Adalimumab Induced Systemic Lupus Erythematosus

Adalimumab Kullanımının Tetiklediği Sistemik Lupus Eritematozus

Songül Çildağ, Taşkın Şentürk

Adnan Menderes University School of Medicine, Department of Immunology-Rheumatology, Aydın, Turkey

Abstract

Tumour necrosis factor alpha is a pivotal cytokine involved in the pathogenesis and progression of rheumatoid arthritis. Anti-tumor necrosis factor-alpha therapy has become a very important modality in the treatment of patients with rheumatoid arthritis. Despite good clinical efficacy and tolerance, the possible occurrence of drug-induced autoimmune disorders remains a matter of concern.The incidence of anti-tumor necrosis factor-alpha therapy induced autoimmune disorders is unknown.We report a new case of adalimumab-induced lupus syndrome with rheumatoid arthritis. *(The Medical Bulletin of Haseki 2012; 50: 27-9)*

Key Words: Adverse effect, anti-TNF therapy, rheumatoid arthritis, systemic lupus erythematosus

Özet

Tümör nekrozis faktör alfa, romatoid artrit patogenezinde ve progresyonunda yer alan önemli bir sitokindir. Romatoid artritli hastaların tedavisinde anti tümör nekrozis faktör alfa oldukça önemli bir tedavi seçeneğidir. İyi tolere edilmesi ve etkinliğinin iyi olmasına rağmen ilacın tetiklediği otoimmün hastalıklar endişe yaratmaktadır. Anti tümör nekrozis faktör alfa kullanımına bağlı otoimmün hastalık gelişim insidansı bilinmemektedir. Bu çalışmada adalimumab kullanımı sonrasında lupus gelişen romatoid artritli bir olgu sunulmuştur *(Haseki Tıp Bülteni 2012; 50: 27-9)*

Anahtar Kelimeler: Anti-TNF tedavisi, romatoid artrit, sistemik lupus eritematozus, yan etki

Introduction

Rheumatoid arthritis (RA) is a chronic disease characterized by an immune mediated inflammatory synovitis leading to joint cartilage and bone destruction (1). Although the causes of RA are not fully understood, laboratory and clinical evidence suggests that proinflammatory cytokines, particularly tumor necrosis factor (TNF) alpha, have an important role in its pathogenesis (2).

TNF-alpha, an inflammatory cytokine that is released by activated monocytes, macrophages, and T lymphocytes, promotes inflammatory responses that are important in the pathogenesis of rheumatoid arthritis (3). TNF alpha concentrations are increased in the synovial fluid of persons with active RA and increased plasma levels of TNF alpha are associated with joint pain (4).

Therapy with anti-TNF-alpha is effective in the management of RA (5,6). The frequent side effects are injection/infusion reactions, infections, autoimmunity, malignancy, congestive heart failure, demyelinating disease, and hematologic disorders. All three anti-TNF agents, infliximab, adalimumab and etanercept, have been associated with the induction of a variety of autoantibodies (7). The mechanism responsible for the production of these autoantibodies during anti-TNF-alpha therapy has not been clearly defined (8). Of concern is the possible induction of lupus-like (or drug-induced lupus) syndromes, but few cases have been reported, most commonly associated with infliximab and etanercept, and rarely related to adalimumab. In all reported cases, the signs disappeared after treatment was stopped (9,10).

We report a new case of adalimumab-induced lupus syndrome with RA, who had clinical response to early methylprednisolone and after anti-TNF therapy was stopped.

Case Report

A 57-year-old woman presented with increasing dyspnea, cough and fever which persisted for 10 days. She was diagnosed as having seropositive RA seven years ago and had been treated with prednisolone, salozopyrine and methotrexate. Since she had continued with active joint inflammation, anti-TNF alpha treatment (40 mg of subcutaneous adalimumab administered in bi-weekly

Address for Correspondence/Yazışma Adresi: Songül Çildağ
Adnan Menderes University School of Medicine, Department of Immunology-Rheumatology, Aydın, Turkey
Phone: +90 256 444 12 56 E-mail: songulcildag@yahoo.com

Received/Geliş Tarihi: 25 March 2011 **Accepted/Kabul Tarihi:** 20 June 2011

injection) was added to the treatment three months ago. Her symptoms started about two months after initiation of adalimumab for RA.

On admission, she was febrile (38,4°C), with tachycardia (102/min) and tachypnea (28/min), blood pressure was 110/90 mmHg. The palpebral conjunctiva was anemic. On auscultation, loud crackles were audible lower the both lungs. Her hands demonstrated typical changes of RA with deformity of her fingers.

Laboratory data revealed the following values: hemoglobin: 8.6 g/dL, hematocrit: 25.9%, reticulocyte index: 1, white blood cell count: 7800/mm³, platelet count: 576000/mm³, direct Coombs IgG: (+++): indirect Coombs - negative, blood urea nitrogen: 45 mg/dl, serum creatinine: 0.9 mg/dL, urinalysis - normal, C3: 68.6 mg/dl (normal: 85-200 mg/dl), C4: 7.3 mg/dl (normal: 15-50 mg/dl), erythrocyte sedimentation rate: 94 mm/h. Antinuclear antibody (ANA) was positive with a titer of 1:320 homogenous pattern, SS-A, SS-B, Ro52, nucleosemes, anti-histone were positive, anti-double- stranded DNA (dsDNA) was negative, rheumatoid factor was positive at 137 U/mL (normal: <18 U/mL), anti-CCP was positive at 50 U/ml (normal: <5 U/ml). Electrocardiogram showed a normal sinus rhythm. Echocardiogram showed pericardial effusion. Her chest radiography revealed bilateral pleural effusion. Chest computerized tomography (CT) demonstrated pneumonia and pleural, pericardial effusion. Her PPD was negative. It had negative stains and cultures for bacteria, M. tuberculosis and fungi. ANA was negative before initiation of adalimumab treatment.

A diagnosis of drug-induced lupus erythematosus was made. Adalimumab treatment was discontinued and high-dose corticosteroid was started. She was maintained on prednisolone 12 mg/day, hydroxychloroquine 400 mg/day with no symptoms at 6-month follow-up. However, she still had high titers of ANA.

Discussion

TNF-alpha plays a central role in the pathogenesis of rheumatic diseases and has become a target molecular structure for antibody or TNF-receptor (TNF-R) based treatment in the past few years (11). TNF inhibitors, such as infliximab, etanercept and adalimumab were shown to be very effective in reducing synovial inflammation and retarding structural damage in RA patients (12). Adalimumab is a recombinant, fully human IgG1 antibody that binds specifically to human TNF-alpha and neutralizes the activity of this citokine. It is administered by subcutaneous injection. It has been approved alone or in combination with methotrexate for the treatment of RA in Europe and the United States. Its side effect profile is favorable when compared with traditional systemic treatments for these diseases (11,13). The most common side effects are injection site reactions. One of the most common side effects is the development of autoantibodies (14).

There are no specific diagnostic criteria for drug-induced lupus, but certain immunologic features of drug-induced lupus help distinguish it from other autoimmune diseases. Patients with drug-induced lupus typically display anti-histone antibodies, which are present in >95% of cases. When associated with TNF antagonists, anti-dsDNA antibodies are usually elevated as well (15). In our patient, ANA was positive after adalimumab therapy. SS-A, SS-B, Ro-52, nucleosemes, anti-histone were positive but anti-double-stranded DNA (dsDNA) was negative.

A French national survey was performed in 2003 to investigate the prevalence and clinical presentation of TNF antagonist-induced autoimmune disease. Of the 866 patients surveyed, only 10 patients had anti-DNA antibodies and skin manifestations classified as limited skin lupus, whereas 12 patients had systemic manifestations and met the American College of Rheumatology lupus criteria. None of the patients had pleural effusions or nephritis, although one patient had a pericardial effusion (16). Our patient had haemolitic anemia, pericardial and pleural effusion, arthritis but there was no renal involvement.

The immunopathological mechanism of the development of SLE upon anti-TNF alpha therapy is unclear. It has been suggested that the drug affects the Th1/Th2 balance. Adalimumab treatment strongly increases cytokines stimulating Th1 activity in contrast to 'anti-inflammatory' and Th2-associated cytokines, which are not significantly changed (14).

There is an increase in the incidence of various antibodies with anti-TNF therapy, but this very rarely results in clinical disease. The British Society for Rheumatology recommends stopping anti-TNF therapy and appropriate treatment if symptoms of an SLE-like syndrome develop on anti-TNF treatment (17).

In summary, here, we report a new case of adalimumab-induced lupus syndrome with RA. We stopped adalimumab therapy and then started prednisolone 12 mg/day, hydroxychloroquine 400 mg/day with no symptoms at 6-month follow-up.

References

1. Lundy SK, Sarkar S, Tesmer LA, Fox D. Cells of the synovium in rheumatoid arthritis. T lymphocytes. Arthritis Res Ther 2007;9:202.
2. Arend WP, Dayer JM. Inhibition of the production and effects of interleukin-1 and tumor necrosis factor a in rheumatoid arthritis. Arthritis Rheum 1995;38:151-60.
3. Choy EH, Panayi GS. Cytokine pathways and joint inflammation in rheumatoid arthritis. N Engl J Med 2001;344:907-16.

4. Beckham JC, Caldwell DS, Peterson BL, et al. Disease severity in rheumatoid arthritis: relationships of plasma tumor necrosis factor-alpha, soluble interleukin 2-receptor, soluble CD4/CD8 ratio, neopterin, and fibrin D-dimer to traditional severity and functional measures. J Clin Immunol 1992;12:353-61.
5. Garrison L, McDonnell N. Etanercept therapeutic use in patients with rheumatoid arthritis. Ann Rheum Dis 1999;58(suppl 1):165-9.
6. Maini R, St Clair EW, Breedveld F, et al. Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. ATTRACT Study Group. Lancet 1999;354:1932-9.
7. Haraoui B, Keystone E. Musculoskeletal manifestations and autoimmune diseases related to new biologic agents. Current Opinion in Rheumatology 2006;18:96-100.
8. Bobbio-Pallavicini F, Alpini C, Caporali R, et al. Montecucco Autoantibody profile in rheumatoid arthritis during long-term infliximab treatment. Arthritis Res Ther 2004,6:R264-72.
9. De Bandt M, Vittecoq O, Descamps V, et al. Anti-TNF alpha-induced systemic lupus erythematosus. Clin Rheumatol 2003;22:56-61.
10. Shakoor N, Michalska M, Harris CA, Block JA. Drug-induced systemic lupus erythematosus associated with etanercept therapy. Lancet 2002;359:579-80.
11. Lee H-H, Song I-H, Friedrich M, et al. Cutaneous side-effects in patients with rheumatic diseases during application of tumour necrosis factor-a antagonists. Br J Dermatol 2007;156:486-91.
12. Via CS, Shustov A, Rus V, Lang T, Nguyen P, Finkelman FD. In vivo neutralization of TNF-promotes humoral autoimmunity by preventing the induction of CTL. J Immunol 2001;167:6821-6.
13. Scheinfeld N. Adalimumab: a review of side effects. Expert Opin Drug Saf 2005;4:637-41.
14. Martín JM, Ricart JM, Alcácer J, Rausell N, Arana G. Adalimumab-induced lupus erythematosus. Lupus 2008;17:676-8.
15. Hess E. Drug-induced lupus. N Engl J Med 1988;318:1460-2.
16. De Bandt M, Sibilia J, Le Loet X, et al. Systemic lupus erythematosus induced by anti- tumour necrosis factor alpha therapy: a French national survey. Arthritis Res Ther 2005;7:545-51.
17. Ledingham J, Deighton C; British Society for Rheumatology Standards, Guidelines and Audit Working Group. Update on the British Society for Rheumatology guidlines for prescribing TNF-blockers in adults with rheumatoid arthritis (update of previous guidelines of April 2001). Rheumatology (Oxford) 2005;44:157-63.