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.

C. RICHEZ[1,3], *MD*
P. BLANCO[2,3], *MD*
C. DUMOULIN[1,3], *MD*
T. SCHAEVERBEKE[1,3], *MD, PhD*

[1]Service de Rhumatologie and [2]Service d'Immunologie, Groupe Hospitalier Pellegrin, CHU de Bordeaux; and [3]University Victor Segalen, Bordeaux, France.

Please address correspondence to: Christophe Richez, MD, Service de Rhumatologie, Hôpital Pellegrin, 6 Place Amélie Raba Léon, 33076 Bordeaux Cedex, France.
E-mail: christophe.richez@club-internet.fr

References

1. ARINGER M, SMOLEN JS: SLE - Complex cytokine effects in a complex autoimmune disease: tumor necrosis factor in systemic lupus erythematosus. *Arthritis Res Ther* 2003; 5: 172-7.
2. PISETSKY DS: Tumor necrosis factor alpha blockers and the induction of anti-DNA autoantibodies. *Arthritis Rheum* 2000; 43: 2381-2.
3. CARLSON E, ROTHFIELD N: Etanercept-induced lupus-like syndrome in a patient with rheumatoid arthritis. *Arthritis Rheum* 2003; 48: 1165-6; author reply 1166.
4. CHARLES PJ, SMEENK RJ, DE JONG J, FELDMANN M, MAINI RN: Assessment of antibodies to double-stranded DNA induced in rheumatoid arthritis patients following treatment with infliximab, a monoclonal antibody to tumor necrosis factor alpha: findings in open-label and randomized placebo-controlled trials. *Arthritis Rheum* 2000; 43: 2383-90.
5. DE RYCKE L, KRUITHOF E, VAN DAMME N *et al.*: Antinuclear antibodies following infliximab treatment in patients with rheumatoid arthritis or spondylarthropathy. *Arthritis Rheum* 2003; 48: 1015-23.
6. LOUIS M, RAUCH J, ARMSTRONG M, FITZCHARLES MA: Induction of autoantibodies during prolonged treatment with infliximab. *J Rheumatol* 2003; 30: 2557-62.
7. SHAKOOR N, MICHALSKA M, HARRIS CA, BLOCK JA: Drug-induced systemic lupus erythematosus associated with etanercept therapy. *Lancet* 2002; 359: 579-80.
8. LEPORE L, MARCHETTI F, FACCHINI S, LEONE V, VENTURA A: Drug-induced systemic lupus erythematosus associated with etanercept therapy in a child with juvenile idiopathic arthritis. *Clin Exp Rheumatol* 2003; 21: 276-7.
9. MIKULS TR, MORELAND LW: Benefit-risk assessment of infliximab in the treatment of rheumatoid arthritis. *Drug Saf* 2003; 26: 23-32.
10. SANDBORN WJ: Optimizing anti-tumor necrosis factor strategies in inflammatory bowel disease. *Curr Gastroenterol Rep* 2003; 5: 501-5.
11. SANDBORN WJ: Strategies for targeting tumour necrosis factor in IBD. *Best Pract Res Clin Gastroenterol* 2003; 17: 105-17.
12. AMIGUES JM, CANTAGREL A, ABBAL M, MAZIERES B: Comparative study of 4 diagnosis criteria sets for mixed connective tissue disease in patients with anti-RNP antibodies. Autoimmunity Group of the Hospitals of Toulouse. *J Rheumatol* 1996; 23: 2055-62.
13. HOCHBERG MC: Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1997; 40: 1725.

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

MEFV-related mutations may explain why amyloidosis due to BD is more common in Middle East and Mediterranean countries than in Japan.

The frequency of MEFV mutations among patients with BD-related amyloidosis has not been investigated previously and our study showed a frequency of 32%. Although the patient with homozygous M680I did not have sufficient clinical findings for FMF, it was not possible to exclude type 2 FMF (4, 5). The main shortage of this study is the absence of a control group (BD patients without amyloidosis), but we can compare our finding with previous studies evaluating MEFV mutations in BD. The frequency of MEFV mutations may vary between regions, countries and ethnic groups and as far as we know, there are three studies evaluating MEFV mutations in BD (one from Turkey, one from Israel and one an international study) (6-8). In an international collaborative study in which we have also participated, the M694V, V726A and E148Q mutations were found to be 2.6%, 2.6% and 5.2%, respectively (7). The other two studies, one from Turkey (6) and one from Israel (8), reported MEFV frequencies of 26% and 30%, respectively. Atagunduz *et al.* have concluded that MEFV mutations are increased in BD and are associated with vascular involvement (6).

A significant difference regarding the frequency of MEFV mutations among patients with BD-related amyloidosis was not found in our study and the absence of a control group does not affect our interpretation. In addition, it should be kept in mind that different ethnic groups, unmentioned patient characteristics (presence or absence of amyloidosis), and differences in the number and type of mutations screened in these studies may influence the integrity of the comparison.

The relationship between rheumatological diseases and MEFV mutations has been reported previously (9, 10). The presented data does not offer conclusive data on MEFV mutations being one of the risk factors for the development of amyloidosis in another inflammatory disease, BD. However, larger studies are needed to clarify whether the altered inflammatory response introduced by the pyrin mutations are one of the predisposing modifying genetic factors for the development of amyloidosis in a patient who already has an inflammatory disease.

Acknowledgement. The authors are grateful to the Cerrahpasa Medical Faculty, Behçet's Disease Study Group for their support of the study.

T. AKPOLAT[1], *Professor*
E. YILMAZ[2], *Associate Professor*
H. ÖZDOGAN[3], *Professor*
M. MELIKOGLU[3], *Assistant Prof.*
E. ALTIOK[4], *Associate Professor*
S. OZEN[2], *Professor*

[1]Ondokuz Mayis University School of Medicine, Samsun; [2]Hacettepe University School of Medicine, Ankara; [3]Istanbul University, Cerrahpasa Medical School, Istanbul; [4]Acibadem Hospital, Istanbul, Turkey.

Address correspondence to: Tekin Akpolat, MD, Ondokuz Mayis Üniversitesi, Tip Fakültesi, Nefroloji Bilim Dali, Samsun, Turkey 55139. E-mail: tekinakpolat@yahoo.com

References

1. AKPOLAT T, AKKOYUNLU M, AKPOLAT I, DILEK M, ODABAS AR, OZEN S: Renal Behçet's disease: a cumulative analysis. *Semin Arthritis Rheum* 2002; 31: 317-37.
2. TUGLULAR S, YALCINKAYA F, PAYDAS S *et al.*: A retrospective analysis for aetiology and clinical findings of 287 secondary amyloidosis cases in Turkey. *Nephrol Dial Transplant* 2002; 17: 2003-5.
3. INTERNATIONAL STUDY GROUP FOR BEHCET'S DISEASE: Criteria for diagnosis of Behçet's disease. *Lancet* 1990; 335: 1078-80.
4. BEN-CHETRIT E, YAZICI H: Thoughts on the proposed links between Behcet's disease and familial Mediterranean fever. *Clin Exp Rheumatol* 2002; 20 (Suppl. 26): S1-2.
5. AKPOLAT T, YILMAZ E, AKPOLAT I *et al.*: Amyloidosis in Behçet's disease and familial Mediterranean fever. *Rheumatology (Oxford)* 2002; 41: 592-3.
6. ATAGUNDUZ P, ERGUN T, DIRESKENELI H: MEFV mutations are increased in Behçet's disease (BD) and associated with vascular involvement. *Clin Exp Rheumatol* 2003; 21 (Suppl. 30): S35-S37.
7. TOUITOU I, MAGNE X, MOLINARI N *et al.*: MEFV mutations in Behcet's disease. *Hum Mutat* 2000; 16: 271-2.
8. BEN-CHETRIT E, COHEN R, CHAJEK-SHAUL T: Familial mediterranean fever and Behcet's disease-are they associated ? *J Rheumatol* 2002; 29: 530-4.
9. BOOTH DR, LACHMANN HJ, GILLMORE JD, BOOTH SE, HAWKINS PN: Prevalence and significance of the FMF gene mutation encoding pyrin Q148. *QJM* 2001; 94: 527-32.
10. OZEN S, BAKKALOGLU A, YILMAZ E *et al.*: Mutations in the gene for FMF: Do they predispose to inflammation ? *J Rheumatol* 2003; 30: 2014-18.

New-onset acute heart failure and ventricular tachycardia after therapy with a tumor necrosis factor antagonist

Sirs,

Numerous adverse effects have been reported with TNF antagonists, mainly infections and lymphomas (1). Other potential adverse effects, cardiac in particular, must be kept in mind (2). We report one case of new onset acute heart failure and one case of ventricular tachycardia during treatment with infliximab.

A woman aged 52 was followed for Behçet's disease. She had no history of cardiovascular disorder. Because of severe joint involvement in spite of treatment with methotrexate, intravenous infliximab 3 mg/kg was prescribed. Initial electrocardiogram and echocardiography were normal. Fifteen minutes after the start of the fourth infusion, she presented an acute heart failure with dyspnea and crepitant rales of both lungs, bilateral alveolar opacity on chest radiograph and sinusal tachycardia on electrocardiogram. After immediate discontinuation of infusion, treatment with intravenous furosemide and nasal oxygen, the episode resolved in a few hours. Search for the cause of this episode by Holter monitoring, echocardiography and cardiac angiography was negative.

A man aged 50 was followed for spondylarthropathy. His only cardiovascular history was arterial hypertension controlled by ramipril. Because of severe axial and peripheral inflammation in spite of treatment with methotrexate, intravenous infliximab 5 mg/kg was prescribed. The initial electrocardiogram was normal. Twenty-four hours after the 9th infusion, he presented lipothymia with a sudden fall in blood pressure, revealing ventricular tachycardia on the electrocardiogram, which was immediately reduced by external electric shock. An implantable defibrillator was placed to prevent recurrence. Search for the cause of this episode revealed signs of lower supra-epicardiac ischemia on the electrocardiogram, a coronary artery spasm reproducing the ventricular tachycardia on cardiac angiography and minimal sequelae of lower necrosis on myocardial scintigraphy.

Behçet's disease may be complicated by pericarditis, myocarditis, endocarditis or coronaritis. Our patient had no such cardiac involvement and no cardiovascular history. Search for the cause of the episode of new-onset acute heart failure was negative. These findings and the chronology suggest a serious adverse event which can be attributed to infliximab. TNF antagonists are contra-indicated in patients with NYHA class III and IV heart failure. This contra-indication results from the premature discontinuation of the ATTACH study which evaluated infliximab in the treatment of heart failure, because of increased mortality and hospital admissions for cardiac decompensation in patients treated with infliximab (3), and from the premature halting of the RECOVER and RENAISSANCE studies which evaluated etanercept in the treatment of heart failure, because of inefficacy of etanercept (4). TNF antagonists may also induce heart failure even in the absence of any cardiovascular history. A recent study revealed 38 cases of new-onset heart failure in patients treated with TNF antagonists, which partially or totally resolved when this treatment was stopped (2).

Spondylarthropathies may be complicated by aortic insufficiency or conduction disturbances. Increased frequencies of myocardial fibrosis and arrhythmias have also been