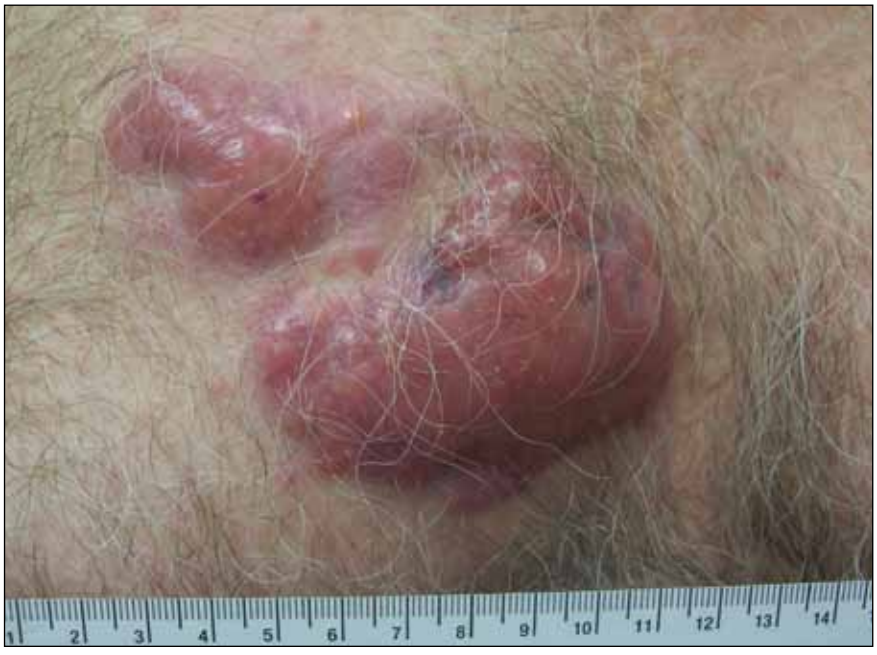
What Is Your Diagnosis?



A 59-year-old white man presented with 2 large erythematous lesions on the right side of the chest wall that had gradually progressed over the last 1.5 years. The patient denied any fever, night sweats, fatigue, unintentional weight loss, or loss of appetite. Physical examination revealed 2 large, well-circumscribed, nearly contiguous, firm, erythematous tumors. One tumor measured 7.5×4.5 cm and the other measured 4×3.5 cm.

PLEASE TURN TO PAGE 249 FOR DISCUSSION

Sean W. Carlson, DO; Savina Aneja, MD; Kord Honda, MD; Kevin D. Cooper, MD

Dr. Carlson was from and Drs. Aneja, Honda, and Cooper are from the Department of Dermatology, University Hospitals Case Medical Center, Cleveland, Ohio. Dr. Carlson currently is from the Department of Radiology, Aultman Hospital, Canton, Ohio. Drs. Honda and Cooper also are from the Multidisciplinary Cutaneous Oncology Program, Seidman Cancer Center, Cleveland, and the School of Medicine, Case Western Reserve University, Cleveland. Dr. Cooper also is from the Case Comprehensive Cancer Center, Cleveland.

The authors report no conflict of interest.

Correspondence: Sean W. Carlson, DO, 2600 Sixth St SW, Canton, OH 44710 (sean.carlson@aultman.org).

The Diagnosis: Cutaneous B-cell Lymphoma

Biopsies from the right side of the chest wall (Figure 1) revealed an atypical dense and diffuse lymphocytic infiltrate throughout the dermis. There was extensive crush artifact throughout the specimen. However, the findings were consistent with cutaneous B-cell lymphoma (CBCL), and the diffuse large B-cell type was favored (Figure 2). Atypical lymphocytes stained positively for antibodies against CD20 (Figure 3), CD79a, and BCL-6, and stained negatively for antibodies against MUM-1 and BCL-2. Although flow cytometry revealed no definitive immunophenotypic lymphoma population, polymerase chain reaction analysis revealed a monoclonal immunoglobulin heavy chain gene rearrangement. Computed tomography (CT) scans of the chest, abdomen, and pelvis were unremarkable. A preliminary diagnosis of primary CBCL (PCBCL) was formulated. Diffuse large B-cell lymphoma (DLBCL) and follicle center lymphoma subtypes were each considered, which triggered further workup to rule out systemic involvement.

A bone marrow biopsy from the posterior iliac crest revealed normocellular bone marrow with normal trilineage hematopoiesis. However, whole-body staging with positron emission tomography (PET)–CT scanning revealed osseous disease in the left proximal humerus (Figure 4) as well as a slightly hypermetabolic right axillary lymph node. Magnetic resonance imaging of the brain showed no evidence of intracranial disease. Because of the apparent systemic involvement, stage IV non-Hodgkin lymphoma (DLBCL) became the new suspected diagnosis. The patient was started on the first of 6 cycles of chemotherapy with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP), and the skin lesions quickly dissipated and flattened. A faint pink discoloration remained over a slightly indented area. A repeat PET-CT scan following 4 cycles of R-CHOP chemotherapy also confirmed a complete response to therapy.

In general, CBCL tends to affect adults and presents as relatively firm and plum-colored papules, nodules, tumors, or plaques, which can be either fast or slow growing. Cutaneous B-cell lymphoma may be primary or secondary to systemic involvement. Primary CBCL refers to a group of non-Hodgkin lymphomas that initially present in the skin with no evidence of extracutaneous involvement at the time of diagnosis.[1,2] Secondary CBCL (SCBCL) refers to cutaneous disease that occurs secondary to systemic B-cell lymphoma.

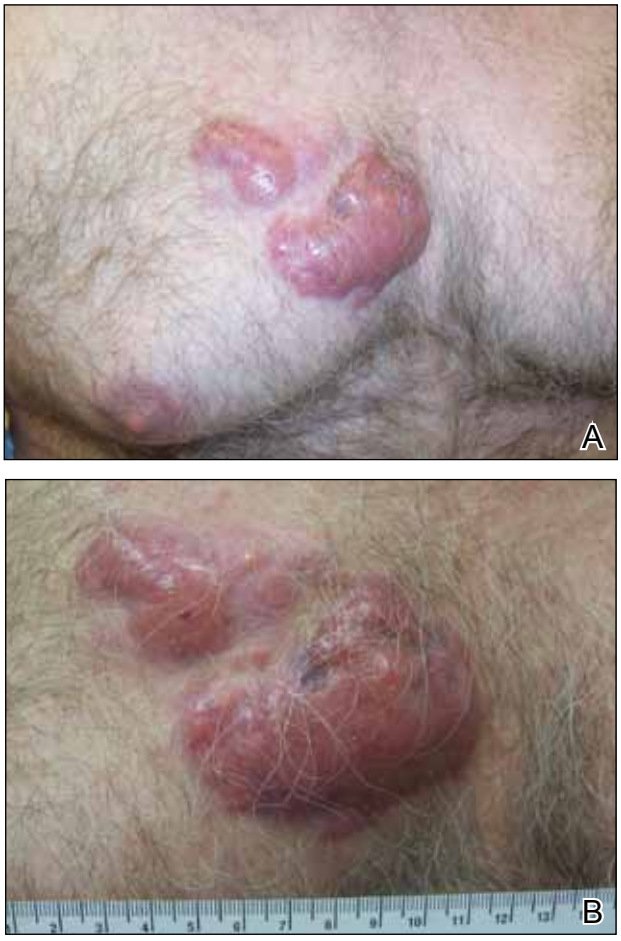
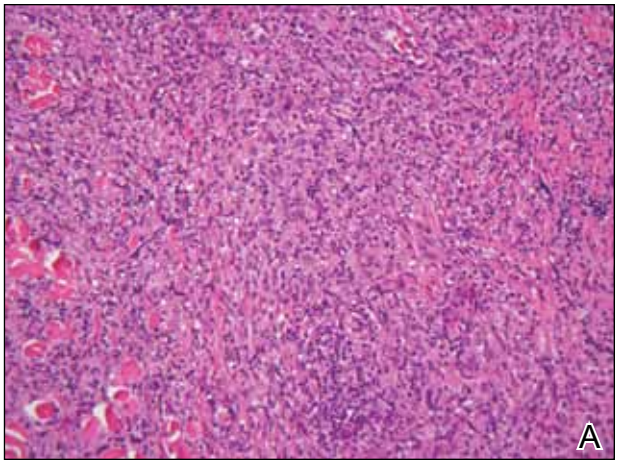


Figure 1. Erythematous firm tumors of the right side of the chest wall (A and B).

Detecting systemic involvement and distinguishing between PCBCL and SCBCL is valuable in determining prognosis and therapeutic options, as subtypes of PCBCL often have an improved prognosis and may be treated with local irradiation.

The initial staging techniques that are preferred for cutaneous lymphomas have been debated.[3-5] For cutaneous lymphomas, except mycosis fungoides and Sézary syndrome, the International Society for Cutaneous Lymphomas and the Cutaneous Lymphoma Task Force of the European Organization of Research and Treatment of Cancer recommends obtaining a complete blood cell count with differential; complete metabolic studies including lactate dehydrogenase; and imaging studies of the chest, abdomen, and



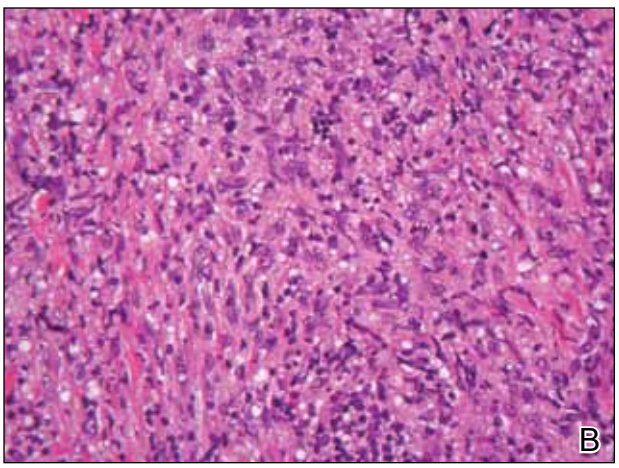


Figure 2. Atypical lymphocytic infiltrate with background crush artifact (A and B)(both H&E, original magnifications ×20 and ×40).

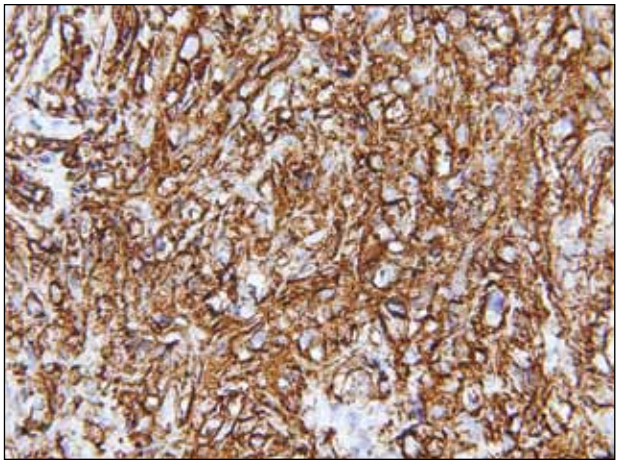


Figure 3. Atypical lymphocytes stained positively for antibodies against CD20 (original magnification ×40).

pelvis. Bone marrow biopsies and imaging studies of the neck or whole-body PET-CT scanning also may be useful depending on the clinical scenario.[3] Although a more limited workup may be sufficient for PCBCLs such as primary cutaneous marginal zone lymphoma,[5] a bone marrow biopsy is recommended for cases of primary cutaneous DLBCL (leg type).[3] Senff et al[5] supported the use of a bone marrow biopsy in the evaluation of follicle center lymphomas first presenting in the skin, though this method is controversial. In our patient, the laboratory results; bone marrow biopsy; and CT scan of the chest, abdomen, and pelvis failed to suggest extracutaneous disease, while the PET-CT scan revealed systemic involvement.

The differential diagnosis of CBCL includes cutaneous lymphoid hyperplasia (pseudolymphoma), which may be the result of insults such as arthropod bites, stings, vaccinations, or trauma. The clinical presentation, histology, and results of molecular studies and immunohistochemistry are essential in differentiating benign versus malignant processes.[6] Lymphomas are expected to be larger and more persistent than benign processes, demonstrating an atypical lymphocytic infiltrate and monoclonality; immunohistochemistry will aid in the distinction between B-cell and T-cell processes and can delineate the type of B-cell lymphoma. Histology for CBCL typically reveals an atypical lymphocytic infiltrate showing a $CD20^+$ and $CD79a^+$ immunophenotype. Staining for antibodies against BCL-2, BCL-6, CD10, and MUM-1 also plays an important role in the diagnosis of cutaneous lymphoma and determining where the lesion(s) falls within the classification schemes. For example, to differentiate between primary cutaneous lymphoma subtypes, BCL-2 negativity and BCL-6 positivity in the context of a $CD20^+$ and $CD79a^+$ immunophenotype supports a follicle center lymphoma or a DLBCL (non–leg type). By contrast, CD20, CD79a, BCL-2, and MUM-1 positivity would favor a DLBCL (leg type).[7]

The natural history and therapeutic options differ greatly between subtypes of CBCL. For example, the prognosis of primary cutaneous follicle center lymphoma is generally favorable with a 5-year disease-specific survival rate of roughly 95%, and radiation therapy is recommended as a first-line therapy for localized disease.[2,8] Conversely, primary cutaneous DLBCL (leg type) frequently spreads to extracutaneous sites[8] and carries a much lower estimated 5-year disease-specific survival rate of 55%.[2] Chemotherapy with R-CHOP is typically included in initial therapy for primary cutaneous DLBCL (leg type).[8] The prognosis of systemic B-cell lymphomas also is highly variable and may depend on the type of B-cell lymphoma, the stage of disease at

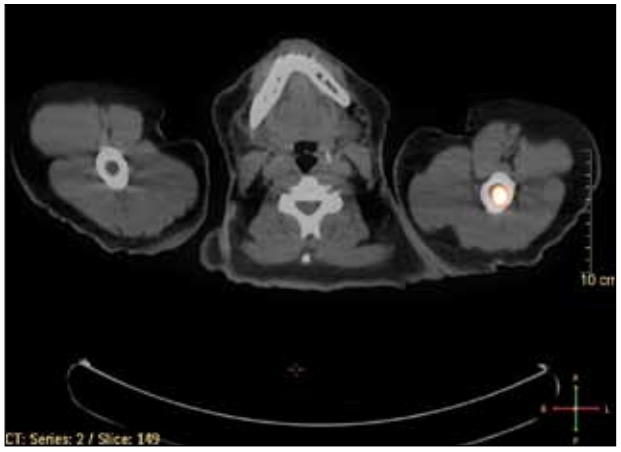


Figure 4. A focus of increased radiotracer deposition is seen in the left proximal humerus on positron emission tomography–computed tomography scanning.

diagnosis, histologic and immunologic characteristics, and the therapy received. Wright et al[9] reported that patients with systemic germinal center B cell–like DLBCL had a 5-year survival rate of 62%, whereas patients with activated B cell–like variants of DLBCL had a 5-year survival rate of 26%. Expression of CD40 may be a favorable prognostic factor following treatment with systemic chemotherapy in patients with DLBCL,[10] whereas FOXP1 protein overexpression is correlated with poor disease-specific survival in certain DLBCL phenotypes.[11]

Although it is uncertain whether the cutaneous lesions preceded systemic disease in our patient, the cutaneous lesions could be arbitrarily classified as secondary because extracutaneous disease was discovered within 6 months of the initial diagnosis.[1] However, classifying the CBCL as primary or secondary did not alter the course of treatment in our patient, as the presumed systemic disease necessitated treatment with systemic chemotherapy; both PCBCLs that develop systemic involvement and SCBCLs (primary extracutaneous disease) usually are treated with systemic chemotherapy. Our case highlights the importance of whole-body staging, as PET-CT scanning changed the course of care by detecting osseous involvement, necessitating systemic therapy as opposed to local radiation therapy alone. A multidisciplinary team with a focus on the diagnosis and management of cutaneous lymphomas helped streamline our patient's laboratory testing and imaging studies, diagnostic and therapeutic decision making, and treatment implementation. Open channels and frequent opportunities for communication among dermatologists, dermatopathologists, medical oncologists, hematopathologists, radiologists, and radiation oncologists are needed to optimize and coordinate care for patients with cutaneous lymphoma who require transdisciplinary care.

Acknowledgment—The authors would like to thank Henry Koon, MD (hematology/oncology), for his input and expertise.

REFERENCES

1. Willemze R, Kerl H, Sterry W, et al. EORTC classification for primary cutaneous lymphomas: a proposal from the cutaneous lymphoma study group of the European organization for research and treatment of cancer. *Blood*. 1997;90:354-371.
2. Willemze R, Jaffe ES, Burg G, et al. WHO-EORTC classification for cutaneous lymphomas. *Blood*. 2005;105:3768-3785.
3. 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;110:479-484.
4. Quereux G, Frot AS, Brocard A, et al. Routine bone marrow biopsy in the initial evaluation of primary cutaneous B-cell lymphoma does not appear justified. *Eur J Dermatol*. 2009;19:216-220.
5. Senff NJ, Kluin-Nelemans HC, Willemze R. Results of bone marrow examination in 275 patients with histological features that suggest an indolent type of cutaneous B-cell lymphoma. *Br J Haematol*. 2008;142:52-56.
6. Gilliam AC, Wood GS. Cutaneous lymphoid hyperplasias. *Semin Cutan Med Surg*. 2000;19:133-141.
7. Burg G, Kempf W, Cozzio A, et al. WHO/EORTC classification of cutaneous lymphomas 2005: histological and molecular aspects. *J Cutan Pathol*. 2005;32:647-674.
8. 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;112:1600-1609.
9. Wright G, Tan B, Rosenwald A, et al. A gene expression-based method to diagnose clinically distinct subgroups of diffuse large B cell lymphoma. *Proc Natl Acad Sci U S A*. 2003;100:9991-9996.
10. Rydström K, Linderoth J, Nyman H, et al. CD40 is a potential marker of favorable prognosis in patients with diffuse large B-cell lymphoma treated with immunochemotherapy. *Leuk Lymphoma*. 2010;51:1643-1648.
11. Hoeller S, Schneider A, Haralambieva E, et al. FOXP1 protein overexpression is associated with inferior outcome in nodal diffuse large B-cell lymphomas with non-gerzminal centre phenotype, independent of gains and structural aberrations at 3p14.1. *Histopathology*. 2010;57:73-80.