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## Infliximab-induced lupus or rheumatoid arthritis (RA) overlapping with systemic lupus erythematosus (SLE) unmasked by infliximab

Sirs,

Various studies have reported no clinical significance of autoantibodies such as antinuclear (ANA) and anti-doubled-stranded DNA (anti-ds-DNA) antibodies in RA patients during anti-TNF-α treatment with infliximab and etanercept (1,2) although several cases of drug-induced lupus (DIL) have been described (1, 3-7). We report the case of an RApatient who developed clinical and laboratory signs of SLE during infliximab treatment, which persisted after drug discontinuation.

A 53-year-old woman with 19-year history of RAwas admitted in May 2001 with morning stiffness 420 min, tender joint count 16, and swollen joint count 26 despite therapy with methotrexate (MTX) 12.5 mg weekly and methylprednisolone 12 mg daily. ESR was 65 mm/h, CRP 63 mg/ml (normal < 5 mg/ml), and RF 1070 IU/ml. ANA, ENA and anti-ds-DNA were negative, C3 and were C4 normal. She was started on infliximab following the usual regimen (3 mg/kg, weeks 0, 2 and 6, and then every 8 weeks), while continuing with the same MTX and methylprednisolone dosage.

Articular manifestations rapidly improved (no morning stiffness, tender joint count 5, swollen joint count 8). ESR was 50 mm/h, CRP 5.1 mg/ml, and ANAand anti-dsDNA were negative. However, 4 weeks after the 4th infusion the patient was re-admitted with acute polyarthritis and photosensitive rash on the face, neck, arms and legs. She had a fever of 37.8ºC and a dry cough. A chest radiograph showed right pleural effusion. ESR was 92 mm/h, CRP 111 mg/ml. Blood and pleural effusion for bacteria were negative. The patient was unsuccessfully treated with gentamycin and amoxycillin with clavulonic acid.

Laboratory tests revealed ANA1:320, anti-dsDNA 64.6 by ELISA (normal < 60), C3 0.66, C4 0.09. ENA and anti-phospholipid antibodies (aPL) were negative, anti-histone antibodies not performed. Hemoglobin was 112g/l. Total white cell, platelet count, renal and liver function tests were normal; there was no proteinuria. A diagnosis of SLE (worsening of polyarthritis, pleural effusion, photosensitive macular rash, positive ANA and anti-dsDNA, low complement levels) was established. Infliximab was discontinued and oral methylprednisolone increased to 32 mg daily. She promptly became afebrile, pleural effusion resolved after 15 days, and arthritis improved slowly. The dosage of MTX was increased to 17.5 mg weekly and methylprednisolone tapered to 12 mg. A year later she had morning stiffness 90 min., tender joint count 14, swollen joint count 15, ESR 45 mm/h, CRP 21 mg/ml, C3 and C4 slightly decreased. ANA was 1:320, anti-ds-DNA139, and there was no anti–ENA and aPL. Photosensitive rash on the face and neck improved slightly after hydroxychloroquine 400 mg daily.

Our patient had RA, with joint erosions documented by X-ray and no previous signs of SLE. After the 4th infusion of infliximab she developed clinical and laboratory signs of acute lupus, raising the question of a possible DIL. The formal diagnostic criteria for DIL, especially in patients with an underlying inflammatory arthritis such as RA, is a matter of concern (7). There are several reports discussing the development of DIL associated with infliximab and etanercept with characteristic resolution of the symptoms after discontinuation of treatment (3-7). However, the cases of some patients with a possible pre-existing overlap with SLE which became overt after exposure to etanercept, but clinically resolved on drug withdrawal, suggest a possible further association of DIL with etanercept (4, 5, 7, 9). We report a patient who had a definitive diagnosis of RA and developed both clinical and laboratory signs of SLE associated with infliximab. Since these criteria did not disappear a year and half after the discontinuation of treatment we cannot speak about DIL. We believe she has RAoverlapping with SLE unmasked by infliximab. Her HLA-haplotype (B8, DR 3) speaks in favour of this hypothesis. Clinicians should be aware that anti-TNF-α therapies may be associated with acute lupus-like symptoms but further monitoring of the patient is needed to evaluate whether it is a real DIL or a pre-existing RA-SLE overlap unmasked by anti-TNF-α therapy.

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