and *IGH@* are seen in less than 10 % of cases. The t(14;18)(q32;q21) also involving *IGH@* and *MALT1* is present in less than 15 % of cases (Cho-Vega et al. 2006; Streubel et al. 2004). Molecular studies looking for a causative microorganism similar to *H. pylori* in gastric marginal zone lymphomas have raised the possibility of *Borrelia burgdorferi*; however, detection of this organism has not been consistent and a potential role has not been established (Ponzoni et al. 2011; Cho-Vega et al. 2006; Goodlad et al. 2000b; Roggero et al. 2000). The

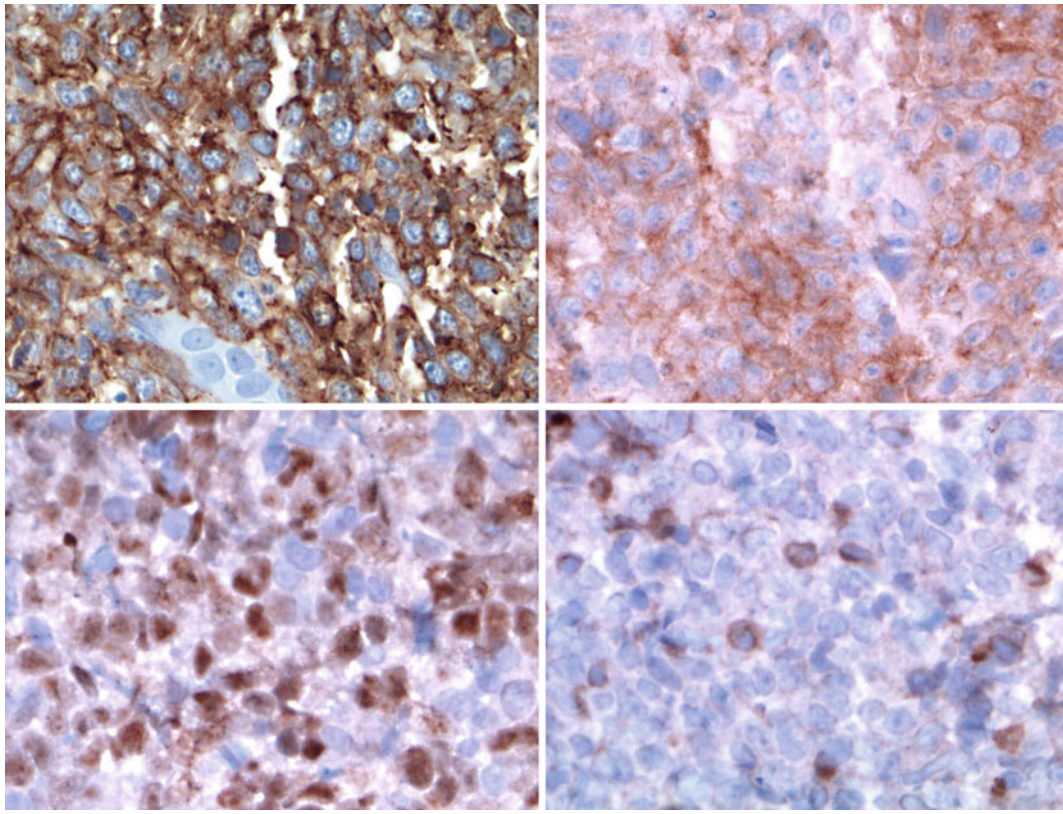

Fig. 19.5 Primary cutaneous follicle center lymphoma immunohistochemistry. The cells express CD20 (*upper left*), CD10 (*upper right*), and BCL6 (*lower left*) but are negative for BCL2 (*lower right*)

IGH@-BCL2 translocation typically seen in nodal follicular lymphoma can be seen in 0–40 % of cases of PCFCL with a follicular growth pattern (Mirza et al. 2002; Streubel et al. 2006; Cerroni et al. 2000). Variation may be related to technique (Streubel et al. 2006). Gene expression profiling studies have shown that the profile resembles germinal center-like diffuse large B-cell lymphomas (Hoefnagel et al. 2005b).

PCDLBL-LT lacks translocations seen in MALT-type lymphomas or follicular lymphoma. However, translocations of *BCL6, MYC*, and *IGH@* and amplification of BCL2 are commonly seen. Deletion in the region of cell cycle inhibitors *CDKN2A* and *CDK2NB* (chromosome 9p21.3) or promoter methylation is frequent and associated with poor outcome (Dijkman et al. 2006; Hallermann et al. 2004). Gene expression profiling shows a distinct profile from PCFCL and similarity to activated B-cell type of diffuse large B-cell lymphoma (Hoefnagel et al. 2005b).

19.7 Differential Diagnosis

The differential diagnosis of PCMZL is often a form of cutaneous lymphoid hyperplasia (CLH) that is B-cell rich due to the presence of reactive follicles. The follicles in CLH should contain preserved mantle zones and the overall immune architecture is preserved, with distinct B- and T-cell areas. Expansion of B cells with a marginal zone appearance away from follicles and demonstration of monotypic plasma cells or monoclonality by molecular methods strongly support lymphoma. As noted above, monoclonality by PCR-based methods can be seen in reactive conditions. In difficult cases, demonstration of the

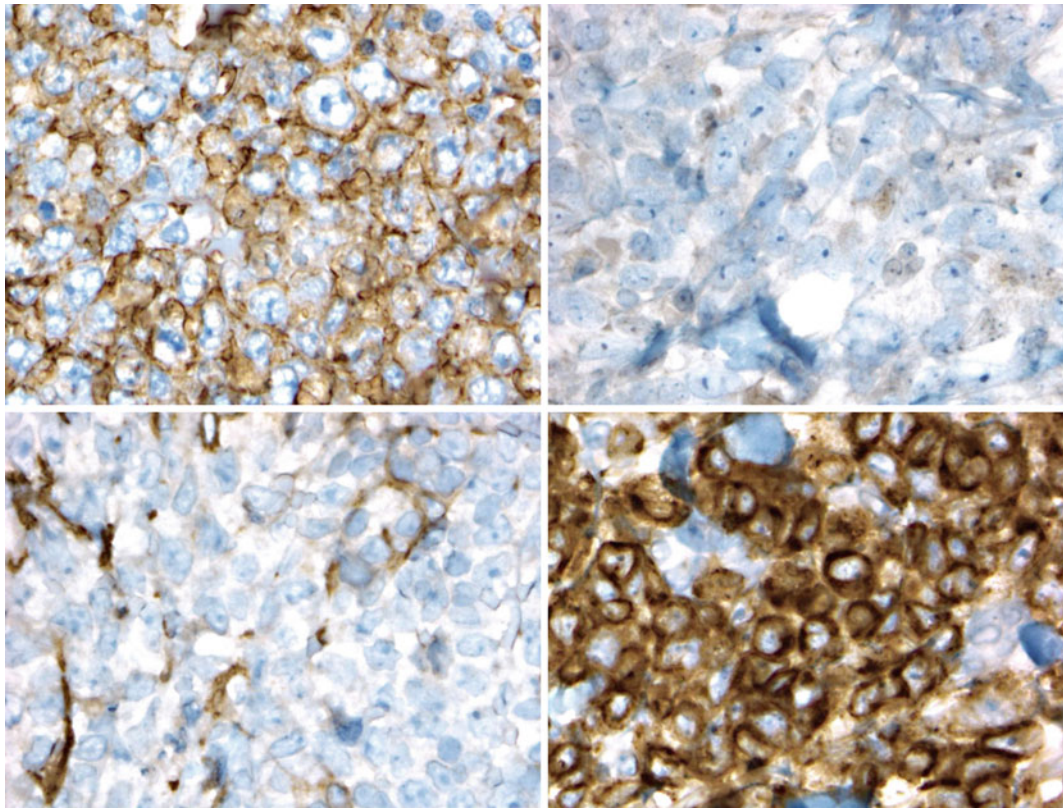

Fig. 19.6 Diffuse large B-cell lymphoma, leg type. Immunohistochemistry shows that the cells express CD20 (*upper left*) and BCL2 (*lower right*) but negative for BCL6 (*lower right*) and CD10

same clone in another lesion or subsequent lesion (identical clone separated in time or space) can help confirm a diagnosis of lymphoma. MZL is at times difficult to differentiate from pseudolymphomas, although increased general awareness between dermatologist and establishment of new markers have facilitated a more accurate diagnosis (Jenni et al. 2011). Skin manifestation of B-CLL can precede its systemic presentation by weeks to months (Cerroni et al. 1996); therefore, the appropriate diagnosis is important since the treatments are completely different. The detection of an immunoglobulin light chain restriction and immunohistochemical staining for CD5, CD23, and CD43 can be helpful in the differentiation of these two entities (Levin et al. 2012). The plasma cell-rich variants of MZL can resemble skin infiltrates by a plasma cell myeloma, but the latter entities can be recognized by adequate staging (Kempf et al. 2012).

PCFCL with a follicular pattern can be differentiated from cutaneous follicular hyperplasia by presence of monomorphous follicles, lack of polarization, and absence of tingible body macrophages in PCFCL. Diffuse forms of PCFCL are usually composed predominantly of large cells, and the diffuse infiltrative pattern of B cells makes CLH unlikely. Differentiation of a diffuse type of PCFCL composed of large cells from PCDLBCL-LT is done on clinical grounds (propensity for the leg of older women), morphology (sheets of centroblasts and immunoblasts), and immunophenotype (B cells that usually express MUM1 and BCL2).

Of course, clinical correlation and staging is required to confirm that the lymphomas represent primary cutaneous disease. It should be noted that bone marrow involvement can be found in up to 11 % of patients with follicle center lymphoma presenting in skin, arguing for routine bone marrow staging studies in these patients (Senff et al. 2008a).

19.8 Prognosis

The 5-year survival rate of 90–95 % for indolent cutaneous BCL is indicative of excellent prognosis. Although cutaneous relapses occur, dissemination to other organs is rare (Cerroni et al. 2000; Garcia et al. 1986).

PCDLBCL-LT is the most aggressive PCBCL and not surprisingly harbors the worst prognosis. The reported 5-year overall survival is approximately 50 % (Senff et al. 2007). Grange et al. attempted to identify characteristics of PCDLBCL-LT that may denote a more aggressive clinical course. They reported the presence of multiple skin lesions and location of the lesion on the leg as the two features with the most negative prognostic value (Grange et al. 2007). Interestingly, patients with tumors on the leg had a 3-year disease-specific survival of 43 %, while those with lesion not on the legs had a 77 % 3-year disease free survival.

19.9 Treatment

The standard treatment for indolent cutaneous B-cell lymphoma (MZL and FCL) depends on the number and size of the lesions as summarized in Table 19.1. Although there is no strong support in the literature for "watch *and* wait," it is recommended by the National Comprehensive Cancer Network (NCCN) guidelines (NCCN guidelines) and practiced by some experts for multifocal lesions or extensive disease.

Total excision and local radiotherapy is commonly considered as first-line therapy especially for solitary lesions. Recent studies have shown treatment with 20–54 Gy radiation could result in 99 % complete response rate, but the relapse rate in these studies widely varied (Senff et al. 2008b). Neelis et al. used low dose (2×4 Gy) in 18 indolent CBCL patients with 72 % complete response rate (Neelis et al. 2009). Low-dose local radiation has considerably less side effects, and moreover, it provides the possibility of repeating radiation when there is evidence of relapse.

In small studies, intralesional interferon-α (Cozzio et al. 2006), intralesional adenovirus-interferon-γ (Audigé et al. 2006), intralesional steroids (Perry et al. 2010; Burg et al. 1994; Wong and Weller 1998), and intralesional rituximab (Heinzerling et al. 2000a; Kyrtsonis et al. 2006) have been administered successfully with an acceptable relapse rate. Systemic rituximab monotherapy is often administered when there is multifocal disease or other therapies are contraindicated or unwanted (Fink-Puches et al. 2005; Gitelson et al. 2006; Heinzerling et al. 2000b). Topical imiquimod, an immune response modulator, is an option in certain cases (Farkas et al. 2009; Coors et al. 2006).

In cases with high suspicion for an infectious trigger such as Borrelia or H. pylori, appropriate antibiotic therapy can be attempted as first-line therapy (Bogle et al. 2005; Grange et al. 2002; Hofbauer et al. 2001; Kutting et al. 1997). Systemic mono- or multiagent chemotherapy such as chlorambucil (Hoefnagel et al. 2005c) or CHOP-like regimens are only considered in cases of extensive disease or failed prior therapies (Senff et al. 2008b).

The treatment of PCDLBCL-LT is extrapolated from the diffuse large B-cell lymphoma, the most common systemic non-Hodgkin lymphoma. Therefore, if manageable, immunotherapy with rituximab plus multiagent anthracycline-based chemotherapy is recommended (Grange et al. 2007; Senff et al. 2008c). Localized radiation therapy to a solitary lesion or grouped lesions has generally fallen out of favor given the significant risk of either cutaneous and/or systemic relapse. The most common regimens used in the up-front management of PCDLBCL-LT are R-CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) or the infusional regimen, dose-adjusted R-EPOCH (cyclophosphamide, doxorubicin vincristine, etoposide, and prednisone). Commonly, full-course therapy with 6–8 cycles are used as there is a lack of evidence for "short-course" combined modality therapy in PCDLBCL-LT despite its use extensively in localized DLBCL (Persky et al. 2008). Rituximab monotherapy for PCDLBCL-LT is thought to be inferior therapy, however remains an option for those unable or intolerant of multiagent chemotherapy (Fenot et al. 2010). The role of consolidative radiation therapy despite full-course therapy in localized presentations remains

controversial although an option. To date, there are no randomized studies to provide guidance. For the patients who experience a relapse of PCDLBCL-LT despite initial multiagent chemotherapy, it can be considered for second-line therapies with intent to perform high-dose therapy with autologous stem cell recue.

19.10 Follow-Up

The follow-up is tailored to patient's needs and extend of disease. However, indolent CBCL patients with inactive disease have usually 6–12 months clinical evaluations; whereas patients under therapy should be seen every 4–6 weeks to access therapeutic response.

The follow-up of PCDLBCL-LT is more characteristic of DLBCL rather than skin-directed surveillance. Therefore, routine physical exam, laboratory evaluation, and a discussion regarding radiographic surveillance for nodal or extranodal recurrence are reasonable but remain individualized. Coordinated follow-ups with a dermatologist and medical oncologist often occur on an every-3-month basis for the first 2 years following completion of therapy then every 6 months thereafter until 5 years.

References

Aberer E, Fingerle V, Wutte N et al (2011) Within European margins. Lancet 377:178

Audigé A, Urosevic M, Schlaepfer E et al (2006) Anti-HIV state but not apoptosis depends on IFN signature in CD4+ T cells. J Immunol 177:6227–6237

Bogle MA, Riddle CC, Triana EM et al (2005) Primary cutaneous B-cell lymphoma. J Am Acad Dermatol 53: 479–484

Bradford PT, Devesa SS, Anderson WF, Toro JR (2009) Cutaneous lymphoma incidence patterns in the United States: a population-based study of 3884 cases. Blood 113:5064–5073

Burg G, Dummer R, Kerl H (1994) Classification of cutaneous lymphomas. Dermatol Clin 12:213–217

Burg G, Kempf W, Cozzio A et al (2006) Cutaneous malignant lymphomas: update 2006. J Dtsch Dermatol Ges 4:914–933

Cerroni L, Kerl H (2001a) Primary cutaneous follicle center cell lymphoma. Leuk Lymphoma 42:891–900

Cerroni L, Kerl H (2001b) Cutaneous follicle center cell lymphoma, follicular type. Am J Dermatopathol 23: 370–373

Cerroni L, Zenahlik P, Höfler G et al (1996) Specific cutaneous infiltrates of B-cell chronic lymphocytic leukemia: a clinicopathologic and prognostic study of 42 patients. Am J Surg Pathol 20:1000–1010

Cerroni L, Zochling N, Putz B, Kerl H (1997) Infection by Borrelia burgdorferi and cutaneous B-cell lymphoma. J Cutan Pathol 24:457–461

Cerroni L, Arzberger E, Putz B et al (2000) Primary cutaneous follicle center cell lymphoma with follicular growth pattern. Blood 95:3922–3928

Cho-Vega JH, Vega F, Rassidakis G, Medeiros LJ (2006) Primary cutaneous marginal zone B-cell lymphoma. Am J Clin Pathol 125(Suppl):S38–S49

Coors EA, Schuler G, Von Den Driesch P (2006) Topical imiquimod as treatment for different kinds of cutaneous lymphoma. Eur J Dermatol 16:391–393

Cozzio A, Kempf W, Schmid-Meyer R et al (2006) Intralesional low-dose interferon alpha2a therapy for primary cutaneous marginal zone B-cell lymphoma. Leuk Lymphoma 47:865–869

Dijkman R, Tensen CP, Jordanova ES et al (2006) Array-based comparative genomic hybridization analysis reveals recurrent chromosomal alterations and prognostic parameters in primary cutaneous large B-cell lymphoma. J Clin Oncol 24:296–305

Dummer R, Asagoe K, Cozzio A et al (2007) Recent advances in cutaneous lymphomas. J Dermatol Sci 48:157–167

Dummer R, Dreyling M, Group EGW (2008) Primary cutaneous lymphoma: ESMO clinical recommendations for diagnosis, treatment and follow-up. Ann Oncol 19(Suppl 2):ii72–ii76

Edinger JT, Kant JA, Swerdlow SH (2010) Cutaneous marginal zone lymphomas have distinctive features and include 2 subsets. Am J Surg Pathol 34:1830–1841

Farkas A, Kemeny L, French LE, Dummer R (2009) New and experimental skin-directed therapies for cutaneous lymphomas. Skin Pharmacol Physiol 22:322–334

Fenot M, Quereux G, Brocard A et al (2010) Rituximab for primary cutaneous diffuse large B-cell lymphoma-leg type. Eur J Dermatol 20:753–757

Fink-Puches R, Wolf IH, Zalaudek I et al (2005) Treatment of primary cutaneous B-cell lymphoma with rituximab. J Am Acad Dermatol 52:847–853

Fujiwara M, Morales AV, Seo K et al (2013) Clonal identity and differences in primary cutaneous B-cell lymphoma occurring at different sites or time points in the same patient. Am J Dermatopathol 35(1):11–8

Garcia CF, Weiss LM, Warnke RA, Wood GS (1986) Cutaneous follicular lymphoma. Am J Surg Pathol 10: 454–463

Geelen FA, Vermeer MH, Meijer CJ et al (1998) bcl-2 protein expression in primary cutaneous large B-cell lymphoma is site-related. J Clin Oncol 16:2080–2085

Gitelson E, Al-Saleem T, Millenson M et al (2006) Cutaneous B-cell lymphoma responds to rituximab: a report of five cases and a review of the literature. Leuk Lymphoma 47:1902–1907

Golling P, Cozzio A, Dummer R et al (2008) Primary cutaneous B-cell lymphomas – clinicopathological, prognostic and therapeutic characterisation of 54 cases according to the WHO-EORTC classification and the ISCL/EORTC TNM classification system for primary cutaneous lymphomas other than mycosis fungoides and Sezary syndrome. Leuk Lymphoma 49:1094–1103

Goodlad JR, Davidson MM, Hollowood K et al (2000a) Primary cutaneous B-cell lymphoma and Borrelia burgdorferi infection in patients from the Highlands of Scotland. Am J Surg Pathol 24:1279–1285

Goodlad JR, Davidson MM, Hollowood K et al (2000b) Borrelia burgdorferi-associated cutaneous marginal zone lymphoma: a clinicopathological study of two cases illustrating the temporal progression of B. burgdorferi-associated B-cell proliferation in the skin. Histopathology 37:501–508

Goodlad JR, Krajewski AS, Batstone PJ et al (2002) Primary cutaneous follicular lymphoma: a clinicopathologic and molecular study of 16 cases in support of a distinct entity. Am J Surg Pathol 26:733–741

Grange F, Wechsler J, Guillaume JC et al (2002) Borrelia burgdorferi-associated lymphocytoma cutis simulating a primary cutaneous large B-cell lymphoma. J Am Acad Dermatol 47:530–534

Grange F, Petrella T, Beylot-Barry M et al (2004) Bcl-2 protein expression is the strongest independent prognostic factor of survival in primary cutaneous large B-cell lymphomas. Blood 103:3662–3668

Grange F, Beylot-Barry M, Courville P et al (2007) Primary cutaneous diffuse large B-cell lymphoma, leg type: clinicopathologic features and prognostic analysis in 60 cases. Arch Dermatol 143:1144–1150

Hallermann C, Kaune KM, Gesk S et al (2004) Molecular cytogenetic analysis of chromosomal breakpoints in the IGH, MYC, BCL6, and MALT1 gene loci in primary cutaneous B-cell lymphomas. J Invest Dermatol 123:213–219

Heinzerling L, Dummer R, Kempf W et al (2000a) Intralesional therapy with anti-CD20 monoclonal antibody rituximab in primary cutaneous B-cell lymphoma. Arch Dermatol 136:374–378

Heinzerling LM, Urbanek M, Funk JO et al (2000b) Reduction of tumor burden and stabilization of disease by systemic therapy with anti-CD20 antibody (rituximab) in patients with primary cutaneous B-cell lymphoma. Cancer 89:1835–1844

Hoefnagel JJ, Vermeer MH, Jansen PM et al (2003) Bcl-2, Bcl-6 and CD10 expression in cutaneous B-cell lymphoma: further support for a follicle centre cell origin and differential diagnostic significance. Br J Dermatol 149:1183–1191

Hoefnagel JJ, Vermeer MH, Jansen PM et al (2005a) Primary cutaneous marginal zone B-cell lymphoma: clinical and therapeutic features in 50 cases. Arch Dermatol 141:1139–1145

Hoefnagel JJ, Dijkman R, Basso K et al (2005b) Distinct types of primary cutaneous large B-cell lymphoma identified by gene expression profiling. Blood 105(9): 3671–3678

Hofbauer GF, Kessler B, Kempf W et al (2001) Multilesional primary cutaneous diffuse large B-cell lymphoma responsive to antibiotic treatment. Dermatology 203:168–170

Jenni D, Karpova MB, Seifert B et al (2011) Primary cutaneous lymphoma: two-decade comparison in a population of 263 cases from a Swiss tertiary referral centre. Br J Dermatol 164:1071–1077

Kempf W, Denisjuk N, Kerl K et al (2012) Primary cutaneous B-cell lymphomas. J Dtsch Dermatol Ges 10: 12–22; quiz 23

Kim YH, Willemze R, Pimpinelli N et al (2007) TNM classification system for primary cutaneous lymphomas other than mycosis fungoides and Sezary syndrome: a proposal of the International Society for Cutaneous Lymphomas (ISCL) and the Cutaneous Lymphoma Task Force of the European Organization of Research and Treatment of Cancer (EORTC). Blood 110:479–484

Kutting B, Bonsmann G, Metze D et al (1997) Borrelia burgdorferi-associated primary cutaneous B cell lymphoma: complete clearing of skin lesions after antibiotic pulse therapy or intralesional injection of interferon alfa-2a. J Am Acad Dermatol 36:311–314

Kyrtsonis MC, Siakantaris MP, Kalpadakis C et al (2006) Favorable outcome of primary cutaneous marginal zone lymphoma treated with intralesional rituximab. Eur J Haematol 77:300–303

Levin C, Mirzamani N, Zwerner J et al (2012) A comparative analysis of cutaneous marginal zone lymphoma and cutaneous chronic lymphocytic leukemia. Am J Dermatopathol 34:18–23

May SA, Netto G, Domiati-Saad R, Kasper C (2005) Cutaneous lymphoid hyperplasia and marginal zone B-cell lymphoma following vaccination. J Am Acad Dermatol 53:512–516

Mirza I, Macpherson N, Paproski S et al (2002) Primary cutaneous follicular lymphoma: an assessment of clinical, histopathologic, immunophenotypic, and molecular features. J Clin Oncol 20:647–655

Morales AV, Arber DA, Seo K et al (2008) Evaluation of B-cell clonality using the BIOMED-2 PCR method effectively distinguishes cutaneous B-cell lymphoma from benign lymphoid infiltrates. Am J Dermatopathol 30:425–430

National Comprehensive Cancer Network 2013 Guidelines. www.nccn.org

Neelis KJ, Schimmel EC, Vermeer MH et al (2009) Low-dose palliative radiotherapy for cutaneous B- and T-cell lymphomas. Int J Radiat Oncol Biol Phys 74:154–158

Nihal M, Mikkola D, Wood GS (2000) Detection of clonally restricted immunoglobulin heavy chain gene rearrangements in normal and lesional skin: analysis of the B cell component of the skin-associated lymphoid tissue and implications for the molecular diagnosis of cutaneous B cell lymphomas. J Mol Diagn 2:5–10

Perry A, Vincent BJ, Parker SR (2010) Intralesional corticosteroid therapy for primary cutaneous B-cell lymphoma. Br J Dermatol 163:223–225

Persky DO, Unger JM, Spier CM et al (2008) Phase II study of rituximab plus three cycles of CHOP and

involved-field radiotherapy for patients with limited-stage aggressive B-cell lymphoma: Southwest Oncology Group study 0014. J Clin Oncol 26:2258–2263

Ponzoni M, Ferreri AJ, Mappa S et al (2011) Prevalence of Borrelia burgdorferi infection in a series of 98 primary cutaneous lymphomas. Oncologist 16:1582–1588

Roggero E, Zucca E, Mainetti C et al (2000) Eradication of Borrelia burgdorferi infection in primary marginal zone B-cell lymphoma of the skin. Hum Pathol 31: 263–268

Rosenberg SA (1977) Validity of the Ann Arbor staging classification for the non-Hodgkin's lymphomas. Cancer Treat Rep 61:1023–1027

Senff NJ, Hoefnagel JJ, Jansen PM et al (2007) Reclassification of 300 primary cutaneous B-Cell lymphomas according to the new WHO-EORTC classification for cutaneous lymphomas: comparison with previous classifications and identification of prognostic markers. J Clin Oncol 25:1581–1587

Senff NJ, Kluin-Nelemans HC, Willemze R (2008a) Results of bone marrow examination in 275 patients with histological features that suggest an indolent type of cutaneous B-cell lymphoma. Br J Haematol 142: 52–56

Senff NJ, Noordijk EM, Kim YH et al (2008b) European Organization for Research and Treatment of Cancer and International Society for Cutaneous Lymphoma consensus recommendations for the management of cutaneous B-cell lymphomas. Blood 112:1600–1609

Servitje O, Gallardo F, Estrach T et al (2002) Primary cutaneous marginal zone B-cell lymphoma: a clinical, histopathological, immunophenotypic and molecular genetic study of 22 cases. Br J Dermatol 147: 1147–1158

Streubel B, Simonitsch-Klupp I, Mullauer L et al (2004) Variable frequencies of MALT lymphoma-associated genetic aberrations in MALT lymphomas of different sites. Leukemia 18:1722–1726

Streubel B, Scheucher B, Valencak J et al (2006) Molecular cytogenetic evidence of t(14;18)(IGH;BCL2) in a substantial proportion of primary cutaneous follicle center lymphomas. Am J Surg Pathol 30:529–536

Sundram U, Kim Y, Mraz-Gernhard S et al (2005) Expression of the bcl-6 and MUM1/IRF4 proteins correlate with overall and disease-specific survival in patients with primary cutaneous large B-cell lymphoma: a tissue microarray study. J Cutan Pathol 32: 227–234

Takino H, Li C, Hu S et al (2008) Primary cutaneous marginal zone B-cell lymphoma: a molecular and clinicopathological study of cases from Asia, Germany, and the United States. Mod Pathol 21:1517–1526

Vermeer MH, Geelen FA, van Haselen CW et al (1996) Primary cutaneous large B-cell lymphomas of the legs. A distinct type of cutaneous B-cell lymphoma with an intermediate prognosis. Dutch Cutaneous Lymphoma Working Group [see comments]. Arch Dermatol 132:1304–1308

Willemze R, Jaffe ES, Burg G et al (2005) WHO-EORTC classification for cutaneous lymphomas. Blood 105: 3768–3785

Wong KC, Weller PA (1998) Primary cutaneous B cell lymphoma: outcomes and treatment. Australas J Dermatol 39:261–264

Wood GS, Kamath NV, Guitart J et al (2001) Absence of Borrelia burgdorferi DNA in cutaneous B-cell lymphomas from the United States. J Cutan Pathol 28: 502–507

Xie X, Sundram U, Natkunam Y et al (2008) Expression of HGAL in primary cutaneous large B-cell lymphomas: evidence for germinal center derivation of primary cutaneous follicular lymphoma. Mod Pathol 21(6):653–659

Zendri E, Venturi C, Ricci R et al (2005) Primary cutaneous plasmacytoma: a role for a triggering stimulus? Clin Exp Dermatol 30:229–231