

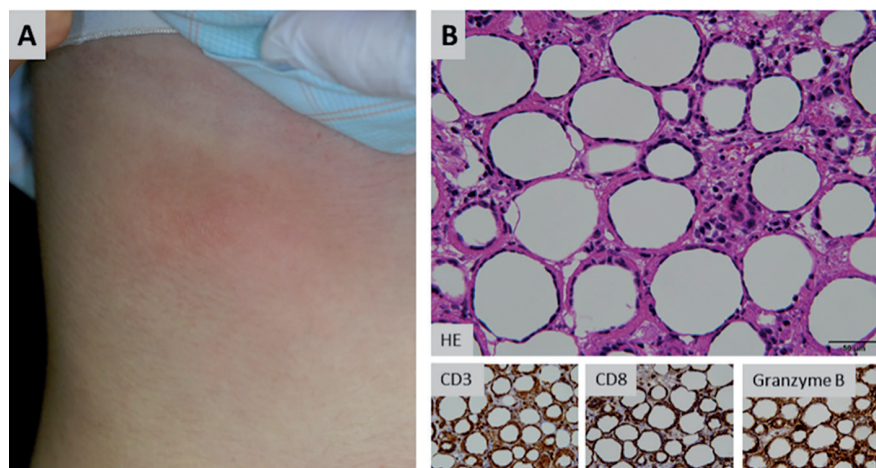
## Subcutaneous panniculitis-like T-cell lymphoma with haemophagocytic syndrome during tocilizumab therapy for juvenile idiopathic arthritis

Sirs,

Subcutaneous panniculitis-like T-cell lymphoma (SPTCL) is a very rare type of cutaneous lymphoma derived from a mature cytotoxic T-cell expressing  $\alpha/\beta$  T-cell receptors. Although its aetiology remains unclear, up to 20% of SPTCL are associated with autoimmune diseases, such as juvenile idiopathic arthritis (JIA) (1). Herein, we present a case of JIA in which SPTCL developed during tocilizumab (TCZ) therapy, discontinuing TCZ led to a remission of SPTCL, and abatacept (ABT) improved JIA without recurrence of SPTCL.

A 21-year-old Japanese woman was admitted to our department due to pyrexia for one week. She had a 7-year history of polyarticular JIA successfully treated with TCZ monotherapy. Six months before admission, she became aware of multiple subcutaneous tumours on the trunk, and leukocytopenia as well as abnormal liver function appeared. Two months before admission, TCZ was discontinued with suspicion of TCZ-related adverse effects. Physical examination on admission revealed multiple, ill-defined, indurated, tender, erythematous, and subcutaneous tumours on the trunk (Fig. 1A). Laboratory findings showed leukocytopenia (2200/ $\mu$ l), lymphocytopenia (260/ $\mu$ l), and elevation of aspartate transaminase (70 U/l), alanine transaminase (37 U/l), lactate dehydrogenase (669 U/l), C-reactive protein (2.37 mg/dl), and ferritin (928 ng/ml) levels. Biopsy of the tumour showed lobular panniculitis-like features with necrotic debris and atypical lymphoid cells which were CD3, CD8, and granzyme B positive forming a rim surrounding individual fat (Fig. 1B). Reconstruction of  $\alpha/\beta$  T-cell receptor gene was confirmed by southern blotting. Based on these findings, the diagnosis of SPTCL was made. The concomitance of haemophagocytic syndrome (HPS) was confirmed by bone marrow aspiration. One week after admission, her symptoms and laboratory abnormalities improved spontaneously. Positron emission tomography-CT confirmed the remission of SPTCL. Eight months after TCZ discontinuation, JIA recurred (simplified disease activity index: SDAI = 22.55). ABT improved her arthritis, and one-year follow-up showed no recurrence of SPTCL.

Most SPTCL patients have a good prognosis, however, SPTCL complicated with HPS requires aggressive chemotherapy due to its poor prognosis (1). Given that discontinuing TCZ led to a remission of SPTCL, TCZ is likely to have been responsible for the development of SPTCL. Although immunosuppressive therapy is associated with a production of lymphoproliferative disorders



**Fig. 1.** A: Erythematous and subcutaneous tumours on the trunk. B: Numerous fat cells are rimmed by lymphoid cells with irregular nuclei, so called "rimming of fat". These atypical lymphoid cells are CD3, CD8, and granzyme B positive.

LPD), there have been only a few case reports of SPTCL associated with immunodeficiency (2, 3). Reactivation of Epstein-Barr virus (EBV) is often observed in immunodeficiency-associated LPD, but not in most of SPTCL (4) including this case. MTX has been shown to be an independent risk factor for LPD in Japan. The dosage of MTX is associated with LPD onset (5). Although not statistically significant in meta-analysis (Peto odds ratio, 2.14; 95% CI, 0.55–8.38) (6), TNF inhibitors have also been suggested to increase the risk of LPD (7). Conversely, TCZ has been suggested to rather decrease the risk of LPD in meta-analysis (Peto odds ratio, 0.05; 95% CI, 0.00–3.19) (6). Furthermore, there have not been any reports of LPD during TCZ therapy. This case had polyarticular JIA with some poor prognostic factors including high titer of anti-cyclic citrullinated protein antibodies and the presence of bone erosions. ABT was selected to improve the prognosis of her joints since there had been no reports that ABT use increased the risk of LPD (8). In addition, several reports have suggested the potential efficacy of T-cell inhibiting therapy for treating SPTCL (9). Recurrence of JIA was successfully treated with ABT, avoiding the recurrence of SPTCL in this case.

This is the first case report of LPD during TCZ therapy, suggesting the association between LPD and IL-6 inhibition. Discontinuation of TCZ would be a treatment option for LPD, leading to a spontaneous remission of SPTCL with HPS in this case.

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