

Nephrotic syndrome as a complication of anti-TNF α in a patient with rheumatoid arthritis

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ABSTRACT

We describe a patient with rheumatoid arthritis (RA) who developed a nephrotic syndrome during treatment with a fully human recombinant monoclonal antibody against TNF α (adalimumab, Humira, Abbott). The proteinuria disappeared spontaneously after cessation of anti-TNF α treatment and relapsed after rechallenge, pointing to anti-TNF α as the culprit. Although renal biopsy disclosed a membranous glomerulopathy, the clinical picture was more compatible with minimal lesion glomerulopathy. The pathogenesis of this side effect is not clear; several mechanisms could in theory lead to these abnormalities.

INTRODUCTION

Blocking the action of tumour necrosis factor α (TNF α) with monoclonal antibodies directed against TNF α has been shown to yield fast and impressive responses in patients with rheumatoid arthritis (RA).^{1,3} Adverse effects are usually mild and except for enhanced susceptibility to certain infections, the most prominent being *M. tuberculosis*,⁴ and rare systemic lupus erythematosus (SLE)-like syndromes, no specific side effects have been reported. We describe a patient who developed a nephrotic syndrome as an adverse effect of treatment with the fully human anti-TNF α monoclonal antibody adalimumab.

CASE REPORT

Our 64-year-old patient was diagnosed with a rheumatoid factor positive, ANA negative erosive rheumatoid arthritis (RA) in 1982. His medical history was unremarkable, except for chronic obstructive pulmonary disease (COPD). In the following years he was treated with D-penicillamine followed by parenteral aurothioglucose. This was stopped in 1984 because of proteinuria up to 1.5 g/l. After cessation of intramuscular gold administration, the proteinuria completely disappeared. Therapy was continued with methotrexate, followed again by aurothioglucose, which was stopped in 1990 because of exacerbation of the RA. Proteinuria did not appear during this second episode of gold therapy nor did it later. Sulphasalazine treatment was initiated, later combined with methotrexate and prednisone. The latter combination therapy was stopped due to lack of efficacy. In light of the persistent disease activity the patient was recruited in May 1997 for a phase I trial with a fully human monoclonal antibody against TNF α (adalimumab, Humira[®], Abbott). Treatment with anti-TNF α was started in a dose of 1.0 mg/kg body weight every two weeks intravenously, later increased to 3.0 mg/kg according to the study protocol. Concomitant medication included prednisone 10 mg a day, diclofenac 75 mg twice a day, alternating calcium and etidronic acid, omeprazol 20 mg twice a day, paracetamol 500 mg as needed, ipratropium-bromide 40 μ g four times a day, salmeterol 100 μ g twice a day and doxycycline 100 mg once daily. There was an excellent clinical response to anti-TNF α treatment: the disease activity score (DAS, a combined disease activity measure for RA) dropped from 5.89 to 2.41 and C-reactive protein levels went from 142 to 24 mg/l. Prednisone was gradually tapered to 2.5 mg/day.

In April 1998, the patient developed progressive pitting oedema of both lower extremities. He also noticed a weight gain from 73 to 84 kg in two weeks. On admission, blood pressure was 150/80 mmHg. Physical examination revealed bilateral leg oedema and evidence of pleural and peritoneal fluid. Laboratory investigations showed serum creatinine 82 $\mu\text{mol/l}$, serum albumin 15 g/l, cholesterol 7.0 mmol/l, haemoglobin 5.5 mmol/l. ANA negative, and normal complement C3 and C4. Proteinuria averaged 16.7 g/24 h, selectivity index was 0.07 (highly selective).

A renal biopsy was performed. By light microscopy segmental irregularities of the glomerular basement membrane (GBM) of all glomeruli were demonstrated, suggestive of a membranous glomerulopathy, such as vacuolisation, spike formation or some ring-like structures. Podocytes, endothelial cells and mesangial areas were normal (figures 1A and 1B). Congo red staining did not reveal amyloid. Immunofluorescence revealed fine granular deposits of particularly IgG and C₃ along the capillary wall in a characteristic membranous pattern (figure 2). No AA amyloid deposits were found using a monoclonal antibody. By electron microscopy, podocytes were hypertrophic and showed retraction of the foot processes (figure 3). In some segments of the GBM, irregularly spaced subepithelial electron dense deposits accompanied by spike formation were observed. Other segments displayed a broad and abnormal GBM, incorporating many complexes that were less electron dense and resolving (figure 3). Several segments of the GBM, however, did not show any alterations or electron dense aggregates.

The patient was treated with diuretics and an angiotensin-converting enzyme inhibitor; anti-TNF α treatment and diclofenac were withdrawn (figure 4). The proteinuria eventually disappeared after three months. Interestingly, symptoms of RA relapsed in the same week that the nephrotic syndrome disappeared. Diclofenac therapy was reinstated but the proteinuria did not reappear until after reintroduction of anti-TNF α treatment. The patient was

treated with prednisone 60 mg daily and cyclophosphamide 100 mg daily. Within one week, proteinuria had completely disappeared. Cyclophosphamide was stopped and prednisone quickly tapered to 10 mg daily. At this point, anti-TNF α was started again. The nephrotic syndrome did not reappear until the prednisone was reduced to a dose of 5 mg daily and subsided again after the dose was increased to 10 mg. Since December 1998, the patient is being treated with anti-TNF α in combination with 10 mg prednisone daily and has retained an excellent clinical response without proteinuria.

DISCUSSION

In our patient a nephrotic syndrome developed during treatment with adalimumab. Renal biopsy disclosed a membranous glomerulopathy. The clinical course strongly incriminated anti-TNF α as the culprit, since proteinuria disappeared after withdrawal of anti-TNF α treatment and reappeared upon rechallenge. Furthermore, we could exclude that the other likely candidate, the NSAID diclofenac, was the cause of the nephrotic syndrome. Membranous nephropathy has been frequently reported in patients with RA. In a series of 110 biopsies in patients with RA, membranous nephropathy was observed in 19 patients (17%).⁵ In most patients with RA and membranous nephropathy, treatment with gold salts or D-penicillamine has been incriminated as the cause. However, it has also been suggested that patients with RA may be prone to the development of membranous nephropathy, even in the absence of gold or D-penicillamine treatment.⁶ It is however unclear if in these latter patients the use of NSAIDs as causative agents was excluded, as an association also exists between NSAID use and membranous nephropathy.⁷ Our patient may thus represent a case of membranous nephropathy caused by anti-TNF α treatment. TNF α has been incriminated in glomerular diseases. *In vitro* studies

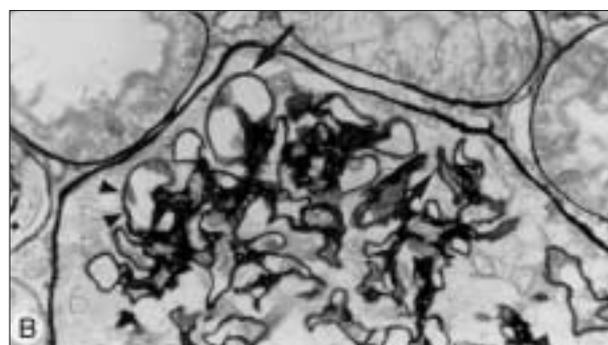
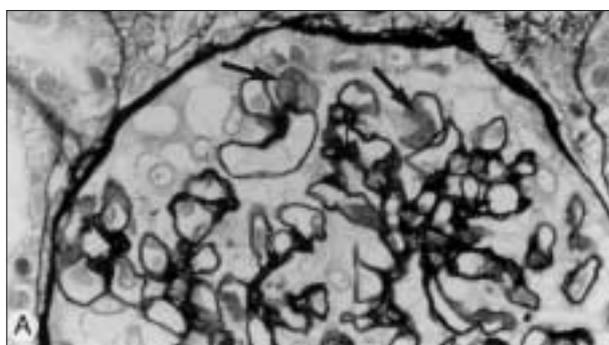


Figure 1

Light microscopy of a part of a glomerulus

Some segments of the GBM (glomerular basement membrane) show extensive vacuolisation (a; arrows), minor irregularities and spike-like conformations (b; arrows) on the epithelial side or bead-like structures (b; arrowheads) ($\times 900$). Silver methenamine staining.

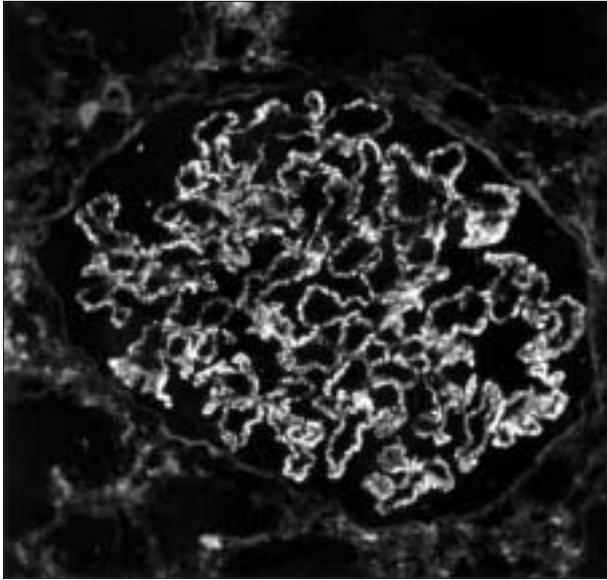


Figure 2
Direct immunofluorescence using FITC-labelled antihuman IgG antibody

Fine granular deposits of IgG are shown along the capillary wall in a characteristic membranous pattern. In some capillary loops only a few granules are present (*400).

have shown that TNF α can increase glomerular permeability, possibly by inducing oxygen radical production.⁸ Glomerular visceral epithelial cells can produce TNF α .⁹ Of particular interest for our case are the observations of Neale *et al.*¹⁰ These investigators have demonstrated the unique presence of TNF α in the visceral epithelial cells and in the subepithelial deposits in patients with membranous nephropathy. TNF α was not found in other forms of glomerular disease. Since membranous nephropathy is the result of an interaction between antibodies and antigens present on the surface of the glomerular epithelial cells,¹¹ one can speculate that in our patient the membranous nephropathy was caused by interaction of the anti-TNF α antibodies with TNF α present on visceral epithelial cells. Infliximab, a chimeric anti-TNF monoclonal antibody, can bind to membrane-bound TNF and bring cells into apoptosis.¹² This characteristic has, however, not yet been demonstrated for adalimumab. Also, to the best of our knowledge, TNF α is only present in the cytoplasm of glomerular epithelial cells and an increased production is only found in patients with established membranous glomerulopathy. Furthermore, we found no evidence for TNF α in the glomerular basement membrane in our patient using biotin-labelled IgG1 anti-TNF α Moab (monoclonal antibody) or a polyclonal anti-human TNF α by indirect immunofluorescence.

The clinical data point to an alternative explanation for the cause of the nephrotic syndrome. The highly selective proteinuria and the immediate and brisk response to

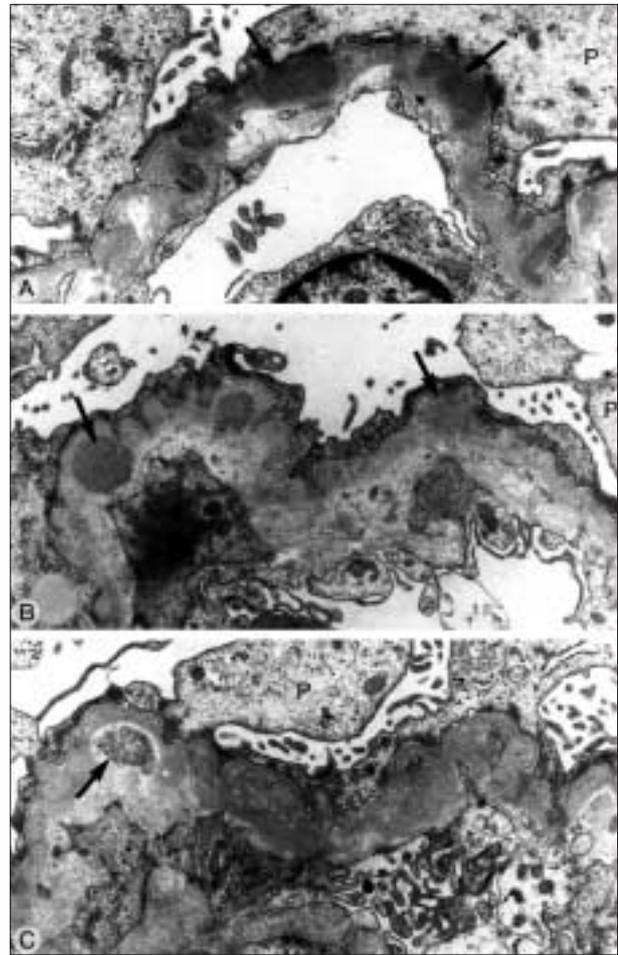


Figure 3
Electron microscopy

Subepithelial electron dense deposits are seen in some segments of the GBM (glomerular basement membrane) (A; arrows). In other segments of the capillary wall the GBM is thickened and extensively altered with incorporation of many resolving deposits showing variable lesser electron density (B and C; arrows). Extensive retraction of the foot processes of the podocytes (P) is present (A, B, C; *17000).

treatment with steroids strongly suggest the presence of minimal change nephropathy.¹³ In patients with established membranous nephropathy proteinuria disappears quite slowly if at all, even during treatment with immunosuppressive agents.¹⁴ We did not observe any complete remissions of proteinuria within three months after the start of treatment in 34 patients with membranous nephropathy who were treated with high-dose prednisone.¹⁵ Likewise, in patients with RA with membranous nephropathy caused by either gold or D-penicillamine, proteinuria disappears gradually; in most patients the maximal proteinuria is even reached one to two months after stopping the offending drug.¹⁶ In such patients, treatment with prednisone apparently does not influence the duration of proteinuria.¹⁷ The finding of subepithelial deposits certainly does not prove that the proteinuria is caused by the membranous

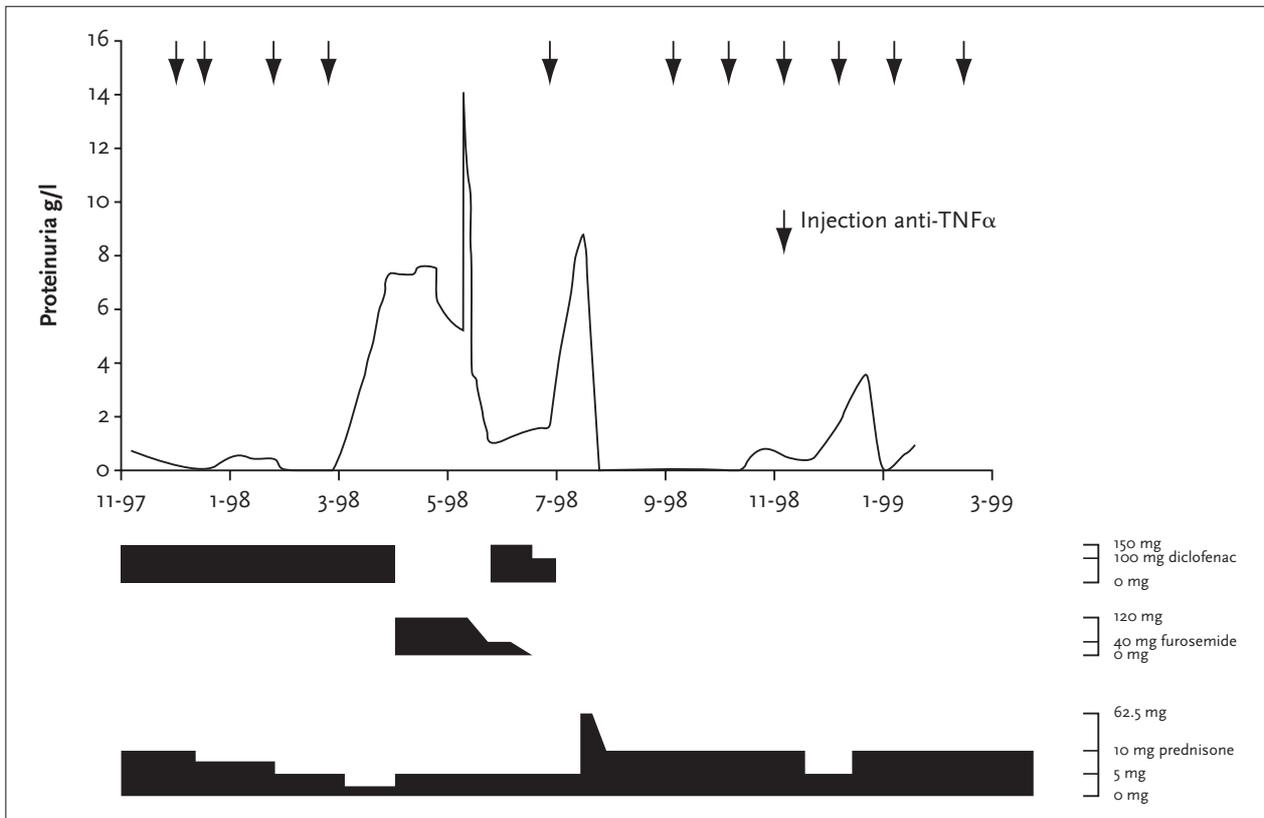


Figure 4

Clinical course of the patient

Proteinuria is depicted over time. Injection of anti-TNF α is indicated by the arrows. There is a clear relationship between the level of proteinuria, the use of anti-TNF α and lowering of prednisone.

nephropathy. In the rat model of membranous nephropathy, injection of monoclonal antibodies against the podocyte antigen megalin results in the formation of small subepithelial deposits that are not paralleled by the development of proteinuria.¹¹ Likewise, a membranous nephropathy with subepithelial deposits in the absence of proteinuria has been observed in hypertensive patients treated with captopril.¹⁸ Notably, in the study mentioned above in patients with RA, three patients were described with membranous nephropathy but no proteinuria.⁵ Furthermore, it is well established that in patients with membranous nephropathy the deposits can remain visible after remission has occurred, even for many years.¹⁹ In our patient, many deposits seem to be old, incorporated in the GBM and dissolving, suggesting that they may have been caused by the previous gold therapy. Alternatively, the deposits may have been induced by the diclofenac treatment.

Experience with infliximab has shown that renal side effects are very rare. Increase of antinuclear and antidouble-stranded DNA antibodies is, however, frequent and a few

cases of drug-induced systemic SLE-like syndromes have been described,²⁰ although these cases did not include renal involvement. As antinuclear and antidouble-stranded DNA antibodies and other signs and symptoms of SLE were absent in our patient, our case does not represent a drug-induced SLE.

As noted, the nephrotic syndrome in our patient was highly steroid sensitive but also steroid dependent. A dose of 10 mg prednisone was able to prevent the reoccurrence of proteinuria. Since a considerable number of patients who receive anti-TNF α are concurrently being treated with prednisone, the potential of anti-TNF α to induce proteinuria may thus be masked. It remains to be established if this side effect becomes more frequent if anti-TNF α treatment is instituted in patients who do not receive steroids.

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