NDT Plus (2008) 4: 221–224
doi: 10.1093/ndtplus/sfn060
Advance Access publication 17 June 2008

NDT PLUS
Nephrology Dialysis Transplantation

Case Report

Clinical and histological features of lupus nephritis induced by anti-TNFα therapy

Tiziana Piccolo, Piero Lisi, Enza Valicenti, Giovanni Pannarale and Pasquale Coratelli

Nephrology Unit 1, Policlinico, Bari, Italy

Abstract

It is known that anti-TNFα therapy has opened a new era in treatment of rheumatoid arthritis, and it is emerging as a new successful treatment in the current rheumatologic practice. Besides, there is evidence that this therapy is an important cause of iatrogenic autoimmune disease. Several studies reported the possible onset of lupus syndrome that can be resolved with withdrawal of anti-TNFα drugs. Our report describes the first lupus nephritis case developing in a rapidly progressive renal failure that required haemodialysis treatment in a patient affected with rheumatoid arthritis, treated with anti-TNFα therapy. So, we confirm the importance of a careful clinic and immunologic evaluation before starting anti-TNFα therapy.

Keywords: anti-tumour necrosis factor α therapy; lupus nephritis

Introduction

It is known that anti-TNFα agents, used in the management of rheumatoid arthritis and other rheumatologic diseases, lead to formation of autoantibodies, flares of vasculitis and reversible lupus-like syndrome. Anti-TNFα agents used in the management of rheumatologic diseases include etanercept, inlfliximab and adalimumab. In a recent review Ramos-Casals *et al.*, through a Medline from January 1990 and December 2006, identified 233 cases of secondary autoimmune diseases (vasculitis in 113, lupus in 92, interstitial lung diseases in 24 and other autoimmune diseases in 4) due to TNFα-targeted therapies. Indeed, among the 92 patients that developed systemic lupus erythematosus/lupus-like disease treated with anti-TNFα therapy, only five cases developed nephropathy (1). Thus, in this study we report on clinical and pathological characteristic of renal involvement in a single case of lupus nephritis following anti-TNFα therapy.

Correspondence and offprint requests to: Tiziana Piccolo, Via G.B. Calò n. 46/b, 70051 Barletta, Italy. E-mail: piccolo.tiziana@libero.it

Case report

A 44-year-old female was admitted with arthritic symptoms, myalgia, oral ulcers, headache, rash, fever and generalized weakness, 9 months after etanercept administration. She had been diagnosed seropositive for rheumatoid arthritis seven years previously, and she had been treated with prednisolone, methotrexate, NSAID and infliximab. Infliximab was stopped because it was not effective, so etanercept was started at twice weekly doses of 25 mg subcutaneously. On admission, serum creatinine was 0.8 mg/dl, urea was 60 mg/dl and serum albumin was 2.5 g/dl. Haemoglobin and platelet counts were normal. Both C3 and C4 components were decreased. Urinalysis showed proteins >400 mg/dl, 1+ red blood cells. Twenty-four-hour urinary protein excretion was 3 g. Serologic tests revealed positive rheumatic factor, positive ANA (1:2560 homogenous pattern) and positive anti-dsDNA (>600). The test for pANCA was positive and for cANCA it was negative. Multiple tests for ANCA and anti-dsDNA in previous years were negative. A renal biopsy was then performed.

Post-biopsy clinical course

A diagnosis of lupus nephritis (Class IV) (Figure 1) (2) was made and etanercept was discontinued. The patient was treated with ciclophosphamide 1 g e.v. and corticosteroids. After 10 days the body temperature was 39°C, total white cells count decreased to 0.60×10^3/Ul and serologic test showed CMV positivity. Ciclophosphamide therapy was then switched to mycophenolate mofetil and granulokine was administered. Total white cell count increased to 2.5×10^3/Ul. Chest and abdomen TC showed pleuric and pericardic effusion and hepatosplenomegaly. Blood pressure was 180/100 mmHg throughout the antihypertensive therapy; the heart rate was 105/min. General conditions worsened, and the patient became lethargic; twenty-four-hour urinary proteins excretion was 11.3 g; heavy dyspnoea appeared, oedema progressively increased till anasarca. The patient underwent an ultrafiltration treatment. After a transient improvement, the patient became anuric and serum creatinine rose to 5.1 mg/dl, urea to 103 mg/dl; haemoglobin went down to 7.3 g/dl and platelet counts to $47 \times 10^3/\mu$l.

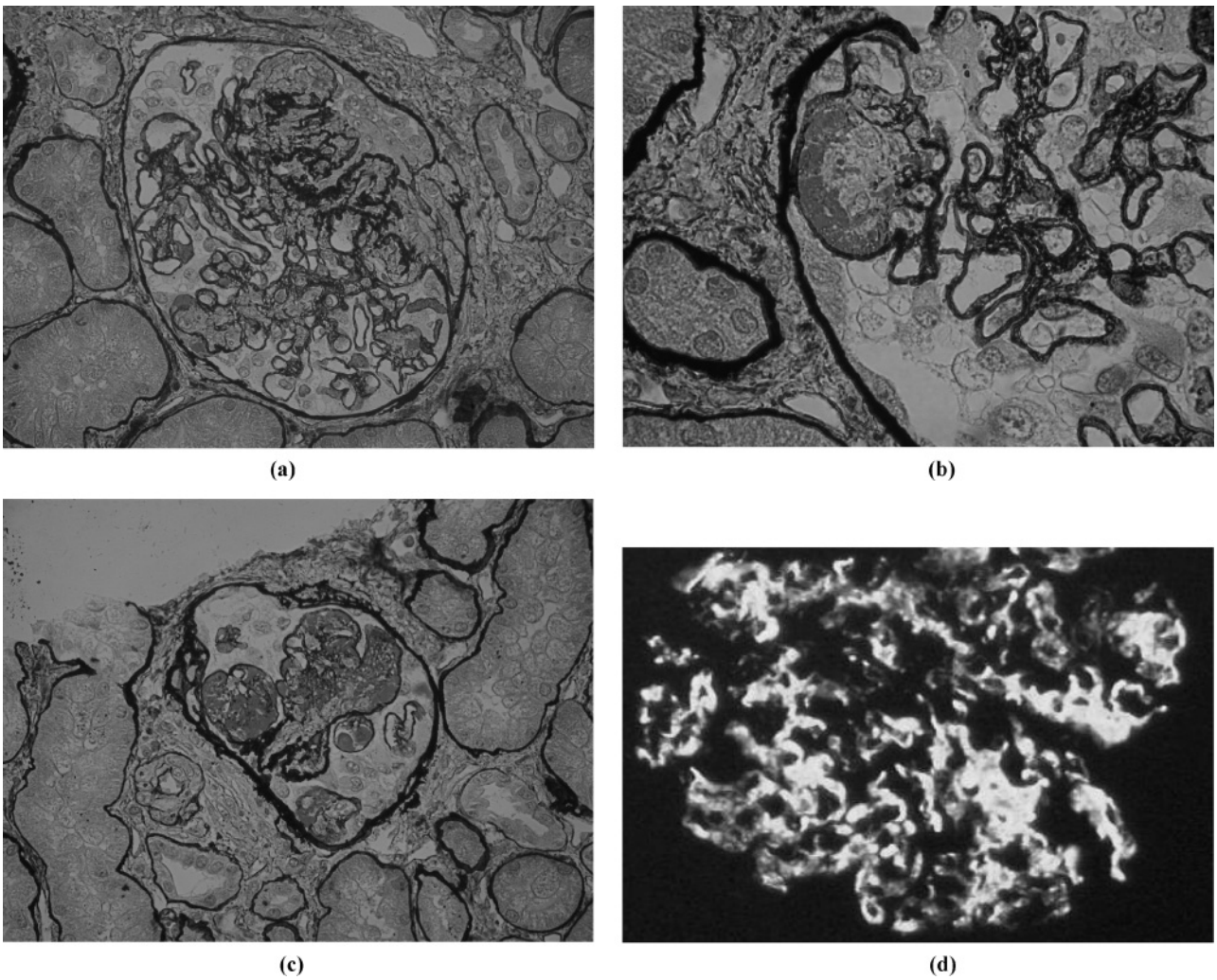

Fig. 1. Segmental solidification of glomerular tuft due to endocapillary hypercellularity and increase of collagenous matrix. (**a**) Evidence of proteinaceous deposits in mesangial areas and along capillary walls. Segmental fibrocellular crescent. (**b**) Large subendothelial deposit. (**c**) Capillary lumina completely obstructed by giant deposits and thromby. (**d**) Marked C1q deposition in mesangium and along the capillary wall.

Mycophenolate mofetil was stopped and the patient underwent haemotransfusion and plasmapheresis. Dialysis was started for a total number of 20 treatments. After 30 days of haemodialysis treatment, diuresis restored, good metabolic balance was reached and patient conditions improved. Serum creatinine progressively went back to 1.3 mg/dl, urea 128 mg/dl, haemoglobin 11.2 g/dl and platelet counts 298 × $10^3/\mu$l. The patient was then discharged with azatioprine 50 mg daily, corticosteroids 25 mg daily, antihypertensive drugs, erythropoietin, and a calcium and vitamin D supplement daily. At this time, upon 14 months of follow-up, the patient is in good health, normotensive, and serologic tests have revealed serum creatinine at 0.7 mg/dl and a 24-h urinary excretion of 1 g/24 h. She continues azatioprine intake, a lower dose of corticosteroids (Figure 2).

Renal biopsy findings

Light microscopy revealed 30 glomeruli. Glomerular tufts displayed diffuse but segmental endocapillary hypercellularity with obliteration of capillary lumina (Figure 1a). Heavy proteinaceous deposits were disclosed, prevalent in subendothelial spaces (Figure 1b), and also seen in mesangial and subepithelial areas and capillary thrombosis (Figure 1c). Crescents, mainly fibrocellular ones, were found in 50% of glomeruli (Figure 1a). Few glomeruli showed small foci of fibrinoid necrosis. No glomerulus was sclerotic, and no tubular atrophy, interstitial fibrosis or arterial vessels damage was identified. Immunofluorescence microscopy disclosed mesangial and glomerular capillary wall staining for IgG, IgM, IgA, C3, C1q and C4 (Figure 1d). The final diagnosis was diffuse proliferative lupus nephritis (Class IV).

Discussion

It is known that anti-TNFα therapy has opened a new era in the treatment of rheumatoid arthritis, and it is emerging as a new successful treatment in the current rheumatologic

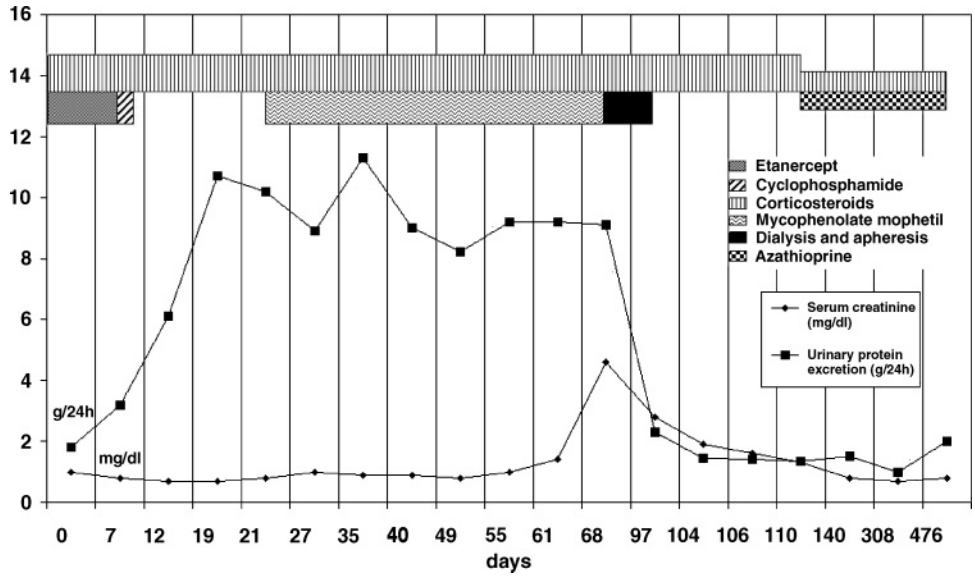

Fig. 2. Course of serum creatinine and urinary protein excretion and modification of therapy with time.

practice. Besides there is evidence that this therapy is an important cause of iatrogenic autoimmune disease, since autoantibody formation was reported at high frequency in anti-TNFα-treated patients. Several studies reported the possible onset of lupus syndrome that can be resolved with withdrawal of anti-TNFα drugs [3,4]. Discontinuation of anti-TNFα agents and administration of immunosuppressive therapy led to improvement in serologic abnormalities and renal function in all the patients, supporting the pathogenetic role of anti-TNFα-induced autoimmunity. An etiologic role for anti-TNFα agents is further supported by the temporal relation between the new onset glomerular disease and administration drug in patients with long-standing RA, and no prior renal disease. Moreover, improvement of clinical symptoms and laboratory abnormalities is observed after drug withdrawal and starting of immunosuppressive therapy in the majority of patients. In the previous reports, timing of the onset and offset of the SLE features strongly supported a drug-related effect of anti-TNFα agents. Most patients developed abnormalities 3–14 months after commencing anti-TNFα therapy and improved rapidly when stopping the treatment. Our report is in agreement to the temporal relation of the new onset of lupus syndrome after 9 months of etanercept therapy that resolved following the discontinuation of etanercept.

In our patient the main clinical feature of SLE was nephropathy. Nephropathy was rapidly progressive and led to uraemia; thus our patient underwent haemodialysis treatment. In previous reports, renal failure was also described in some cases [6], but no patient required dialysis.

In a recent review, Ramos Casals *et al.* identified, through a Medline from January 1990 and December 2006, 233 cases of secondary autoimmune diseases due to TNFα-targeted therapies. The autoimmune disease identified was classified in four groups: vasculitis (113), lupus (92), interstitial lung diseases (24) and other autoimmune diseases (4) [1]. Among the 92 patients that developed systemic lupus erythematosus/lupus-like disease, after starting anti-TNFα therapy, only in five cases nephropathy was observed. More recently Haake described another case of focal proliferative lupus nephritis during anti-TNFα therapy for psoriasic arthritis [5]. So, clinical and histological features of nephropathy caused by anti-TNFα therapy are still poorly described. Stokes *et al*. reported five patients with long-standing RA who developed new onset of glomerular disease while receiving TNFα antagonist. Among these, three patients were receiving etanercept, one adalimumab and another one infliximab. Renal biopsies showed proliferative lupus nephritis in two patients, pauci-immune necrotizing and crescentic glomerulonephritis in other two subjects and immune complex-mediated renal vasculitis in another patient [6]. Both cellular and humoral mechanisms appeared to cooperate in determining renal damage. Moreover, renal biopsy findings showed chronic characteristics as in long-standing RA or previous drugs damage (ciclosporine, non-steroidal antinflammatory drugs, methotrexate). In our report, there is an endocapillary proliferation with heavy subendothelial fuchsinophilic deposits as a result of a prevalent humoral mechanism, as described in the case reported by Adam Mor *et al*. [7]. The mechanism of anti-TNFα-induced autoimmunity has not been yet clarified. TNFα is a citokine that plays a pro-inflammatory role in the pathogenesis of rheumatic disease. Inhibition of TNFα with etanercept (a p75 TNF receptor fusion protein conjugated to the Fc region of human IgG), infliximab (a chimeric monoclonal antibody against TNFα) and adalimumab (a human anti-TNFα monoclonal antibody) has recently emerged as an effective therapy for treating rheumatic diseases. Charles *et al*. have proposed that TNFα blockade induces apoptosis of cells that express TNFα releasing immunogenic nucleosomal antigens, which promote anti-dsDNA antibody formation [8]. However, the evidence is in conflict since in the mouse model of lupus (NZB/NZW F1 strain) TNFα appears to be protective, improving lupus nephritis [9,10].

This is, however, a complex area that requires clarification by further study.

Through our report, we described the first lupus nephropathy case, among the RA patients treated with anti-TNFα therapy, that developed uraemia and underwent haemodialysis treatment. So, we confirm the importance of a careful clinic and immunologic evaluation before starting anti-TNFα therapy.

Conflict of interest statement. None declared.

References

1. Ramos-Casals M, Brito-Zeron P, Munoz S *et al*. Autoimmune diseases induced by TNF-targeted therapies. Analysis of 233 cases. *Medicine* 2007; 86: 242–251
2. Weening JJ, D'Agati VD, Schwartz MM *et al*. The classification of glomerulonephritis in systemic lupus erythematosus revisited. *J Am Soc Nephrol* 2004; 15: 241–250
3. 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: 1932–1939
4. Shakoor N, Michalska M, Harris CA *et al*. Drug-induced systemic lupus erythematosus associated with etanercept therapy. *Lancet* 2002; 359: 579–580
5. Haake H, Koneke J, Amann K *et al*. Development of systemic lupus erythematosus with focal proliferative lupus nephritis during anti-TNF-alpha therapy for psoriatic arthritis. *Med Klin* 2007; 102: 852–857
6. Stokes MB, Foster K, Markowitz GS *et al*. Development of glomerulonephritis during anti-TNF-alpha therapy for rheumatoid arthritis. *Nephrol Dial Transplant* 2005; 20: 1400–1406
7. Mor A, Bingham CO III, Barisoni L *et al*. Proliferative lupus nephritis and leukocytoclastic vasculitis during treatment with etanercept. *J Rheumatol* 2005; 32: 740–743
8. Charles PJ, Smeenk RJ, De Long J *et al*. 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: 2383–2390
9. Gordon C, Ranges GE, Greenspan JS *et al*. Chronic therapy with recombinant tumor necrosis factor-alpha in autoimmune NZB/NZW F1 mice. *Clin Immunol Immunopathol* 1989; 52: 421–434
10. Pisetsky DS. Tumour necrosis factor α blockers and the induction of anti-DNA autoantibodies. *Arthritis Rheum* 2000; 43: 2381–2382

Received for publication: 15.4.08
Accepted in revised form: 6.5.08