Type B Follicular Lymphomatoid Papulosis

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We report a 48-year-old woman who presented with waxing and waning papulovesicles of 4 years' duration. Histologic examination revealed a folliculotropic, small cell dominant, T cell lymphocytic infiltrate unaccompanied by follicular mucin deposition and with scattered intrafollicular and perifollicular CD30$^+$ cells. A diagnosis of type B follicular lymphomatoid papulosis (LyP), rather than mycosis fungoides (MF), was made on the basis of her clinical presentation, which included spontaneously resolving, waxing and waning papules that healed with scarring. Type B follicular LyP is a rare form of LyP.

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Initially described by Macaulay[1] in 1968, lymphomatoid papulosis (LyP) is a disorder characterized by remitting and recurring papules and nodules that contain atypical lymphocytes. Individual lesions usually persist for weeks to months and then spontaneously heal, often with scarring. The World Health Organization and European Organization for Research and Treatment of Cancer (WHO-EORTC) classification system labels LyP as a primary cutaneous CD30$^+$ lymphoproliferative disorder (CD30$^+$ LPD).[2] Approximately 20% of patients with this condition have or will eventually develop an additional cutaneous or extracutaneous lymphoid dyscrasia, most commonly mycosis fungoides (MF), anaplastic large cell lymphoma (ALCL), or Hodgkin lymphoma.[3,4] A rare variant of LyP, follicular LyP, was presented by Pierard et al[5] in 1980. The infiltrate in this variant surrounds hair follicles. A total of 12 cases of follicular LyP have been reported in the literature according to a PubMed search of articles indexed for MEDLINE using the term *follicular lymphomatoid papulosis*.[5-11] We present an additional case of follicular LyP.

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The authors report no conflict of interest.

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Case Report

A 48-year-old obese woman with a history of genital herpes presented to our clinic with intermittent nonpruritic papulovesicles on her torso of 4 years' duration. The papulovesicles would wax and wane approximately every 3 months, and she associated them with flulike symptoms of fatigue and myalgia. She had seen 2 other dermatologists for her condition and both diagnosed folliculitis after multiple skin biopsies. A retrospective review of these prior biopsies revealed a relatively dense folliculotropic infiltrate. She took several medications throughout the last 4 years; however, the onset of her skin condition had no consistent temporal association with medication intake. On physical examination, she was noted to have red papulovesicles on the trunk and arms, some with excoriation and ulceration and some with scale (Figure 1). No lymphadenopathy or hepatosplenomegaly was present. Complete blood cell count, erythrocyte sedimentation rate, blood chemistries, antinuclear antibody titer, rheumatoid factor, and rapid plasma reagin levels were all within reference range or negative.

A 3-mm skin biopsy revealed a folliculotropic and patchy perivascular infiltrate in the superficial dermis with small perivascular aggregates in the mid dermis (Figure 2). Small to medium–sized lymphocytes also were seen infiltrating the overlying epidermis adjacent to the follicle. The infiltrate consisted of a population of polymorphous lymphocytes including larger atypical lymphocytes. The dominant small cell lymphoid populace had nuclear atypia and contour irregularities including occasional cerebriform outlines. No admixed neutrophils were noted and rare eosinophils were present. Immunohistochemical studies revealed that the population of larger atypical lymphocytes exhibited characteristic cytoplasmic staining for CD30. This population was found predominantly in the hair follicle (Figure 3). Review of prior biopsies taken from the patient revealed a similar though more sparse population. Additional immunohistochemical markers revealed diffuse CD3$^+$ and no staining for CD79a or CD20, confirming an exclusively T cell infiltrate. Alcian blue staining at pH 2.5

failed to demonstrate follicular mucinosis. Staining for CD4 and CD8 cells was not performed and was not thought to have any diagnostic utility in this case. Additional immunohistochemical staining for herpes simplex virus (HSV) types 1 and 2 was negative.

The histologic differential diagnosis included type B follicular LyP, folliculotropic MF, follicular-based drug reactions, folliculotropic pityriasis lichenoides chronica, mucin-poor alopecia mucinosa, and folliculocentric HSV. Many drugs have been reported to cause an LyP-type reaction, including anticonvulsants, antihypertensives, and even gold acupuncture, but the clinical picture of waxing and waning papules in this patient without correlation to drug intake ruled out a drug-induced pseudolymphoma.[12] Pityriasis lichenoides chronica, which generally heals without scarring, and alopecia mucinosa, which presents with alopecia, also were ruled out based on the clinical presentation.[13,14] Chronic or healed herpetic lesions may resemble the histologic findings seen in LyP, particularly if there are no classic cytologic features of herpes infection (ie, effaced chromatin with beading of the nuclear membrane, multinucleation, hypereosinophilia of the cytoplasm, acantholysis). An atypical lymphoid infiltrate including a population of $CD30^+$ cells has been well-described in chronic or healed herpetic infection. However, $CD30^+$ cells in HSV infection typically are scattered throughout the infiltrate, while they are clustered in LyP, as seen in our case. In addition, herpetic infections often have a variable number of admixed B lymphocytes,[15] which was not a prominent feature in this case. Negative staining for HSV provided additional evidence against this diagnosis. In rare cases, the histologic features of LyP and herpetic infection may be indistinguishable, and clinical correlation is essential for a correct diagnosis. Based on the clinical presentation, we limited the differential diagnosis to type B follicular LyP and folliculotropic MF. Further workup for systemic malignancy, including flow cytometry and positron emission tomography–computed tomography, was negative. T-cell receptor (TCR) γ chain gene polymerase chain reaction (PCR) was performed and did not demonstrate a clonally rearranged population. Taken together with the clinical features, the findings are most consistent with type B follicular LyP. The patient currently is deferring therapy.

Comment

Lymphomatoid papulosis generally occurs in adults (average age, 45 years) with a male predominance.[2] This disease falls under the umbrella of $CD30^+$ LPDs. In addition to LyP, $CD30^+$ LPDs include primary cutaneous $CD30^+$ large cell lymphoma of anaplastic, immunoblastic, or pleomorphic cytomorphology, as well as borderline types.[2,11] CD30 is a cytokine belonging to the tumor necrosis factor superfamily. Additional $CD30^+$ T cell infiltrates that do not fall under the $CD30^+$ LPD umbrella include drug-induced eruptions and chronic or healed herpetic infections.[13] Hyperplasia of $CD30^+$ cells also may be seen in arthropod assaults, most notably in association with scabies infestation.[16,17] Histologically distinguishing $CD30^+$ LPDs from other causes of $CD30^+$ infiltrates can be challenging, occasionally necessitating clinical correlation to arrive at the correct diagnosis.

Lymphomatoid papulosis contains atypical lymphoid cells that usually express CD4 (90%), but $CD4^-CD8^+$ and $CD4^-CD8^-$ variants occasionally are encountered. Typically there is variability of the T-cell antigens, CD2, CD3, CD5, and CD7.[3]

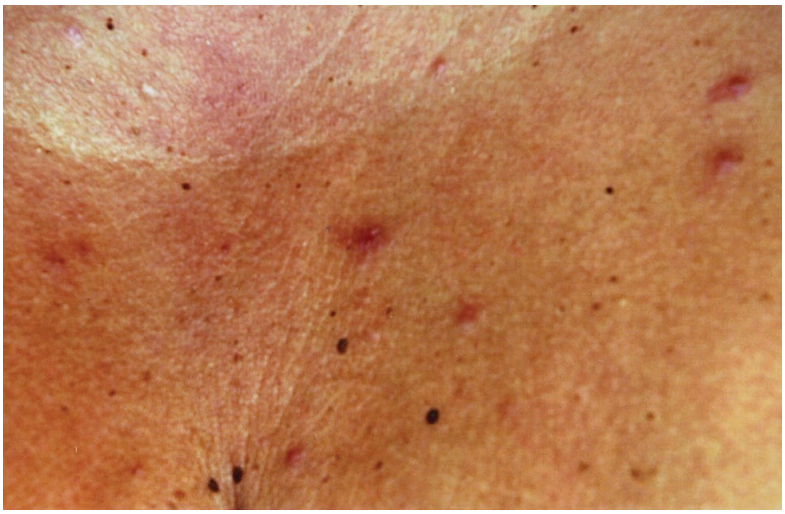

Figure 1. Follicular-based erythematous papules with central scarring on the chest of a 48-year-old woman.

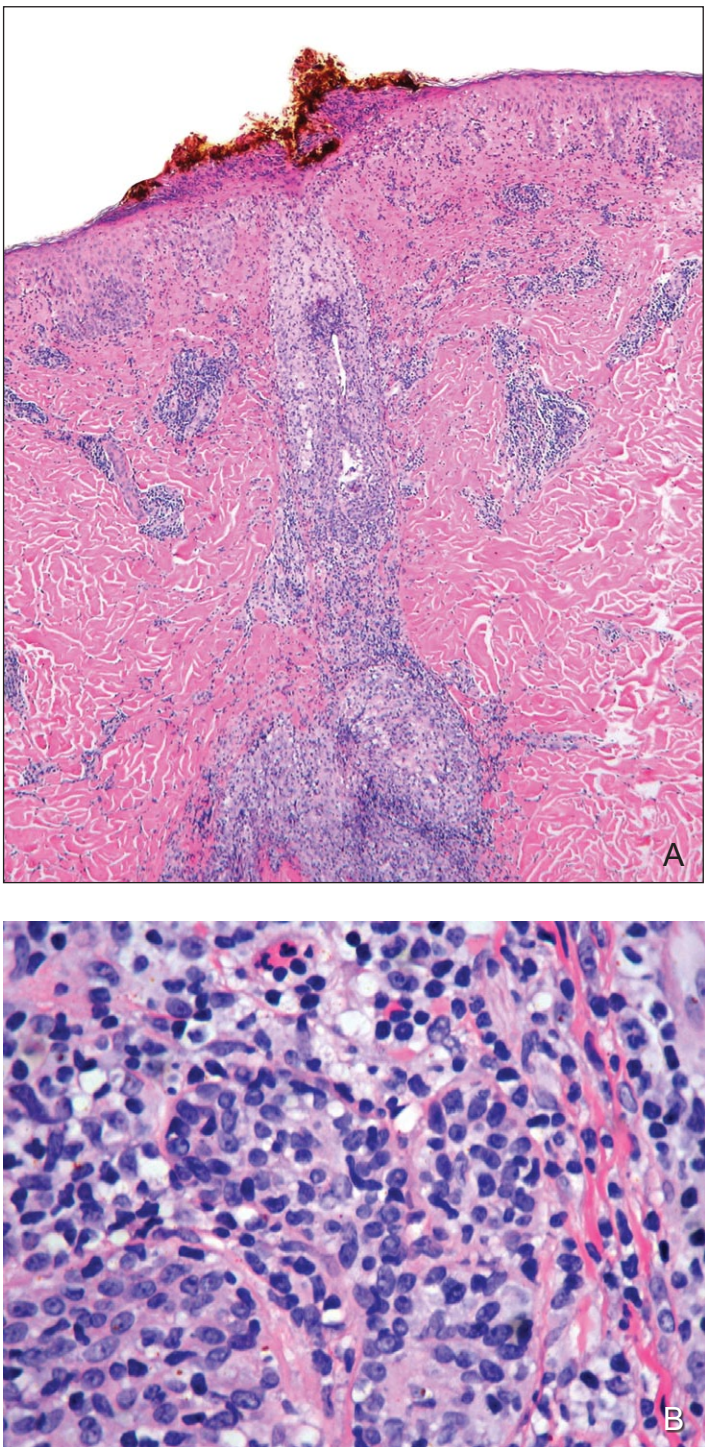

Figure 2. A folliculotropic and perivascular dermal infiltrate of small to medium–sized lymphocytes. Small to medium–sized lymphocytes also infiltrated the overlying epidermis (A)(H&E, original magnification ×100). Within the follicle, the infiltrate included larger atypical lymphocytes (B)(H&E, original magnification ×400).

Lymphomatoid papulosis has been histopathologically classified into 3 different subtypes: A, B, and C. Overlap between the 3 variants has been well-described.[11] Type A LyP, or the histiocytic type, consists of a wedge-shaped infiltrate and is the most common presentation of LyP. The infiltrate contains large anaplastic $CD30^+$ cells, often accompanied by inflammatory cells such as neutrophils, eosinophils, and histiocytes.[11,13] Occasionally, type A lesions have multinucleated or Reed-Sternberg–like cells. Type C LyP also contains $CD30^+$ cells, but they are greater in number and often arranged in clusters or sheets; therefore, type C LyP histologically resembles ALCL but still is differentiated by its clinical presentation. Anaplastic large cell lymphoma usually is confined to one extremity or body area and

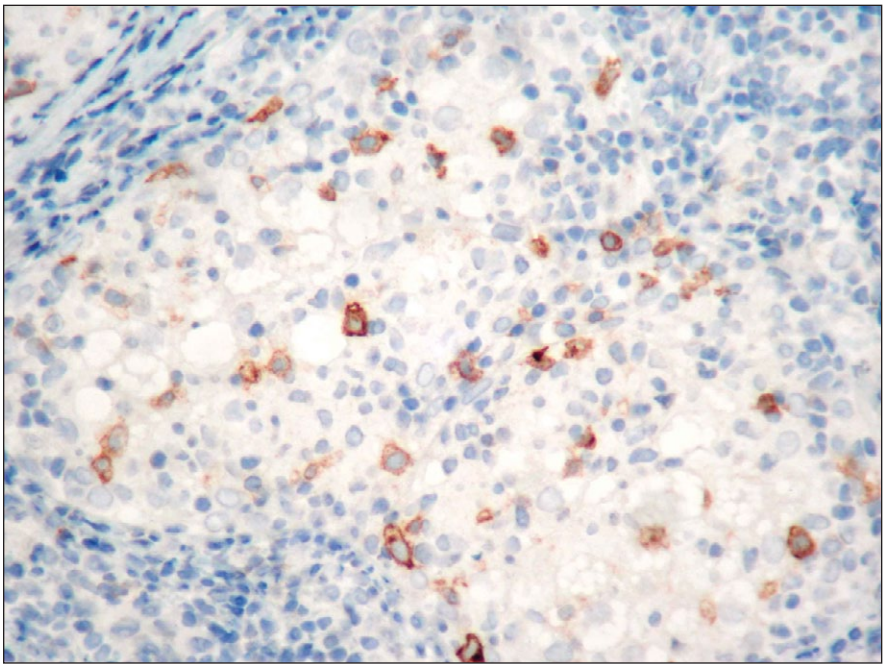

Figure 3. Anti-CD30 antibody staining of type B follicular lymphomatoid papulosis. The population of larger atypical lymphocytes revealed characteristic cytoplasmic immunohistochemical staining for CD30 (original magnification ×400).

does not remit and relapse, while LyP waxes and wanes. Because there are many similarities between types A and C LyP, Kempf[13] postulated that these 2 types represent a spectrum of disease.

Type B LyP, the lymphocytic variant, resembles MF.[2,11] It consists of a small to medium–sized infiltrate of lymphocytes with cerebriform nuclei and is the least common subtype of LyP. Lymphocytes of this subtype may not express the CD30 antigen, different from our case, but are generally $CD3^+$, $CD4^+$, and $CD8^-$.[2] Monoclonal rearrangement of TCR genes occurs in less than half of all types of LyP when assayed with automated high-resolution PCR fragment analysis on paraffin-embedded tissue. However, a negative result with this modality does not rule out the possibility of a lymphoproliferative disorder.[13,14,18,19] Steinhoff et al[20] demonstrated the monoclonality of LyP through an even more sensitive technique with frozen-tissue assay and PCR analysis of TCRγ rearrangements using individual $CD30^+$ cells. Because the histologic features of type B LyP and MF can be identical, they must be correlated with the clinical presentation to arrive at the correct diagnosis. Clinically, type B follicular LyP has waxing and waning papules, resolves spontaneously, and heals with scarring. Folliculotropic MF has persistent papules, resolves only following treatment, and most often heals without scarring.[21]

Kato and Matsue[7] reviewed the first 6 cases of follicular LyP presented in the literature. Two men and 4 women (age range, 22–60 years) were reported. Two showed type A histology, 2 showed type B histology, 1 showed a combination of both types A and B, and 1 was not given a subtype classification.[7] The 5 cases reported since then do not specify histologic subtype.[5,6,8-11] The origin of follicular LyP remains to be elucidated, but some consider it to be an abnormal reaction to folliculitis or a response to a foreign body.[8] Others consider it to be a spectrum of typical LyP whereby the lymphoproliferative reaction occurs in the vicinity of hair follicles, causing hyperplastic proliferation of the follicular epithelium, which results in the follicular papules seen clinically.[7]

Treatment of follicular LyP does not differ from any other form of LyP. Therapy is aimed at suppressing the development of new skin lesions. Unfortunately, shortly after the cessation of most therapies, the disease reappears. Psoralen plus UVA light, topical chemotherapy (eg, carmustine, nitrogen mustard), or low-dose methotrexate are the most common treatments. Other therapies include systemic interferon alfa-2a, etretinate, bexarotene, and excision with radiotherapy.[22,23] A case report describes positive results with imiquimod cream 5%.[24]

Lymphomatoid papulosis typically has a benign prognosis but can be associated with or progress to malignancy. Most cases, though remitting and recurring for many years, end without long-term sequelae. The prognosis of follicular LyP cannot be predicted confidently because of the paucity of case reports. Favorably, none of the cases described to date have reported systemic malignancy associated

with follicular LyP. Our patient, for example, had no evidence of a systemic lymphoproliferative disorder after 4 years of symptoms. While systemic malignancies can occur in up to 20% of patients with LyP, no risk factors appear to determine which patients will develop further disease.[25] Evidence suggests that fascin, an actin-building protein, may be a marker of malignant degeneration.[26] The malignancies that occur most commonly in patients with LyP include other lymphoid dyscrasias, such as MF, ALCL, or Hodgkin lymphoma. Therefore, it is important to monitor these patients carefully for systemic disease until a reliable marker for prognosis is found.

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