REVIEW ARTICLE

Update in Diagnosis and Management of Primary Cutaneous B-Cell Lymphomas

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Abstract

Primary cutaneous lymphomas are a rare group of diseases, with an estimated incidence of 0.5–1 case per 100,000 people per year. Primary cutaneous B-cell lymphomas (pCBCLs) represent 25–30% of all primary cutaneous lymphomas. There are three main subtypes of pCBCL: primary cutaneous marginal zone lymphoma, primary cutaneous follicle center lymphoma, and primary cutaneous diffuse large B-cell lymphoma, leg type. Cutaneous B-cell lymphomas have a broad spectrum of clinical presentations, which makes diagnostic and therapeutic strategies challenging. To date, treatment recommendations for cutaneous B-cell lymphomas have been largely based on small retrospective studies and institutional experience. Recently, the pharmacotherapeutic landscape has expanded to include drugs that may modify the underlying disease pathology of pCBCLs, representing new therapeutic modalities for this rare group of diseases. Novel therapies used for other systemic B-cell lymphomas show promise for the treatment of pCBCLs and are being increasingly considered. These new therapies are divided into five main groups: monoclonal antibodies, immune checkpoint inhibitors, small-molecule inhibitors, bispecific T-cell engaging, and chimeric antigen receptor T cell. In this review, we discuss the clinical, histopathological, molecular, and cytogenetic features of the most common pCBCL subtypes with a focus on current and innovative therapeutic developments in their management. These emerging treatment strategies for B-cell lymphomas and cutaneous B-cell lymphomas may represent novel first-line options for the management of these rare diseases.

1 Introduction

Primary cutaneous B-cell lymphomas (pCBCLs) constitute a heterogeneous group of extra-nodal B-cell non-Hodgkin lymphomas (B-NHLs). Defined as being present only in the skin at the time of diagnosis, pCBCLs are a rare entity, representing only 25–30% of all primary cutaneous lymphomas [1]. Incidence is estimated at < 1 per 100,000 persons/year and increases with age [2].

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Key Points
Primary cutaneous B-cell lymphomas have a broad spectrum of clinical presentations, which makes diagnostic and therapeutic strategies challenging.
To date, treatment recommendations for primary cutaneous B-cell lymphomas have been largely based on small retrospective studies and institutional experience.
The pharmacotherapeutic landscape has recently expanded to include drugs that may modify the underlying disease pathology.

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classifies pCBCL into three major subtypes: primary cutaneous marginal zone lymphoma (PCMZL), primary cutaneous follicle center lymphoma (PCFCL), and primary cutaneous diffuse large B-cell lymphoma, leg type (PCDLBCL, LT). Primary cutaneous follicle center lymphoma and PCMZL

portend an indolent clinical course with 5-year survival rates of over 90% and up to 98%, whereas PCDLBCL, LT is a more aggressive variant with associated 5-year survival between 20 and 70%. [3] Intravascular large B-cell lymphoma is a rare and aggressive subtype of large B-cell lymphoma with a 3-year survival rate of 56% in patients with only cutaneous manifestations and 22% in those with disseminated disease. Primary cutaneous diffuse large B-cell lymphoma not otherwise specified, and Epstein–Barr virus-positive mucocutaneous ulcer are very rare pCBCL subtypes. Primary cutaneous diffuse large B-cell lymphoma not otherwise specified has a 5-year survival around 90% and Epstein–Barr virus-positive mucocutaneous ulcer portends an indolent self-limited course [1, 2, 4].

An accurate pathologic diagnosis of the subtype is the most important first step in the management of pCBCLs. Basic clinicopathologic evaluation is the same for each subtype, although some further evaluation may be useful in certain circumstances to clarify a particular diagnosis. To appropriately confirm the diagnosis of pCBCL, systemic involvement must be ruled out. As such, a thorough work-up is necessary and includes a detailed history and physical examination, tissue sampling, molecular studies, and laboratory studies. Cytogenetics and flow cytometry of the blood and/or lesional tissue are helpful in certain conditions [5–7]

Management of pCBCL is complex and requires coordination of a multidisciplinary care team comprising dermatologists, pathologists, hematology-oncologists, and radiation oncologists. There is a scarcity of large randomized trials in pCBCL, and current therapeutic guidelines are based on small retrospective studies [3, 8–10]. This review aims to describe the pathophysiological, epidemiological, clinicopathological, immunohistochemical, molecular, and cytogenetic features of the most common pCBCL subtypes with a focus on current and innovative therapeutic developments in their management.

2 Primary Cutaneous Marginal Zone Lymphoma (PCMZL)

2.1 Epidemiology/Prognosis

Primary cutaneous marginal zone lymphoma represents 9% of all primary cutaneous lymphomas and is the second most common variant [2, 11, 12]. This lymphoma affects middle-aged adults with a median age at diagnosis of 55 years. Although rare, PCMZL comprises the majority of pCBCL cases in the pediatric population [11–13]. Overall prognosis is favorable, with a 5-year survival rate of 95–100%. While local recurrence is common, with cutaneous relapse in up to 50% of patients, extracutaneous dissemination is rare and reported in approximately 4% of patients [2, 3, 14–18].

2.2 Etiology

The etiology of PCMZL remains unknown but likely occurs in the setting of chronic antigen stimulation. The association of PCMZL with *Borrelia burgdorferi* is debated, as only European cases have been described [19, 20]. Additional associations of PCMZL reported in the literature include *Helicobacter pylori* colonization of the stomach, immunization against influenza or hepatitis A, arthropod bites, traumatic injuries, tattoos, gastrointestinal disorders, and autoimmune diseases [13, 18, 21, 22].

2.3 Clinical Presentation

Primary cutaneous marginal zone lymphoma most commonly presents as asymptomatic, red-to-violaceous cutaneous nodules on the extremities and trunk and has an indolent clinical course (Fig. 1) [2]. While studies have shown nearly 44% of patients are asymptomatic at the time of diagnosis, local symptoms including pruritus have been reported to occur in up to 47.5% of patients [13]. Systemic symptoms such as fever, night sweats, and weight loss are exceedingly rare [11, 14, 17, 23–25].

2.4 Histology

Primary cutaneous marginal zone lymphomas comprise a heterogeneously mixed infiltrate with small lymphocytes and centrocyte-like B cells, lymphoplasmacytoid cells, plasma cells, reactive T cells, and centroblasts. Eosinophils are seen in approximately 25% of cases [11]. The infiltrate is arranged in a nodular or diffuse dermal pattern with the presence of a grenz zone sparing the epidermis and superficial papillary dermis (Fig. 2) [2, 4, 9, 26].

2.5 Immunohistochemical, Cytogenetic, and Molecular Features

Two sub-types of PCMZL are described based on distinct immunophenotypes [27, 28]. The first and most common type is characterized by class-switched immunoglobins, IgG more frequently than IgA or IgE [28]. IgG4 expression is a common variant with distinct features, demonstrating a predominance of T cells in a T-cell helper type 2 environment, and is associated with more prominent CD21-positive follicular dendritic cells [27, 29–32]. The second type of PCMZL is characterized by diffuse proliferation or large nodules composed of B cells expressing IgM and often CXCR3 [2].

Primary cutaneous marginal zone lymphoma cells are characteristically positive for CD20, CD79a, PAX5, CD43, MUM-1, and B-cell leukemia/lymphoma-2 (bcl-2) and

Fig. 1 Patient presenting with primary cutaneous marginal zone lymphoma. (**a**) Erythematous nodule on the left forearm and (**b**) smooth erythematous plaque on the right side of the chest
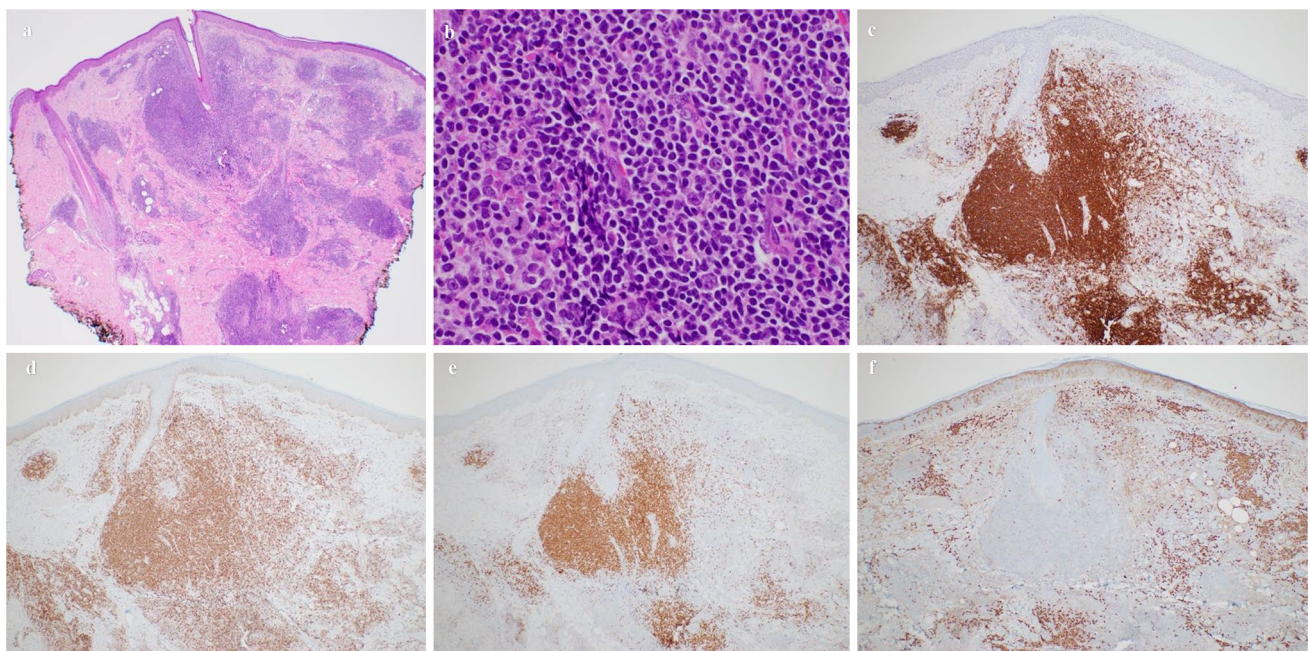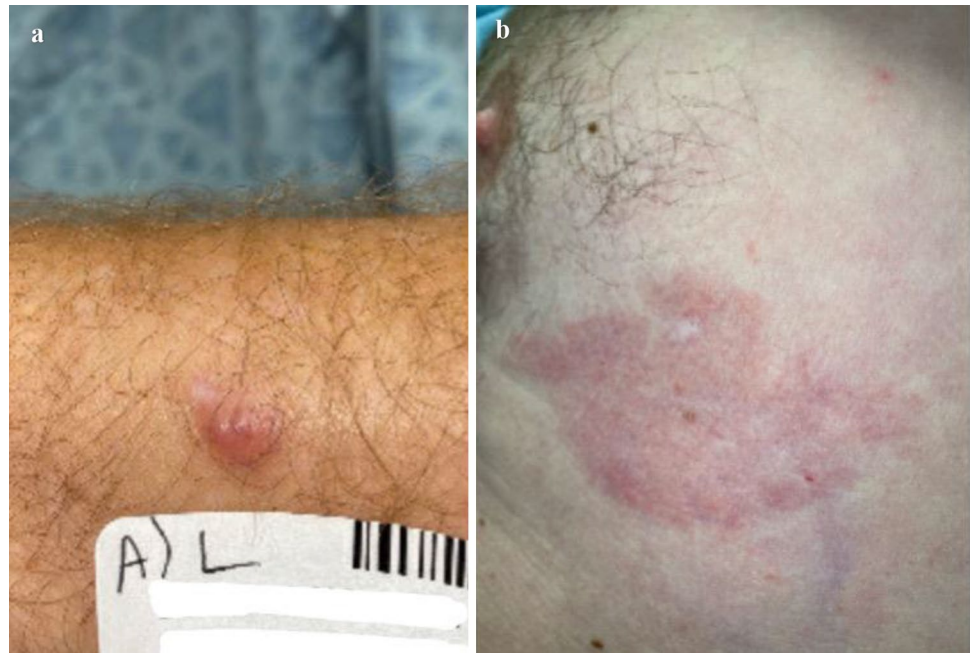

Fig. 2 Primary cutaneous marginal zone lymphoma. Histological sections show a multinodular, superficial, and deep lymphoid infiltrate of reactive germinal centers surrounded by tumor cells with prominent Grenz zones (**a**) composed of small lymphocytes admixed with numerous plasma cells, and rare larger atypical lymphocytes (**b**). Immunohistochemical staining shows a nodular aggregate of CD20-positive B cells (**c**) expressing Bcl-2 (**d**) and PAX5 (**e**). CD10 is negative. The plasma cells show lambda light chain restriction (**f**) and are negative for kappa light chain. (**a**, **b**, hematoxylin-eosin stain; **c**, immunoperoxidase stain, anti-CD20; **d**, immunoperoxidase stain, anti-Bcl-2; **e**, immunoperoxidase stain, anti-PAX5; original magnifications: **a**, ×20; **b**, ×400; **c–f**, ×40)

negative for CD5, CD10, FOXP1, and Bcl-6 [2, 33]. Plasma cells are positive for CD79a and CD138 without CD20 and demonstrate monotypic expression of kappa or lambda light chain [2, 10, 26]. Recurrent alterations in the *FAS* gene, a gene responsible for programmed cell death, have been described, highlighting the role of apoptotic downregulation in PCMZL's indolent course [34]

While less common in PCMZL than nodal marginal zone lymphoma, translocations such as *t*(14;18), *t*(3;14), and *t*(11;18) are observed in approximately 25%, 10%, and 7% of PCMZL cases, respectively, and involve the *MLT* gene located on chromosome 18 and immunoglobulin heavy chain (IgH) on chromosome 14. Polymerase chain reaction-based detection of clonal B cells is useful in confirming the diagnosis (vs benign lymphoid hyperplasia) [9, 35, 36].

2.6 Staging

In addition to immunohistochemical, molecular, and cytogenetic studies, staging should include appropriate laboratory studies (including a complete blood count, comprehensive serum chemistries, serum lactate dehydrogenase, and serum protein electrophoresis). *Borrelia* testing via serology and DNA on lesional skin by polymerase chain reaction (preferred) should also be performed particularly in European cases. However, infection with *B. burgdorferi* is not a frequent finding nor is it a geographically stable occurrence. Radiographic imaging with contrast-enhanced computed tomography (CT), positron emission tomography (PET), or PET/CT of the chest, abdomen, pelvis, and neck (in cases of head involvement) is also indicated. Bone marrow biopsy and polymerase chain reaction for B-cell clonality are not routinely performed unless other biological tests are abnormal (e.g., unexplained cytopenias) or if there is high clinical suspicion for extracutaneous involvement [37, 38].

2.7 Treatment

First-line treatment for a solitary lesion or a single site of involvement is surgical excision with curative intent or radiation therapy (RT) [8]. Both have response rates around 90% [8, 39]. However, local recurrences are common. There are no guidelines for margin assessment in pCBCL, and thus pathologists cannot determine if the histological margins are clear after an excision. Further, the side effects of surgery include scarring and disfiguration, which poses a challenge when multiple lesions are present and in cases of relapse or recurrence. For a few localized lesions, RT is a better treatment option. However, the side effects of RT therapy are common including acute toxicities (local erythema, pain, edema, pruritus, anesthesia, and immediate pigmentation) and long-term side effects (alopecia, pruritus, pigmentation changes, atrophy, and telangiectasia). While the recommended total dose for PCMZL ranges between 4 and 36 Gy, multiple recent studies recommend the use of low-dose RT (4 Gy) because of improved efficacy and decreased toxicities [39]. Antibiotic treatment is indicated in cases positive for *B. burgdorferi* infection. There is no clear consensus regarding antibiotic indication, efficacy, and treatment course in

cases negative for *Borrelia*. Senff et al. described 14 patients treated with a course of oral cephalosporins and tetracyclines over 3 weeks, with 43% of patients achieving complete remission. They also observed superior results with intravenously administered cephalosporins (vs high-dose oral tetracyclines) in a small cohort of eight patients. Topical treatments such as clobetasol and cryosurgery are efficacious in the treatment of small solitary lesions. Additional options for such lesions include imiquimod and nitrogen mustard; however, these require several months to achieve response and produce inconsistent results [8, 40, 41].

Intralesional triamcinolone, interferon-α, and rituximab are non US Food and Drug Administration (FDA)-approved treatments that are considered second-line therapy in patients with solitary lesions, or first-line therapy in patients with multiple localized lesions [27, 42, 43]. The efficacy of these therapies is confined to case series and reports, with reported 44% complete response (CR) rates to intralesional triamcinolone, 100% to intralesional interferon-alpha, and 71–89% to intralesional rituximab [7, 39, 40]. Side effects include triamcinolone-induced injection-site atrophy, interferon-alpha-induced fever, malaise, local erythema, pruritus and guttate psoriasis, and injection-site pain during intralesional rituximab administration [8, 39, 42, 43]. Treatment of multiple lesions include systemic treatments such as intravenous rituximab or oral chlorambucil, or multisite local RT [8, 25, 44]. There are no randomized trials to compare these treatments. Intravenous rituximab data have a lower reported complete remission of 67% compared with intralesional administration for cutaneous B-cell lymphomas [8]. Side effects of intravenously administered rituximab include infusion-related reactions such as dyspnea, erythema, hyperhidrosis, flushing, hypotension, and rash, seen in 77% of patients. Other side effects include hematologic, cardiovascular, and infection-related adverse events. The most common cytopenia associated with systemic rituximab is neutropenia, but leukopenia and thrombocytopenia are also observed. Prolonged B-cell depletion places rituximab-treated patients at an increased risk of infections, and approximately 30–55% of patients in clinical trials developed bacterial or viral infections during treatment including localized *Candida*, herpes zoster, cytomegalovirus, and reactivation of hepatitis B [45, 46].

In PCMZL, as in other indolent lymphomas, observation with a close follow-up is an option, as lesions may spontaneously regress or enlarge slowly if left untreated, often over years. Follow-up every 6 months with a thorough skin and lymph node examination is recommended. If the patient develops systemic symptoms, bulky masses, or a high tumor burden defined as lesions > 7 cm, symptomatic splenomegaly, progressive leukemization, or serum effusions, re-staging studies and treatment are indicated [1, 9, 40, 47].

3 Primary Cutaneous Follicle Center Lymphoma (PCFCL)

3.1 Etiology

The etiology of PCFCL is unknown as no specific genetic mutations have been identified (unlike in systemic follicular BCL). There is a proposed role for lectins from commensal skin bacteria in the pathogenesis of this rare mature B-cell lymphoma [48].

3.2 Epidemiology/Prognosis

Primary cutaneous follicle center lymphoma is the most common type of pCBCL, representing 13% of all primary cutaneous lymphomas. This variant most commonly affects middle-aged and older patients with a median age of onset of 60 years, though few pediatric cases are reported in the literature [2, 12, 49–51]. Like PCMZL, the course of PCFCL is indolent, with growth occurring over months or years in certain cases. While frequent recurrence is common (with possible phases of spontaneous regression), occurring in 46% of cases, extracutaneous metastasis is rare [52]. Overall prognosis is good, with a 5-year survival rate of 95%, although localization to the lower extremities is associated with a worse prognosis and a 5-year survival of 41%. Additional negative prognostic indicators include concomitant diffuse large B-cell lymphoma as well as transformation to either diffuse large B-cell lymphoma or progression to a more aggressive form. The overall rate of transformation of PCFCL is unknown, but a 3% annual risk of transformation is reported for follicular lymphoma [4, 9, 49, 53].

3.3 Clinical Presentation

Clinically, PCFCL presents as one or more slow-growing papules, plaques, or tumors that are pink to purple with or without peripheral erythema with a predilection for the scalp, forehead, and posterior torso (Fig. 3). Lesions are grouped or widespread and may reveal peripheral erythema. The indolent course of growth differentiates PCFCL from the more aggressive PCDLBCL, LT variant, which demonstrates rapid growth [2, 52].

3.4 Histology

The dermal infiltrate occurs in one of three indistinct growth patterns that exist on a spectrum: follicular, follicular diffuse, and diffuse. The pattern of growth has no association with clinical behavior or prognosis. There is sparing of the epidermis via a grenz zone. The cellular infiltrate is primarily

Fig. 3 Nodule on the central frontal scalp of a patient presenting with primary cutaneous follicle center lymphoma

composed of centrocytes derived from germinal center B cells and reactive processes are not seen (Fig. 4) [4, 26, 52].

3.5 Immunohistochemical, Cytogenetic, and Molecular Features

Neoplastic B cells are positive for CD20, CD79a, PAX-5, and bcl-6 and negative for CD5, CD43, bcl-2, and IgM. Expression of CD10 is variable. Co-expression of CD10 and bcl-2 suggests a systemic follicular lymphoma with secondary cutaneous involvement. MUM1/IRF4 and FOXP1 are negative, consistent with the germinal center B-cell origin of this cellular infiltrate [10, 49, 54].

Translocation t(14;18) is exceedingly rare in PFCL as opposed to primary nodal follicular lymphoma [10, 49]. Absence of the MYD88 L265P in PCFCL is helpful in differentiating this from PCDLBCL, LT, an important distinction as the prognosis and treatment course are vastly different for these types of pCBCLs [3, 37]. Surface immunoglobulins will show monoclonal restriction to either kappa or lambda light chains.

3.6 Staging

Staging is similar to that for PCMZL and includes a thorough history and physical examination in addition to appropriate laboratory and imaging studies (with PET/CT increasingly utilized in PCFCL). Systemic involvement at presentation is low (8–9%) in PCFCL; however, it is higher than PCMZL. Bone marrow biopsy in PCFCL should be considered in cases positive for bcl-2, CD10, or t(14,18) translocation at presentation [37, 40, 54, 55].
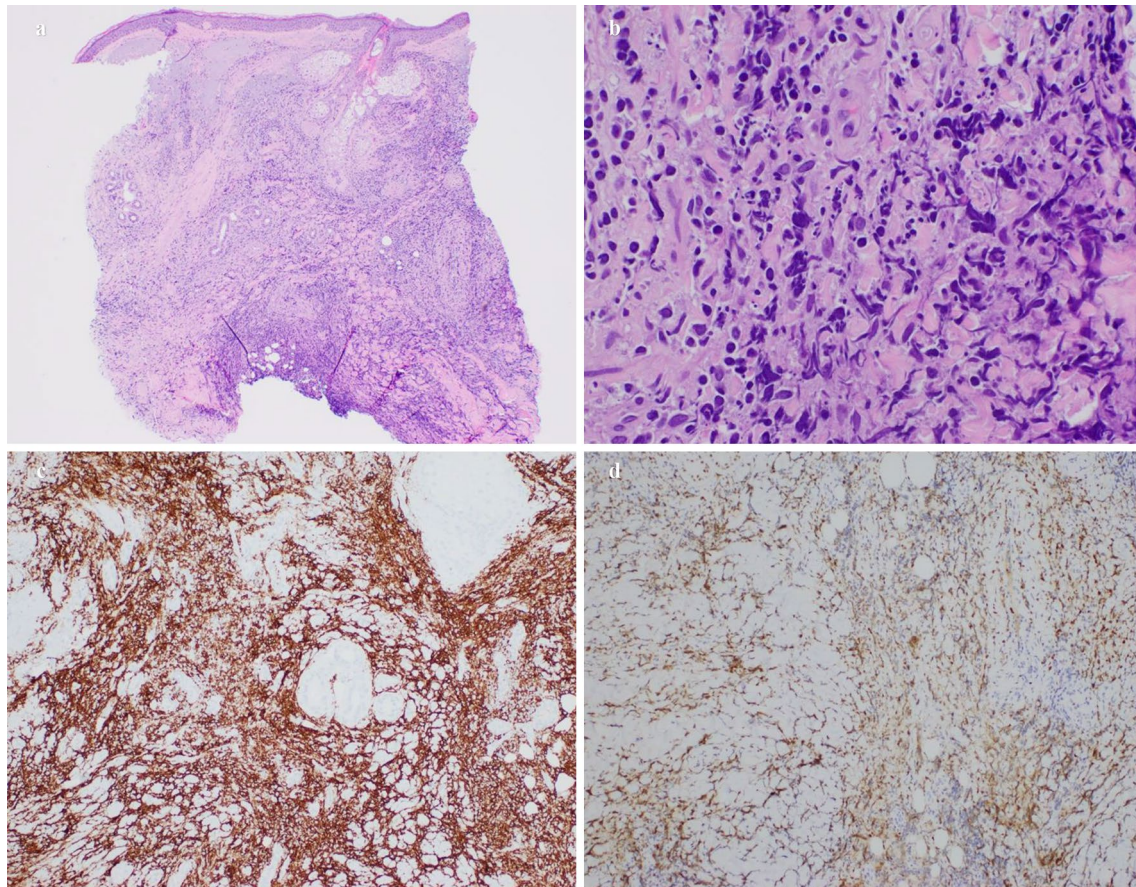
Fig. 4 Primary cutaneous follicle center lymphoma. Histological sections show a nodular atypical lymphohistiocytic infiltrate in the dermis (**a**). The atypical lymphocytes are small in size (**b**). Immunohistochemical studies reveal that the atypical lymphocytes are positive for CD20 and Bcl-6 (**c** and **d**), but are negative for CD5, CD10, Bcl-2, CD23, and Bcl-1. (**a, b**, hematoxylin-eosin stain; **c**, immunoperoxidase stain, anti-CD20; **d**, immunoperoxidase stain, anti-bcl-6; original magnifications: **a**, ×40; **b**, ×400; **c**, ×100; **d**, ×100)

3.7 Treatment

Primary cutaneous follicle center lymphoma portends an indolent course like PCMLZ. As such, management is similar. First-line treatment for solitary lesions includes RT in addition to surgical excision with curative intent [8]. Low-dose RT (4 Gy) is recommended owing to an improved outcome and reduced acute toxicity profile in indolent pCBCL [39]. For patients with multiple localized lesions, treatment with multi-site low-dose RT, topical therapies (i.e., corticosteroids, nitrogen mustard, imiquimod, cryosurgery), or intralesional therapies (i.e., corticosteroids, rituximab) is appropriate [8, 47].

Systemic therapies such as intravenous rituximab are efficacious treatments in patients with generalized skin disease. Albeit rare, patients may present with diffuse extracutaneous disease, in which case, combination treatment with rituximab and multi-agent chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) is indicated. There is less evidence regarding the benefit of this treatment in PCFCL as opposed to PCMZL. Recommended follow-up is 6 months with a complete cutaneous and nodal examination. Because PCFCL is an indolent lymphoma, the wait-and-see approach may be taken with treatment only for asymptomatic lesions [9, 40, 47].

4 Primary Cutaneous Diffuse Large B-Cell Lymphoma, Leg Type (PCDLBCL, LT)

4.1 Etiology

The etiology of PCDLBCL, LT is poorly understood, though continued advancements in genetic studies have contributed to an enhanced understanding of the molecular mechanisms involved in the pathogenesis.

4.2 Epidemiology/Prognosis

Primary cutaneous diffuse large B-cell lymphoma, leg type is the least common variant of pCBCL, accounting for 2% of all primary cutaneous lymphomas. This lymphoma affects elderly patients with a median age of diagnosis between 70 and 82 years, with a female sex predilection. While rare, PCDLBCL, LT portends a particularly aggressive course. The 5-year survival rate is 56% and extracutaneous dissemination occurs in 10% of cases [9, 40].

4.3 Clinical Presentation

Primary cutaneous diffuse large B-cell lymphoma, leg type usually occurs with solitary or multiple rapidly enlarging plaques or nodules that are localized to either one or both legs. The rapid growth kinetic of this primary cutaneous lymphoma variant is important in its differential diagnosis to other indolent primary cutaneous lymphomas [2]. Lesions may be associated with pain with or without necrosis and ulceration (Fig. 5). Atypical presentations have been reported and include patches and/or thin plaques. B symptoms are unusual, though patients may have an impaired general condition mostly secondary to advanced age [4, 9, 56].

4.4 Histology

The histologic picture of PCDLBCL, LT is characterized by a dense and diffuse infiltrate, extending from the papillary dermis to the subcutaneous tissue. A monomorphic population of large atypical cells resembling centroblasts is arranged in confluent sheets, with frequent mitotic figures and occasional immunoblasts. There is a minimal reactive

Fig. 5 Multiple violaceous nodules on the right lower extremity in a patient presenting with primary cutaneous diffuse large B-cell lymphoma, leg type

T-cell component compared with other pCBCL subtypes. Rarely, there is epidermal involvement with large neoplastic B-cells resembling Pautrier microabscesses seen in cutaneous T-cell lymphoma and/or ulceration [26, 57, 58].

4.5 Immunohistochemical, Cytogenetic, and Molecular Features

The neoplastic cells of PCDLBCL, LT are positive for CD20, bcl-2, C79a, PAX5, IRF4/MUM1, and FOXP1. High expression of the post-germinal center markers IRF4/MUM1 and FOXP1 markers is associated with worse prognosis [59]. Bcl-6 expression is variable and CD10 is negative. Expression of cMYC is present in 75% of cases. This is a highly proliferative lymphomatous infiltrate with a Ki-67 index between 60 and 90% (Fig. 6) [2].

Several genetic abnormalities have been identified and serve as diagnostic and prognostic markers. These include translocations of *Bcl-6*, *IgH*, and *cMYC* genes, and BLIMP-1 deletions. Inactivation of the CDKN2A locus on chromosome 9p21 via deletion or promoter methylation may occur and is associated with a worse prognosis [60]. The genetic landscape of PCDLBCL, LT is similar to that of activated B-cell type diffuse large B-cell lymphoma and diffuse large B-cell lymphoma of the central nervous system with mutations in the activated B-cell pathway elicited with massive parallel sequencing [18, 61, 62]. Mutations in MYD88 L265P (60–70% of cases) and additional NFκB pathway markers CD79B, PIM1, TNFAIP3/A20, and CARD11 are also observed. These B-cell receptor mutations are associated with a lower response rate to R-polychemotherapy [61, 63, 64]. MYD88 L265P mutations are absent in other forms of diffuse large B-cell lymphoma, and when present are a diagnostic marker for PCDLBCL, LT [65].

4.6 Tumor Immune Microenvironment

The tumor microenvironment of PCDCBL, LT comprises two distinct cell populations: CD33+ myeloid-derived suppressor cells and CD163+ M2 macrophages with differential expressions of membrane-bound PD-L1 in both cell populations [66, 67]. Upregulation of PD-L1/PD-L2 is also observed within the microenvironment of high-grade lymphomas, and is not seen in low-grade lymphomas [68]. The culmination of these findings suggests a mechanism of immune surveillance escape contributing to the poor prognosis in PCDLBCL, LT. Decreased expression of CD4 and FOXP3 as well as significantly decreased C4/FOXP3 ratio are also seen in PCDLBCL, LT as opposed to indolent PCBCL, indicating a role for T helper cells in limiting tumor progression [69].
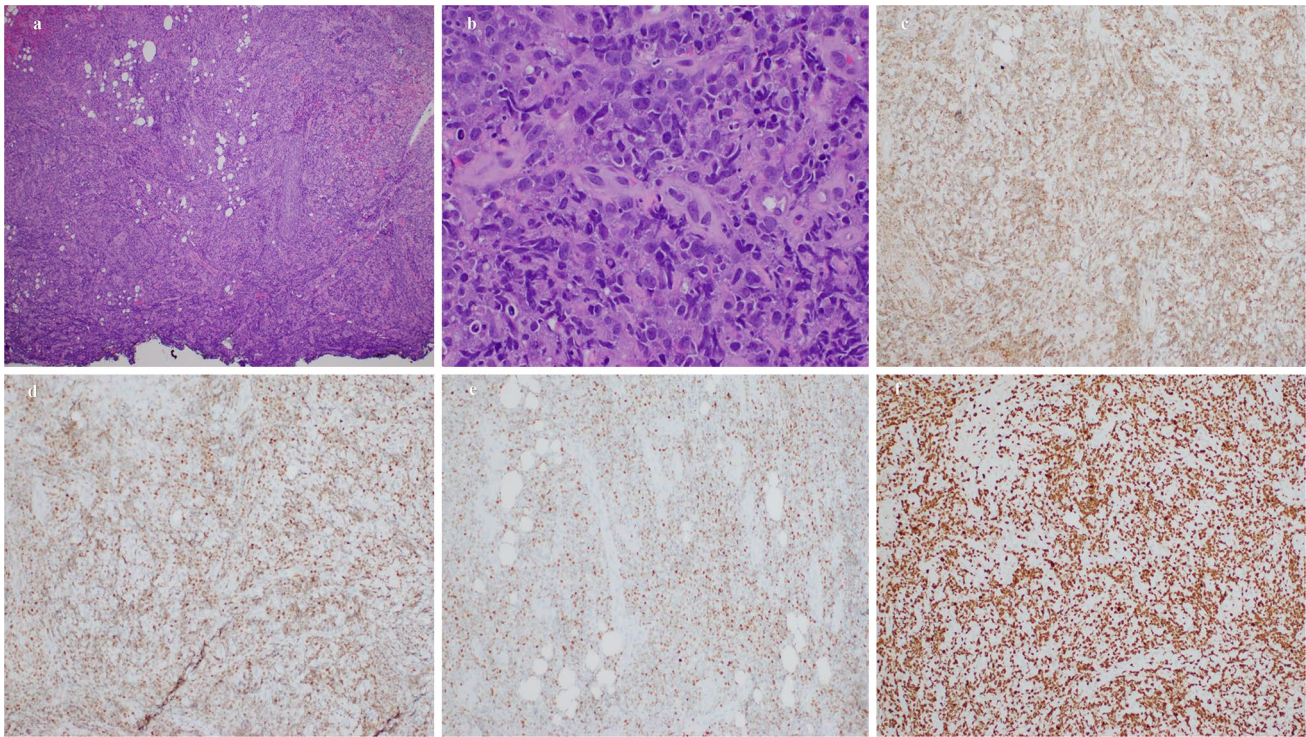
Fig. 6 Primary cutaneous diffuse large B-cell lymphoma, leg type. Histological sections show sheets of medium-to-large monomorphic lymphocytes with an immunoblastic morphology (**a**, **b**). Immunohistochemical studies reveal that the atypical lymphocytes are positive for Bcl-2, Bcl-6, and MUM1/IRF4 (**c–e**), but are negative for CD10. This is a highly proliferative lymphomatous infiltrate with a Ki-67 index of ~70%. (**a**, **b**, hematoxylin-eosin stain; **c**, immunoperoxidase stain, anti-bcl-2; **d**, immunoperoxidase stain, anti-bcl-6; **e**, immunoperoxidase stain, anti-MUM1/IRF4; **f**, immunoperoxidase stain, anti-ki67; original magnification: **a**, ×40; **b**, ×400; **c–f**, ×100)

4.7 Staging

Imaging (PET/CT) and laboratory studies (complete blood count, comprehensive metabolic panel), as well as a bone marrow biopsy are recommended for diagnosis and staging, to rule out systemic disease, and direct treatment. The risk/benefit ratio of performing a bone marrow biopsy must be carefully considered, specifically when it does not change the management of PCDLBCL in elderly patients. In this scenario, a bone marrow biopsy should only be completed if there are unexplained abnormalities found on hematologic testing.

4.8 Treatment

As an aggressive lymphoma primarily affecting the elderly population, management of PCDLBCL, LT proves challenging. An oncogeriatric evaluation should be discussed for the final therapeutic choice in elderly patients and may include adapted poly-chemotherapy regimens. Response to primary treatment is rare, with a high recurrence rate. Recurrence in the central nervous system after treatment is particularly common [2, 70].

Patients with generalized disease are treated as nodal diffuse large B-cell lymphoma with the current first-line treatment being rituximab plus combination chemotherapy with R-CHOP [8, 40]. In a large retrospective study evaluating the efficacy of R-CHOP, Grange et al. demonstrated an improved prognosis of PCDLBCL, LT with R-CHOP treatment, particularly with age-adapted treatment [71]. After showing promise in the treatment of primary cutaneous T-cell lymphoma, pegylated liposomal doxorubicin was used to treat PCDLBCL, LT in a phase II pilot trial with a median of 3 months until CR in all patients [72]. In a multicenter phase II trial, Fabbri et al. studied the combination of rituximab and pegylated liposomal doxorubicin in 12 patients with refractory disease. Of these 12 patients (four with PCFCL, five with PCMZL, and three with PCDLBCL, LT), the overall response rate (ORR) was 66% with one patient achieving a CR, one with a partial response, and one with progressive disease. Minimal side effects were noted with no dose interruptions required [73].

For patients with solitary lesions, local therapy demonstrates good initial efficacy, but relapses are common [74]. Thus, local RT and surgical excision may be used as palliative treatment or in combination with R-CHOP [8, 40, 75].

5 Innovative Therapeutic Approaches

Among B-cell lymphomas, only relapsed/recurring diffuse large B-cell lymphoma (rrDLBCL) has approved FDA treatments including monoclonal antibodies, chimeric antigen receptor T cells (CAR-T), and a selective inhibitor of nuclear transport. However, there are currently no FDA-approved treatments for pCBCLs, including PCFCL and PCMZL. Additional treatment approaches are needed for patients with pCBCLs, particularly those with generalized, relapsed, or refractory disease. Novel therapies used for B-cell lymphomas show promise for the treatment of pCBCLs and are being increasingly considered. Below, we review many of the most applicable treatments used in B-cell lymphomas and select cases of pCBCL that may be applicable to pCBCLs broadly, including treatment efficacy and significant therapy-related adverse events (Table 1).

5.1 Monoclonal Antibodies (mAbs)

Monoclonal antibodies (mAbs) have been successful in the treatment of pCBCL owing to their ability to target B-cell associated cell-surface markers. CD20 is a B-cell-specific differentiation antigen present on all stages of B cells except early progenitors and late plasma cells that is thought to regulate calcium transport, B-cell activation, and proliferation. The two mAbs most frequently used for pCBCL are type I anti-CD20 antibodies, rituximab and ofatumumab [76]. While rituximab is generally effective in the treatment of pCBCL, relapse is common in both indolent and aggressive variants [8]. Newer generations of mAbs exhibit increased affinity for the CD20 receptor, lower immunogenicity, and an improved side-effect profile [77]. Of these, ofatumumab is the most studied in the treatment of pCBCL [78–80]. Additionally, a new generation of mAbs are anti-CD20 antibodies conjugated with radioisotopes, which demonstrate improved efficacy compared with mAb monotherapy. Currently, two anti-CD20 radioconjugates, Y-ibritumomab tiuxetan and I-tositumomab, are FDA approved for the treatment of B-NHL and demonstrate an ORR of 76.2% and 77.2%, respectively [81–86]. Intralesional or topical formulations may be translatable for the future treatment of pCBCL.

Additional mAbs are also being investigated. Dacetuzumab is a humanized IgG1 antibody targeting the CD40 cell surface antigen. CD40 is a molecule expressed on several types of B-cell neoplasms that, when stimulated by CD40L on T cells, is responsible for antibody isotype switching and differentiation to plasma cells. Rather than inhibiting the function of CD40, dacetuzumab exerts its anti-tumor effect by acting as a partial agonist. In a recent phase II trial, dacetuzumab monotherapy treatment of rrDLBCL showed only modest efficacy with an ORR of 9%

and frequent grade 3–4 lymphopenias. However, 37% of patients achieved significant disease control defined as total complete remission plus partial remission plus stable disease, suggesting a potential role for some alternative dosing or combination therapy regimen in the treatment of pCBCL [87, 88]. CD19 is expressed on B cells and enhances receptor signaling and tumor cell proliferation. Tafasitamib, an Fc-enhanced humanized CD19 antibody, causes antibody-dependent cellular cytotoxicity and antibody-dependent cellular phagocytosis. The efficacy of tafasitamib and lenalidomide combination treatment of rrDLBCL was investigated in a recent phase II trial and demonstrated an ORR or 58% [89].

5.2 Bispecific T-Cell Engaging (BiTE) Antibodies

Bispecific T-cell Engaging (BiTE) antibodies are novel immunotherapy agents of interest in the treatment of B-cell malignancies. They exhibit dual specificity for tumor-specific antigens and tumor immune cells, resulting in a robust anti-tumor immune response. Among these is the drug blinatumomab, which binds to CD19 on B cells and CD3, a T-cell co-receptor involved in the activation of CD8+ and CD4+ cells, on T cells. The binding of CD3 that occurs with blinatumomab causes potent target cell lysis at extremely low concentrations, as low as 10 pg/mL [90]. While its current main treatment focus is B-precursor acute lymphoblastic leukemia, recent studies show promising results regarding its efficacy in the treatment of rrDLBCL, LT, with an ORR up to 89% [91–94]. Additionally, there is an ongoing phase I trial investigating combination treatment of relapsed, refractory non-Hodgkin lymphoma (rrNHL) with blinatumomab and lenalidomide (NCT02568552) [95].

Mosunetuzumab exhibits anti-CD3 and anti-CD20 activity and showed efficacy and improved safety in a phase II trial treating rrB-NHL. Of 218 patients, the ORR was 64.1% and 34.7% in indolent and aggressive lymphoma subtypes, respectively [96–98]. A subcutaneous formulation of mosentuzumab is being investigated in a phase II trial of relapsed, refractory follicular lymphoma (rrFL) [99]. A phase III trial is also investigating combination therapy with mosentuzumab plus lenalidomide versus lenalidomide plus rituximab in patients with rrFL (NCT04712097). Another phase III trial is enrolling patients with untreated diffuse large B-cell lymphoma to be treated with mosentuzumab plus CHP (cyclophosphamide, doxorubicin, prednisone) and polatuzumab vedotin-piiq, versus rituzimab, CHP, and polatuzumab (NCT03677141).

REGN1979 is another anti-CD20/CD3 BiTE antibody that is being investigated in a phase I clinical trial for rrDLBC and rrFL with promising early results (100% and 40% ORR, respectively) [NCT03888105]. The anti-CD20/CD3 BitE, CD20-TCB (RG6026), plus pretreatment with

Table 1 Innovative therapeutic approaches in primary cutaneous B-cell lymphomas

Author	Indication	Target	Intervention	Route	Dose and frequency	Study design	n	ORR (%)	CR (%)	PFS (months)	Side effects
Monoclonal antibodies											
Galanina et al. [79]	rrDLBCL	CD20	Ofatumumab	IV	1000 mg weekly × 8 weeks	II	11	18	0	2	Diarrhea, anorexia, hyponatremia, fatigue
Rosenbaum et al. [80]	FL	CD20	Ofatumumab	IV	1000 mg/week × 4 doses followed by 1 dose/8 weeks × 4 doses	III	36	84	16	1.9	Lymphopenia, anemia, thrombocytopenia, neutropenia, leukocytosis, pain, fatigue, dyspnea, insomnia, nausea, hyperglycemia, hyponatremia, infection
Moore et al. [108]	rrPCDLBCL-LT	CD20 (+CD40, +BTK)	Rituximab (+ lenalidomide + ibrutinib)	IV, PO	Ibrutinib 560 mg daily, lenalidomide 20 mg days 1–21/month, rituximab 375 mg/m²/month	CS	2	100	100	ND	Fatigue, neutropenia, rash
de Vos et al. [88]	rrDLBCL	CD40	Dacetuzumab	IV	Dose-escalation to 8 mg/kg/week × 5 weeks, then 8 mg/kg/week × 4 weeks	II	46	9	4	1.2	Fatigue, headache, chills, fever, nausea, DVT, lymphopenia, neutropenia, thrombocytopenia, reversible ocular event
Salles et al. [89]	rrDLBCL	C19 (+ proteasome)	Tafasitamib (+ lenalidomide)	IV, PO	Tafasitamib 12 mg/kg and lenalidomide 25 mg/day up to 12, 28-day cycles	II	81	54	32	16.2	Neutropenia, thrombocytopenia, pneumonia, febrile neutropenia, pulmonary embolism, bronchitis, atrial fibrillation, congestive cardiac failure
Bispecific T-cell engager antibodies											
Viardot et al. [91]	rrDLBCL	CD19/CD3	Blinatumomab	IV	112 mcg/day for 2 cycles (8 weeks + 4 weeks)	II	21	43	19	3.7	Tremor, pyrexia, fatigue, edema, thrombocytopenia, pneumonia, diarrhea, leukopenia

Table 1 (continued)

Author	Indication	Target	Intervention	Route	Dose and frequency	Study design	n	ORR (%)	CR (%)	PFS (months)	Side effects
Coyle et al. [93]	rrB-NHL	CD19/CD3	Blinatumomab	IV	9 mcg/day for 7 days, 28 mcg/day for 7 days, 112 mcg/day for 42 days	II	41	37	22	2.5	Back pain, pyrexia, headache, tremor, peripheral edema, neutropenia, anemia, confusion, aphasia
Katz et al. [94]	DLBCL	CD19/CD3	Blinatumomab	IV	9 mcg/day for 7 days, 28 mcg/day for 7 days, 112 mcg/day for 42 days	II	28	89	ND	ND	Neurotoxicity, neutropenia, neurologic events
Poh et al. [95]	rrB-NHL	CD19/CD3 (+ proteasome)	Blinatumomab (+ lenalidomide)	IV, PO	Blinatumomab 9 mcg/day to 112 mcg/day days 1–56 and lenalidomide 10 or 20 mg/day days 29–49	I	12	83	50	8.3	Lymphopenia, hypophosphatemia, hyponatremia, neurotoxicity
Schuster et al. [96]	rrB-NHL	CD20/CD3	Mosunetuzumab	IV	1/2/60 mg (step-up days 1, 8, 15) cycle 1, then fixed dose day 1 of each subsequent 21-day cycle	I/Ib	218	43.8	25	ND	Cytokine release syndrome, headache, insomnia, dizziness
Immune checkpoint inhibitors											
Tuscano et al. [103]	rrB-NHL	CTLA-4 (+ CD20)	Ipilimumab (+ rituximab)	IV	Rituximab 375/m², ipilimumab 3 mg/kg on day 1 and every 3 weeks × 4 doses	I	33	2	6	2.6	Neutropenia, skin infection, diarrhea, abdominal pain, dyspnea, maculopapular rash
Ansell et al. [129]	rrB-NHL	CTLA-4	Ipilimumab	IV	3 mg/kg then 1 mg/kg/month × 3 months, then 2 mg/kg × 4 months	I	18	11	ND	16	Fatigue, diarrhea, abdominal pain, thrombocytopenia
Di Raimondo et al. [102]	rrPCDLBCL, LT	PD1 (+ CD20, + proteasome)	Pembrolizumab (+ rituximab, + lenalidomide)	IV, PO	Rituximab 375 mg/m² × 4 weeks, lenalidomide 10 mg/day 1–21, pembrolizumab 200 mg × 2 cycles	CR*	1	100	100	ND	Neutropenia, pneumonia

Table 1 (continued)

Author	Indication	Target	Intervention	Route	Dose and frequency	Study design	n	ORR (%)	CR (%)	PFS (months)	Side effects
Small-molecule inhibitors											
Gupta et al. [81]	PCDLBCL, LT	BTK	Ibrutinib	PO	560 mg/day	CR*	1	100	100	ND	N/A
Leonard et al. [130]	rrB-NHL	Proteasome (+ CD20)	Lenalidomide (+ rituximab)	PO, IV	Lenalidomide 20 mg/day days 1–21, rituximab 375 mg/m^2 every 7 days, then once/week × 5 cycles	III	178	78	34	39.4	Neutropenia, diarrhea, constipation, cough, fatigue, pyrexia
Beylot-Barry et al. [106]	rrPCDLBCL, LT	Proteasome	Lenalidomide	PO	25 mg/day days 1–21 of 28-day cycle × 12 cycles	II	19	26.3	4.9	19.4	Thrombocytopenia, neutropenia, anemia, asthenia, diarrhea, constipation, neuropathy, skin rash, atrial fibrillation, death
Crump et al. [109]	DLBCL	PKCβ	Enzastaurin	PO	500 mg/day × 3 years	III	758	80	ND	ND	Chromaturia, QTc prolongation, diarrhea, feces discoloration
Forero-Torres et al. [110]	rrB-NHL	PI3Kδ	Parsaclisib	PO	5–45 mg/day dose escalation, 20 and 30 mg/day dose expansion	I/II	72	20–100	0–44	ND	Diarrhea/colitis, nausea, fatigue, rash, pyrexia, hypotension, sepsis
Davids et al. [110, 112]	rrB-NHL	Bcl-2	Venetoclax	PO	200–1200 mg/day dose escalation	I	106	44	14/106	6	Anemia, neutropenia, thrombocytopenia
CAR-T											
Bao et al. [120]	rrDLBCL	Anti-CD19 CAR-T	IM19 CAR-T	IV	3 × 10^6/kg cells once	I	5	75	50	ND	Cytopenia, transient aphasia
Neelapu et al. [118]	rrDLBCL	CD19 CAR-T	Axicabtagene-ciloleucel	IV	2 × 10^6/kg cells once	II	111	82	54	5.8	Neutropenia, anemia, thrombocytopenia, cytokine release syndrome, neurologic events
Schuster et al. [117]	rrDLBCL	CD19 CAR-T	Tisagenlecleucel	IV	Mean 11 × 10^8 cells total	II	93	52	54	5.8	Cytokine release syndrome, anemia, neutropenia, pyrexia, neutropenia, thrombocytopenia, leukopenia, diarrhea

Table 1 (continued)

Author	Indication	Target	Intervention	Route	Dose and frequency	Study design	n	ORR (%)	CR (%)	PFS (months)	Side effects
Cao et al. [122]	rrDLBCL	CD19 CAR-T (+ PD-1)	CD19 CAR-T (+ nivolumab)	IV	Median 8 × 10⁶/kg cells total	NA	11	81.8	45.4	6	Cytopenia fever, fatigue, nausea, neurotoxicity

B-NHL B-cell non-Hodgkin lymphoma, *BTK* Bruton tyrosine kinase, *CAR-T* chimeric antigen receptor T cells, *CR* complete remission, *CR** case report, *CS* case series, *DLBCL* diffuse large B-cell lymphoma, *DVT* deep vein thrombosis, *FL* follicular lymphoma, *IV* intravenous, *ORR* overall response rate, *PCDLBCL-LT* primary cutaneous diffuse large B-cell lymphoma, leg type, *PFS* progression-free survival, *PO* oral, *QTc* corrected QT, *rr* relapsed/refractory, *rrB-NHL* relapsed, refractory B-cell non-Hodgkin lymphoma

obinutuzumab is currently being assessed in patients with rrNHL in a phase I clinical trial where it has demonstrated an ORR of 38% at doses of ≥300 µg (NCT0307569).

5.3 Immune Checkpoint Inhibitors

Improved understanding of the lymphomatous tumor micro-environment and mechanisms of escaping immune surveillance lends to therapeutic targets of interest in pCBCL; however, immune checkpoint inhibitor monotherapy demonstrated a lack of efficacy in B-NHL including diffuse large B-cell lymphoma [100, 101]. Efficacy of immune checkpoint blockage in B-cell lymphomas is more encouraging with the use of mAbs combined with mAbs targeting other surface molecules. A recent case report demonstrated the efficacy of triple therapy with rituximab, the proteasome inhibitor lenalidomide, and the PD-L1 inhibitor pembrolizumab in an elderly patient with relapsed/recurrent primary cutaneous diffuse large B-cell lymphoma, leg type (rrPCDLBCL, LT) [102]. In a phase I trial, rituximab was used in combination with ipilimumab in the treatment of 33 patients with relapsed/refractory B-cell lymphomas. While overall ORR was modest at 24% between all subtypes, ORR for patients with follicular lymphoma was 58%, suggesting a role for this combination treatment [103].

5.4 Small-Molecule Inhibitors

Small-molecule inhibitors are of increasing interest in the treatment of diffuse large B-cell lymphoma. Ibrutinib, an inhibitor of the Bruton tyrosine kinase pathway, is one of the first among its class to be used in this regard. Bruton tyrosine kinase plays an important role in B-cell development and modulates downstream pathways during B-cell signaling. In a case report, treatment with ibrutinib 560 mg per day resulted in a CR in a patient with rrPCDLBCL, LT at a 3-month follow-up. The authors indicated that the patient remained at a CR at the time of manuscript writing [81]. Pang et al. described a case of rrPCDLBCL, LT positive with a swift CR with low-dose ibrutinib treatment, which was sustained for over 2 years and addictive with a near-immediate relapse of disease upon drug discontinuation [104]. There are several genomic aberrations that allow for bypassing of Bruton tyrosine kinase inhibition and may confer ibrutinib resistance in PCDLBCL, LT. These include two activating mutations of CARD-11, a deleterious mutation of NF-kB, and IgH-IRF8 translocation [105].

Lenalidomide is an oral immunomodulating agent commonly used in multiple myeloma. This drug exhibits antineoplastic effects through various mechanisms and demonstrated efficacy in the treatment of PCDLBCL, LT with an ORR of 26% in a phase II trial treating 26 patients with PCDLBCL, LT [106]. Combination treatment using

small-molecule inhibitors with mAbs shows promising efficacy in the treatment of pCBCLs. Lenalidomide treatment with rituximab and ibrutinib treatment of rrDLBCL demonstrated good safety and efficacy in a phase Ib study, with an ORR of 44% and a CR of 28% [107]. In a recent case series, Moore et al. utilized this combination regimen of rituximab, lenalidomide, and ibrutinib in the treatment of two patients with rrPCDLBCL, LT, both of whom experienced a CR of disease [108].

Activated by constituent signaling through B-cell receptors, the PI3K/mTOR pathway regulates the growth and survival pathways of cancer cells. Inhibitors of the PI3K/AKC and mTOR pathways are efficacious in the treatment of rrNHL and offer a favorable therapeutic target in pCBCL, specifically PCDLBCL, LT [109]. In the treatment of rrDLBCL, mTOR inhibitors everolimus and tesirolimus demonstrated an ORR of 30% with a 5.7-month median duration of response [110, 111].

B-cell leukemia/lymphoma-2 is an anti-apoptotic protein found on B-cell mitochondria that, when overexpressed, is fundamental to the development of many NHL subtypes. Despite high expression of bcl-2 in diffuse large B-cell lymphoma, trials with the bcl-2 inhibitor, venetoclax, in the treatment of rrDLBCL showed insufficient response as monotherapy [112, 113]. Walter et al. demonstrated successful use of venetoclax monotherapy in the treatment of one patient with PCDLBCL, LT, with a CR noted after 4 weeks of treatment. However, relapse did occur immediately upon discontinuation [114]. The use of bcl-2 inhibitors in the treatment of pCBCL has yet to be explored, and there may be value in a combination approach of venetoclax with other agents.

5.5 Chimeric Antigen Receptor T Cells (CAR-T)

Chimeric antigen receptor T cells are genetically engineered to express specific chimeric antigen receptors enabling them to recognize and subsequently kill target tumor cells. Tisagenlecleucel, lisocabtagene maraleucel, and axicabtagene ciloleucel are FDA-approved CD19-directed CAR-T regimens for the treatment of rrDLBCL in patients not responding to two or more systemic treatments and have demonstrated potent clinical efficacy with sustainable results and improved patient survival outcomes [115–118]. Important considerations include their significant side-effect profile including neurotoxicity and cytokine release syndrome [117–119]. Additionally, resistance to CAR-T therapy does occur secondary to evasion of the immunosurveillance mechanism and/or CAR-T redistribution [120]. To this regard, combination treatment of CAR-T with cytokines or immune checkpoint inhibitors is being explored as it may enhance the efficacy of CAR-T in the treatment of

lymphomas [121, 122]. The future implication of these therapeutic options for PDLCBL, LT may be valuable.

5.6 Modified Viruses

Two forms of genetically modified viruses have been studied for the treatment of pCBCL: adenovirus interferon-γ and talimogene laherparepvec. These treatments are particularly appealing because of their intralesional application and ability to selectively target tumor cells, leaving healthy tissue unharmed. Adenovirus interferon-γ (TG1042) is a non-replicating adenovirus type 5 vector encoding the human interferon-γ gene that exerts its immunomodulatory effects by prolonging local production of interferon-γ. TG1042 has been shown to be successful in phase II trials of both primary cutaneous T-cell lymphoma and pCBCL, including relapsing pCBCL [123, 124]. Among 13 enrolled participants, repeated intralesional administration of TG1042 resulted in 11 (85%) patients showing an objective response, including seven (54%) with a CR and four (31%) with a partial response [124]. Side effects of TG1042 included fever, chills, fatigue, lymphopenia, and injection-site reactions [124, 125].

Talimogene laherparepvec is a replicating oncolytic virus based on herpes simplex virus type 1 with deletions of the herpes virus neurovirulence factor gene (*ICP34.5*) and *ICP47* gene as well as insertion of the gene encoding human granulocyte macrophage colony-stimulating factor. The combined effects of these modifications reduce viral pathogenicity, enhance tumor-selective replication, and induce local production of granulocyte macrophage colony-stimulating factor to increase antigen-presenting cell activity [126]. Talimogene laherparepvec is the first oncolytic therapy approved by the FDA following phase III trials showing success for the treatment of stage IIIB–IV melanoma not surgically resectable [127, 128]. A phase I clinical trial investigating repeated intralesional talimogene laherparepvec in non-melanoma skin cancer, including cutaneous lymphomas, is currently underway (NCT03458117).

6 Conclusions

Food and Drug Administration-approved therapies and large-scale clinical trials for the treatment of pCBCL are extremely limited, and current/future directions are confined to therapies that have proven efficacious in the treatment of B-cell NHLs. These treatments, though largely successful, comprise systemic oral or intravenous administration that is associated with a wide array of systemic adverse effects. However, by definition, pCBCLs are often localized to small areas of the skin and may respond best to more targeted topical or intralesional therapies that are less likely to cause

systemic adverse reactions. This gap in management of pCB-CLs represents a niche of pharmaceutical innovation that, if successful, could provide much needed treatment options for aggressive or relapsing/recurring pCBCL.

Declarations

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