

# Vesicles and Bullae on the Leg

Marissa Ceresnie, DO; Mojgan Hosseinipour, DO; Kalliope Kyrkiades, DO; Paul Chu, MD; Charles Gropper, DO; Cindy Hoffman, DO



A 60-year-old man presented to the emergency department with slowly progressing edema of the lower legs of 3 months' duration. In the week prior to presentation to the emergency department, he noticed a sudden eruption of vesicles and bullae on the right leg that drained clear fluid and healed with brown crust. The lesions were associated with mild burning, pruritus, and pain. He denied fever, chills, recent travel, or injury. His medical history was notable for poorly controlled diabetes mellitus, congestive heart failure, hypertension, chronic kidney disease, hyperlipidemia, and chronic anemia. Physical examination revealed multiple scattered erythematous vesicles and bullae on the right leg on a background of hyperpigmentation. Bilateral 2+ pitting edema of the legs also was present. A punch biopsy of a lesion was performed.

## WHAT'S YOUR DIAGNOSIS?

- bacillary angiomatosis
- cutaneous B-cell lymphoma
- elephantiasis nostras verrucosa
- filariasis
- Kaposi sarcoma

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Dr. Ceresnie was from Nova Southeastern University, Dr. Kiran C. Patel College of Osteopathic Medicine, Fort Lauderdale, Florida, and currently is from Largo Medical Center, Florida. Drs. Hosseinipour, Kyrkiades, Chu, Gropper, and Hoffman are from the Department of Dermatology, St. Barnabas Hospital, Bronx, New York. Dr. Chu also is from Bridge Dermatopathology Services, PLLC, Tarrytown, New York.

The authors report no conflict of interest.

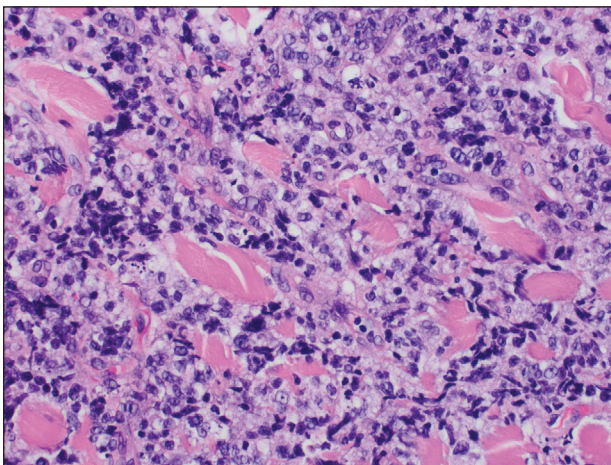
Correspondence: Marissa Ceresnie, DO (marissa.ceresnie@gmail.com).

doi:10.12788/cutis.0219

## THE DIAGNOSIS: Cutaneous B-cell Lymphoma

**H**istopathology revealed a dense and diffuse lymphocytic infiltrate throughout the dermis with occasional individual cell necrosis. On closer inspection, the infiltrate consisted of intermediate-sized lymphocytes, some with a vesiculated nucleus and ample amount of cytoplasm, while others contained hyperchromatic nuclei (Figure 1). These cells stained strongly positive for B-cell marker (CD20), while only a few mature lymphocytes demonstrated T-cell phenotype (CD3)(Figure 2).

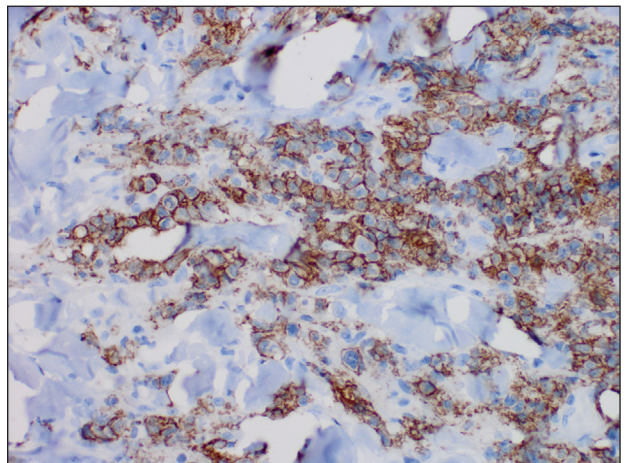
Although the patient recounted a 3-month history of lower leg edema, he also reported that the rash began a few weeks after his diagnosis of systemic B-cell follicular lymphoma. Throughout this time, he was seen by various physicians who attributed the edema and skin changes to chronic stasis, peripheral venous insufficiency, and diabetic peripheral neuropathy. His primary care physician prescribed an antifungal lotion, which he discontinued on his own due to lack of improvement. Upon arrival to the emergency department, he was started on intravenous cefazolin and subcutaneous heparin. Doppler ultrasonography of the legs was ordered to rule out a deep venous thrombosis. Dermatology was consulted and proceeded with a punch biopsy to investigate for cutaneous B-cell lymphoma (BCL) with a plan to follow up as an outpatient for results upon discharge. He also was prescribed triamcinolone ointment 0.1% twice daily for symptomatic relief.



**FIGURE 1.** Cutaneous B-cell lymphoma. Punch biopsy showed a dense and diffuse lymphocytic infiltrate throughout the dermis with occasional individual cell necrosis. Intermediate-sized lymphocytes either contained a vesiculated nucleus and ample amount of cytoplasm or hyperchromatic nuclei with minimal cytoplasm (H&E, original magnification  $\times 400$ ).

The patient's left axillary lymph node was biopsied for pathologic evaluation. Immunohistochemical staining revealed expression of B-cell markers CD20, CD79a, and PAX5, along with the antiapoptotic markers BCL-2 and BCL-6. Fluorescence in situ hybridization displayed gene rearrangements of BCL-2, BCL-6, and t(14;18)/IgH-BCL2 in the majority of cells. CD3 and CD5 immunostains were negative, indicating that T cells were not involved in this process. Flow cytometry identified a monoclonal  $\kappa$  B-cell population in 40% to 50% of the total cells, which co-expressed CD10, CD19, CD22, and CD38; the cells were negative for CD5, CD20, and CD23. Cell size was variably enlarged and CD71 positive, otherwise known as transferrin receptor 1, indicating the mediation of iron transport into cells of erythroid lineage that is necessary for proliferation.<sup>1</sup> Bone marrow core biopsy did not identify features of bone marrow involvement by the lymphoma. Based on these results, the patient was diagnosed with systemic B-cell follicular lymphoma grade 3b stage IIIA. Oncology initiated a systemic chemotherapy regimen with obinutuzumab, cyclophosphamide, doxorubicin hydrochloride (hydroxydaunorubicin), vincristine sulfate, and prednisone.

Skin involvement in B-cell follicular lymphoma can be primary or secondary. Although all subtypes of BCL can have secondary cutaneous involvement, it is most common in advanced-stage disease (stages III or IV).<sup>2</sup> Cutaneous manifestations of primary cutaneous follicle-center lymphoma (PCFCL) and systemic/nodal follicular lymphoma secondarily involving the skin can be difficult to distinguish clinically and histopathologically; both



**FIGURE 2.** Cutaneous B-cell lymphoma. Positive immunohistochemical staining of lymphocytes for the CD20 B-cell marker (original magnification  $\times 400$ ).

appear as solitary or grouped plaques and nodules most commonly on the head, neck, or trunk, and rarely on the legs.<sup>3</sup> Although the pathologic features of these two diagnoses can seem almost identical, it is important to differentiate them due to their differing prognosis and management. Patients with follicular lymphoma involving the skin are more likely than those with PCFCL to develop lymphadenopathy and B symptoms.<sup>3</sup> Primary cutaneous follicle-center lymphoma also generally runs an indolent course and requires local therapy, while secondary involvement of the skin due to systemic/nodal follicular lymphoma has a worse prognosis and requires systemic chemotherapy treatment.<sup>4</sup>

Immunohistochemical markers are the most helpful tool used to distinguish PCFCL from systemic/nodal follicular lymphoma involving the skin. Tumors of B-cell origin are expected to express associated B-cell markers such as CD20, CD79a, and PAX5<sup>2</sup>; BCL-6, a marker of germinal center cells, also is expected to stain positive.<sup>2</sup> CD10 is positive in a majority of cases with a follicular growth pattern, while those with a diffuse pattern of growth may have a negative stain.<sup>2</sup> The most valuable histopathologic indicator differentiating primary and secondary skin involvement is the intensity of BCL-2 expression.<sup>5</sup> The prognostic significance of the t(14;18)/IgH-BCL2 rearrangement is controversial, with rearrangement identified in more than 75% of systemic/nodal follicular lymphoma cases and less commonly found in PCFCL, with one report arguing an incidence ranging from 1% to 40%.<sup>5</sup>

A comprehensive history and physical examination are necessary to develop a differential diagnosis. Our

patient's lower leg edema and extensive medical history made the diagnosis more complicated. Pitting edema was present on physical examination, making elephantiasis nostras verrucosa less likely, as it would instead present with nonpitting edema and a woody feel.<sup>6</sup> Our patient did not have epidemiologic exposure to filariasis through foreign travel and did not present with any classic signs or symptoms of lymphatic filariasis, such as fever, eosinophilia, chyluria, or hydrocele.<sup>7</sup> Although a negative history of HIV makes Kaposi sarcoma and bacillary angiomatosis less likely diagnoses, a biopsy would be useful to rule out these conditions. Positive inguinal lymphadenopathy present on physical examination may have contributed to lymphatic flow obstruction leading to the leg lymphedema in our patient.

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