Chapter 3
Primary Cutaneous B-cell Lymphomas: FL, MCL, Differential Diagnosis

Robert E. LeBlanc

Primary Cutaneous B-Cell Lymphomas

Primary cutaneous lymphomas are non-Hodgkin lymphomas that arise in the skin. At the time of presentation, they generally do not have clinical evidence of extracutaneous disease [1]. Primary cutaneous B-cell lymphomas (PCBCL) comprise roughly a quarter of the lymphomas in this broad and heterogeneous category [2]. These lymphomas pose three main diagnostic challenges for the healthcare team: PCBCL must be distinguished from cutaneous lymphoid hyperplasias and other inflammatory diseases that mimic lymphoma, PCBCL subtypes must be distinguished from one another, and PCBCL must be distinguished from extracutaneous lymphomas that secondarily involve the skin. When a patient does not have a previous diagnosis of an extracutaneous B-cell lymphoma or has a previous diagnosis of an extracutaneous B-cell lymphoma but no tissue available for a comparative clonality assessment, a pathologist may not be able to determine whether a lymphoma is of cutaneous or extracutaneous origin. Therefore, a multidisciplinary approach to the diagnosis is necessary.

In general, PCBCL have a higher prevalence among men and among patients of middle to advanced age [3]. Per the World Health Organization (WHO) updated 2016 classification, there are three main diagnostic entities comprising this group: primary cutaneous marginal zone lymphoma (PCMZL), primary cutaneous follicle center lymphoma (PCFCL), and primary cutaneous diffuse large B-cell lymphoma, leg-type (PCDLBCL-LT) [2]. Both PCMZL and PCFCL are indolent diseases with rare exceptions. In contrast, PCDLBCL-LT is an aggressive lymphoma with a propensity to disseminate beyond the skin. Reports of skin-limited B-cell lymphomas that warrant consideration for other WHO classifications are exceptional, and less is

R. E. LeBlanc (✉)
Pathology and Laboratory Medicine, Dermatopathology Fellowship Program, Dartmouth Hitchcock Medical Center, One Medical Center Drive, Lebanon, NH, USA
e-mail: Robert.E.LeBlanc@hitchcock.org

P. Kaur (ed.), *Follicular Lymphoma and Mantle Cell Lymphoma*, Molecular and Translational Medicine, https://doi.org/10.1007/978-3-030-49741-5_3

known about their biologic potentials. For instance, the skin rarely hosts the initial clinical manifestations of mantle cell lymphoma. While the concept of a primary cutaneous mantle cell lymphoma has been discussed, many reported cases with clinical follow-up show that patients have occult nodal disease concomitant with their skin findings or develop extracutaneous dissemination on follow-up, which is in keeping with the multisystemic involvement attributed to this aggressive malignancy [4]. Nonetheless, it is important to consider a broad differential diagnosis for any robust cutaneous lymphoid infiltrate since a wide variety of B-cell lymphomas and other lymphocyte-rich processes can disseminate to the skin and be mistaken for primary cutaneous lymphoma. This list includes intravascular large B-cell lymphoma (IVLBCL), which is exceedingly rare but can be diagnosed on skin biopsies. The classification and our understanding of these lymphomas continue to evolve with advancements in immunobiology and molecular pathology.

Primary Cutaneous Marginal Zone B-Cell Lymphoma

Primary cutaneous marginal zone B-cell lymphoma (PCMZL) is subsumed under the WHO classification category of extranodal marginal zone lymphoma of mucosal-associated lymphoid tissue (MALT). Skin is the second most common site for MALT-type lymphoma after the gastrointestinal tract, and PCMZL is the second most common PCBCL accounting for approximately 25% of lymphomas in the category [2, 3]. An association between PCMZL and *Borrelia burgdorferi* has been established in some Western European cohorts; however, this association has not been made in North American and Asian populations [5, 6]. While the etiology is obscure for a majority of patients, an increased incidence of autoimmunity, allergies, and various gastrointestinal pathologies is diagnosed in patients with PCMZL as compared to the general population [7, 8]. Patients are twice as likely to be male than female and have a median age of 50; however, there is a wide age range from 6 to 93 years [9–12]. PCMZL can be comprised of single or multiple, clustered red to violaceous plaques or nodules. They occasionally have an annular rim of erythema [2, 9, 13]. PCMZL is more likely to arise on the trunk, upper extremities, and head and neck than elsewhere [9, 10, 14]. Patients lack constitutional symptoms, and a majority of patients have localized disease. Overall, 5-year overall survival is 97%, and it approximates 100% for patients with solitary lesions [2, 10, 15]. Dissemination beyond skin is rare with sporadic reports of nodal dissemination and exceptional reports of transformation to a large cell phenotype [9, 10, 15–17]. Approximately 93% of patients with solitary or localized lesions and 75% with broader cutaneous dissemination achieve a complete response to therapy [9]. Treatment of solitary or localized lesions can include intralesional steroids, radiotherapy, or surgical excision. Radiation has been associated with superior clearance rates [18–20]. Rate of relapse is 39% for patients with solitary or localized lesions and 77% for patients with multifocal disease [9]. Per National Comprehensive Cancer Network (NCCN) guidelines, patients receiving a putative histologic

diagnosis of PCMZL should be screened for extracutaneous disease with a workup that includes physical examination, complete blood count with differential, comprehensive metabolic panel, lactate dehydrogenase, and CT chest/abdomen/pelvis with contrast [21].

Histomorphology

There are two histologically (and likely etiologically) distinct subsets of PCMZL [8, 22]. While both comprise nodular and diffuse, bottom-heavy dermal lymphoid infiltrates that spare the epidermis and involve the subcutis (Fig. 3.1a), one subset does not undergo heavy chain class switching and resembles its extracutaneous MALT lymphoma counterparts replete with sheets of neoplastic B-cells that colonize germinal center follicles and efface adnexa. The other subset undergoes heavy chain class switching and is accompanied by a polymorphous infiltrate that is sometimes

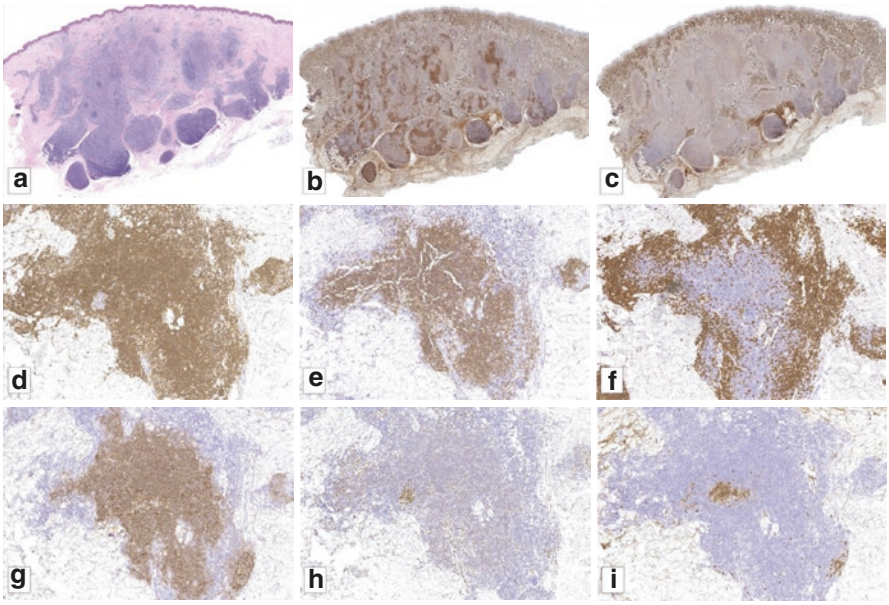

Fig. 3.1 Primary cutaneous marginal zone lymphoma. A nodular and diffuse, bottom-heavy lymphoid infiltrate spares the epidermis, occupies much of the reticular dermis, and extends into the subcutis (**a**. 10×). A kappa light chain-restricted population is evident on low power given the preponderance of kappa-positive cells (**b**. 10×) in comparison to Lambda expression (**c**. 10×). Another example illustrates colonization of a germinal center follicle by lymphoma cells that express both CD20 (**d**. 20×) and BCL2 (**e**. 20×). T-cells co-express BCL2 and CD3 (**f**. 20×) around the periphery of the infiltrate. CD21 highlights an irregular, follicular dendritic cell network with lysis at the periphery underlying the B-cell infiltrate (**g**. 20×); however, only a small, atretic residuum of the colonized follicle is revealed with BCL6 (**h**. 20×) and CD10 staining (**i**. 20×)

histologically indistinguishable from cutaneous lymphoid hyperplasia. There has been some discussion as to whether all PCMZL are bona fide lymphomas or if, in some instances, they represent an indolent clonal expansion of B-cells in the skin in the setting of T-cell-mediated B-cell hyperplasia [23]. In keeping with this hypothesis, clonal B-cells may comprise a small minority of the infiltrate in class-switched PCMZL, which is enriched for T-cells and reactive germinal center follicles. The clonal B-cells in both subtypes of PCMZL are small and can have variable morphologies including monocytoid cells, cells with cleaved nuclei, and cells with rounded nuclear contours. They may be cytomorphologically indistinguishable from the accompanying lymphocytes, particularly when they comprise a minority of the infiltrate.

Plasmacytic differentiation in PCMZL is highly variable, ranging from sparse cells scattered around the periphery of lymphoid nodules to lymphomas with exclusive plasmacytoid differentiation. The latter has previously been referred to as immunocytoma [24]. Plasma cell cytologic atypia, including binucleated cells and Dutcher bodies, can be prevalent and may serve as a clue to the diagnosis of lymphoma. Immunohistochemistry and in situ hybridization can demonstrate light chain restriction in cases with significant plasmacytic differentiation (Fig. 3.1b, c). This method offers greater sensitivity for establishing clonality in PCMZL than IgH clonality studies using PCR-capillary gel electrophoresis [11, 25]. In very rare reports, PCMZL has undergone transformation to an aggressive lymphoma characterized by blastic cytomorphology, [26] although blastoid features present in PCMZL at disease onset do not always portend aggressive behavior [27].

Ancillary Studies

As previously mentioned, there is ongoing discussion as to whether a majority of PCMZL, in light of their excellent clinical outcomes, represent a benign clonal B-cell expansion as opposed to a bona fide lymphoma [23, 28, 29]. Aiding this hypothesis is the observation that B-cell clonality has been well-documented in the setting of cutaneous lymphoid hyperplasias [30, 31]. Nonetheless, the presence of rare chromosomal translocations [32, 33] and *FAS* gene alterations [34] in a subset of PCMZL strongly supports a neoplastic origin for at least a minority of cases, as do exceedingly rare and exceptional reports of PCMZL progressing to an aggressive disease. Nonetheless, it is well-established that peripheral lymphomas can evolve in the setting of various inflammatory milieus. It is therefore not surprising that biopsies of developing lesions sometimes reveal histomorphologic findings that are diagnostically equivocal. From a strict nosological perspective, there is no single consensus on what diagnoses these borderline cases should receive or on which histologic features predict persistent growth and local recurrence. However, an unequivocal lymphoma diagnosis may provoke significant patient anxiety, even in cases where the clinical management would not differ significantly for a patient with a firm histologic diagnosis of unilesional PCMZL versus a provisional diagnosis of

cutaneous lymphoid hyperplasia with mention of features equivocal for an evolving PCMZL. Contrasting with these borderline cases, lesions of PCMZL that are diagnostically straightforward from a clinical and histopathologic perspective should be carefully distinguished from PCFCL and from cutaneous dissemination of extracutaneous lymphomas, particularly marginal zone lymphoma, chronic lymphocytic leukemia/small cell lymphoma, and mantle cell lymphoma.

The basic, nonspecific mature B-cell immunophenotype of PCMZL (BCL2+, BCL6-, CD10-) distinguishes PCMZL from PCFCL; however it cannot distinguish PCMZL from cutaneous lymphoid hyperplasia and other indolent T-cell-rich lymphoid processes. In contrast with extracutaneous marginal zone lymphomas, a number of PCMZL have been shown to be CD43 negative [35]. The marker may be especially challenging to interpret in cases of PCMZL and cutaneous lymphoid hyperplasia where CD43-positive T-cells predominate. The distinction between PCMZL and cutaneous lymphoid hyperplasia cannot always be made on histologic grounds; however, clues to a PCMZL diagnosis include dense, diffuse sheets of monotonous lymphocytes, colonization of germinal center follicles by a monomorphous B-cell infiltrate (Fig. 3.1d–i), cases demonstrating a light chain-restricted plasma cell population, the presence of cytomorphologically abnormal plasma cells, and lesions that show extensive plasmacytic differentiation. PCMZLs with extensive plasmacytic differentiation will often show decreased or absent CD20 expression but express other mature B-cell markers, including CD79a and CD19 [36]. Many of these cases express the IgG4 isotype, which is true of a majority of class-switched PCMZL; however, IgG4 expression should not be used in isolation to exclude the possibility of an extracutaneous lymphoma secondary involving the skin [37, 38]. CD5 is negative in PCMZL, except in exceedingly rare reported cases of transformed blastic PCMZL. It is therefore useful for distinguishing PCMZL from chronic lymphocytic leukemia/small cell lymphoma (CLL/SLL) and mantle cell lymphoma. It is particularly important to distinguish PCMZL from mantle cell lymphoma given the propensity of the latter to behave aggressively. A majority of mantle cell lymphomas also express Cyclin D1, which is neither expressed in PCMZL nor in CLL/SLL. Sox11, which is positive in rare mantle cell lymphomas lacking Cyclin D1 expression, may also be helpful for excluding the possibility of mantle cell lymphoma, but staining should be interpreted with caution as reactivity has been reported in a subset of marginal zone lymphomas of splenic origin [39]. In contrast with diffuse large B-cell lymphoma, PCMZL is comprised of small, mature-appearing lymphocytes and Ki-67 stains only a minority of nuclei.

Class-switched PCMZL, which can be particularly challenging if not impossible to distinguish from cutaneous lymphoid hyperplasia both clinically and histologically (Fig. 3.2), frequently expresses IgG4, does not express CXCR3, and develops in association with a T-cell helper type 2 microenvironment [8, 22, 37]. In contrast, non-class-switched PCMZL expresses IgM and is CXCR3 positive in keeping with their extracutaneous MALT lymphoma counterparts. Clinical correlations should be sought in these cases in order to evaluate for the possibility of an extracutaneous MALT lymphoma secondarily involving the skin. While routine histomorphologic features may not permit for this distinction, the translocations' characteristic of

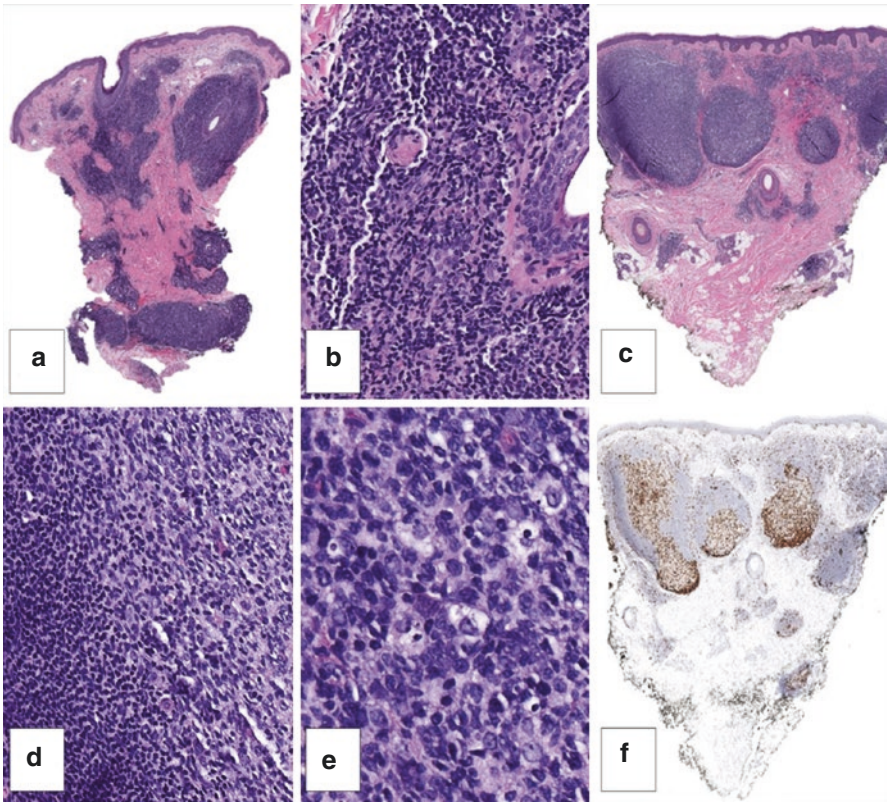

Fig. 3.2 Benign mimics of lymphoma. Pseudolymphomatous folliculitis can extend deep to the subcutis mimicking lymphoma; however, the inflammation often conforms to the shape of a hair follicle and surrounds adnexa while sparing the intervening dermal interstitium (**a**. 20×). The infiltrate is comprised of small, mature-appearing lymphocytes (**b**. 200×). Cutaneous lymphoid hyperplasia can exhibit variably sized and shaped germinal center follicles that mimic the appearance of lymphoma. Note that the follicles in this example involve only the superficial to mid-reticular dermis (**c**. 20×). Furthermore, a prominent mantle zone surrounds the follicle (**d**. 200×). Numerous tingible body macrophages are present in the germinal center in association with centrocytes and centroblasts (**e**. 400×). Ki-67 labels a majority of the germinal center B-cells with obvious polarization (**f**. 20×)

extracutaneous MALT lymphomas has a significantly lower prevalence in PCMZL. For instance, t(14;18)(q32;q31) is present in only 15% of PCMZL, [33, 40] and t(3;14)(p14.1;q32), which has a higher prevalence in thyroidal MALT lymphomas, is present in 10% of PCMZL [32].

Rare B-cell lymphomas exhibit epidermotropism with single cells. Many reported examples have an immunophenotype that is compatible with PCMZL, and interestingly, several of these rare patients share a distinct clinical presentation of recurrent crops of pink, variably pruritic papules on their torsos and extremities. Extracutaneous involvement has been documented, but these rare

cases have been associated with excellent survival approaching that of PCMZL. Some of the patients in this unusual subgroup of lymphomas have had clinical findings that could support a clinical diagnosis of splenic diffuse red pulp small B-cell lymphoma, including splenomegaly and bone marrow involvement at the time of diagnosis [41, 42]. Other patients have had no evidence of extracutaneous involvement at the time of diagnosis, supporting the idea that these cases represent a novel, de novo primary cutaneous lymphoma [43]. It has not been established whether epidermotropic B-cell lymphomas represent a heterogeneous group of lymphomas or a lymphoma with a propensity to involve the skin, spleen, and marrow in varying proportions. The nosological distinction may be an academic one since each patient with an epidermotropic B-cell infiltrate requires a comprehensive clinical evaluation for systemic disease. However, the indolent behavior of these unusual entities to date suggests that aggressive management may be unnecessary. Importantly, the clinical presentation and gross morphology of all epidermotropic B-cell lymphomas reported to date have been distinct from that of mycosis fungoides, a T-cell disease comprising the majority of cutaneous lymphomas. Although myriad clinical variants are described, mycosis fungoides generally manifests as erythematous patches with scale and arises in a photoprotected anatomic distribution. While there are rare reports of mycosis fungoides exhibiting aberrant CD20 expression, the aforementioned clinical morphology that characterizes mycosis fungoides would cast doubt on a diagnosis of B-cell lymphoma. The pattern of single cell epidermal infiltration described in epidermotropic B-cell lymphomas is also distinct from the intraepidermal lymphoid aggregates that characterize developed lesions of mycosis fungoides. Additional mature T-cell and B-cell markers should be used to confirm the lineage if there is any diagnostic uncertainty [44].

Lastly, a subset of posttransplant lymphoproliferative disease (PTLD) can have the appearance and phenotype of PCMZL. In contrast with conventional PCMZL, however, they are EBER positive, and a majority of these rare reported cases are IgA positive [45]. Additional EBV-positive PCMZL has been documented in the settings of congenital immunodeficiency, immunosuppression, and immunosenescence in patients of advanced aged [46].

Primary Cutaneous Follicle Center Lymphoma

Primary cutaneous follicle center lymphoma (PCFCL) is the most common PCBCL comprising 60% of lymphomas in the category [2]. Male patients outnumber female patients with a median age of onset of 50 years [2]. Clinically, PCFCL presents as slow-growing, smooth red-to-violaceous nodules with a tendency to arise on the head and neck, trunk, and upper extremities [2, 47, 48]. Although 80% of patients have multiple discrete lesions at the time of diagnosis, disease is generally localized [2, 47, 48]. Prognosis is excellent with posttreatment survival approaching 99% [2]. Wide cutaneous dissemination would suggest an alternative diagnosis. A minority

of patients present with large infiltrated papules and plaques on their back, and another small subset present with agminated miliary papules; however, these clinical variants do not influence prognosis [47, 49, 50]. Despite the overall indolent behavior associated with PCFCL, persistent local growth is common, and relapse occurs in a third of patients. Extracutaneous spread is rare and would raise alternative consideration for a diagnosis of follicular lymphoma secondarily involving the skin [2]. Prognosis is independent of disease multifocality with one critically important exception: PCFCL localized to the leg is associated with a marked decreased in survival approaching that of PCDLBCL-LT [47].

Since PCFCL and follicular lymphomas of nodal origin show substantial clinical, histologic, and immunophenotypic overlap in the skin, NCCN guidelines indicate that patients receiving a putative histologic diagnosis of PCMZL should be screened for extracutaneous disease with a workup that includes physical examination, complete blood count with differential, comprehensive metabolic panel, lactate dehydrogenase, and CT chest/abdomen/pelvis with contrast [21]. Treatment options for PCFCL are similar to those of PCMZL.

Histomorphology

Two predominant architectural patterns attributable to PCFCL are irregular, overlapping nodules that recapitulate germinal center follicles and diffuse sheets of cells with a germinal center phenotype. These patterns can be combined in a single lesion. PCFCL spares the epidermis, fills the dermis, and regularly extends to the subcutis. The lesional B-cells are medium-sized and resemble centrocytes and centroblasts that comprise benign germinal center follicles. In contrast with benign follicles, the follicular structures of PCFCL show a loss of polarization, an absence of tingible body macrophages, underdeveloped or absent mantle zones, and extension of neoplastic cells beyond the borders of the underpinning follicular dendritic cell networks. Neoplastic B-cells resemble cleaved centrocytes with a widely variable number of accompanying centroblasts that predominate in some cases (Fig. 3.3a–c). In contrast with nodal follicular lymphomas, however, PCFCL is not assigned a histologic grade regardless of architecture and cytomorphology [47]. Nonetheless, dense sheets of centroblasts without smaller accompanying lymphocytes, the presence of immunoblasts, significant cytologic atypia, prominent mitotic activity, and single cell necrosis are features that would challenge a diagnosis of PCFCL and raise histologic consideration for diffuse large B-cell lymphoma. PCFCL with a preponderance of centroblasts generally has small accompanying lymphocytes in contrast with the monomorphous infiltrates of PCDLBCL-LT. Dermal sclerosis is also commonly identified in PCFCL and is less often reported in diffuse large B-cell lymphomas. Rarely PCFCL demonstrates bizarre Reed-Sternberg-like cells [51, 52] or a sarcomatoid appearance with spindled B-cells dissecting through the dermal interstitium; however, these cytomorphologic variations have not been shown to effect prognosis [53–56].

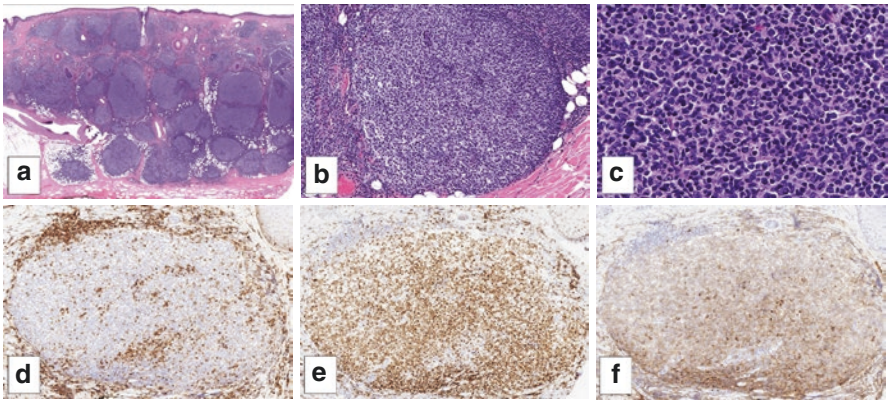

Fig. 3.3 Primary cutaneous follicle center lymphoma. Variably sized intradermal and subcutaneous nodules recapitulating germinal center follicles (**a**. 10×). However, these abnormal follicles lack polarity and mantle zones (**b**. 100×). Enlarged, neoplastic centrocytes with cleaved nuclei and scattered centroblasts with conspicuous nucleoli are present, and there is a relative paucity of tingible body macrophages (**c**. 400×). The lymphoma cells are BCL2-negative (**d**. 100×), BCL6-positive (**e**. 100×), and weakly CD10-positive (**f**. 100×)

Ancillary Studies

The three most common diagnostic conundrums entail distinguishing PCFCL from cutaneous lymphoid hyperplasias, distinguishing PCFCL from follicular lymphomas of nodal origin that secondarily involve the skin, and distinguishing PCFCL from diffuse large B-cell lymphomas. All cases of PCFCL express germinal center follicle markers, definitionally BCL6 with varied and heterogeneous coexpression of CD10 (Fig. 3.3d–f). In contrast with follicular lymphoma, however, PCFCL is more likely to be CD10 negative, particularly in cases with diffuse architecture [9, 47]. When the diagnosis is in question, it may be helpful to incorporate additional germinal center follicle markers to aid in diagnosis. In order of decreasing sensitivity, these markers include STMN1, LMO2, HGAL, and AID [57]. BCL2 can be positive or negative in PCFCL and therefore cannot reliably distinguish PCFCL from nodal follicular lymphoma. Mutually exclusive rearrangements involving *BCL2* and loss of 1p36 can be identified in both of these lymphomas, albeit the prevalence is reportedly lower in PCFCL [58, 59]. While the majority of follicular lymphomas have an associated t(14;18)(IGH;BCL2), data are conflicting on its prevalence in PCFCL, reportedly ranging from 0% to 51% [60–63]. Variation may reflect different methods used for detection. The presence of this translocation in PCFCL has been shown to correlate with BCL2 expression by immunohistochemistry, which is often faint in contrast with stronger expression evident in follicular lymphomas that secondarily involve the skin [61–63]. Limited data suggest that the detection of t(14;18)(IGH;BCL2) in a case of suspected PCFCL does not indicate a worse prognosis; however, its presence in a cutaneous lymphoid infiltrate showing strong CD10 and BCL2 coexpression should prompt consideration for clinically

occult nodal disease [63]. Deletions of 1p36 involving the CD10 locus are common in both PCFCL and follicular lymphoma and also should not be used to distinguish them [58, 64, 65].

Cases of PCFCL with a predominance of large centrocytes generally have a similar excellent response to therapy and survival [66, 67]. However rare cases of PCFCL can undergo transformation to an aggressive large cell phenotype [68]. Similarly, there are de novo primary cutaneous lymphomas that have features ambiguous for PCFCL and PCDLBCL. Ki-67 expression is low in PCFCL, and staining will reveal a loss of the germinal center polarization that is characteristic of cutaneous lymphoid hyperplasias. By comparison, Ki-67 is markedly elevated in diffuse large B-cell lymphomas, staining a majority of the lymphoma nuclei. PCDLBCL-LT generally demonstrates an activated B-cell (ABC) phenotype with expression of MUM1, FOX-P1, and IgM, which can be helpful for distinguishing it from PCFCL with a preponderance of large cells. In contrast, fewer than 30% of the B-cells comprising PCFCL express these markers [69, 70]. Kappa and lambda stains or in situ hybridization is generally unhelpful in establishing a diagnosis of PCFCL; however, IgH gene rearrangement studies can demonstrate clonality if necessary. While clonality cannot reliably distinguish lymphoma from lymphoid hyperplasia, it could potentially aid in the comparison of a diffuse large B-cell lymphoma to a prior or concomitant biopsy of PCFCL when transformation is suspected.

Primary Cutaneous Diffuse Large B-Cell Lymphoma, Leg-Type

Primary cutaneous diffuse large B-cell lymphoma, leg type (PCDLBCL-LT), is an aggressive malignancy that comprises slightly less than 20% of all PCBCL [2]. In contrast with PCMZL and PCFCL, PCDLBCL-LT has a median age of onset in the 70s and a predilection to involve women on their lower extremities [2]. Clinically, this lymphoma presents as large red-to-violaceous nodules. Despite its nomenclature, 15% of cases arise on non-leg locations; however, a unifying feature is that a majority of cases described manifest in the skin as a de novo lymphoma and share an ABC phenotype [2, 48, 66]. Altogether, PCDLBCL-LT has a 5-year disease-specific survival of 50%–70% [2]. Negative prognostic indicators include the presence of multiple lesions, age greater than 75 years, and leg involvement, which alone is associated with a 5-year disease-specific survival of 43% owing to a higher risk of extracutaneous dissemination [67]. Per NCCN guidelines, patients with a new diagnosis of DLBCL involving the skin should be staged with PET-CT, bone marrow biopsy, and peripheral blood flow cytometry in order to exclude the possibility of secondary skin involvement by an extracutaneous lymphoma, which has a higher incidence than PCDLBCL-LT, occurring in approximately 10% of patients with extracutaneous DLBCL [68, 71]. Additionally, male patients should undergo testicular ultrasonography since testicular DLBCL and PCDLBCL-LT are histomorphologically indistinguishable [72]. The mutational profile of PCDLBCL-LT

overlaps with both testicular lymphoma and primary central nervous system lymphoma (PCNSL) [73]. The standard treatment includes rituximab, combination chemotherapy, and radiotherapy [74–76]. Relapses and extracutaneous dissemination of PCDLBCL-LT are common [2, 67].

Histomorphology

Sheets of large, often monomorphous lymphoid cells fill the dermis and can involve the subcutis. The overlying epidermis is sometimes ulcerated. There are few to no accompanying small lymphocytes and granulocytes, in contrast with cases of PCFCL with a predominance of centroblasts and with other diffuse large B-cell lymphoma subtypes. The cells comprising PCDLBCL-LT show an immunoblastic, centroblastic, or mixed appearance with frequent mitoses.

Ancillary Studies

PCDLBCL-LT should be distinguished from PCFCL and extracutaneous large B-cell lymphomas whenever possible. Some cutaneous large cell lymphomas lack an ABC phenotype and present as sheets of monomorphous blasts including immunoblasts [77].

The majority of PCDLBCL-LT has an ABC phenotype demonstrable by gene expression profiling [9, 78] and exhibits a corresponding immunophenotype (MUM1+/BCL2+/CD10-). PCDLBCL-LT is further characterized by *MYD88* L265P mutations in 70% of cases [79–82]. Ki-67 highlights the vast preponderance of lesional blasts (Fig. 3.4) in contrast with the relatively low percentage of Ki-67-positive nuclei encountered in indolent PCBCL. PCDLBCL-LT commonly co-expresses BCL6. This marker is therefore of little diagnostic aid in distinguishing PCDLBCL-LT from PCFCL and from extracutaneous diffuse large B-cell lymphomas. FOX-P1, IgM, and p63-positivity in >30% of the lymphoid infiltrate can help distinguish PCDLBCL-LT from PCFCL with a preponderance of large cells [69, 70]. CD21-positive follicular dendritic cell networks are not present in PCDLBCL-LT. EBER in situ hybridization is negative in PCDLBCL-LT and should be performed to exclude an Epstein-Barr virus-associated DLBCL.

PCDLBCL-LT controlled for cases with an ABC phenotype has an exceedingly low prevalence of *MYC* rearrangements. The rearrangement has been identified in only 4.5% of such cases [78, 83–86]. Other studies permitting greater immunophenotypic variety for a diagnosis of PCDLBCL-LT have demonstrated *MYC* rearrangements in 32% of cases [87]. In general, *MYC* rearrangements are more prevalent in diffuse large B-cell lymphomas exhibiting a GCB phenotype [88]. In some case series, up to 10% of PCDLBCL-LT were described as lacking the

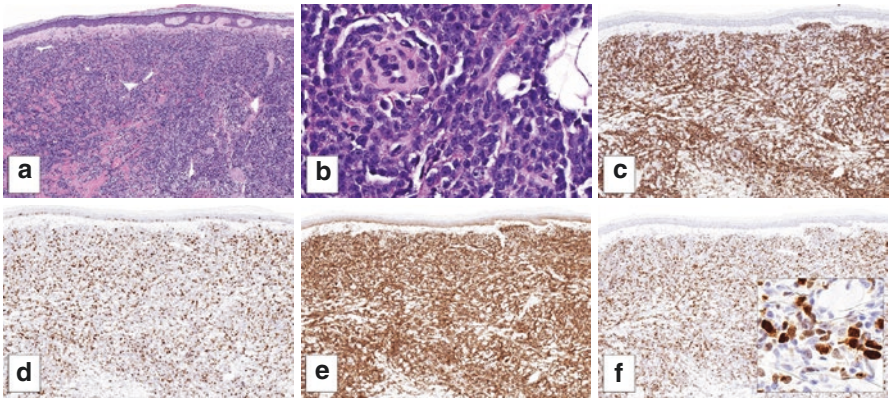

Fig. 3.4 Diffuse large B-cell lymphoma, leg type. Sheets of lymphoid cells fill the reticular dermis and spare the epidermis (**a**. 40×). A preponderance of enlarged lymphoid cells with prominent central nucleoli crowds the dermis (**b**. 400×). The lymphoma cells express CD20 (**c**. 40×), Ki-67 (**d**. 40×), BCL2 (**e**. 40×), and MUM1 (**f**. 40×, inset 400×)

requisite BCL2 and MUM1 expression to classify the lymphoma as ABC [2, 89, 90], and some cases of PCDLBCL with a BCL2-/BCL6+ immunophenotype behave aggressively in keeping with their ABC counterparts. Thus, there is ongoing discussion as to how these lymphomas are best classified [79]. In general, a diagnosis of PCDLBCL-LT should be reconsidered when the infiltrate is polymorphous with numerous accompanying small lymphocytes, an ABC immunophenotype cannot be established, and no *MYD88* L265P mutation is identified [84, 91]. Reports of double-hit translocations in PCDLBCL-LT are exceedingly rare in all studies regardless of diagnostic criteria [87]. Loss of 9p21.3 including the *CDKN2A* locus is present in 75% of cases [92–94]; however, this finding is identified in other diffuse large B-cell lymphoma subtypes [95].

Other B-Cell Lymphoma that Involve Skin

Mantle cell lymphoma is an aggressive mature B-cell malignancy that occasionally involves the skin [4, 96–100]. As noted previously, there are exceptional reports of cutaneous mantle cell lymphomas that initially manifest in the skin; however, these lymphomas have a propensity for wide dissemination and poor outcomes [4, 101]. A majority of mantle cell lymphomas are characterized by the t(11;14)(q13;q32) rearrangement involving *CCND1* and *IGH*. These lymphomas generally express Cyclin D1 by immunohistochemistry. The lymphoma comprises a monotonous infiltrate of small to slightly enlarged lymphoid cells with mildly irregular nuclear contours, coarse nuclear chromatin, small inconspicuous nucleoli, and little cytoplasm; however, both the cytomorphology and architecture can vary in the skin. Centrocyte-like, blastoid and pleomorphic cytomorphologic variants are known, and cases with

diffuse, nodular and diffuse, and perivascular architectural patterns have been described. A majority of mantle cell lymphomas express Cyclin D1, SOX11, FMC7, and CD5 by immunohistochemistry, which can help distinguish them from PCMZL and PCFCL. CD23 is negative, in contrast with CLL/SLL. CLL/SLL in the skin often manifests as exaggerated host reactions to neoplasms, arthropod exposures, and other inflammatory phenomena and infrequently as cutaneous plaques in asymptomatic patients who lack a preceding diagnosis. There are exceptionally rare cases of cutaneous CLL/SLL in patients with a normal peripheral blood count [102, 103]. Importantly, CLL/SLL can lack CD20 expression if the patient has been treated with rituximab. Other mature B-cell markers, such as CD79a and CD19, should be considered to confirm B-cell origin. Otherwise, expression of CD5, CD23, and LEF1 and the absence of staining with Cyclin D1, SOX11, and germinal center follicle markers help distinguish CLL/SLL from other mature B-cell lymphomas.

Precursor B-cell acute lymphoblastic leukemia/lymphoma (B-ALL/LBL) expresses CD10, which is a potential diagnostic pitfall; however, it generally shows a loss of CD20 in keeping with an immature B-cell phenotype. B-cell lineage can be confirmed with CD79a, which is usually retrained. B-ALL/LBL also expresses TDT. These markers should be considered to evaluate for any B-cell lymphoma exhibiting a lymphoblastic appearance, particularly in pediatric and young adult patients [104].

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