# Lymphomatoid Papulosis Type B in a Patient with Crohn's Disease Treated with TNF-Alpha Inhibitors Infliximab and Adalimumab

Dear Editor,

Lymphomatoid papulosis (LP) is a chronic, recurrent, usually self-limited papulonecrotic or papulonodular skin disease, which belongs to the group of primary cutaneous CD30+ lymphoproliferative disorders (1). Three main histological subtypes of LP have been recognized: type A (histiocytic), type B (mycosis fungoides-like), and type C (anaplastic large cell lymphoma-like). Recently, new histologic LP variants classified as type D (CD8-positive, cytotoxic form) and type E (angioinvasive form) have also been described. The etiology of LP has not been determined to date (2-4). Herein we report a case of LP type B evolving in a patient with Crohn's disease after treatment with infliximab and adalimumab.

A 38-year-old man suffering from terminal ileitis form of luminar Crohn's disease for 10 years presented at our department. During the last 10 years, the patient had been treated with a number of conventional disease-modifying anti-inflammatory drugs including non-steroid anti-inflammatory drugs, mesalazine, and immunomodulatory agents such as corticosteroids and azathioprine. As the disease was not sufficiently controlled, TNF-α inhibitor therapy was initiated. Infliximab was administered in standard dosage (5 mg/kg body weight every 8 weeks after the induction period) for one year. Concomitant therapy with azathioprine was established to reduce the risk of adverse immunological reactions. Since the patient showed only partial clinical response, infliximab was switched to adalimumab (40 mg biweekly), resulting in notable improvement. 18 months after the initiation of adalimumab treatment, asymptomatic, small, red to brown papules developed on the extremities. Multiple lesions were observed, initially on the legs, but the symptoms rapidly progressed to the arms and trunk (Figure 1). An acquired ichthyosis further complicated the disease course by extended, extremely xerotic, scaling skin lesions. Neither systemic symptoms nor significant lymphadenopathy was observed.

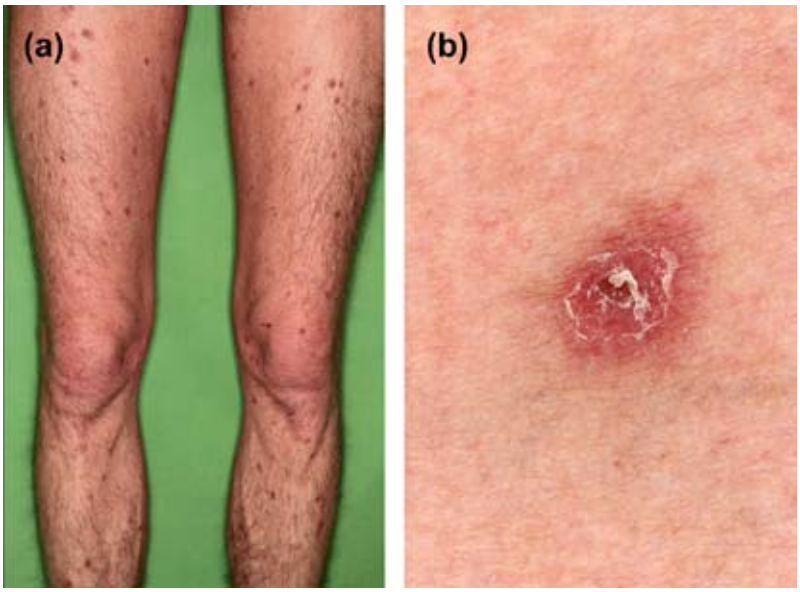


**Figure 1.** Clinical manifestation. (a) Multiple papules on the legs. (b) Scaling papules with a crusted necrotic center.

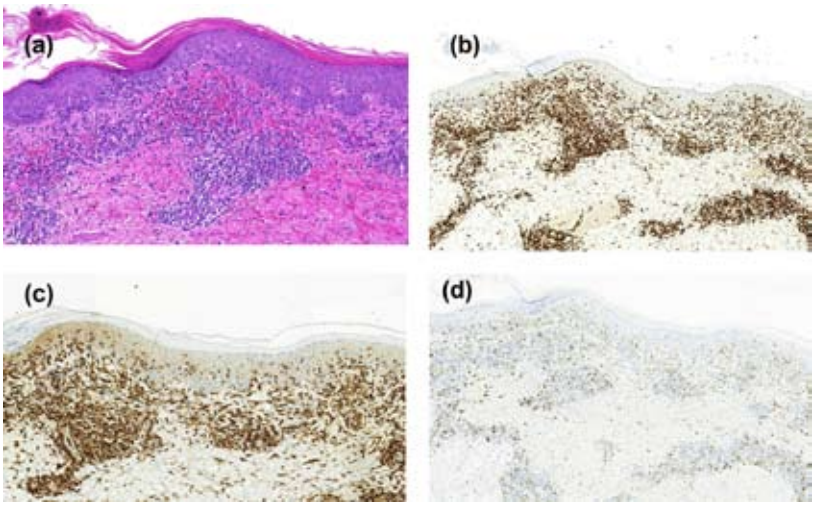


**Figure 2.** Histopathology showing perivascular and periadnexal dense, small-to-medium sized lymphoid cell infiltration with focal epidermotropism, and hemorrhage (hematoxylin and eosin staining (HE), ×100 magnification). (a) Epidermotropic infiltration by small-to-medium sized atypical lymphocytes (HE, original magnification ×100). (b-d) Immunohistochemical staining of infiltrating lymphocytes for (b) CD3, (c) CD4 and (d) CD30 (×100 magnification).

The clinical picture suggested either ichthyosiform mycosis fungoides or a coincidence of LP and acquired ichthyosis. The histology of a typical papule showed perivascular and periadnexal lymphoid infiltration with massive hemorrhage in the dermis. The infiltration was dense, composed of small-to-medium-sized lymphoid cells showing focal significant epidermotropism (Figure 2). Most observed epidermal lymphocytes were CD3+, CD4+, and CD30+, while the dermal infiltration had higher CD4 and lower CD30 expression (10-15%). Polymerase chain reaction (PCR) analysis of skin and peripheral blood samples did not show clonal rearrangement of T-cell receptor gamma (TcRgamma) genes. Normal phenotypes of lymphocyte subsets were detected by flow cytometry of peripheral blood. Ichthyosiform mycosis fungoides was excluded since histology of ichthyosiform skin lesions showed only hyperkeratosis with a reduced granular layer. While the cutaneous CD4+ epidermotropic infiltrate was suspicious of either mycosis fungoides or LP type B, the complexity of clinicopathological data confirmed the diagnosis of LP type B. The peripheral blood counts, serum biochemical tests, and urinalysis were within normal range, while the elevated serum anti-Saccharomyces cerevisiae antibodies (ASCA) of IgG and IgA subclasses indicated the activity of Crohn's disease. Adalimumab and azathioprine were discontinued, and oral budesonide therapy was started in combination with topical corticosteroids and PUVA phototherapy. The skin lesions resolved with hyperpigmentation, and there was no relapse during the twelve-month follow-up.

Recent data suggest that LP occurs more commonly in immunocompromised patients, especially in those with solid organ or bone marrow transplants (3). Though TNF-α inhibitors have dramatically advanced the treatment of various diseases, the risk of lymphoma associated with their use remains controversial (5). Several cases of cutaneous lymphoproliferative disorders associated with TNF-α inhibitor treatment have been reported, including two patients with LP (6). One of the two patients with LP received infliximab for Crohn's disease (7), while the other one had juvenile rheumatoid arthritis and received adalimumab (8). Our case is the third report on LP developing under TNF-α inhibitor therapy and the first LP type B in a patient with Crohn's disease treated with infliximab and later with adalimumab. A further interesting aspect of our case is that it also represents an example of the known association of acquired ichthyosis with inflammatory bowel disease (9). Multidisciplinary management was needed to provide optimal care and disease outcome for our patient. Since it is usually difficult to prove causality in most of such cases, it is important to collect similar clinical observations.

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