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Case Presentation

Primary cutaneous follicle-center lymphoma

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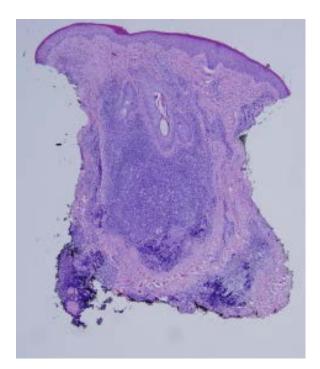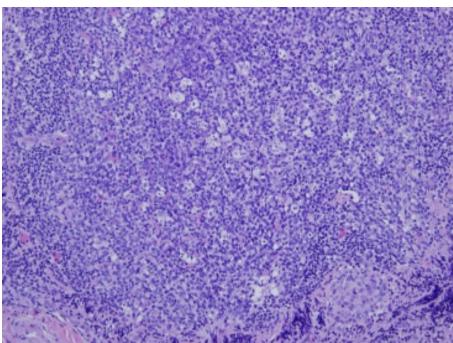
Abstract

We present a 64-year-old man with a three-year history of pruritic, pink papules and nodules of the face who was found to have a clonal lymphoproliferative B-cell disease that was characterized by a clonal IGH rearrangement. Although morphologic features present in the biopsy specimen were consistent with a reactive process, additional clinicopathologic correlation (anatomic presentation of lesions on the face, the absence of t(14:18) translocation, and bcl-2 and MUM1 expression) reinforced suspicion of a cutaneous B-cell lymphoma. Systemic work-up with CT/PET and a bone marrow biopsy ultimately excluded systemic disease and primary cutaneous follicle-center lymphoma (PCFCL) was a strong diagnostic consideration. The patient was treated with systemic rituximab with a partial resolution of the facial lesions. The case demonstrates both clinical and pathologic challenges to the diagnosis of primary cutaneous B-cell lymphoma (PCBCL). Furthermore, despite a newly refined classification system, the case also specifically highlights the persistent requirement for flexible clinical reasoning and pathologic correlation. Such reasoning is necessary to generate individualized strategies for diagnosis and treatment when cutaneous B-cell lymphoma is suspected.

Case synopsis

History: A 63-year-old man presented to the Manhattan Campus of VA New York Harbor Healthcare System for treatment of pruritic papules and nodules on the face. The patient, originally from Puerto Rico, lived in the New York. He initially presented to the Dermatology Clinic in February, 2010, with a one-month history of papules and nodules on the forehead and temple. Metronidazole gel and hydrocortisone cream were prescribed with no improvement. A punch biopsy specimen of the left cheek showed granulomatous inflammation. Over the subsequent 18 months, the patient was managed for a presumptive diagnosis of granulomatous rosacea with oral and topical medications, which included topical metronidazole gel, topical tacrolimus ointment, topical clindamycin, oral doxycycline, oral minocycline, topical dapsone, topical crotamiton, topical permethrin, and sulfacetamide/sulfur lotion. Despite these interventions, he experienced an increasing number of facial lesions and pruritus. A second biopsy of the right cheek showed a reactive lymphocytic infiltrate with germinal centers and prominent blood vessels with plump endothelial cells. The possibility of angiolymphoid hyperplasia with eosinophilia was raised. Review of this specimen noted a dense, nodular, lymphohistocytic infiltrate within the dermis, and the possibility of a pseudolymphoma also was raised. The findings were, nonetheless, considered consistent with the clinical diagnosis of granulomatous rosacea.

Past medical history included depression. He denied any systemic symptoms, which included fever, chills, night sweats, or weight loss. The patient pursued a second opinion at the Bronx Campus of VA New York Harbor Healthcare System Dermatology Clinic and a repeat punch biopsy of the cheek was performed.

Physical examination: There were multiple, erythematous, 1 to 2-cm, pink-to-purple, indurated plaques and nodules over the right and left preauricular skin. There was no cervical, submental, posterior auricular, occipital, axillary, or inquinal lymphadenopathy.

Laboratory: A complete blood count and chemistry profile were normal. A positron emission tomography/computed tomography scan and a bone marrow biopsy specimen did not show disease.

Histopathology: There is a dense, nodular, lymphoid infiltrate in the dermis without appreciable epidermotropism. The nodules appear to be well-defined follicles, which show a predominance of lymphocytes in addition to tingible body macrophages and scattered eosinophils. Immunostains show that the lymphocytes are mostly follicle-center B cells, which are positive for CD20, Pax5, CD10, and Bcl-6, but are negative for Bcl-2. Ki-67 shows a high proliferative rate. Per report, a clonal B-cell population was detected upon PCR analysis for immunoglobulin heavy-chain gene rearrangement.

Discussion

Diagnosis: Primary cutaneous follicle-center lymphoma, likely

Comment: The consensus WHO-EORTC classification for cutaneous lymphomas was established in 2005 [1]. This classification was the culmination of two independent European meetings in 2003 and 2004 that were attended by representatives from both organizations. Although the WHO-EORTC system encompasses lymphoproliferative diseases of mature T-cells, NK-cells, mature B-cells, and immature hematopoietic cells, the endeavor was undertaken in large part to specifically resolve confusion and debate regarding definitions and terminologies among subsets of cutaneous T- and B-cell lymphomas. Specific focus and effort were placed on the classification of B-cell lymphoma subtypes and large-cell phenotypes with noted differences in clinical behavior and prognosis.

The three most common subtypes of primary cutaneous B-cell lymphomas under the WHO-EORTC classification are primary cutaneous follicle-center lymphoma (PCFCL), primary cutaneous marginal-zone lymphoma (PCMZL), and primary cutaneous diffuse large B-cell lymphoma of the leg (PCDLBCL-leg) [1, 2]. Distinctive histomorphologic, immunophenotypic, and genetic features characterize each subtype.

Clinically, PCFCL commonly presents as pink-to-violaceous nodules and plaques on the head and neck. The differential diagnosis commonly includes rosacea, folliculitis, acne, insect bites, merkel-cell carcinoma, cutaneous lymphoid hyperplasia, and basal-cell carcinoma. Histopathologic features of PCFCL include dermal and subcutaneous proliferations of CD20+ centrocytes and centroblasts, either in follicular or diffuse growth patterns [1-3]. Early lesions of PCFCL often show a perivascular or periadnexal, lymphocytic infiltrate and often are mistaken for pseudolymphoma initially. PCFCL is notable for an absence of Bcl-2, MUM1/IRF4, and FOX-P1. Malignant B-cells in PCFCL do not harbor the t(14;18) translocation that is commonly observed in the nodal variant form of this disease. PCFCL carries a favorable prognosis with a 95% five-year survival; prognosis is not affected by histopathologic growth pattern or the presence of multifocal lesions [3-5]. Because nodal follicle center lymphoma has a poor prognosis, PET/CT and bone marrow biopsy, only in cases where PET/CT is positive, is indicated to verify its skin-only location.

PCMZL commonly presents as red-to-violaceous papules, nodules, or plaques on the face, trunk, and arms. Differential diagnosis of PCMZL often includes urticaria, leukemia cutis, pseudolymphoma, and insect bites. Histopathologic features of PCMZL include dermal and subcutaneous nodular-to-diffuse marginal zone B-cells, lymphplasmacytoid mononuclear cells, evident plasma cells, centro/immunoblast-like cells, and reactive T-cells [1-3]. Malignant cells are CD20+, Bcl-2+, and MUM-1/IRF4+ [6,7]. Genetic translocations that are found in PCMZL include t(14;18) in <25% of cases [8,9]. Less commonly t(11;18) and t(3;14) translocation are observed as well. PCMZL also carries a very good prognosis with a 99% five-year survival rate [3].

PCDLBCL-leg presents as red-to-blue nodules or plaques on the lower extremities. Like PCFCL, PCDLBCL-leg also is of follicular origin and is composed of large B-cells with a diffuse dermal growth of centroblasts and immunoblasts [1-3]. In contrast to PCFCL, the malignant B-cells in PCDLBCL-leg express MUM1/IRF4, FOX-P1, IgM, and bcl-2 [10,11]. Although the t(14;18) translocation is not present characteristically, many other chromosomal aberrations are common [12-14]. Prognosis associated with PCDLBCL-leg is less favorable, with studies demonstrating a 50% 5-year survival rate [15,16]. This striking survival difference makes the distinction of PCDLBCL-leg from PCFCL of utmost importance. Under the WHO-EORTC classification, criteria are available to properly classify PCFCL and PCDLBCL-leg using clinical, histopathologic, genetic, and immunophenotypic methods. Classification then may better inform clinicians regarding optimal treatment strategies and prognosis.

For the patient presented, the anatomic distribution of facial nodules and plaques, with an evident follicular pattern growth and the absence of bcl-2, t(14;18), and MUM-1 expression were demonstrated. However, histopathologic review showed prominent features that were consistent with a reactive lymphocytic process or pseudolymphoma. After identification of a monoclonal IgH rearrangement via PCR, a cutaneous B-cell lymphoma could not be excluded. Subsequent systemic evaluation with PET/CT and a bone marrow biopsy specimen did not show evidence of extracutaneous disease. In this scenario, PCFCL remained a strong consideration. The patient underwent treatment with intravenous rituximab with partial resolution.

This case highlights the challenging pathobiologic aspects of cutaneous lymphoproliferative processes, but the clinical presentation that was consistent with granulomatous rosacea represented a clinical diagnostic challenge. A series of cases that described granulomatous rosacea and rhinophyma-like presentations of PCBCL recently has been reported [17]. In this study of 12 patients with PCBCL that simulated rosacea, four patients were classified as having PCFCL, six others as having PCMZL, and four as chronic lymphocytic leukemia (CLL). Clinicopathologic correlation and establishment of B-cell clonality was required for the final diagnostic classification in all cases. Chronic antigenic stimulation, perhaps from *Demodex folliculorum*, has been suggested as a potential etiology for the development of rosacea-like presentations of PCBCL, which is analogous to *Borrelia* associated with PCMZL and leukemic cutaneous infiltrates of CLL associated with zoster. Alternatively, isomorphic phenomena at sites of preexisting rosacea/rhinophyma also have been hypothesized to contribute to rosacea-like presentations of PCBCL.

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