Primary cutaneous B-cell lymphomas—clinical and histopathologic features, differential diagnosis, and treatment

Steven T Chen, MD, MPH[1,2,3]; Jeffrey Barnes, MD, PhD[1,3,4]; and Lyn Duncan, MD[1,5]

Abstract

Cutaneous B-cell lymphomas (CBCLs) are a heterogeneous group of diseases that can have variable presentations, prognoses, and treatments. The proper identification of a CBCL hinges on proper histopathologic and clinical evaluation. Comprising 25% to 30% of the primary cutaneous lymphomas, incident cases of CBCL are rare. Given the variable natural history of the CBCL, proper classification is critical so that patients are treated appropriately. CBCLs can be divided into 2 main groups: indolent and aggressive. Indolent CBCLs include primary cutaneous follicle center lymphoma and primary cutaneous marginal zone lymphoma. These subtypes usually do not affect a patient's lifespan but can lead to substantial symptomatology, prompting the need for treatment. The aggressive subtypes of CBCL include diffuse large B-cell lymphoma leg type and intravascular large B-cell lymphoma. These are treated as systemic lymphomas, and their prognoses are not as good. In this article, we discuss the clinical features, differential diagnoses, histopathologic features, and treatment options for each of the 4 types of CBCL. The proper categorization of these diseases can allow physicians to properly treat a patient with CBCL, including the avoidance of unnecessary therapy.

Semin Cutan Med Surg 37:49-55 © 2018 Frontline Medical Communications

In 2017, there will be an estimated 72,000 cases of non-Hodgkin lymphoma.[1] Less than 5% of these will be a form of primary cutaneous lymphoma.[1] Primary cutaneous lymphoma occurs at an incidence of 0.5 to 1 per 100,000 persons annually.[2,3] Cutaneous B-cell lymphomas (CBCLs) make up approximately 25% to 30% of all primary cutaneous lymphomas. The majority of primary cutaneous lymphomas are cutaneous T-cell lymphomas.[2,3]

The CBCLs can be further subdivided into those with indolent behavior and those with aggressive clinical behavior.[2] The indolent CBCLs include primary cutaneous marginal zone lymphoma (PCMZL) and primary cutaneous follicle center lymphoma (PCFCL). The aggressive clinical behavior group includes diffuse large B-cell lymphoma leg type (DLBCL-LT) and intravascular large B-cell lymphoma (IVLBCL), a subtype of diffuse large B-cell lymphoma other.[2] The treatments and workup pursued for each type of B-cell lymphoma can vary widely. As such, the diagnosis is critical in ensuring appropriate management. Proper diagnosis depends on clinical features consistent with the diagnosis and a review of histopathologic features.

Indolent cutaneous B-cell lymphomas

The 2 subtypes of CBCL that are indolent are PCFCL and PCMZL.[2] The clinical features, workup, and treatment options for these two entities are quite similar. Histopathology differentiates the two, but otherwise management is largely identical.

Clinical features

Both PCFCL and PCMZL are more commonly found on the head, neck, and shoulders and usually present with an edematous pink erythematous to violaceous papule or plaque (Figure 1).[4] Patients often report suspecting a mosquito or other insect bite but present to a physician when the lesion does not resolve. Lesions can be pruritic and are seldom painful. A skin biopsy (either excisional or punch) is the diagnostic procedure of choice.[4]

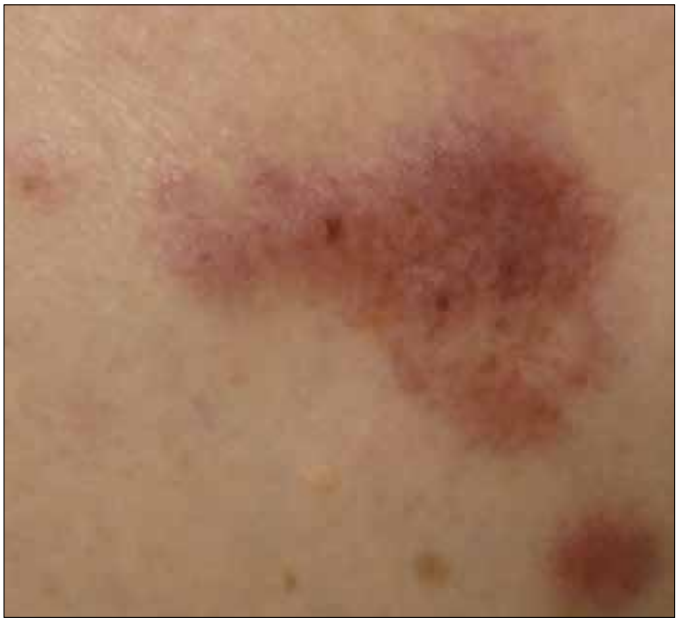


FIGURE 1. PCMZL. On the right upper shoulder, there is a large erythematous to violaceous plaque approximately 4 centimeters in size. Inferior to this plaque is a smaller erythematous to violaceous plaque approximately 1 centimeter in size. PCMZL, primary cutaneous marginal zone lymphoma.

[1]Harvard Medical School, Boston, Massachusetts.
[2]Department of Dermatology, Massachusetts General Hospital, Boston, Massachusetts.
[3]Department of Internal Medicine, Massachusetts General Hospital, Boston, Massachusetts.
[4]Division of Hematology and Oncology, Massachusetts General Hospital, Boston, Massachusetts.
[5]Pathology Service, Massachusetts General Hospital, Boston, Massachusetts.

Disclosures: The authors have nothing to disclose.

Correspondence: Steven T Chen, MD, MPH; stchen@partners.org

1085-5629/13$-see front matter © 2018 Frontline Medical Communications
DOI: https://doi.org/10.12788/j.sder.2018.014

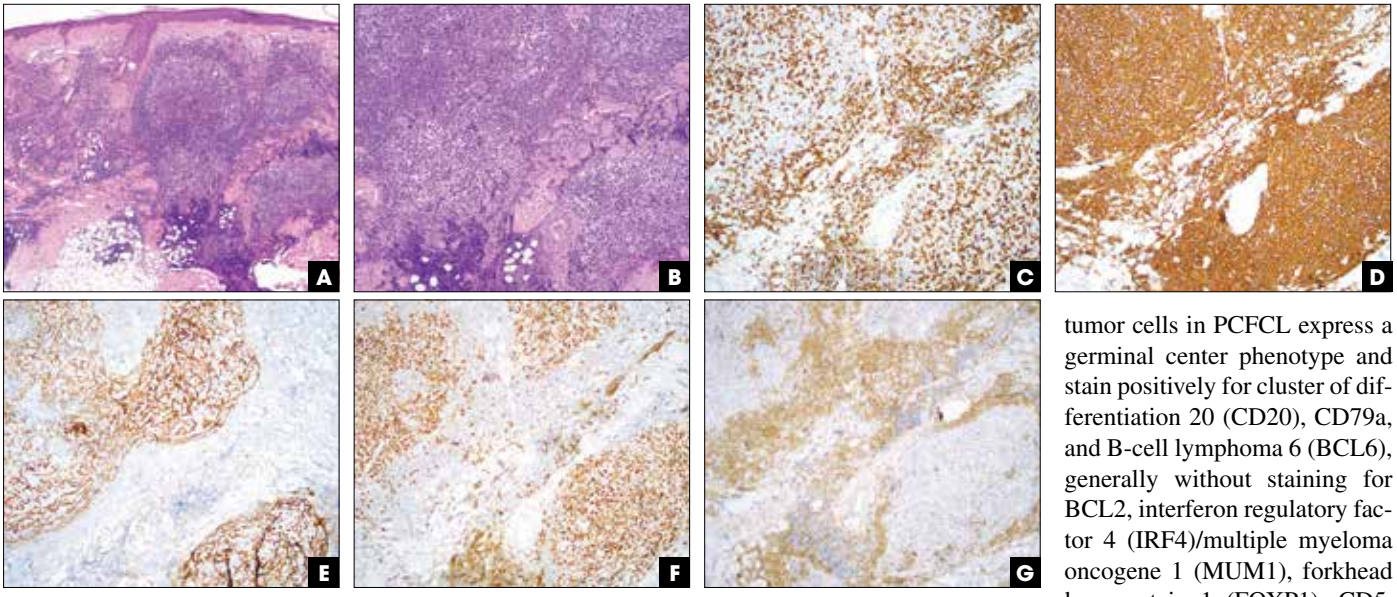


FIGURE 2. PCFCL. **(A)** Scanning magnification reveals a dermal and subcutaneous lymphocytic infiltrate; **(B)** irregularly shaped proliferations of follicle center cells; **(C)** admixed CD3+ T cells; **(D)** the tumor cells stain positively for CD20; **(E)** CD21 revealed irregularly shaped follicular dendritic cell meshworks; **(F)** the tumor cells stain positively for BCL6; **(G)** the tumor does not stain for BCL2. Abbreviations: BCL6, B-cell lymphoma 6; CD3, cluster of differentiation 3; PCFCL, primary cutaneous follicle center lymphoma.

The differential diagnosis for these lesions usually includes reactive lymphoid hyperplasia, a hypersensitivity reaction secondary to insect bites or other inflammatory trigger, nonmelanoma skin cancers, and systemic lymphomas that may have secondarily involved the skin.

Of note, cases of PCMZL in Europe have been associated with infection by *Borrelia burgdorferi*,[5] and as such, antibiotics have been included in some treatment algorithms.[6] This association has not been reported in the United States.[7]

Histopathology

Both PCFCL and PCMZL are characterized histopathologically by a predominantly dermal, somewhat nodular lymphoid infiltrate usually separated from the overlying epidermis by a grenz zone of uninvolved papillary dermis. These infiltrates may be subtle and involve only the superficial dermis or extend deep into the subcutaneous fat. It is important to note that numerous T cells are often present in association with CBCL.

PCFCL may have a follicular, follicular and diffuse, or diffuse growth pattern.[8,9] In the follicular pattern of growth, there is usually a nodular pattern in which the lesional cells form irregularly shaped follicles, often supported by expanded follicular dendritic cell meshworks. When these collections of tumor cells are without a mantle zone and are directly apposed to the reticular dermal collagen they may be termed "naked follicles." Occasionally, this proliferation of centrocytes and centroblasts surrounds collections of small T cells and B cells, forming so-called "inside-out follicles" (Figure 2). In the diffuse pattern of growth, there are typically diffuse sheets of lesional lymphocytes, and the aberrant follicle formation seen in the follicular pattern is not present. The tumor cells in PCFCL express a germinal center phenotype and stain positively for cluster of differentiation 20 (CD20), CD79a, and B-cell lymphoma 6 (BCL6), generally without staining for BCL2, interferon regulatory factor 4 (IRF4)/multiple myeloma oncogene 1 (MUM1), forkhead box protein 1 (FOXP1), CD5, and CD43.[8,10-13] Light chain-restricted plasma cells are not present. Clonal immunoglobulin rearrangement may be detected with polymerase chain reaction. BCL2 rearrangement is typically absent in PCFCL. Point mutations in BCL6, MYC, RhoH/TTF, and paired box protein 5 (PAX5) secondary to aberrant somatic hypermutation have been observed.[13,14]

PCMZL is characterized by a neoplastic proliferation of monocytoid B cells, lymphoplasmacytoid cells, and plasma cells (Figure 3).[15-18] Plasma cells may be prominent or inconspicuous; in cases with few plasma cells, there is usually a predominance of monocytoid B cells. Reactive lymphoid follicles are usually present and may be colonized by neoplastic B cells.[19] Dutcher bodies (intranuclear PAS+ immunoglobulin pseudo-inclusions found in plasma cells) may be seen. Formation of lymphoepithelial lesions in adnexal structures (groups of 3 or more marginal zone cells with epithelial destruction) is rarely observed but helpful when present. The neoplastic B cells typically have a CD20+, BCL2+, CD79a+, BCL6− immunophenotype. Light chain restriction in plasma cells is detected by immunohistochemistry or in situ hybridization in 70% of cases.[20] Plasma cells in PCMZL usually express immunoglobulin G (IgG), in contrast to MZL at other extranodal sites, which typically express IgM.[16] Abnormalities in the MALT1 gene and trisomy 18 are infrequent.[15] Aberrant somatic hypermutation of PAX5, RhoH/TTF, cMYC, and PIM1 has been described.[16,21]

Further investigation

A relatively recent proposal from the International Society of Cutaneous Lymphomas (ISCL) and the United States Cutaneous Lymphoma Consortium (USCLC) advocates for staging these patients.[22] This includes a history and physical exam, laboratory investigations, and imaging studies including computed tomography (CT). The need for a bone marrow biopsy is somewhat debated in the literature, although most studies suggest that probably is not

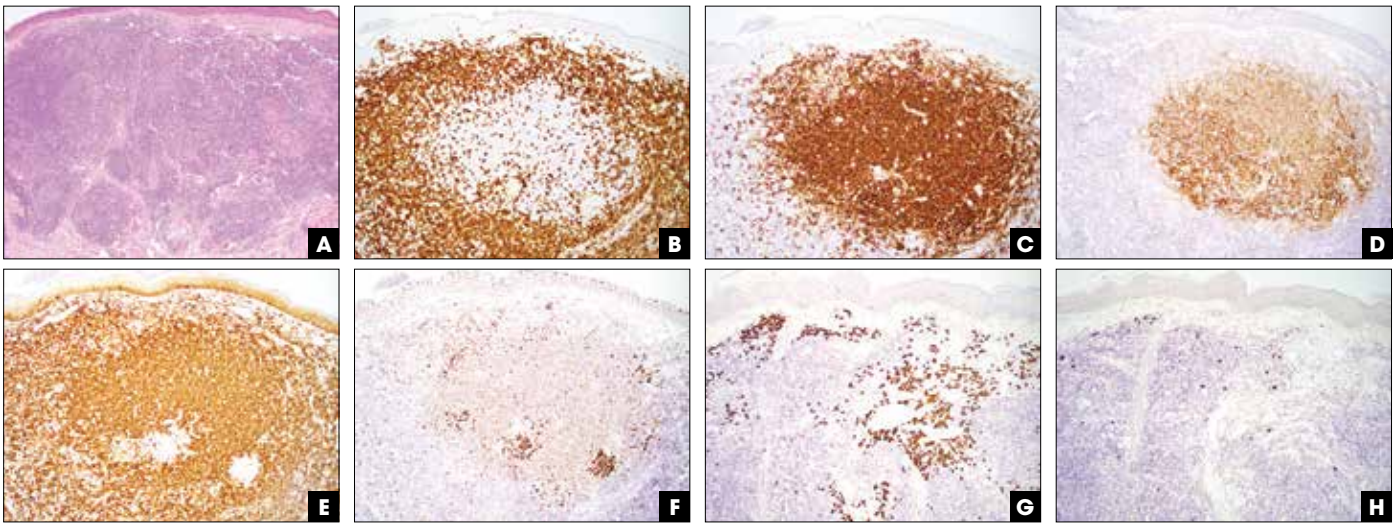


FIGURE 3. Primary cutaneous marginal zone B-cell lymphoma. **(A)** Scanning magnification reveals a dermal infiltrate with minimal involvement of the overlying epidermis; **(B)** $CD3^+$ T cells surround the tumor cells; **(C)** the tumor cells stain positively for CD20; **(D)** CD21 stain reveals a dispersed oval meshwork of follicular dendritic cells; **(E)** BCL2 stains the reactive T cells and neoplastic B cells, and negative zones correspond to residual non-neoplastic follicle center cells; **(F)** the non-neoplastic aggregates of follicle center cells stain positively for BCL6; **(G)** lambda light chains are detected in most of the plasma cells, consistent with light chain restriction; **(H)** a minor population of plasma cells stain for kappa light chains.

necessary. It is suggested that the clinician follow the standard of care of his or her regional practice.

Patients present with either solitary lesions or multiple lesions spread over the cutaneous surface, making a complete skin exam important in the evaluation of these patients.[4] Attention should be paid to the lymph node exam and a full review of systems taken. In PCFCL and PCMZL, the review of systems is usually negative for any "B symptoms" such as weight loss, fevers, or night sweats. Any lymphadenopathy or positive symptoms on review should prompt a consideration of a systemic lymphoma that has secondarily affected the skin. Certain histopathologic features, such as strong positive staining for BCL2 in FCL or expression of IgM in MZL, should also prompt consideration of systemic lymphoma. Regardless, given the higher incidence of systemic lymphomas yearly than primary cutaneous lymphomas, our practice, in agreement with the recently published proposals of the ISCL and USCLC,[22] includes a full staging evaluation in order to exclude systemic involvement. This includes checking a complete blood count (CBC), a comprehensive metabolic panel (CMP), lactate dehydrogenase (LDH), and a CT scan of the chest, abdomen, and pelvis. Some institutions prefer the use of positron emission tomography (PET) scans.

Treatment

Given the indolent nature of these tumors, treatment is not overly aggressive and therefore very well tolerated. There is a preference to treat patients with radiation therapy, given the good clinical result with complete resolution in most cases, the lack of severe side effects, and the lack of scarring that can occur with other treatment modalities.[23] If the lymphoma recurs, it generally occurs outside of the original field of treatment. One nuance for the radiation dosed is the number of lesions present on presentation. If only one lesion is noted, definitive dosing is often used with 10 to 12 fractions of 2 gray, amounting to a total of 20 to 24 gray total. However, if multiple lesions are present, palliative dosing is used, given the patient's propensity to develop more lesions. This dosing is usually 2 gray given twice over 2 consecutive days.[24]

Indolent CBCL can also be treated with surgical excision, but this leaves the patient with a scar, and there is a paucity of evidence regarding appropriate clinical margins and rate of recurrence. For that reason, surgical excision might be avoided as a first-line treatment.

Topical steroids can be trialed, but response is variable given the depth of the neoplastic infiltrate. Intralesional steroids injected directly into the lesion can have a good effect; however, the tumor may recur, and skin atrophy, erythema, and other local adverse effects are possible.[25]

Finally, in rare cases in which patients have too many lesions to easily treat with any of the aforementioned modalities, we consider treatment with rituximab, an anti-CD20 monoclonal antibody that targets B cells.[26]

Follow-up

Follow-up intervals for patients with indolent CBCL are usually at every 6 months for a complete cutaneous and lymph node exam. Any new lesions that are consistent with the patient's original lymphoma are often biopsied to confirm diagnosis. However, if the patient continues to present with more lesions, the diagnosis is then usually made clinically in the future. If recurrent disease occurs, they are again referred to radiation oncology for palliative dosing as detailed previously. Some patients prefer to trial other treatment modalities, and as such, patient preference plays a significant role in deciding on future therapy. It is important to note that CT scans and blood work are seldom repeated af-

ter initial diagnosis. We will only repeat these tests if the patient reports new "B symptoms" or presents with new signs on exam (such as lymphadenopathy), in part to evaluate for the possibility of systemic lymphoma.

Aggressive cutaneous B-cell lymphomas

Although classified as a primary cutaneous lymphoma, the two entities within this category may be considered from a clinical approach to be systemic diseases, requiring systemic treatment. Unlike the indolent lymphomas, the two subtypes of aggressive CBCL are rather different and will be presented separately.

Diffuse large B-cell lymphoma leg type

Primary cutaneous DLBCL-LT usually presents with an aggressive clinical course and is associated with a 5-year survival of less than 50%.[27,28] This subtype makes up roughly 20% of all primary CBCLs.

Clinical features

DLBCL-LT presents as solitary or multiple red to violaceous nodule(s) or tumors commonly arising on the legs, either bilaterally or unilaterally.[9,27] Despite the name, 10% of cases can present at a site other than the leg (Figure 4).[9] In fact, prognosis is better for these patients with DLBCL-LT not on the leg.[16] Disease can be multifocal in 20% of patients with dissemination to nodal and visceral sites.[27,28] Given the often systemic nature of this disease, patients may complain of "B symptoms," such as fever, night sweats, and weight loss. Biopsy of a skin lesion is important for the diagnosis; staging scans, including PET and bloodwork, are also critical components of the workup. A bone marrow biopsy is recommended according to recent ISCL/USCLC guidelines.[22] Given the systemic illness often felt by the patient, the differential diagnosis usually includes other neoplastic diseases, other non-Hodgkin systemic lymphoma, or leukemia. Solid malignancies can also present similarly in rare instances. Other diseases that can cause diffuse lymphadenopathy and B symptoms include infectious diseases and connective tissue diseases as well as systemic hypersensitivity reactions.

Histopathology

DLBCL-LT is a neoplasm predominantly of centroblasts or immunoblasts, or a combination of both, that usually diffusely effaces the dermis and may extend into the subcutaneous fat. The tumor may be ulcerated, or the epidermis may be uninvolved (Figure 5).[29] The neoplastic B cells have large, round, noncleaved nuclei and typically express CD20, CD79a, PAX5, IRF4/MUM1, BCL2, and FOXP1. BCL6 may be present, dim, or absent. Approximately 10% of cases lack BCL2 and/or IRF4/MUM1 expression. Mitoses are common. In contrast to the indolent CBCL, fewer reactive T cells are observed in association with DLBCL-LT.[29,30] Most DLBCL-LTs demonstrate chromosomal imbalances. Approximately two-thirds of tumors have deletion of 9p21.3 (containing the *CDKN2A* and *CDKN2B* genes); reduced expression of the *CDKN2A* and *CDKN2B* genes resulting from deletion or hypermethylation is associated with a poor prognosis.[21,29,31] Amplification of 18q21.31-q21.33, a region that includes the genes *BCL2* and *MALT1*, is often detected, whereas the t(14;18) translocation is typically absent. Additional markers that have been associated with a poor prognosis include IRF4/MUM1, organic cation transporter 2 (OCT2), and FOXP1 and inactivation of the *CDKN2A* gene.[21,29,32,33] By contrast, tumor cell expression of FOXP3 and the presence of regulatory T cells has been associated with a better prognosis.[34]

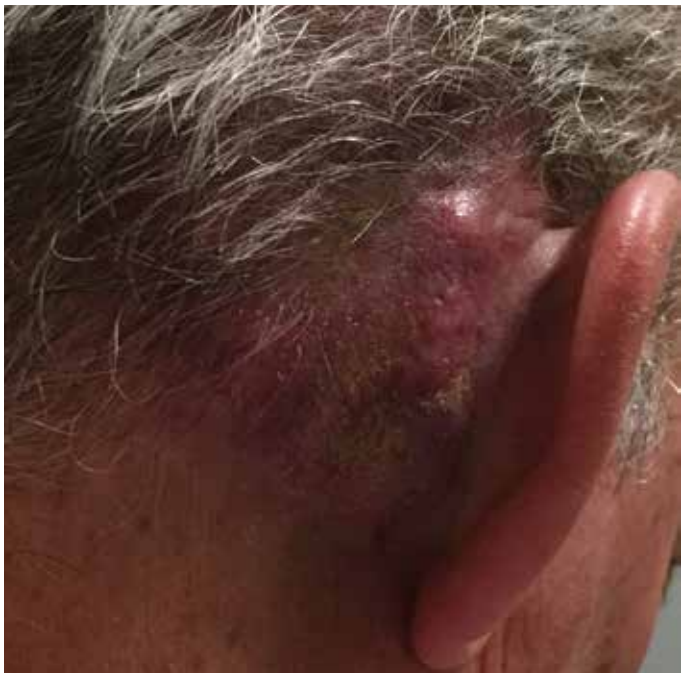


FIGURE 4. Diffuse large B-cell lymphoma. On the right postauricular area, there is a 4-centimeter erythematous and violaceous tumor.

Further investigations

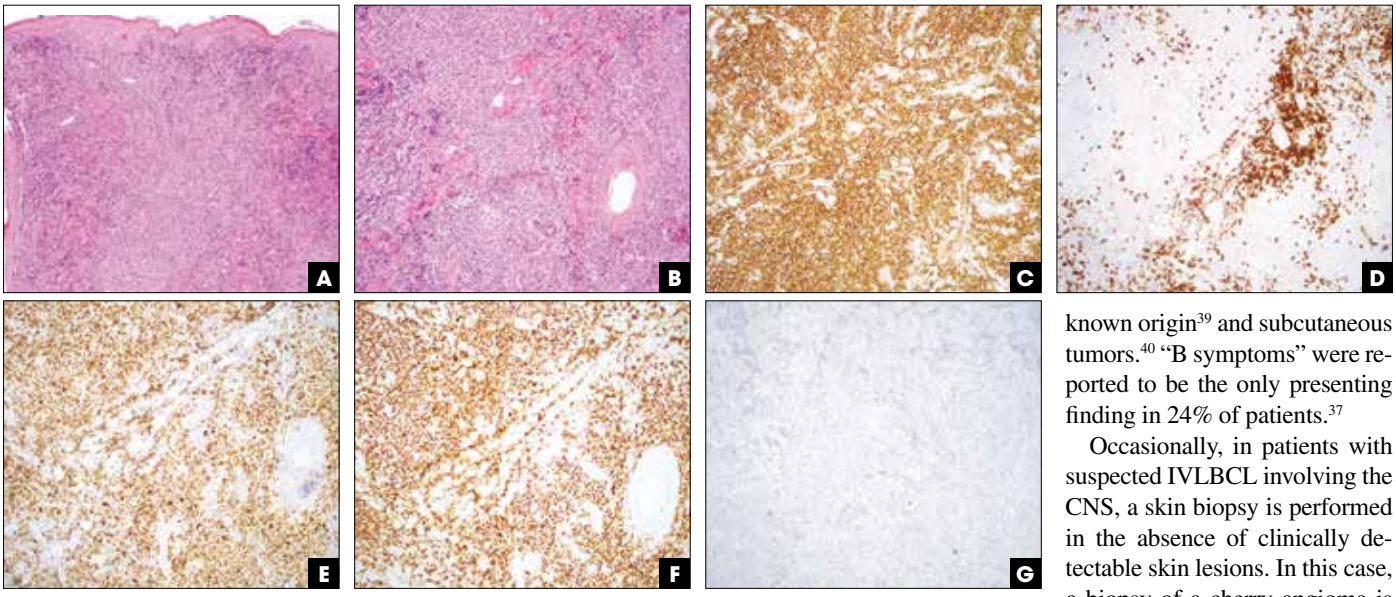
Patients will undergo laboratory workup, including CBC, CMP, LDH, and uric acid. CT scan of the chest, abdomen, and pelvis with PET is critical to complete staging evaluation. Given that treatment often includes anthracyclines, an echocardiogram is also recommended. As discussed above, bone marrow biopsy is advised in this diagnosis.[22]

Treatment

Most patients with DLBCL-LT are best treated with Rituximab, Cyclophosphamide, Adriamycin, Oncovin, and Prednisone (R-CHOP).[9,26,27,36] Patients are dosed as per oncology protocol and usually undergo 6 cycles of therapy. Patients who do not respond to R-CHOP therapy may require subsequent therapy that may include salvage chemotherapy with autologous stem cell transplant, radiation, and/or clinical trial enrollment.

Follow-up

Patients with DLBCL-LT are usually advised to follow up with their oncologists every 3 months soon after initial treatment. Provided patients do well, they will space their visits out accordingly and eventually graduate to a yearly follow-up visit. At follow-up



■ **FIGURE 5.** DLBCL-LT. **(A)** Scanning magnification reveals a diffuse dermal proliferation of atypical lymphocytes; **(B)** the tumor cells have round nuclei and resemble centroblasts; **(C)** CD20 stains the tumor cells; **(D)** CD3-positive non-neoplastic T cells are present; **(E)** Ki67 reveals a high proliferation fraction; **(F)** the tumor stains positively for IRF4/MUM1; **(G)** $CD21^{+}$ follicular dendritic cell meshworks are absent. Abbreviations: CD20, cluster of differentiation 20; DLBCL-LT, diffuse large B-cell lymphoma leg type; IRF4, interferon regulatory factor 4; MUM1, multiple myeloma oncogene 1.

appointments, laboratory evaluation including CBC with differential, complete blood panel, and LDH along with physical exam are performed to monitor for any suggestion of disease recurrence.

Intravascular large B-cell lymphoma

This diagnosis completes the pair of B-cell lymphomas involving the skin that have an aggressive clinical behavior. First described in 1959 as "angioendotheliomatous proliferans," this B-cell lymphoma is manifested as an intravascular neoplasm most commonly in the skin and central nervous system (CNS).

Clinical features

Although the two most common sites of involvement by IVLBCL are the skin and CNS, patients can also have hepatosplenic and bone marrow involvement.[37] Widely disseminated extranodal disease is common; however, lymph nodes are usually spared.[37] Although this tumor often presents in the skin, roughly one-third of patients do not develop significant skin involvement.[37] Clinically apparent cutaneous lesions may appear as erythematous or violaceous plaques, painful blue-red nodules, ulcerated tumors, and small red papules.[37] Lesions are commonly reported on the upper arms, thighs, and legs, as well as the lower abdomen and breast regions.[37] A report of predominantly female patients with IVLBCL limited to the skin had a significantly better prognosis.

Other than cutaneous findings, patients may have neurological symptoms (34% of patients) which include a heterogeneous group of findings including sensory and motor deficits, meningoradiculitis, paresthesias, aphasia, dysarthria, hemiparesis, seizures, myoclonus, transient visual loss, vertigo, and/or altered mental status.[37,38] Patients may present with other nonspecific findings, including fever of unknown origin[39] and subcutaneous tumors.[40] "B symptoms" were reported to be the only presenting finding in 24% of patients.[37]

Occasionally, in patients with suspected IVLBCL involving the CNS, a skin biopsy is performed in the absence of clinically detectable skin lesions. In this case, a biopsy of a cherry angioma is recommended.[41] Laboratory testing usually reveals an elevated LDH and beta2-microglobulin.[37] Anemia, leukopenia, and thrombocytopenia are also reported. An elevated erythrocyte sedimentation rate is reported in 43% of cases. A monoclonal gammopathy has been reported in 14% of cases and hepatic, renal, and thyroid dysfunction in 16% of cases.[37]

Histopathology

IVLBCL is characterized by the presence of large neoplastic B cells within small- and medium-sized cutaneous vessels (Figure 6). The tumor cells are confined to the lumen without involvement of the surrounding tissue.[42] Angiodestruction is rare; however, associated hemorrhage, fibrin thrombi, and necrosis may be present.[42] The neoplastic B cells have large nuclei with multiple nucleoli and coarse nuclear chromatin and express CD20, BCL2, and IRF4/MUM1. They occasionally stain for CD5 and CD10, and cases without CD10 are nearly always positive for IRF4/MUM1. Clonal immunoglobulin rearrangement is usually present.[43]

Further investigations

No consensus guidelines guide the staging evaluation of this entity. Given the heterogeneity of presentations, a high index of suspicion is required, and diagnosis ultimately is made by biopsy of the involved site. There are case reports of random skin biopsy of normal skin being the diagnostic test required.[44] However, a recent study showed the limited utility of random skin biopsies of clinically normal skin.[45]

Once a diagnosis of IVLBCL is made, standard staging with blood work (CBC, CMP, and LDH), bone marrow biopsy, and imaging studies including PET are advisable (if not already done). Given the propensity for this process to involve the CNS, MRI of the CNS could be considered, but often imaging is driven by the patient's signs and symptoms.

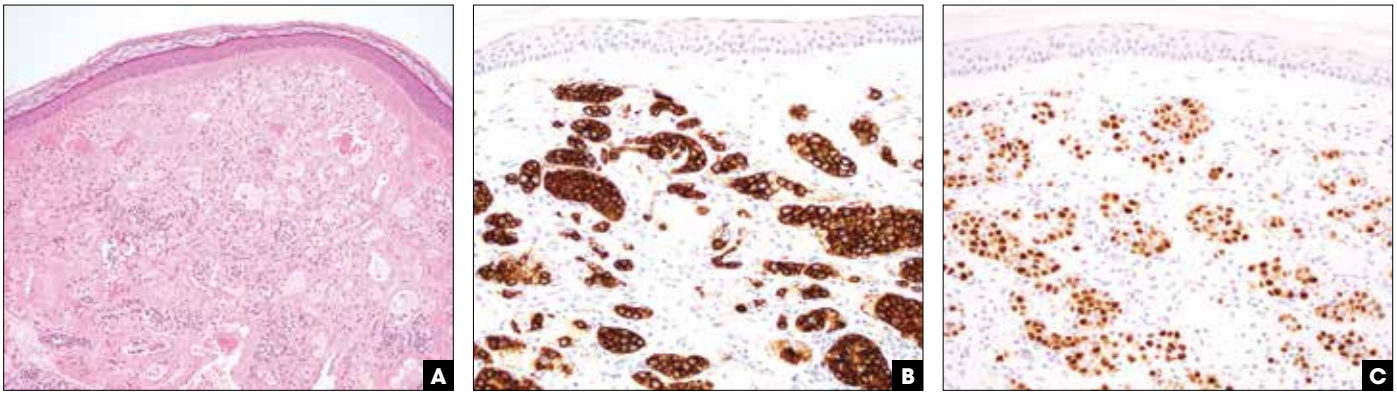


FIGURE 6. IVLBCL. **(A)** The tumor cells have large blastic nuclei and fill the lumina of dermal blood vessels; **(B)** the tumor cells stain positively for CD20; **(C)** nuclear staining of the tumor for MUM1 is also seen. Abbreviations: IVLBCL, intravascular large B-cell lymphoma; MUM1, multiple myeloma oncogene 1.

Treatment

The choice of therapeutic regimens for IVLBCL varies widely. Anthracycline-based chemotherapy is often used, with or without autologous stem cell transplantation.[37,46] Given the risk of CNS involvement, careful consideration of CNS-directed therapy with methotrexate should be considered. Allogeneic stem cell transplantation has also been reported.[47] Additionally, surgical excision has also been reported as monotherapy.[37] Ultimately, treatment will depend on patient characteristics and preexisting conditions that may affect tolerability of chemotherapeutic regimen. Referral to an academic medical center with experience treating IVLBCL may be advised.

Follow-up

Patients with the "cutaneous only" variant have a better prognosis with higher rates of survival.[37] Other patients who respond to chemotherapy with or without stem cell transplantation should be followed periodically after initial treatment. Any recrudescence of symptoms, including suggestion of CNS pathology, should be taken seriously, with consideration of repeat imaging and workup.

Conclusion

The primary CBCLs are a collection of diseases with both indolent and aggressive behavior. The workup, treatment, and monitoring of each patient depends on a combination of factors, including the tumor type, patient characteristics, and any potential complications from the treatment or the disease itself.

Histopathology is critical in the evaluation of these tumors. Clinicopathologic correlation, as well as frequent communication between pathologists and clinicians, is important to ensure appropriate, timely, and accurate diagnosis.

Treatment algorithms differ depending on the institutional practices at play. Future work may move toward standardization of care so that patients with these diagnoses can be appropriately treated regardless of the institution they may visit.

References

1. Lymphoma of the Skin. American Cancer Society website. https://www.cancer.org/cancer/skin-lymphoma.html. Updated 2017. Accessed October 16, 2017.
2. Willemze R, Jaffe ES, Burg G, et al. WHO-EORTC classification for cutaneous lymphomas. *Blood*. 2005;105(10):3768-3785. doi:10.1182/blood-2004-09-3502.
3. Wilson LD, Hinds GA, Yu JB. Age, race, sex, stage, and incidence of cutaneous lymphoma. *Clin Lymphoma Myeloma Leuk*. 2012;12(5):291-296. doi:10.1016/j.clml.2012.06.010.
4. Wilcox RA. Cutaneous B-cell lymphomas: 2016 update on diagnosis, risk-stratification, and management. *Am J Hematol*. 2016;91(10):1052-1055. doi:10.1002/ajh.24462.
5. Cerroni L, Zöchling N, Pütz B, Kerl H. Infection by borrelia burgdorferi and cutaneous B-cell lymphoma. *J Cutan Pathol*. 1997;24(8):457-461.
6. Dreno B. Standard and new treatments in cutaneous B-cell lymphomas. *J Cutan Pathol*. 2006;33 Suppl 1:47-51. doi:10.1111/j.0303-6987.2006.00544.x.
7. Wood GS, Kamath NV, Guitart J, et al. Absence of borrelia burgdorferi DNA in cutaneous B-cell lymphomas from the United States. *J Cutan Pathol*. 2001;28(10):502-507.
8. Willemze R, Swerdlow SH, Harris NL, Vergier B. Primary cutaneous follicle centre lymphoma. In: Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, et al, eds. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Revised 4th ed. Lyon, France: International Agency for Research On Cancer; 2017: 282-284.
9. Senff NJ, Hoefnagel JJ, Jansen PM, et al. Reclassification of 300 primary cutaneous B-cell lymphomas according to the new WHO-EORTC classification for cutaneous lymphomas: Comparison with previous classifications and identification of prognostic markers. *J Clin Oncol*. 2007;25(12):1581-1587. doi:10.1200/JCO.2006.09.6396.
10. de Leval L, Harris NL, Longtine J, Ferry JA, Duncan LM. Cutaneous B-Cell Lymphomas of Follicular and Marginal Zone Types Diagnosis and Classification. *Am J Surg Pathol*. 2001;25(6):732-741.
11. Gellrich S, Rutz S, Golembowski S, et al. Primary cutaneous follicle center cell lymphomas and large B cell lymphomas of the leg descend from germinal center cells. A single cell polymerase chain reaction analysis. *J Invest Dermatol*. 2001;117(6):1512-1520. doi:10.1046/j.0022-202x.2001.01543.x.
12. Hoefnagel JJ, Dijkman R, Basso K, et al. Distinct types of primary cutaneous large B-cell lymphoma identified by gene expression profiling. *Blood*. 2005;105(9):3671-3678. doi:10.1182/blood-2004-04-1594.
13. Hoefnagel JJ, Vermeer MH, Jansen PM, Fleuren GJ, Meijer CJ, Willemze R. Bcl-2, Bcl-6 and CD10 expression in cutaneous B-cell lymphoma: further support for a follicle centre cell origin and differential diagnostic significance. *Br J Dermatol*. 2003;149(6):1183-1191.
14. Dijkman R, Tensen CP, Jordanova ES, et al. Array-based comparative genomic hybridization analysis reveals recurrent chromosomal alterations and prognostic parameters in primary cutaneous large B-cell lymphoma. *J Clin Oncol*. 2006;24(2):296-305. doi:10.1200/JCO.2005.02.0842.
15. Hoefnagel J, Vermeer MH, Jansen PM, et al. Primary cutaneous marginal zone B-cell lymphoma: Clinical and theraputic features in 50 cases. *Arch Dermatol*. 2005;141(9):1139-1145. doi:10.1001/archderm.141.9.1139.
16. Cook JR, Isaacson PG, Chott A, Nakamura S, Muller-Hermelink HK, Harris NL, Swerdlow SH. Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma). In: Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, et al, eds. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*. Revised 4th ed. Lyon, France: International Agency for Research On Cancer; 2017: 259-262.
17. Dalle S, Thomas L, Balme B, Dumontet C, Thieblemont C. Primary cutaneous mar-

ginal zone lymphoma. *Crit Rev Oncol Hematol*. 2010;74(3):156-162. doi:10.1016/j.critrevonc.2009.09.003.
18. Servitje O, Gallardo F, Estrach T, et al. Primary cutaneous marginal zone B-cell lymphoma: a clinical, histopathological, immunophenotypic and molecular genetic study of 22 cases. *Br J Dermatol*. 2002;147(6):1147-1158.
19. Cho-Vega JH, Vega F, Rassidakis G, Medeiros LJ. Primary Cutaneous Marginal Zone B-Cell Lymphoma. *Am J Clin Pathol*. 2006;125 Suppl:S38-S49.
20. Cerroni L, Signoretti S, Höfler G, et al. Primary cutaneous marginal zone B-cell lymphoma: a recently described entity of low-grade malignant cutaneous B-cell lymphoma. *Am J Surg Pathol*. 1997;21(11):1307-1315.
21. Deutsch AJ, Frühwirth M, Aigelsreiter A, Cerroni L, Neumeister P. Primary Cutaneous Marginal Zone B-Cell Lymphomas Are Targeted by Aberrant Somatic Hypermutation. *J Invest Dermatol*. 2009;129(2):476-479. doi:10.1038/jid.2008.243.
22. Kim YH, Willemze R, Pimpinelli N, et al. TNM classification system for primary cutaneous lymphomas other than mycosis fungoides and Sézary syndrome: A proposal of the International Society for Cutaneous Lymphomas (ISCL) and the Cutaneous Lymphoma Task Force of the European Organization of Research and Treatment of Cancer (EORTC). *Blood*. 2007;110(2):479-484. doi:10.1182/blood-2006-10-054601.
23. Bekkenk MW, Vermeer MH, Geerts ML, et al. Treatment of multifocal primary cutaneous B-cell lymphoma: A clinical follow-up study of 29 patients. *J Clin Oncol*. 1999;17(8):2471-2478. doi:10.1200/JCO.1999.17.8.2471.
24. Neelis KJ, Schimmel EC, Vermeer MH, Senff NJ, Willemze R, Noordijk EM. Low-dose palliative radiotherapy for cutaneous B- and T-cell lymphomas. *Int J Radiat Oncol Biol Phys*. 2009;74(1):154-158. doi:10.1016/j.ijrobp.2008.06.1918.
25. Perry A, Vincent BJ, Parker SR. Intralesional corticosteroid therapy for primary cutaneous B-cell lymphoma. *Br J Dermatol*. 2010;163(1):223-225. doi:10.1111/j.1365-2133.2010.09798.x.
26. Senff NJ, Noordijk EM, Kim YH, et al. European organization for research and treatment of cancer and international society for cutaneous lymphoma consensus recommendations for the management of cutaneous B-cell lymphomas. *Blood*. 2008;112(5):1600-1609. doi:10.1182/blood-2008-04-152850.
27. Grange F, Beylot-Barry M, Courville P, et al. Primary cutaneous diffuse large B-cell lymphoma, leg type: Clinicopathologic features and prognostic analysis in 60 cases. *Arch Dermatol*. 2007;143(9):1144-1150. doi:10.1001/archderm.143.9.1144.
28. Kheterpal M, Mehta-Shah N, Virmani P, Myskowski PL, Moskowitz A, Horwitz SM. Managing patients with cutaneous B-cell and T-cell lymphomas other than mycosis fungoides. *Curr Hematol Malig Rep*. 2016;11(3):224-233. doi:10.1007/s11899-016-0322-5.
29. Willemze R, Vergier B, Duncan LM. Primary cutaneous diffuse large B-cell lymphoma, leg type. In: Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, et al, eds. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*. Revised 4th ed. Lyon, France: International Agency for Research On Cancer; 2017: 303-304.
30. Swerdlow SH, Quintanilla-Martinez L, Willemze R, Kinney MC. Cutaneous B-cell lymphoproliferative disorders: report of the 2011 Society for Hematopathology/European Association for Haematopathology workshop. *Am J Clin Pathol*. 2013;139(4):515-535.
31. Senff NJ, Zoutman WH, Vermeer MH, et al. Fine-mapping chromosomal loss at 9p21: correlation with prognosis in primary cutaneous diffuse large B-cell lymphoma, leg type. *J Invest Dermatol*. 2009;129(5):1149-1155. doi:10.1038/jid.2008.357.
32. Hallermann C, Kaune KM, Gesk S, et al. Molecular cytogenetic analysis of chromosomal breakpoints in the IGH, MYC, BCL6, and MALT1 gene loci in primary cutaneous B-cell lymphomas. *J Invest Dermatol*. 2004;123(1):213-219. doi:10.1111/j.0022-202X.2004.22720.x.
33. Espinet B, García-Herrera A, Gallardo F, et al. FOXP1 molecular cytogenetics and protein expression analyses in primary cutaneous large B cell lymphoma, leg-type. *Histol Histopathol*. 2011;26(2):213-221. doi:10.14670/HH-26.213.
34. Felcht M, Heck M, Weiss C, et al. Expression of the T-cell regulatory marker FOXP3 in primary cutaneous large B-cell lymphoma tumour cells. *Br J Dermatol*. 2012;167(2):348-358. doi:10.1111/j.1365-2133.2012.10987.x.
35. Grange F, Bekkenk MW, Wechsler J, et al. Prognostic factors in primary cutaneous large B-cell lymphomas: A european multicenter study. *J Clin Oncol*. 2001;19(16):3602-3610. doi:10.1200/JCO.2001.19.16.3602.
36. Hamilton SN, Wai ES, Tan K, Alexander C, Gascoyne RD, Connors JM. Treatment and outcomes in patients with primary cutaneous B-cell lymphoma: The BC cancer agency experience. *Int J Radiat Oncol Biol Phys*. 2013;87(4):719-725. doi:10.1016/j.ijrobp.2013.07.019.
37. Ferreri AJ, Campo E, Seymour JF, et al. Intravascular lymphoma: Clinical presentation, natural history, management and prognostic factors in a series of 38 cases, with special emphasis on the 'cutaneous variant'. *Br J Haematol*. 2004;127(2):173-183. doi:10.1111/j.1365-2141.2004.05177.x.
38. Savard M, Verreault S, Gould PV, Bernier V, Bouchard JP. Intravascular lymphoma with conus medullaris syndrome followed by encephalopathy. *Can J Neurol Sci*. 2008;35(3):366-371.
39. di Fonzo H, Contardo D, Carrozza D, et al. Intravascular large B cell lymphoma presenting as fever of unknown origin and diagnosed by random skin biopsies: A case report and literature review. *Am J Case Rep*. 2017;18:482-486.
40. Yin W, Li M, Gao Z, Huang F, Da J, Liu C. Intravascular large B-cell lymphoma with involvement of the abdominal subcutis: A case report and literature review. *Int J Hematol*. 2009;89(3):348-351. doi:10.1007/s12185-009-0262-0.
41. Cerroni L, Zalaudek I, Kerl H. Intravascular large B-cell lymphoma colonizing cutaneous hemangiomas. *Dermatology*. 2004;209(2):132-134. doi:10.1159/000079597.
42. Orwat DE, Batalis NI. Intravascular large B-cell lymphoma. *Arch Pathol Lab Med*. 2012;136(3):333-338. doi:10.5858/arpa.2010-0747-RS.
43. Nakamura S, Ponzoni M, Campo E. Intravascular large B-cell lymphoma. In: Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri S, Stein H, et al, eds. *WHO Classification of Tumours of Haematopoietic Lymphoid Tissues*. Revised 4th ed. Lyon, France: International Agency for Research On Cancer; 2017: 317-318.
44. Barnett CR, Seo S, Husain S, Grossman ME. Intravascular B-cell lymphoma: The role of skin biopsy. *Am J Dermatopathol*. 2008;30(3):295-299. doi:10.1097/DAD.0b013e31816c745f.
45. Cho HG, Sheu SL, Kuo KY, et al. Limited role of random skin biopsy in the diagnosis of intravascular lymphoma in adult patients with hemophagocytic lymphohistiocytosis. *Acta Haematol*. 2017;138(1):33-38. doi:10.1159/000476027.
46. Baldolli A, Chuffart M, Geffray L, Verneuil L, Reman O. Interest of an intensive chemotherapy for intravascular large B cell lymphoma. *Bull Cancer*. 2013;100(4):317-321. doi:10.1684/bdc.2013.1733.
47. Adam DN, Beleznay KM, Randhawa RS, Marton M, Zhou Y. Review of intravascular lymphoma with a report of treatment with allogenic peripheral blood stem cell transplant. *Cutis*. 2008;82(4):267-272.