SHORT COMMUNICATION

Primary Cutaneous B-cell Lymphoma Leg-type Related to a Tumour Necrosis Factor Alpha Inhibitor

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Tumour necrosis factor alpha inhibitors (TNFαi) have demonstrated remarkable efficacy in various inflammatory disorders and are widely used in rheumatology, gastroenterology, ophthalmology and dermatology. There is a debated risk of neoplasia, including lymphoproliferation, induced by this class of treatment (1). Rare cases of non-Hodgkin lymphoma have been reported, including exceptional cases of primary cutaneous lymphomas (PCL) (2). However, most of these cases of PCL were found to be progression of undiagnosed PCL after TNFαi, mainly mycosis fungoides or Sézary syndrome initially misdiagnosed as psoriasis or eczema (3). Exact mechanisms by which TNFαi could promote cancer development remain under investigation (1, 4, 5). We report here a case of primary cutaneous B-cell lymphoma leg-type (PCBCL-LT) probably induced by TNFαi.

CASE REPORT

A 63-year-old woman was followed in rheumatology for an HLA-B27-positive spondylarthritis treated with oral methotrexate, 10 mg per week, and adalimumab. She had taken methotrexate for 8 years, while adalimumab had been initiated 6 months earlier. She had no other significant medical history. She was referred to the dermatology department for a 1-month history of a growing lumbar cutaneous lesion. Physical examination revealed a solitary thick, violaceous plaque, 6×4 cm (**Fig. 1**), with no enlarged lymph nodes. No fatigue, fever or pruritus were present.

Histological examination of the skin revealed a monomorphic dermal proliferation of large centroblast-like cells with large round, sometimes irregular, nuclei. Only rare reactive small cells were present. The infiltrate spared the epidermis, with a grenz zone. The tumour cells were positive for CD45, CD20, bcl2, bcl6, MUM1, highly proliferating (Ki67 95%), and negative for CD3, CD30, CD10 and EBV/EBER (**Fig. 2**). No CD21- or CD23-positive follicular dendritic cell network was identified. Fluorescence in situ hybridization showed no BCL2, BCL6 or CMYC rearrangement, while high-resolution melting identified the MYD88 L265P mutation. A monoclonal neoplastic B-cell population was identified by PCR. Body fluorodeoxyglucose positron emission tomography and computed tomography (FDG-PET/CT) showed a single hypermetabolic activity corresponding to the cutaneous lesion, without distant tumours.

Although the *Borrelia burgdorferi* serology was negative, a 15-day course of doxycycline, 200 mg daily, was given. A diagnosis of PCBCL-LT was finally reached, and adalimumab (but not methotrexate) was discontinued. The tumour disappeared completely within 4 months after discontinuation. No other TNFαi were given subsequently. No recurrence was observed after a follow-up of 4 years.

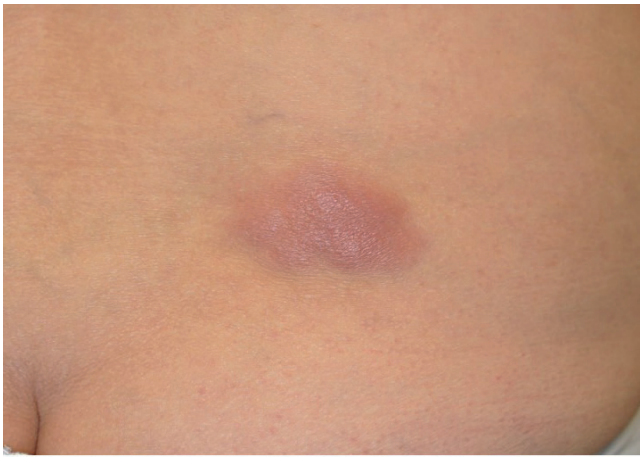

Fig. 1. Rapidly growing violaceus lumbar plaque.

DISCUSSION

To our knowledge, this is the first reported case of PCBCL-LT induced by a TNFαi. A retrospective study and literature review found 2 cases of indolent types of PCBCL, possibly induced by TNFαi: 1 primary cutaneous follicular B-cell lymphoma after 1 month of adalimumab and 1 marginal zone B-cell lymphoma after 8 months of etanercept (3). In contrast to indolent PCBCL, PCBCL-LT is more aggressive, with frequent extracutaneous dissemination and only exceptional spontaneous regressions, constantly followed by recurrences (6–8). Drug-induced PCBCL-LT has been described in organ-transplant recipients receiving immunosuppressive drugs (9). In addition, cutaneous large B-cell lymphomas morphologically and immunophenotypically similar to PCBCL-LT have been described in patients treated with methotrexate, with frequent expression of EBV by the tumour cells (10).

In the current patient, the diagnosis of PCBCL-LT was assessed by the histological and genetic features, including the monomorphic proliferation of large $CD20^+$, $Bcl2^+$, $Mum1^+$, $CD10^-$ B cells, the B-cell clonality and the MYD88 L265P mutation, as reported previously (11). The role of methotrexate, although not ruled out as a cofactor, is unlikely because of the absence of EBV expression, and complete regression, while methotrexate was continued. Long-term remission after adalimumab discontinuation, however, strongly argues for the role

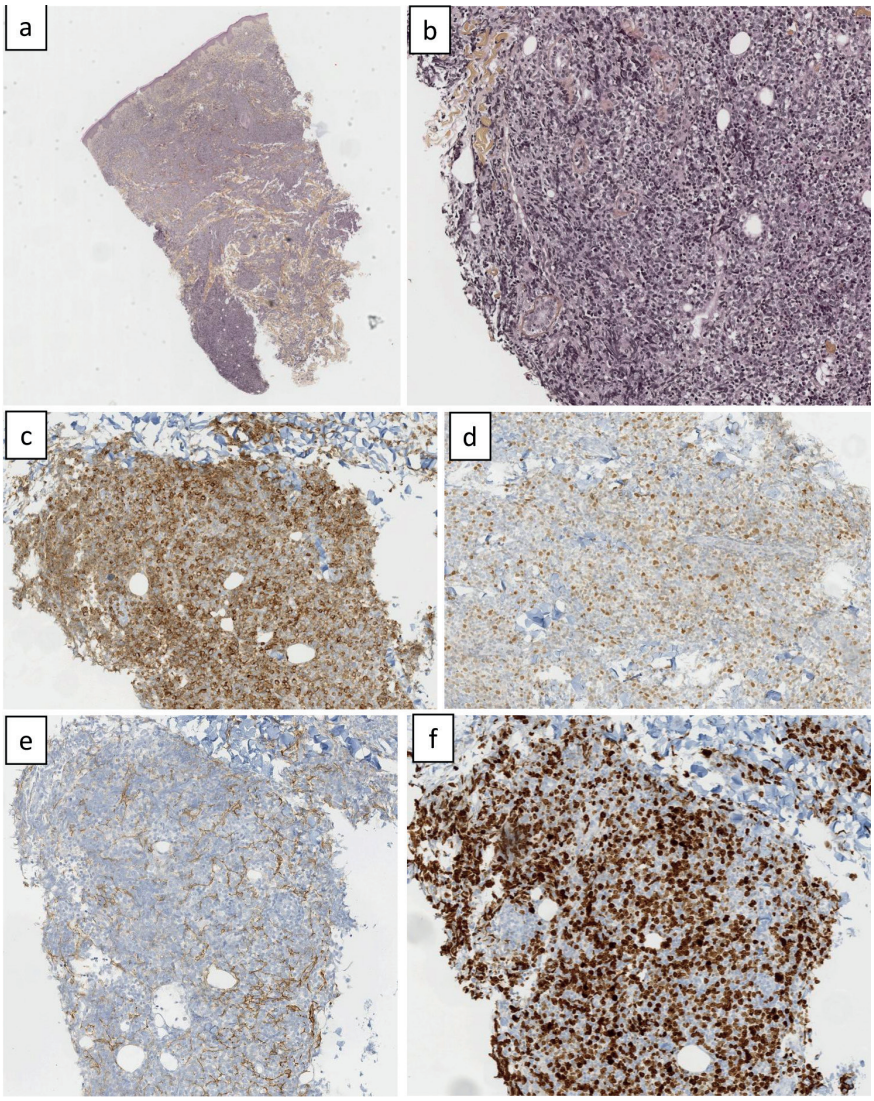

Fig. 2. Histological and immunohistochemical features: dense monomorphic dermal proliferation of large cells with round nuclei. (a, b) Haematoxylin, phloxine, saffron; (c) positive Bcl2 staining (90%); (d) positive MUM1 staining (40%); (e) negative CDIO. (f) Positive Ki67 staining (95%). The original magnifications are x1 (a), x10 (b;f).

of this treatment in the occurrence of this potentially aggressive lymphoma.

The authors have no conflicts of interest to declare.

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