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A case series of primary cutaneous B-cell lymphomas with atypical presentations: diagnostic and therapeutic challenges

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Primary cutaneous B cell lymphomas (PCBCL) are defined as B-cell lymphomas of the skin without nodal, bone marrow, or visceral involvement at time of diagnosis.\textsuperscript{1} They represent approximately 25\% of primary cutaneous lymphomas.\textsuperscript{1,2} Histopathological diagnosis of PCBCL can be challenging in certain instances where overlapping features are present. Nevertheless, identification of the correct subtype of PCBCL is imperative for determining the prognosis and avoiding inappropriate aggressive treatments which could lead to unnecessary morbidity.\textsuperscript{3} Here we present a series of three cases that highlight the distinguishing features between two subtypes of PCBCL.

The first case was a 57-year-old African-American man with multiple pruritic nodules on his abdomen that appeared and rapidly progressed in size six months prior to presentation (Figure 1A). Review of systems was negative for pain, weight loss, night sweats or fevers. Blood flow cytometry analysis was normal, and PET scan was negative for metabolically active lymph nodes or systemic disease. Skin biopsy demonstrated sheets of large atypical lymphoid aggregates with centroblast morphology extending into the entire thickness of the dermis with accompanying significant reactive small-sized lymphocytic infiltrate (Figure 2B). The large cells expressed CD20 and BCL6 but were negative for CD10, BCL2, and MUM-1 on immunostaining (Figure 1D, E, F, G, H). Ki67 stain showed a proliferation rate of 30-40\%. B-cell receptor clonality assay (clonoseq) identified two dominant immunoglobulin heavy chain sequences. An initial diagnosis of Diffuse Large B-cell Lymphoma (DLBCL) was considered, but a complete histopathological review with clinical correlation rendered the final diagnosis of Primary Cutaneous Follicle Center Lymphoma (PCFCL) with diffuse pattern. Three large lesions were excised and local radiation therapy provided total regression of the rest of the abdominal tumors without recurrence to date (two years).

The second case was an 83-year-old Caucasian male presenting with an erythematous, asymptomatic growth on the forehead that had increased in size to 6 x 7 cm over six months (Figure 2A). The patient had no systemic symptoms of fevers, night sweats, weight loss, or lymphadenopathy. Punch biopsy of the lesion demonstrated a dense lymphocytic neoplasm composed of centroblasts and immunoblasts positive for CD10, CD20, and BCL6 but negative for MUM1. Small-sized reactive lymphocytes were BCL2 positive (Figure 2B, D, E, F, G, H). Immunoglobulin heavy chain gene-rearrangement studies were positive for monoclonality. Blood flow cytometry analysis and PET scan were negative for blood or systemic involvement. This case was also initially diagnosed as DLBCL, but a secondary histopathological review combined with
clinical correlation led to a diagnosis of PCFCL with diffuse pattern. Radiation therapy provided complete regression of the tumor without recurrence to date (one and a half years).

The third case was a 72-year-old gentleman with a history of stage III chronic kidney disease and heart failure who presented with a tender pink tumor on his scalp that abruptly appeared as a small papule but rapidly grew in size to 4 x 4 cm over one month (Figure 3A). History was negative for fever, lymphadenopathy, fatigue, night sweats, and systemic symptoms. Punch biopsy revealed a sheet-like diffuse dense infiltrate composed of cells with immunoblastic morphology and high mitotic activity (Figure 3B). The atypical lymphocytes stained positive for CD10, CD20, BCL2, BCL6, and MUM1 (Figure 3D, E, F, G, H) with more than 80% proliferative population based on Ki-67 positivity. Fluorescent in-situ hybridization (FISH) test was positive for a BCL-6 gene rearrangement (18% of nuclei) and negative for rearrangement of MYC, CCND1, and BCL2. A dominant immunoglobulin heavy chain sequence with a 99% frequency of all nucleated cells was identified by immunosequencing (ClonoSeq). PET scan revealed a hypermetabolic scalp lesion with no evidence of lymph node or systemic involvement, and blood flow cytometry analysis was normal. The patient was diagnosed with Primary Cutaneous Diffuse Large B-Cell Lymphoma, Leg Type (PCDLBCL, LT). Combination chemotherapy with R-CHOP was not initiated due to poor ejection fraction (48%). Instead, given his comorbidities and life expectancy, he received radiation therapy with complete resolution of lesion, confirmed with PET scan. Due to his aggressive diagnosis, the patient was closely monitored by oncology without recurrence for two years until he passed due to cardiac arrest from his comorbidities.

The three cases presented here highlight the challenge of distinguishing between PCFCL and PCDLBCL-LT, two of the three main subtypes of PCBCL. The first two cases of PCFCL were originally diagnosed as DLBCL without specification. The correct diagnosis of diffuse PCFCL was made after a secondary histological consultation along with clinical correlation. The third case illustrates the fact a PCDLBCL, LT can present on the scalp.

For the first two cases, the absence of follicular pattern and diffuse sheets of atypical large cells gave an initial impression of DLBCL while the lack of expression of MUM1 and the presence of reactive infiltrate clearly pointed to the diagnosis of PCFCL. Although all cases showed a diffuse infiltrate on histology, their histomorphology, immunophenotype, pattern of molecular aberration on FISH analysis, and clinical presentation distinguished the correct diagnosis. This underscores the importance of recognizing PCFCL with diffuse pattern to avoid overcalling DLBCL and the resulting unnecessary aggressive treatment.
Histomorphology should be interrogated in detail to arrive to the correct diagnosis in PCBCLs. Although diffuse sheets of cells were seen in all cases, a close evaluation of cellular morphology clearly distinguishes DLBCL from other subtypes. Large cells with multiple mitotic figures and nuclear atypia in PCDLBCL, LT directly contrast with smaller cells and condensed nuclei seen in PCFCL cases (Figure 1C, 2C, 3C).

Immunohistochemistry is an essential tool in diagnosing the subtypes of PCBCLs. MUM-1 positivity precludes PCFCL and must be investigated before making a diagnosis of all subtypes of PCBCLs. BCL-2 is not expressed by malignant cells in PCFCL, but it may be present in reactive T-cells. In the second case of the series, BCL-2 was originally called positive but upon further evaluation it was clear that only reactive cells expressed BCL-2. FISH studies can be utilized in cases of PCDLBCL, LT, and we found a positive BCL-6 gene rearrangement in our case.

Overall, these cases demonstrate the architectural, histomorphological, and immunohistochemical features that can distinguish PCFCL from PCDLBCL, LT and highlight the diagnostic challenges that arise as a result of overlapping characteristics. The clinical impact of this overlap is most acutely felt in PCDLBCL, LT, because of its more aggressive course and the fact that radiation therapy alone is generally considered inadequate. While there is currently no evidence-based standard of care, most patients with PCDLBCL, LT are treated as systemic DLBCL, with rituximab and CHOP chemoimmunotherapy, often with CNS prophylaxis, due to high risk of CNS dissemination. The addition of radiation therapy to chemoimmunotherapy was found to be important in a recent case series. Despite historical data showing that the outcomes of patients with PCDLBCL,LT have improved since the introduction of modern chemoimmunotherapy, outcomes remain relatively poor. In addition, many patients are unfit for chemotherapy, due to age or comorbidities. In the cohort of Grange et al (2014) about 50% of the patients were older than 80 years. At the moment, front line radiation therapy, especially for localized, unifocal disease, is an acceptable option for elderly and frail patients, and some, including case three presented here, have durable responses and long progression free survival.

The clinical and histological findings for B-cell lymphomas can vary widely. The clinical picture in the first case reminds readers that it is possible to have multiple lesions in PCFCL, including multifocal lesions, although it is often thought to present as a solitary lesion. The second case emphasizes that histological and immunohistochemical results must be assessed together, without relying on one over the other. Case three cautions physicians that PCDLBCL, LT can occur
elsewhere on the body while having overlapping histological features with PCFCL. Due to the complexity of cutaneous lymphomas, it is imperative for physicians to work together in a multidisciplinary team with dermatology, oncology, dermatopathology and radiation oncology in order to provide the best care for these patients
REFERENCES:


**Figure 1.** Primary Cutaneous Follicle Center Lymphoma designated by various features. A) Three firm ill-defined pink tumors, 2 to 3 cm in size, with surrounding erythematous plaques and significant induration on the mid abdomen B-C) dense lymphocytic infiltrate of small to medium sized lymphocytes with condensed nuclei (H&E, B. 40x C. 100x) that are D) CD10- E) CD20+ F) BCL2- G) BCL6+ H) MUM1-

**Figure 2.** A different presentation of Primary Cutaneous Follicle Center Lymphoma is shown. A) Single firm erythematous tumor on right forehead B-C) dense infiltrate of medium sized centroblasts and immunoblasts in the dermis (H&E, B. 40x C. 100x) that are D) CD10+ E) CD20+ F) BCL2- on large cells, BCL2+ on reactive cells G) BCL6+ H) MUM1-

**Figure 3.** Primary Cutaneous Diffuse Large B-Cell Lymphoma, Leg Type is defined by features seen in this figure. A) Well-defined tumor on left parietal scalp with B-C) diffuse proliferation of large polygonal lymphocytes with high mitotic activity, large nuclei, and little cytoplasm (H&E, B. 40x C. 100x) that are D) CD10+ E) CD20+ F) BCL2+ G) BCL6+ H) MUM1+