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LETTER

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Polymyositis associated with infliximab treatment for rheumatoid arthritis

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To the Editor:

Therapies using anti-tumor necrosis factor (TNF)α hold the promise of exciting new strategies for the treatment of rheumatoid arthritis (RA).[1] Although the anti-TNFα antibody infliximab has been shown to be efficacious, well tolerated, and safe, very rare reports have described induction of autoimmune phenomena (anti-double standard DNA [dsDNA] antibodies) and development of systemic lupus erythematosus.[2] In addition, polymyositis (PM) develops on rare occasions with the use of infliximab. We report on the first confirmed case in Japan.

A 52-year-old Japanese woman had a 33-year history of severe, disabling, and seropositive destructive RA with radiological changes and pulmonary fibrosis, and had recently received treatment with the nonsteroidal anti-inflammatory drugs methotrexate (6 mg/week) and prednisolone (2 mg/day). Erythrocyte sedimentation rate (ESR) was 82 mm/h. C-reactive protein (CRP) level was 2.5 mg/dl. KL-6 level was 471 IU/ml (normal, <500 IU/ml), and was not indicative of the severity of interstitial pneumonia (IP). Serum aminotransferase levels were within normal ranges. No previous history of any muscular disorder was identified. The patient was started on infliximab in May 2004 following the standard regimen (3 mg/kg, intravenous administration, weeks 0, 2, and 6, and then every 8 weeks) in association with methotrexate (6 mg/week) and prednisolone (2 mg/day). After the third course of injections, marked clinical improvement was observed, and ESR and CRP levels decreased promptly to 39 mm/h and 0.6 mg/dl, respectively. No appreciable changes were seen in KL-6 level. Therapy with prednisolone was discontinued in June, while methotrexate was continued at the same dose.

In February 2005, after the seventh course of injections, the patient was admitted to our hospital due to proximal muscle weakness in both lower extremities, general fatigue, dyspnea, and appetite loss. Physical examination revealed dry crepitations in the lower lung fields on inspiration. Initial laboratory tests revealed: serum ESR, 86 mm/h; CRP, 5.8 mg/dl; creatine kinase (CK), 3399 U/l (normal, <144 U/l); CK-MB isozyme, 58 U/l (normal, <25 U/l); myoglobin, 3079 ng/ml (normal, <70 ng/ml); aspartate aminotransferase (AST), 320 U/l (normal, <38 U/l); alanine aminotransferase (ALT), 183 U/l (normal, <44 U/l); lactate dehydrogenase, 716 U/l (normal, <200 U/l); and KL-6, 1100 IU/ml (normal, <500 IU/ml). Antinuclear antibody was positive at a titer of 1:640 (both homogeneous and speckled type). Anti-dsDNA immunoglobulin (Ig)G was negative and anti-dsDNA IgM antibody was positive (131 U/ml), anti-Ro/SSA was negative, anti-U1RNPantibody was negative, and myeloperoxidase anti-neutrophil cytoplasmic antibody was negative. Anti-Jo-1 antibody was positive (>500 U/ml, enzyme-linked immunosorbent assay [ELISA]).

Chest radiography and high-resolution computed tomography revealed interstitial shadowing in both lung fields, primarily on the dorsal aspect of the lungs. These findings had been present for 2 years, but symptoms were negligible. Blood gases were normal. Muscle biopsy showed changes typical for myositis, including infiltration with lymphocytes and differences in size of muscle fibers due to degeneration. These findings, including weakness of proximal muscles, elevation of muscle-related enzymes, anti Jo-1 antibody, and results of muscle biopsy, resulted in a diagnosis of PM associated with infliximab. After the diagnosis of PM, infliximab was discontinued as the probable causative agent, and treatment was continued with middle-dose prednisolone (30 mg/day). This resulted in marked improvement in muscle strength, and levels of CK, AST, and ALT decreased within 4 weeks (CK, 101 U/l; AST, 60 U/l; ALT, 39 U/l).

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Initially, although infliximab was discontinued and status of the patient was observed for 1 year, myositis-induced infection, metabolic or hereditary disorders, and cancer were excluded based on history and additional investigations. Blood samples were taken from the patient starting from before the initiation of infliximab treatment, and the serum was stored at −120°C. Samples from before the first injection displayed positive results for antinuclear antibody (1:640) and anti-Jo-1 antibodies (>500 U/ml ELISA). However, anti-dsDNA IgG and anti-dsDNA IgM antibodies were negative. The patient was discharged after 63 days, and as of 1 year later was in good condition with improved pulmonary fibrosis; KL-6 decreased to within the normal range (392 U/ml) following treatment with 10 mg/day prednisolone and 3 mg/day tacrolimus.

To the best of our knowledge, the first case of severe PM associated with anti-TNFα therapy was reported in 2003,[3] and no similar reports appear to have been described since. This report is thus the second report in the world, and the first from Japan.

Rheumatoid arthritis might have been complicated with PM by chance.[4,5] Interstitial pneumonia is a comparatively common complication of long-term RA, and most likely resulted from the development of PM. In addition, IP is likely to develop earlier than myositis in PM.

Compared with anti-TNFα therapy for RA, the efficacy of anti-TNFα therapy for PM/dermatomyositis (DM) remains unclear, and while many reports have noted the effect of anti-TNFα therapy on PM/DM,[6] negative links have also been reported.[7] Antinuclear antibody has been found preceding infliximab treatment in several RA patients.[8] However, no reports appear to have measured anti-Jo-1 antibody before infliximab administration. The influence of infliximab on RA with anti-Jo-1 antibody remains uncertain. Moreover, we could only identify one case of IP and anti-Jo-1 antibodies detected in an RA patient, but without any signs of myositis.[9] The hypothesis that IP in this case actually represented a prodrome of PM and that symptoms of myositis subsequently became apparent over time is thus extremely attractive. However, the involvement of infliximab to some extent is difficult to completely deny.

As for safety in such cases, if anti-Jo-1 antibody can be measured at any time before injection, a conclusion might be reached. However, until such a time, all suitable patients will be strictly monitored so that treatment can be started as needed.

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