

## Letter to the Editor (Case report)

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**Minimal change nephrotic syndrome due to certolizumab pegol, an anti-tumor necrosis factor-alpha monoclonal antibody for treatment of rheumatoid arthritis**

**Key message**

- Anti-TNF- $\alpha$  therapy is known to cause immunological renal disease in RA.

DEAR EDITOR, TNF- $\alpha$  has an important role in the onset and maintenance of various autoimmune diseases, and TNF- $\alpha$ -blocking therapy has been accepted as an effective treatment for RA [1].

Anti-TNF- $\alpha$  therapy is associated with some adverse effects, including infectious events, congestive heart failure [2] and new-onset immunological disorders. We encountered a case of a renal disorder and nephrotic proteinuria that developed after the intake of certolizumab pegol (CZP).

A 75-year-old Japanese woman was admitted to our department because of massive proteinuria. She had no past medical history of primary renal disease or other systemic disorders that could cause secondary renal disease. Her current medication was eldecalcitol, weekly alendronate and omeprazole. She had been suffering from RA for 30 years and had been taking weekly MTX and etanercept for the last 10 years. Owing to the attenuated effects of this treatment regimen, her medication was switched to CZP 2 years ago.

She underwent subtotal gastrectomy because of advanced gastric cancer. In the perioperative period, CZP was withdrawn for 3 weeks. Two months later, her rheumatologist noticed proteinuria and bilateral leg oedema, for which CZP was discontinued immediately. However, as she gained 13 kg in body weight, urinary protein rose to 750 mg/dl, and serum albumin dropped to 1.9 g/dl. Serum creatinine was 0.68 mg/dl, and the estimated glomerular filtration rate was 64 ml/min/1.73 m<sup>2</sup>. The serological findings were as follows: ANA titre,  $\times 80$ ; anti-dsDNA antibody, negative; CH50, 34.2 U/ml; IgM-RF (64 U/ml) and ACPA (25.3 IU/ml) were positive.

Increasing serum creatinine levels of up to 2.00 mg/dl indicated acute kidney injury. Oral prednisolone at a dose of 40 mg/day was initiated. Renal biopsy was performed the day before the start of CS therapy. The amount of proteinuria decreased rapidly, from 15.4 to 0.59 g/day in 10 days, and reached 0.16 g/day in

3 weeks. The dose of prednisolone was decreased to 10 mg in 10 months. Abatacept was added as the therapy for RA. The disease activity of arthritis and nephrotic syndrome subsided at this time (the clinical course in our case is shown in [Supplementary Fig. S1](#), available at *Rheumatology Advance in Practice* online).

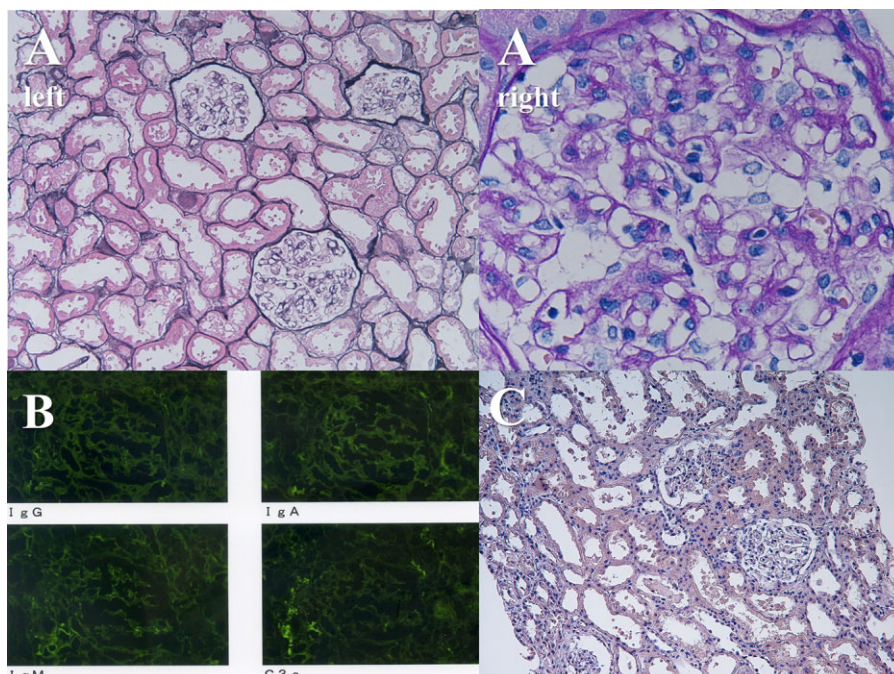
Renal histopathology revealed minor abnormalities ([Fig. 1](#)). Evidence of epithelial immune complex deposition in glomeruli was not observed even with electron microscopy. Amyloid protein was not detected with Congo Red staining. These findings indicated a diagnosis of minimal change disease (MCD).

Pathological findings of renal manifestations in RA have been reported in 110 cases, and among these, three cases of MCD may have been associated with malignancy and gold compounds [3]. However, gold compounds were not prescribed for our patient. Furthermore, the pathogenesis of proteinuria is thought to be attributable to subepithelial immune complex deposition; however, this was not the case in our patient.

In terms of the association with malignancy, the most solid cancer-associated cases are usually membranous glomerulonephritis, not MCD. Furthermore, haematological malignancy had been reported in most cases associated with MCD [4]. Moreover, in our patient the gastric cancer was removed completely; there was no evidence of metastases or residual disease remaining. We concluded that nephrotic syndrome was not affected by gastric cancer.

Biologics-induced autoimmune renal disorders have been reported in patients with rheumatic diseases [5]. Anti-TNF- $\alpha$  therapy can induce a cytokine imbalance that leads to ANA production, often resulting in a lupus-like syndrome [6]. In addition, some patients receiving anti-TNF- $\alpha$  therapy develop new-onset glomerular disease followed by anti-dsDNA antibody or MPO and ANCA production [7]. However, these autoantibodies were not apparent in our patient.

In terms of the pathogenesis of MCD, TNF- $\alpha$  has been reported to be increased in the serum and overexpressed in peripheral leucocytes, whereas the expression of T-cell cytokines was not identified [8]. From another perspective, regulatory T cells, which can maintain immune homeostasis and prevent autoimmunity, might be associated with the onset of minimal change nephrotic syndrome [7]. Such T cells are reported to be downregulated by TNF, and the essential regulatory protein FOXP3 is increased during anti-TNF- $\alpha$  therapy [9]. In our case, the withdrawal from CZP could have triggered the nephrotic syndrome. TNF- $\alpha$  activity might have been upregulated extremely through the surgical procedure or the immunological response against the malignant tumour. Restarting CZP might then have affected the

**Fig. 1** Renal biopsy consistent with minimal change nephrotic syndrome

Minor glomerular abnormality in Periodic Acid–Schiff staining (**A**; magnification: left  $\times 100$ , right  $\times 400$ ), no immunoglobulin or complement deposition (**B**), and amyloid protein is not detected with Congo Red staining (**C**).

cytokine imbalance and expression of regulatory T cells, leading to the onset of MCD.

Abatacept (CTLA4-Ig) was added as an alternative therapy for RA in our patient. Given that CD80 overexpression on podocytes can cause proteinuria in MCD patients [10], the inhibition of co-stimulatory molecules via the CD28–CD80 pathway not only affects anti-TNF therapy-associated proteinuria but is also effective for RA treatment.

In conclusion, our RA patient treated with CZP exhibited minimal change nephrotic disease. Her renal manifestations subsided with the discontinuation of the biologic therapy, and remission was maintained with CS and CTLA4-Ig treatment.

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**Patient consent.** Informed consent was obtained from the patient before publication.

### Data availability statement

The data underlying this article will be shared on reasonable request to the corresponding author.

### Supplementary data

Supplementary data are available at *Rheumatology Advances in Practice* online.

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