Review Article

Primary Cutaneous Diffuse Large B-Cell Lymphoma, Leg Type: A Narrative Review

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ABSTRACT

Primary cutaneous lymphomas are rare manifestations of extranodal lymphomas. Comprising the majority of cutaneous lymphoma cases with neoplastic B-cell origins, three main subtypes exist. In general, grossly and microscopically these subtypes are similar. However, these are three distinct variants with diverse clinicopathologic, cytogenetic, molecular, and prognostic features. Primary cutaneous diffuse large B-cell lymphoma, leg type is an exceedingly rare and aggressive variant of primary cutaneous B-cell lymphomas. Thus, increased clinical awareness is needed to differentiate between the three subtypes because earlier identification not only leads to the appropriate treatment, but also improved survival. Here, characteristic features of the three predominant variants of primary cutaneous B-cell lymphomas are presented while remaining focused on the most aggressive subtype—primary cutaneous diffuse large B-cell lymphoma, leg type.

Introduction

Primary cutaneous lymphomas represent a rare manifestation of extranodal lymphomas. T-cell malignancies are the predominant etiologic agent for most cutaneous lymphomas [1]. Primary cutaneous B-cell lymphoma (PCBCL) accounts for approximately 25% of all primary cutaneous lymphoma cases [1, 2]. Comprising the majority of cutaneous lymphoma cases with neoplastic B-cell origins, three main subtypes have been described (Table 1). Grossly and microscopically these subtypes are primarily similar. Non-epidermotropic, or epidermis-sparing, infiltrates of monotonous centroblasts and immunoblasts admixed with local cells is characteristic (Table 2) [3, 4]. Although morphological similar, these variants have distinct clinicopathologic, cytogenetic, molecular, and prognostic features.

Discussion

I Epidemiology, Clinical, and Prognosis

PCDLBCL-LT is exceedingly rare, accounting for less than 5% of all cutaneous lymphomas [5]. Compared to the typically indolent PCFCL and PCMZL, the clinical course of PCDLBCL-LT is characteristically aggressive, and preferentially affects elderly females [6]. As its name implies, PCDLBCL-LT almost exclusively involves the legs. However, it has been reported to initially present at other dermatologic sites [3, 7]. PCFCL is the most common subtype of PCBCL and predominantly develops on the scalp and trunk of middle-aged males (Table 3). Increased clinical awareness of PCBCLs and its variants is needed as the distinction between them has important treatment implications. A small majority of PCFCLs develop on the legs [1, 3]. Interestingly, leg involvement of any PCBCL subtype correlates with a worse prognosis.

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Poor prognostic factors for PCBCLs have been identified, such as multiple skin lesions, extracutaneous disease, elevated serum lactate dehydrogenase, BCL2 expression, and presence of a mutated MYD88 gene [8-10]. If PCDLCL-LT is confirmed by excisional skin biopsy and treatment is started, refractory disease, recurrence, and extracutaneous dissemination is common [11]. Thus, compared to the more indolent neoplasic cutaneous B-cell entities, PCDLCL-LT has a worse prognosis with only about 50% of patients achieving 5-year survival after completing first-line therapy [1]. Although no risk factors have been identified, several genetic mutations have been recently studied for their possible key roles in neoplastic cutaneous B-cell disorders. *Borrelia burgdorferi*’s role in PCMZL remains controversial and debated [12].

Table 1: Three main subtypes of primary cutaneous B-cell lymphoma according to World Health Organization classification [1].

| Distinctive variants |
|----------------------|
| Primary cutaneous diffuse large B cell lymphoma, leg type, PCDLCL-LT |
| Primary cutaneous follicle center lymphoma, PCFCL |
| Primary cutaneous marginal zone lymphoma, PCMZL |

Table 2: Summary of the common histologic findings for the main subtypes of primary cutaneous B-cell lymphoma.

| PCDLCL-LT | PCFCL | PCMZL |
|-----------|-------|-------|
| **Histology** | | |
| Diffuse non-epidermotropic infiltrates; commonly sheets of monotonous large rounded cells; many mitotic figures are common | Nodular or diffuse non-epidermotropic infiltrates consisting of monotonous follicular cells | Nodular or diffuse non-epidermotropic infiltrates |
| **Cytopathology** | | |
| Centroblasts and immunoblasts; small B-cells and reactive T-cells are rare | Centrocytes with centroblasts and immunoblasts; admixed with follicular dendritic cells and numerous reactive T-cells; follicular architecture often ill-defined | Lymphocytes, marginal zone B-cells, centrocyte-like cells, plasma cells, centroblasts, immunoblasts, and lymphoplasmacytoid cells; reactive T-cells and germinal centers |

PCDLCL-LT: primary cutaneous diffuse large B cell lymphoma- leg type; PCFCL: primary cutaneous follicle center lymphoma; PCMZL: primary cutaneous marginal zone lymphoma [3, 4].

Table 3: Summary of etiopathogenesis and characteristic clinical features of primary cutaneous B-cell lymphoma variants.

| Epidemiology | PCDLCL-LT | PCFCL | PCMZL |
|--------------|-----------|-------|-------|
| - 20% of all primary B-cell lymphomas | - 60% of all primary B-cell lymphomas | - fifth and sixth decades |
| - seventh decade | - fifth decade | - male predominance |
| - female predominance [11] | - male predominance[3] | - male predominance |

Pathogenesis | | | |
| - no identifiable risk factors or hereditary tendencies [13] | | |
| - MYC, BCL6, IGH, MALT1, CDKN2A/2B, PDL1/2, FOXP1, PAX5, PIM1, MYD88, CARD11, CD79B, and TNFAIP3/A20 mutations [10, 13] | | |
| - *Borrelia burgdorferi* [6] | | |

Clinical | | | |
| - violaceous papules, plaques, or nodule(s) +/- ulceration | - violaceous papules, plaques, or nodule(s) +/- ulceration | - violaceous papules, plaques, or nodule(s) +/- ulceration |
| - multifocal | - 75% solitary | - 50% solitary |
| - 80% leg involvement | - head/scalp > trunk | - trunk > arms |
| - aggressive | - 5% on the legs | - indolent |
| - high relapse rate, in general | - indolent | - higher relapse rate if multiple skin lesions present |
| - 60% extracutaneous dissemination [1,3,11] | - 10% extracutaneous dissemination [1,3] | - extracutaneous dissemination rare |

First-line therapy [4] | Polychemotherapy | Radiotherapy, surgery | Radiotherapy, surgery |

Additional therapies [4] | | |
| - Radiotherapy, surgery | Polychemotherapy | Polychemotherapy |
| - Monoclonal antibodies | | |
| - Lenalidomide | | |
| - Ibrutinib | | |

Prognosis | | |
| 5-year overall survival, 50-60% [1] | 5-year overall survival, 95% [1] | 5-year overall survival, 97% [8] |

PCDLCL-LT: primary cutaneous diffuse large B cell lymphoma- leg type; PCFCL: primary cutaneous follicle center lymphoma; PCMZL: primary cutaneous marginal zone lymphoma; MYC: proto-oncogene; BCL6: B-cell lymphoma 6; IGH: Immunoglobulin heavy locus; MALT1: Mucosa-associated lymphoid tissue lymphoma translocation protein 1; CDKN2A/2B: cyclin-dependent kinase inhibitor 2A/2B; PDL1/2: programmed death-1/2; FOXP1: Forkhead box P; PAX5: Paired Box 5; PIM1: proto-oncogene and serine/threonine kinase; MYD88: Myeloid differentiation primary response protein; CARD11: Caspase recruitment domain-containing protein 1; CD79B: Cluster of differentiation 79B; TNFAIP3/A20: Tumor necrosis factor, alpha-induced protein 3 or A20; Polychemotherapy, e.g. rituximab, cyclophosphamide, doxorrubicin, vincristine, and prednisone.
II Immunohistochemistry

MUM1 and BCL2 expression can allow for the distinction between PCDLBCL-LT from the less-aggressive PCFCL subtype. However, approximately 10% of PCDLBCL-LT case specimens lack MUM1 or BCL2 immunoreactivity. As a result, careful clinicopathologic correlation is required for definitive diagnosis [19]. While the germinal center marker CD10 is usually negative, BCL6 is variably positive [20-22]. CD20, PAX5, and CD79a immunoreactivity can also be used to help confirm the diagnosis. [19-22].

Table 4: Immunophenotypes of primary cutaneous B-cell lymphoma variants.

| PCBCL variants | B-cell markers | GC-markers | PG/PC markers | Other markers |
|----------------|----------------|------------|---------------|---------------|
|                | CD20 | CD79a | PAX5 | CD10 | BCL6 | MUM1 | CD138 | MYC | BCL2 | CD30 | PD-1 |
| PCDLBCL-LT | +    | +    | -    | -    | +/-  | +    | -    | +/-  | +    | -    | +/-  |
| CL-LT         | +    | +    | +/-  | +    | -    | +/-  | -    | +/-  | -    | -    | -    |
| PCFCL         | +    | +    | +/-  | +    | -    | +/-  | -    | +/-  | -    | -    | -    |
| PCMZL         | +/-  | +/-  | +/-  | +/-  | +/-  | +/-  | +/-  | +/-  | +/-  | +/-  | +/-  |

PCBCL: primary cutaneous B-cell lymphoma; PCDLBCL-LT: primary cutaneous diffuse large B cell lymphoma- leg type; PCFCL: primary cutaneous follicle center lymphoma; PCMZL: primary cutaneous marginal zone lymphoma; GC: germinal center; PG: post-germinall; PC: plasma cell; PAX5: Paired Box 5; BCL6: B-cell lymphoma 6; MUM1: Multiple Myeloma 1; BCL2: B-cell lymphoma 2; PD-1: programmed death-1; N/A: data not available; +, more commonly cases are positive; +/-, commonly cases are positive; +/-, less commonly cases are positive; -, more commonly cases are negative [1, 4, 6, 11, 12, 14-18].

III Genes and Molecular Studies

Extracutaneous dissemination is more characteristic of PCDLBCL-LT and PCFCL [1]. When metastatic disease occurs, regional lymph nodes and the bone marrow are typically involved. PCDLBCL-LT has also been reported to disseminate to the central nervous system [19, 20, 24]. For PCFCL, it remains unclear which genetic aberrations lead to a more aggressive disease course since this specific PCBCL variant rarely, if at all, harbor MYD88 mutations and translocations in BCL6, MYC, and IGH [1].

The high prevalence of MYD88 mutations in PCDLBCL-LT patients suggests its putative role as a driver event of carcinogenesis [9,10]. Determining MYD88 mutation status is necessary for diagnosis, prognosis, and management [25]. MYD88 proto-oncogene mutations promote activated B-cell survival through nuclear factor kappa B (NF-kB) pathway activation. Alterations in MYD88 gene are present in up to 75% of PCDLBCL-LT cases, and is associated with decreased survival [4, 8-10]. Although the MYD88 mutation is deleterious and associated with a poor prognosis, NF-kB pathway activation can block by targeted BTK-inhibitor therapy, such as with ibrutinib [26, 27]. Although ibrutinib therapy appears promising for PCDLBCL-LT patients, much works remains to further elucidate the molecular mechanisms that could explain tumor recurrence or resistance [26, 27]. Earlier identification of aberrant NF-kB or B-cell receptor signaling pathways and use of targeted therapies like ibrutinib could improve quality of life and survival in PCDLBCL-LT patients.

Similarly, inactivation of 9p21.3 (associated with the CDKN2A tumor-suppressor gene) has recently been associated with disease progression and a poor prognosis in PCDLBCL-LT patients [28]. It remains unclear if the co-occurrence of MYD88 and CDKN2A mutations synergistically impose a worse prognosis. However, this thought warrants further considerations, especially since BTK- and CDK inhibitors are already available and widely used, such as ibrutinib and abemaciclib, respectively. Although little is known about the significance of this co-occurrence in PCDLBCL-LT, much could potentially be gained by turning the attention to primary central nervous system lymphoma (PCNSL). Recent molecular work using matched primary and recurrent malignant tissue from PCNSL patients suggest simultaneous genetic alterations in the MYD88 and CDKN2A genes may predict recurrence [29]. This case report could serve as a basis to launch such investigations in PCDLBCL-LT patients. Finally, PCDLBCL-LT hosts the highest incidence of MYC rearrangement (32%) of any diffuse large B-cell lymphoma subtype. The presence of the MYC rearrangement is significantly associated with a reduced 5-year disease-specific survival and disease-free survival [30].

IV Treatment

PCBCL treatment is based on the specific subtype, extent of disease, and risk stratification [4]. Anecdotally, various therapeutic options exist, but indications lack support from randomized controlled trials to help guide clinical decisions. Due to the more indolent courses of PCFCL and PMZL less aggressive first-line therapeutic modalities are recommended. First-line polychemotherapy is indicated for PCLBCL-LT initially due to its associated worse prognosis, and advanced or refractory PCFCL and PCMZL. The relapse rate is high for PCLBCL-LT, which often requires additional lines of treatment with more targeted therapies (Table 3) [4].

Spontaneous regression of PCDLBCL-LT without treatment is extremely rare with only four cases reported in the literature [31-33]. Histology findings from 75% of the reported cases showed a significant dermal T-cell infiltrate [32, 33]. This suggests an inadequate T-cell immune response may play an important role in the disease pathogenesis and progression [32]. Whether or not this could potentially contribute to
future use of immune checkpoint inhibitors in PCDLBCL-LT remains unknown.

First-line treatment for PCDLBCL-LT is anthracycline-based chemotherapy combined with rituximab [34]. However, not all patients are eligible for this treatment owing to age and comorbidity. Therefore, different rituximab plus polychemotherapy (R-PCT) combinations are alternatively used, regardless of the clinical stage. R-PCT with or without anthracyclines significantly increases 5-year survival rates [1, 35]. However, patients often progress despite treatment [35, 36].

Lenalidomide, an oral immunomodulatory agent, has shown promise against activated B-cell diffuse large B-cell lymphomas (ABC-DLBCL) by enhancing the activity of cytotoxic T and NK-cells. It exhibits both anti-proliferative and anti-angiogenic effects through upregulation of tumor suppressor genes [37]. By these mechanisms, lenalidomide has been shown to have a direct effect on DLBCL cell lines by decreasing NF-κB signaling pathway activity in pre-clinical trial [38]. Previous studies have shown efficacy of lenalidomide in relapsing and refractory DLBCL, improving overall response rate [8, 38, 39]. Moreover, lenalidomide appears to have an exceptional safety profile in elderly patients with non-germinal center B-cell / activated B-cell line phenotypes [40-43]. However, the presence of an MYD88 mutation in PCDLBCL-LT is associated with a lower 6-month overall response rate, rendering it a limited therapeutic option in relapsing or refractory PCDLBCL-LT [36].

BTK, a key signaling molecule in B-cell receptor and NF-κB signaling pathway, is constitutively activated in ABC-DLBCL due aberrant genetic alterations [44]. Ibrutinib, an irreversible inhibitor of BTK, is an established therapeutic agent in a variety of B-cell lymphoproliferative disorders. It disrupts the B-cell receptor signaling pathway, thereby arresting disease progression in B-cell lymphomas. It has been demonstrated to be effective in patients with ABC-DLBCL, particularly those with CD79B and MYD88 co-mutations [27]. However, ibrutinib is associated with an increased incidence of infections in patients with B-cell malignancies. Patients receiving ibrutinib should be vigilantly monitored for development of infections [45, 46]. Life-threatening HBV reactivation is considered to be one of the potential infectious complications of ibrutinib. Physicians should be aware of the potential risks of HBV reactivation that can occur following ibrutinib therapy in patients with past or chronic HBV infection [47]. Also, notably ibrutinib is associated with increased risk of atrial fibrillation and bleeding diathesis [48, 49].

**Conclusion**

PCBCLs are unique and rare manifestations of extranodal lymphomas. Of the three main subtypes, PCDLBCL-LT is the most aggressive characterized by frequent extracutaneous dissemination, high rates of relapse, and a significantly lower 5-year overall survival. Despite more aggressive therapeutic modalities, such as polychemotherapy, being recommended as first-line treatment recurrence is common in PCDLBCL-LT patients compared to the more indolent PCFCL and PCMZL variants. When PCDLBCL-LT is diagnosed by skin biopsy, treatment should be started immediately, and routine close monitoring is recommended since patients often do not achieve complete remission early in their disease course. Much work has revealed PCDLBCL-LT patients harbor unique genetic aberrations. Although no randomized controlled trials studying newer, targeted therapies specifically in PCDLBCL-LT patients exist, certain therapeutic modalities used in other neoplastic B-cell disorders have shown to be efficacious.

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