

## Cutaneous Gamma/Delta T-cell Lymphoma During Treatment with Etanercept for Rheumatoid Arthritis

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Sir,

Tumour necrosis factor-alpha (TNF- $\alpha$ ) antagonists, such as etanercept, infliximab and adalimumab, are used increasingly in the treatment of chronic inflammatory diseases, such as rheumatoid arthritis (RA), ankylosing spondylitis, psoriatic arthritis, moderate to severe psoriasis and Crohn's disease (1). In recent years there has been an increasing number of reports on malignant lymphomas developing in patients using TNF- $\alpha$  blocking agents, mostly infliximab or etanercept. Most lymphomas developing in patients using anti-TNF- $\alpha$  therapy are B-cell lymphomas (2). Reports on T-cell lymphomas as a result of this treatment, especially those primarily involving the skin, are rare (3–11). We report here an unusual case of cutaneous  $\gamma\delta$  T-cell lymphoma (CGD-TCL) in a patient with RA receiving anti-TNF- $\alpha$  treatment.

### CASE REPORT

A 67-year-old man with a 40-year history of RA had been successfully treated with etanercept 25 mg subcutaneously twice weekly and dexamethasone per os 0.5 mg per day for the last 3 years. In August 2006 he presented with generalized skin lesions, night sweats and weight loss. These symptoms had been present for 3 weeks. Physical examination revealed multiple indurated bluish red nodules on the trunk and extremities. There was no peripheral lymphadenopathy or hepatosplenomegaly and no signs of disease activity of rheumatoid arthritis. Laboratory investigations showed no abnormalities except for a raised lactate dehydrogenase of 791 U/l.

A skin biopsy showed extensive infiltration of the subcutaneous fat and the upper dermis by a population of mainly medium-sized lymphoid cells with pleomorphic nuclei and often prominent nucleoli (Fig. 1a–c). So-called "rimming" of the atypical lymphocytes around individual adipocytes was frequently seen (Fig. 1b). Scat-

tered histiocytes showed erythrophagocytosis (Fig. 1c). There was little epidermal involvement. Immunohistochemically, the tumour cells were positive for CD2 and CD3 (Fig. 2a), showed partial loss of CD5, but were completely negative for both CD4 and CD8 as well as for CD56 and  $\beta$ F1. *In situ* hybridization on Epstein-Barr virus-encoded RNA (EBER) was negative. The cytotoxic markers TIA-1 and Granzyme B (Fig. 2b) were strongly positive. The neoplastic cells were positive for monoclonal antibody TCR1153, recognizing the human TCR  $\gamma$ -chain constant region (Fig. 2c). Based on these clinical, histological and phenotypical data, a diagnosis of cutaneous  $\gamma\delta$  T cell lymphoma (CGD-TCL) was made (12).

At this point, the etanercept treatment was discontinued and the dosage of dexamethasone was increased from 0.5 mg to 1.0 mg a day. This resulted in a rapid improvement in the skin lesions and systemic symptoms, and after several weeks the lesions had resolved completely. The patient continued dexamethasone treatment and started methotrexate 4 months after disappearance of all skin lesions. Skin lesions have not returned and the patient has died of natural causes, most probably unrelated to the lymphoma (sudden death of unknown cause), after 1.5 years of follow-up.

### DISCUSSION

According to the criteria of the WHO classification 2001 (13) our case should be classified as a subcutaneous panniculitis-like T-cell lymphoma (SPTL). However, in the recent WHO-EORTC classification (14) as well as in the updated WHO classification 2008 (12), the term SPTL is only used for SPTL expressing the  $\alpha\beta$  T-cell receptor (SPTL-AB), while cases expressing the  $\gamma\delta$  T-cell receptor (formerly classified as SPTL-GD) are nowadays reclassified as CDG-TCL. In general, SPTL-AB is confined to the subcutis, shows a CD4 $^-$ , CD8 $^+$ , CD56 $^-$ ,  $\beta$ F1 $^+$  T-cell phenotype, is uncommonly associated with a haemophagocytic syndrome (HPS), and has an excellent prognosis

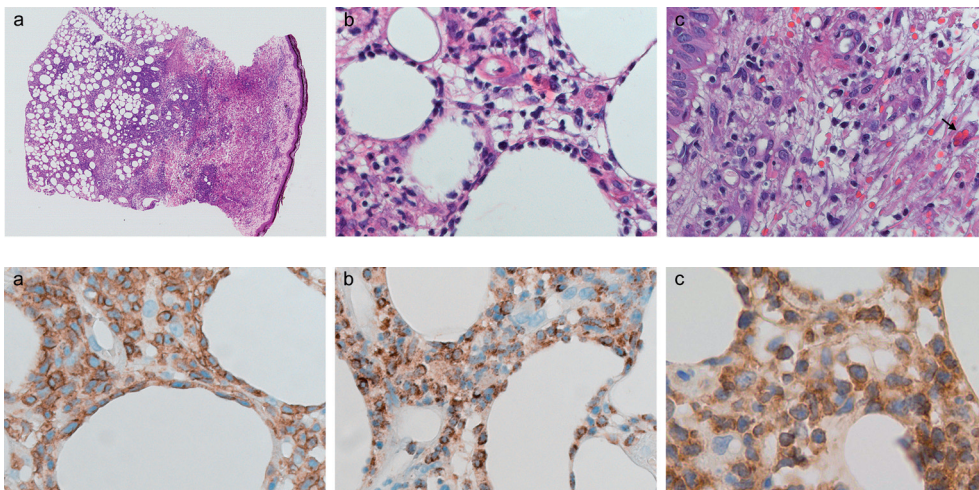


Fig. 1. (a) Low-power view showing extensive infiltration of the subcutaneous fat and the lower dermis by medium-sized lymphoid cells. (b) Rimming of atypical lymphocytes around individual adipocytes, (c) Erythrophagocytosis in the dermis (arrow). H&E; a:  $\times 2.5$ , b, c:  $\times 40$ .

Fig. 2. (a) CD3 positivity in the neoplastic cells. (b) Granzyme B positivity in the neoplastic cells. (c) Positive staining for monoclonal antibody TCR1153 Dr John Choi, Children's Hospital of Philadelphia, University of Pennsylvania, confirming a  $\gamma\delta$  T-cell phenotype of the neoplastic cells. IHC;  $\times 40$ .

(5-year survival 82%) (15). In contrast, CGD-TCL often shows both subcutaneous and (epi)dermal involvement, reflected by ulcerating skin lesions in over 50% of cases, displays a CD4<sup>-</sup>, CD8<sup>-</sup>, CD56<sup>+/-</sup>,  $\beta$ F1<sup>-</sup> T-cell phenotype, is associated with HPS in over 50% of cases, and has a poor prognosis. In a recent EORTC study 15 out of 20 cases of CGD-TCL died of lymphoma, with a 2-year survival of only 30% (15).

The clinical course in our patient, with rapid disappearance of all skin lesions and no relapse during follow-up, is highly unusual for patients with CGD-TCL. While partial or complete remissions following drug withdrawal are quite common in methotrexate-associated malignant lymphomas in patients with RA, in particular in those associated with EBV, there are very few reports on spontaneous regression of malignant lymphomas following withdrawal of anti-TNF- $\alpha$  (2–4). The disappearance of all skin lesions following cessation of etanercept strongly suggests a direct causal relationship between etanercept therapy and the development of CGD-TCL in our patient. An additional effect of the increased dose of dexamethasone from 0.5 to 1.0 mg daily cannot be excluded completely, but seems highly unlikely in this type of lymphoma.

Nevertheless, the exact role of anti-TNF- $\alpha$  therapy in the development of these lymphomas is a matter of debate. For instance, patients with RA are known to have an increased risk to develop a malignant lymphoma, whether or not they receive methotrexate or anti-TNF- $\alpha$  therapy (16). Thus, in individual patients it is difficult to ascertain whether the development of a lymphoma is due to the immune dysregulation related to the underlying disease or to the TNF- $\alpha$  blocking agent.

To our knowledge, only a few cases of primary cutaneous lymphoma during anti-TNF- $\alpha$  treatment were reported previously (3–11). Most reports concerned cases of mycosis fungoides. All these patients survived through adequate therapy and one patient showed spontaneously resolution of lymphoma after abrogation of anti-TNF- $\alpha$  therapy (3). Mahe et al. (4) reported a CD30<sup>+</sup> T-cell lymphoma in a patient showing regression after cessation of anti-TNF- $\alpha$  treatment. Two other reports described cases of Sezary syndrome, one of which was fatal despite aggressive systemic treatment (5). Finally, Michot et al. (6) recently reported a patient with SPTL-AB, requiring systemic chemotherapy to achieve complete remission.

In a recent report, Beyer et al. (17) reported an association between anti-TNF- $\alpha$  therapy and hepatosplenic T-cell lymphoma (HSTCL) in patients with inflammatory bowel disease. Like CGD-TCL, HSTCL is a highly aggressive extranodal T-cell lymphoma, usually with a  $\gamma\delta$  T-cell receptor phenotype. Interestingly, no patients with dermatological or rheumatic disease were reported to develop HSTCL during anti-TNF- $\alpha$  therapy, which might suggest that the type of  $\gamma\delta$  T-cell lymphoma development during anti-TNF- $\alpha$  therapy is related to the specific subpopulation of  $\gamma\delta$  T-cells involved in the underlying disease.

## REFERENCES

- Valesini G, Iannuccelli C, Marocchi E, Pascoli L, Scalzi V, Di Franco M. Biological and clinical effects of anti-TNF $\alpha$  treatment. *Autoimmun Rev* 2007; 7: 35–41.
- Brown SL, Greene MH, Gershon SK, Edwards ET, Braun MM. Tumor necrosis factor antagonist therapy and lymphoma development: twenty-six cases reported to the Food and Drug Administration. *Arthritis Rheum* 2002; 46: 3151–3158.
- Lourari S, Prey S, Livideanu C, Jamard B, Lamant L, Cantagrel A, et al. Cutaneous T-cell lymphoma following treatment of rheumatoid arthritis with tumour necrosis factor- $\alpha$  blocking agents: two cases. *J Eur Acad Dermatol Venereol* 2009; 23: 967–968.
- Mahe E, Descamps V, Grossin M, Fraitag S, Crickx B. CD30<sup>+</sup> T-cell lymphoma in a patient with psoriasis treated with ciclosporin and infliximab. *Br J Dermatol* 2003; 149: 170–173.
- Adams AE, Zwicker J, Curiel C, Kadin ME, Falchuk KR, Drews R, et al. Aggressive cutaneous T-cell lymphomas after TNF- $\alpha$  blockade. *J Am Acad Dermatol* 2004; 51: 660–662.
- Michot C, Costes V, Gerard-Dran D, Guillot B, Combes B, Dereure O. Subcutaneous panniculitis-like T-cell lymphoma in a patient receiving etanercept for rheumatoid arthritis. *Br J Dermatol* 2009; 160: 889–890.
- Dauendorffer JN, Rivet J, Allard A, Bachelez H. Sezary syndrome in a patient receiving infliximab for ankylosing spondylitis. *Br J Dermatol* 2007; 156: 742–743.
- Sanli H, Ataman S, Akay BN, Yilmaz A, Yildizlar D, Gurgey E. Mycosis fungoides in a patient with ankylosing spondylitis during infliximab therapy. *J Drugs Dermatol* 2007; 6: 834–836.
- Dalle S, Balme B, Berger F, Hayette S, Thomas L. Mycosis fungoides-associated follicular mucinosis under adalimumab. *Br J Dermatol* 2005; 153: 207–208.
- Bucher C, Degen L, Dirnhofer S, Pless M, Herrmann R, Schraml P, et al. Biologics in inflammatory disease: infliximab associated risk of lymphoma development. *Gut* 2005; 54: 732–733.
- Lafaille P, Bouffard D, Provost N. Exacerbation of undiagnosed mycosis fungoides during treatment with etanercept. *Arch Dermatol* 2009; 145: 94–95.
- Gaulard P, Berti E, Willemze R, Jaffe ES. Primary cutaneous peripheral T-cell lymphomas, rare subtypes. In: Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, et al, editors. *World Health Organization classification of tumours of haematopoietic and lymphoid tissues*. Lyon: IARC Press; 2008, p. 302–303.
- Jaffe ES, Ralfkiaer E. Subcutaneous panniculitis-like T-cell lymphoma. In: Jaffe ES, Harris NL, Stein H, Vardiman JW, editors. *World Health Organization classification of tumours. Pathology and tumours of haematopoietic and lymphoid tissue*. Lyon: IARC Press; 2001, p. 212–213.
- Willemze R, Kerl H, Sterry W, Berti E, Cerroni L, Chimenti S, et al. EORTC classification for primary cutaneous lymphomas: a proposal from the Cutaneous Lymphoma Study Group of the European Organization for Research and Treatment of Cancer. *Blood* 1997; 90: 354–371.
- Willemze R, Jansen P, Cerroni L, Berti E, Santucci M, Assaf C, et al. Subcutaneous panniculitis-like T-cell lymphoma: definition, classification and prognostic factors. An EORTC cutaneous lymphoma group study of 83 cases. *Blood* 2008; 111: 838–845.
- Wolfe F, Michaud K. The effect of methotrexate and anti-tumor necrosis factor therapy on the risk of lymphoma in rheumatoid arthritis in 19,562 patients during 89,710 person-years of observation. *Arthritis Rheum* 2007; 56: 1433–1439.
- Beyer M, Steinhoff M, Anagnostopoulos I, Assaf C, Sterry W. Hepatosplenic T-cell lymphomas and therapy with TNF- $\alpha$ -blocking biologics: a risk for psoriasis patients? *J Dtsch Dermatol Ges* 2009; 7: 191–194.