Clinical and Experimental Rheumatology 2008; 26: 1116-1118.

Drug-induced lupus-like syndrome in ankylosing spondylitis treated with infliximab

A. Mounach, M. Ghazi, A. Nouijai, I. Ghozlani, L. Achemlal, A. Bezza, A. El Maghraoui

Rheumatology and Physical Rehabilitation Department, Military Hospital Mohammed V, Rabat, Morocco.

Aziza Mounach, MD
Mirieme Ghazi, MD,
Abderrazak Nouijai, MD
Imad Ghozlani, MD
Lahsen Achemlal, MD, Professor
Ahmed Bezza, MD, Professor
Abdellah El Maghraoui, MD, Professor

Please address correspondence and reprint requests to:
Prof. A. El Maghraoui, Rheumatology and Physical Rehabilitation Department, Military Hospital Mohammed V, P.O. Box 1018, Rabat, Morocco.
E-mail:aelmaghraoui@gmail.com

Received on January 31, 2008; accepted in revised form on July 24, 2008.

Key words: Ankylosing spondylitis, infliximab, lupus-like syndrome.

Competing interests: none declared.

ABSTRACT

Specific antagonists of tumour necrosis factor (TNF-α) have rapidly gained popularity for the treatment of rheumatoid arthritis and ankylosing spondylitis (AS). Reported side effects from these agents include drug-induced autoimmune disorders. The monoclonal antibody against TNF-α, infliximab, has been associated with induction of systemic lupus erythematosus (SLE) in only one patient with AS in the literature. However, there have been no published reports of drug induced lupus-like syndrome (LLS) with positive anti-histone antibodies. We describe a 59-year-old woman with a 12-year history of refractory axial AS who developed signs and symptoms of LLS during treatment with infliximb with positive antinuclear and anti-histone antibodies. On diagnosis of LLS, infliximab was discontinued and the LLS-related symptoms promptly resolved.

Introduction

Drug-induced lupus (DIL) was firstly reported by Hoffman in 1945, in a patient who developed hypersensitivity syndrome similar to acute systemic lupus erythematosus (SLE) after taking sulfadiazine (1). Up to 80 kinds of drugs have been known to induce lupus-like syndrome (LLS), composing approximately 10% of the all SLE cases (2). Anti-TNF agents including infliximab have recently been considered as drugs that can potentially induce lupus, since new autoantibodies such as antinuclear antibodies (ANAs) and anti-double stranded DNA (anti-dsDNA) antibodies were detected in anti-TNF treated patients (3-5). The development of those antibodies has been observed in 63.8% and 13% of RA patients and in 49.1% and 21.5% of Crohn's disease patients, respectively (4-7). Early induction of those antibodies has been commonly reported in Behçet's disease patients treated with infliximab (8).

Tumor necrosis factor (TNF-α) contributes to the inflammation of ankylosing spondylitis (AS), and specific anti-TNF-α therapy has been an important advance in treatment for this disease. The induction of auto antibodies in the treatment of ankylosing spondylitis with infliximab has also been described. Perez-Garcia *et al*. (9) have reported the first and only case of DIL in a patient with AS, treated with infliximab. We describe the first case reported in the literature of LLS with positive anti-histone antibodies in a patient with refractory AS, treated with infliximab.

Case report

We report the case of a 59-year-old woman with a 12-year history of severe axial inadequately controlled AS. She never complained of peripheral joint involvement. The patient had been treated with several NSAIDs for up to 11 years. Sulfasalazine was tried but stopped due to an allergic reaction. The patient complained of refractory inflammatory low back pain. The Bath Ankylosing Spondylitis Functional Index (BASFI) was 50/100, the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) 68/100, and spinal mobility measures were as follows: Schober test 1 cm; and occiput–wall 7cm. Antinuclear antibodies and HLA B27 antigens were negative.

Infliximab infusions were initiated at a dose of 5 mg/kg at weeks 0, 2, 6 and then every 8 weeks. Within 2 weeks, she reported improved clinical symptoms, with decrease in biochemical and clinical parameters (Table I). In the sixth week of treatment with infliximab, the patient presented an ASAS (Assessment in Ankylosing Spondylitis Response Criteria) response of 50. However, the patient continued to take the same NSAID she had before the beginning of infliximab. Before the fifth infusion of infliximab, the patient developed symmetric polyarthralgia of the hands and wrists with eight synovitis interesting the first and the second metacarpophalangeal joints, the proximal interphalangeal joints of the hands and the wrists. Morning stiffness was of 120 minutes. No other systemic or cutaneous manifestations was present. Biological exams showed: erythrocyte sedimentation rate 45 mm/h, CRP 28 mg/dl (normal value <0.8 mg/dl) and normal blood cells count. Renal function was normal as well as urinary sediment. Urinanalysis was negative

Table I. Clinical and biological outcome with infliximab therapy in our patient.

	Start	Week 2	Week 6	Week 14	Week 22
VAS pain (100mm scale)	80	50	40	20	50
PGA disease (100mm scale)	70	50	40	20	60
DGA disease (100mm scale)	70	50	40	20	50
BASDAI	68	60	30	30	60
BASFI	50	41	28	30	60
BASMI	6	4	4	4	3
ESR (mm)	40	18	12	20	45
CRP (mg/l)	9,9	1	3,4	4	28
ANA	Negative	-	-	-	1/3000
Anti ds-DNA (IU/ml)	Negative	-	-	-	-
Anti-histone (IU/ml)	Negative	-	-	-	600
ASAS response			50	70	

ASAS: Assessment in Ankylosing Spondylitis; DGA: doctor's global assessment of disease; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; PGA: patient's global assessment of disease; VAS: visual analogic scale.

for protein. Serological tests by indirect immunofluorescence on Hep2 cells showed antinuclear antibodies of 1:3000 (screening 1/200). Antibodies against double-stranded DNA were negative. Histone antibodies (H2A-H2B) were 600 (normal <1). Antibodies against ribonucleoprotein, Ro/SS-A, La/SS-B and Smith were negative. Drug-induced LLS associated with infliximab was diagnosed and treatment with corticosteroids was introduced. Within two weeks, a rapid reduction of the clinical symptoms and biological parameters was seen; the ANA and antihistone antibodies disappeared after three months.

Discussion

TNF plays a key role in the pathogenesis of many chronic inflammatory and rheumatic diseases, in particular, Crohn's disease, rheumatoid arthritis, and AS. Serious and unexpected adverse events, such as DIL, have been reported in patients receiving TNF inhibitor therapy (10). The role of TNF-α in the pathogenesis of SLE is complex. It is clearly an important component of the inflammatory response, and concentrations are raised in SLE (11). However, in NZB/NZW F1 mice, exogenous TNF-α actually delays the onset and progression of SLE, implying a potentially protective role (12). Induction of autoantibodies could be a predictable consequence of anti-TNF-α blockade because this blockade could promote humoral autoimmunity by inhibiting the induction of cytotoxic T lymphocyte response, which normally suppresses autoreactive B-cells (13). Infliximab might also act by neutralizing the biological activity of TNF-α by binding the soluble forms of TNF-α, thereby preventing the interaction of TNF-α with its cellular receptors, p55 and p75. Infliximab also binds the transmembrane form of TNF-α and could induce antibody-dependent or complement dependent cellular cytotoxicity of the cells expressing the cytokine (14). Furthermore, infliximab has been shown to increase the number of apoptotic T lymphocytes in the lamina propria (15) and apoptotic monocytes in peripheral blood in Crohn's disease (16). In this case, one hypothesis concerning the development of SLE is that an increased apoptotic process could promote the release of numerous autoantigens, leading to the development of auto antibodies against cytoplasmic and nuclear compounds such as ANA and dsDNA (17), especially if production of these auto antibodies is no longer suppressed by the action of infliximab on the suppressor T cell population. Several mechanisms are postulated: Cairns *et al*. (18) suggested that TNF-α may upregulate cellular expression of the adhesion molecule CD44, which has a role in apoptotic neutrophil clearance. Reduction of TNF-α activity by this class of medications will thus reduce the expression of CD44 and impair clearance of apoptotic cells; and, interestingly, both reduced expression of CD44 and impaired clearance of apoptotic cells have been described in association with SLE (18). Others have postulated that anti-TNF-α medications induce apoptosis, which causes the release of nucleosomal antigens that lead to anti-dsDNA auto-antibody production in susceptible individuals (19).

It has been shown that in mice, a lack of serum amyloid P, which is the murine analogue of the acute-phase protein C-reactive protein, results in a decrease in clearance of chromatin (20). The profound down-regulation of C-reactive protein in humans after infliximab might result in a similar decrease of clearance of nuclear material and, hence, prolonged exposure to the immune system of excessive amounts of intracellular material, which could potentially induce and maintain an ANA response by repeated stimulation (21).

References

1. HOFFMAN BJ: Sensitivity to sulfadiazine resembling acute disseminated lupus erythematosus. *Arch Dermatol Syphilis* 1945; 51: 190-2.
2. ANTONOV D, KAZANDJIEVA J, ETUGOV D, GOSPODINOV D, TSANKOV N: Drug-induced lupus erythematosus. *Clin Dermatol* 2004; 22: 157-66.
3. PISETSKY DS: Tumor necrosis factor blockers and the induction of anti-DNA autoantibodies. *Arthritis Rheum* 2000; 43: 2381-2.
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. *Arthritis Rheum* 2000; 43: 2383- 90.
5. ERIKSSON C, ENGSTRAND S, SUNDQVIST KG, RANTAPÄÄ-DAHLQVIST S: Autoantibody formation in patients with rheumatoid arthritis treated with anti-TNF. *Ann Rheum Dis* 2005; 64: 403-7.
6. HANAUER SB: Safety of infliximab in clinical trials. *Aliment Pharmacol Ther* 1999; 13: 16-22.
7. VERMEIRE S, NOMAN M, VAN ASSCHE G *et al*.: Autoimmunity associated with anti-tumor necrosis factor alpha treatment in Crohn's disease: a prospective cohort study. Gastroenterology 2003; 125: 32-9.
8. ELEZOGLOU A, KAFASI N, KAKLAMANIS PH *et al*.: Infliximab treatment-induced formation of autoantibodies is common in Behçet's disease. *Clin Exp Rheumatol* 2007; 25 (Suppl. 45): S65-9.
9. PEREZ-GARCIA C, MAYMO J, LISBONA PEREZ MP, ALMIRALL BERNABE M, CARBONELL ABELLO J: Drug-induced systemic lupus

erythematosus in ankylosing spondylitis associated with infliximab. *Rheumatology* 2006; 45: 114-6.
10. CUSH JJ: Unusual toxicities with TNF inhibition: heart failure and drug induced-lupus. *Clin Exp Rheumatol* 2004; 22 (Suppl. 35): S141-7.
11. STUDNICKA-BENKE A, STEINER G, PETERA P, SMOLEN JS: Tumour necrosis factor alpha and its soluble receptors parallel clinical disease and autoimmune activity in systemic lupus erythematosus. *Br J Rheumatol* 1996; 35: 1067-74.
12. GORDON C, RANGES GE, GREENSPAN JS, WOFSY D: Chronic therapy with recombinant tumor necrosis factor-α in autoimmune NZB/W F1 mice. *Clin Immunol Immunopathol* 1989; 52: 421-34.
13. VIA CS, SHUSTOV A, RUS V, LANG T, NGUYEN P, FINKELMAN FD: *In vivo* neutralization of TNF-alpha promotes humoral autoimmunity by preventing the induction of CTL. *J Immunol* 2001; 167: 6821-6.
14. ZIMMERMANN-NIELSEN E, AGNHOLT J, THORLACIUS-USSING O, DAHLERUP JF, BAATRUP G: Complement activation in plasma before and after infliximab treatment in Crohn's disease. *Scand J Gastroenterol* 2003; 38: 1050-4.
15. TEN HOVE T, VAN MONTFRANS C, PEPPELENBOSCH MP, VAN DEVENTER SJ: Infliximab treatment induces apoptosis of lamina propria T lymphocytes in Crohn's disease. *Gut* 2002; 50: 206-11.
16. LUGERING A, SCHMIDT M, LUGERING N, PAUELS HG, DOMSCHKE W, KUCHARZIK T: Infliximab induces apoptosis in monocytes from patients with chronic active Crohn's disease by using a caspase- dependent pathway. *Gastroenterology* 2001; 121: 1145-57.
17. BELL DA, MORRISON B: The spontaneous apoptotic cell death of normal human lymphocytes in vitro: the release of, and immunoproliferative response to, nucleosomes *in vitro*. *Clin Immunol Immunopathol* 1991; 60: 13-26.
18. CAIRNS AP, DUNCAN MK, HINDER AE, TAGGART AJ: New onset systemic lupus erythematosus in a patient receiving etanercept for rheumatoid arthritis. *Ann Rheum Dis* 2002; 61: 1031-2.
19. FAVALLI E, SINIGAGLIA L, VARENNA M, ARNOLDI C: Drug-induced lupus following treatment with infliximab in rheumatoid arthritis. *Lupus* 2002; 11: 753-5.
20. BICKERSTAFF MC, BOTTO M, HUTCHINSON WL *et al.*: Serum amyloid P component controls chromatin degradation and prevents antinuclear auto-immunity. *Nat Med* 1999; 5: 694-7.
21. CASIANO CA, TAN EM: Recent developments in the understanding of antinuclear autoantibodies. *Int Arch Allergy Immunol* 1996; 111:308-13.