
Borrelia burgdorferi-associated primary cutaneous B cell lymphoma: complete clearing of skin lesions after antibiotic pulse therapy or intralesional injection of interferon alfa-2a

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We report two patients with low-grade malignant primary cutaneous B cell lymphoma in association with *Borrelia burgdorferi* infection. Extracutaneous manifestations were ruled out by standard staging procedures. Infection with *Borrelia burgdorferi* was confirmed by cultivation from lesional skin in both patients. In the first patient skin lesions cleared completely after pulse therapy with cefotaxime, whereas in the second patient antibiotic treatment failed. In this patient, however, skin lesions completely cleared after intralesional injection of interferon alfa-2a. Antibiotic treatment or intralesional injection of interferon alfa-2a should be considered as a first-line treatment of *Borrelia burgdorferi*-associated primary cutaneous B cell lymphoma before more aggressive conventional therapeutic modalities (e.g., radiation therapy) are applied. (*J Am Acad Dermatol* 1997;36:311-4.)

The association of malignant lymphoma, especially B cell lymphoma, and acrodermatitis chronica atrophicans had been noted before *Borrelia burgdorferi* was identified.^{1,2} These observations suggested a potential involvement of *B. burgdorferi* in the development of cutaneous B cell lymphoma. In 1988 Garbe et al.³ initially described the association of low-grade malignant B cell lymphoma of the skin with chronic *B. burgdorferi* infection confirmed by positive serologic studies.³ Three years later, Garbe et al.⁴ described four more cases⁴ and emphasized the benign course of these lymphomas. In this report we describe two additional cases of *B. burgdorferi*-associated B cell lymphoma that promptly responded to antibiotic therapy or intralesional injection of interferon alfa-2a. In our cases *B. burgdorferi* infection could be proved for the first time not only by serologic parameters but also by cultivation from lesional skin.

CASE REPORTS

Case 1

A 28-year-old man noticed a few erythematous papules and plaques on his right arm in November 1992 (Fig. 1). Seven months later a reddish nodule appeared at the same site. In June 1994 a few subcutaneous nodules were detected on the other arm.

A skin biopsy specimen from a subcutaneous nodule revealed a dense infiltrate of lymphoid cells with formation of germinal centers in the deeper dermis and subcutaneous fat (Fig. 2). Higher magnification showed two main cell populations: small lymphoid cells and medium-sized cells with abundant clear cytoplasm. Both cell types expressed the B cell-associated antigen CD 20/L 26 (Dako, Dakopatts, Denmark). A few, reactive, CD3-positive (Dako) T-lymphocytes were also found. The neoplastic nature of the B-lymphocytes was confirmed by showing monoclonal restriction of light chain with expression of K chain and absence of λ chain. A diagnosis of low-grade malignant B cell lymphoma, possibly of the marginal zone type, was established. Extracutaneous manifestations were ruled out by blood cell count, chest radiograph, bone marrow biopsy, and abdominal and nodal sonography.

Although *B. burgdorferi* serology revealed only marginally elevated titers (Lyme-Elisa-IgG—neg.; Lyme-Elisa-IgM—0.354), lymphocyte transformation test showed high activity. Moreover, *B. burgdorferi* could be cultured from lesional skin on a modified Kelly's me-



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Fig. 1. Case 1. Erythematous papules and plaques on upper part of arm right.

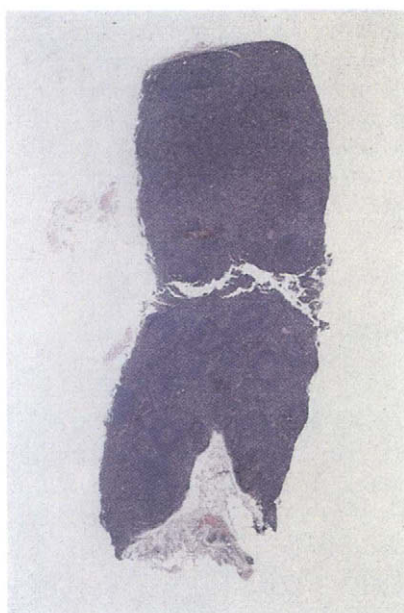


Fig. 2. Case 1. Histologic specimen of subcutaneous nodule showing dense infiltrate of lymphoid cells with formation of germinal centers in deeper dermis and subcutaneous tissues.

dium. Specific DNA sequences were also detected within lesional tissue specimens by polymerase chain reaction (PCR) analysis. Antibiotic treatment with ceftriaxone, 2 gm/day intravenously for 2 weeks, and oral doxycycline 200 g/day for 3 weeks, was unsuccessful. However, skin lesions cleared after pulse therapy with cefotaxime (3 × 4 g/day intravenously on two successive days, every 8 days, for a total of eight cycles).

The patient has been in complete remission for 14 months.

Case 2

A 38-year-old man has had recurrent erythematous papules and plaques on his back since 1991 (Fig. 3). A

biopsy specimen revealed a dense infiltrate in the entire dermis, involving the subcutaneous fat. Higher magnification showed a mixed population of small lymphocytes and larger cells with features of centrocytes, centroblasts, and immunoblasts. Immunohistochemistry showed findings similar to those in case 1. A diagnosis of low-grade malignant B cell lymphoma of the follicular center cell type was established.

Extracutaneous involvement could not be detected by standard staging procedures.

B. burgdorferi was cultured from lesional skin. However, serologic titers were only marginally elevated (Lyme Immunoblot IgG—negative; Lyme Immunoblot IgM—positive with p41/i: pBi). PCR analysis for *B. burgdorferi* infection failed. Antibiotic treatment with ceftriaxone, doxycycline, and cefotaxime was unsuccessful, but skin lesions cleared after intralesional injection of interferon alfa-2a in a cumulative dosage of 64.5 million I. U. in a 3 week period (Fig. 4).

The patient has been without recurrence for 7 months.

DISCUSSION:

Study of our two patients confirms the association between some cases of primary cutaneous B cell lymphoma and infection with *B. burgdorferi*, as described by Garbe et al.^{3,4} The clinical and histopathologic features in both patients were consistent with the diagnosis of malignant lymphoma. However, the differentiation between cutaneous pseudolymphoma and malignant lymphoma by clinical or histologic criteria can be difficult in some cases.⁵ Several cases diagnosed in the past as pseudolymphoma have been reclassified as true B cell lymphomas of low-grade malignancy. In our patients, the neoplastic nature of the infiltrates was confirmed by immunohistochemical detection of monoclonality. Both cases revealed immunoglobulin light chain restriction with expression of the K chain and



Fig. 3. Case 2. Erythematous papules and plaques on patient's back.



Fig. 4. Case 2. Complete clearing of skin lesions after intralesional injection of interferon alfa-2a.

absence of the λ chain. In contrast, benign lymphocytic infiltrates are characterized by a polyclonal pattern with both K-positive and λ -positive cells. In cases in which no immunoglobulin expression can be detected, molecular biologic approaches such as analysis of the rearrangement of the immunoglobulin heavy chain genes⁶ can help identify the neoplastic nature of the infiltrates. Ashton-Key et al.,⁷ however, demonstrated that immunohistologic results are more reliable than PCR in providing evidence of monoclonality in B cell lymphomas.

Infection with *B. burgdorferi* was confirmed in both of our patients by culture of lesional skin. Culture is the most specific and reliable way of diagnosing *B. burgdorferi* infection. *B. burgdorferi*-specific DNA sequences could be detected by PCR only in our first patient. The negative result in the second patient is probably related to differential sensitivity of primers for OspB, p41 and the 16S ribosome gene. The negative PCR result may also be explained by the fact that the amount of specific

DNA was below the limit of detection. In contrast to the report by Garbe et al.,⁴ we could not find high titers of IgG antibodies to *B. burgdorferi*. *B. burgdorferi* infection may be present in lesions of cutaneous B cell lymphoma in patients with negative serologic tests. Culture of these organisms from lesions of cutaneous B cell lymphoma should be attempted even when serologic tests are negative.

In the first patient skin lesions cleared completely after modified pulse therapy with cefotaxime as initially described by Hassler et al.⁸ for the treatment of persistent *B. burgdorferi* infection in cases of Lyme arthritis. This high-dose cefotaxime therapy had been successful in two cases of Lyme-Borreliose refractory to standard antibiotic therapies. The success of this therapeutic approach might be caused by the extremely long generation cycle of *B. burgdorferi* (7 to 33 hours). However, *B. burgdorferi* is sensitive only to antibiotics in its time of generation.

The complete clearing of skin lesions in our first patient is analogous to the observation that *Helico-*

bacter pylori-associated gastric lymphoma may regress after eradication of the organism.⁹⁻¹² We speculate that chronic antigenic stimulation by *B. burgdorferi* or *H. pylori* may result in cutaneous or gastric B cell lymphomas, respectively.¹³ Because of their favorable prognosis, cutaneous B cell lymphomas have been considered similar to the lymphomas of "mucosa-associated lymphoid tissue" (so-called MALT-lymphomas).¹⁴

In our second patient antibiotic treatment, including pulse therapy with ceftriaxone failed but the skin lesions cleared after intralesional injection of interferon alfa-2a. Similar results were reported by Zenone et al.,¹⁵ who observed complete regression in a patient with primary cutaneous B cell lymphoma after intralesional injection of interferon alfa-2a. Because interferon alfa-2a has been used with success in the treatment of low-grade malignant cutaneous B cell lymphoma,¹⁶ we tried it in our second patient after the failure of antibiotics.

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