Lupus erythematosus manifestations exacerbated by etanercept therapy in a patient with mixed connective tissue disease

Sirs,

Several authors have discussed the potential benefit of TNF-α blockers in systemic lupus erythematosus (SLE), a condition in which new therapeutic agents are needed (1-3). Nevertheless, the induction of anti-DNA antibodies in patients with rheumatoid arthritis (RA) treated with TNF-α blockers has been noted since the earliest clinical trials with etanercept and infliximab, a phenomenon emphasized in two recent papers (4, 5). However, although these biological abnormalities frequently occur in 20 to 60% (6), only a few lupus-like syndromes have been reported in patients treated with TNF-α antagonists (3, 7-11). Thus, it remains unclear whether the appearance of antinuclear antibodies (ANA) in RA patients treated with TNF-α blockers could compromise the use of such agents in SLE patients. We report the case of a patient presenting with a mixed connective tissue disease (MCTD) according to the criteria of Amigues *et al*. (12) who was treated by TNF-α antagonists which precipitated manifestations of SLE.

A 27-year-old woman was admitted because of symmetrical destructive polyarthritis, Raynaud's phenomenon, sclerodactyly and pericarditis. Immunological investigations revealed positive ANAs (titer 1: 8000), anti-double-stranded DNA antibodies (anti-dsDNA, 21.5 Units/ml; negative < 7) (IgG isotype), anti-RNP antibodies and anti-Ro antibodies, but no rheumatoid factor. There were no antineutrophil cytoplasmic antibodies (ANCA) or cryoglobulinemia. She was unsuccessfully given hydroxychloroquine, then leflunomide (20 mg/day) and finally methotrexate (up to 20mg/week IM). Considering the severity of the polyarthritis and the lack of efficacy of the corticosteroids (up to 20 mg/day of prednisone) and methotrexate, she was given etanercept 25 mg twice a week.

One month later, she presented with polyarthritis and a generalized urticarian skin eruption suggesting a lupus–like syndrome. Laboratory results disclosed the following results: erythrocyte sedimentation rate 46 mm/hour, elevated C-reactive protein (45.3 mg/l; normal < 10), low lymphocyte count (0.5×10^9/l; normal $1.5 - 4 \times 10^9$) and a relevant increase in ANAs (titer 1:64000) and anti-dsDNA antibodies (41 U/ml) (IgG isotype). CH50 was low (59 U/ml; normal 63-145) and the C4 level was below 10 mg/dl (normal 15-35). There was no proteinuria. Histological skin analysis showed a perivascular lymphocytic infiltrate in the dermal portion compatible with the diagnosis of lupus. Etanercept was withdrawn and mycophenolate mofetil 2000mg/day was started. One month later, she was symptom-free. No relapse of clinical SLE symptoms had occurred after one year of follow-up and immunological parameters including ANAs and anti-DNA antibodies had improved.

MCTD may overlap rheumatoid arthritis and SLE and could be an interesting model for studying the impact of TNF antagonists in the treatment of such diseases, because it can naturally evolve into SLE as well as RA. Interestingly, under etanercept therapy, which was justified considering the severity of the rheumatologic manifestations, our patient added clinical symptoms strongly suggestive of SLE (13) and worsen biological abnormalities. In this cases, anti-TNF treatment have not induced lupus but have exacerbated the SLE symptoms of the MCTD. Because TNF blockers have been proposed for treating lupus patients (1-3), the present case highlights the need to establish the subgroup of SLE patients in whom it could represent a valuable tool. Moreover, MCTD with features of SLE at disease onset may not represent a suitable indication for TNF antagonists.

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Do MEFV mutations play a role in the development of Behçet's disease related amyloidosis?

Sirs,

Familial Mediterranean fever (FMF) and Behçet's disease (BD) may be complicated by AA type amyloidosis; however this is much rarer in BD compared to FMF (1, 2). In order to evaluate the possible role of MEFV (the gene for FMF) mutations in BD related amyloidosis, we studied the common mutations in patients with BD and amyloidosis.

Nineteen patients (17 male, 2 female, mean age 47.2 years) with BD and amyloidosis were included in the study. All patients fulfilled the diagnostic criteria of International Study Group for BD (3). All patients denied recurrent abdominal pain and fever attacks during childhood. Exon 10 mutations (M694V, M680I, V726A, M694I) and Exon 2 mutation (E148Q) were studied by denaturing gradient gel electrophoresis and restriction enzyme analysis, respectively. MEFV mutations [homozygous M680I (1), heterozygous M694V (3), heterozygous V726A (1) and heterozygous E148Q (1)] were detected in 6 patients (32%).

In recent years, the possible association between FMF and BD has been of interest (4, 5). The clinical features of BD show variation according to the geographic area and/or ethnic group. Most of the cases with BD and amyloidosis have been reported from Middle East and Mediterranean countries rather than Japan where FMF or MEFV mutations have rarely been reported (1). It may be speculated that the possible role of