Tocilizumab-induced remission of nephrotic syndrome accompanied by secondary amyloidosis and glomerulonephritis in a patient with rheumatoid arthritis

Shunsuke Yamada · Akihiro Tsuchimoto · Yoshiki Kaizu ·
Masatomo Taniguchi · Kosuke Masutani · Hiroshi Tsukamoto ·
Hiroaki Ooboshi · Kazuhiko Tsuruya · Takanari Kitazono

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Abstract Rheumatoid arthritis (RA) is an autoimmune-mediated systemic disorder that primarily affects the musculoskeletal system. Patients with RA often present with kidney diseases, such as nephrotic syndrome. Causes of nephrotic syndrome include membranous nephropathy, IgA nephropathy and secondary amyloidosis. Recently, biological agents, including anti-tumor necrosis factor alpha and anti-interleukin 6 (IL-6) receptor antibodies, have been used for the treatment of RA. Anti-IL-6 receptor antibody therapy is believed to ameliorate RA-related kidney diseases, as IL-6 plays a central role in the pathogenesis of RA. We, herein, present the case of a patient with RA and related nephrotic syndrome whose proteinuria completely disappeared 1 month after tocilizumab treatment. A light microscopic examination of the pretreatment kidney biopsy specimen showed active glomerulonephritis with fibrocellular crescents and the deposition of amorphous substances stained weakly with hematoxylin–eosin

and strongly with the Dylon method. Electron microscopy revealed the accumulation of microtubules ranging from 10 to 20 μm in width, primarily in the mesangial lesion. Amyloid A (AA) protein was positively stained in the mesangial area and vascular wall on immunohistochemistry. The final histologic diagnosis was RA-related glomerulonephritis and secondary AA amyloidosis. This case indicates that biological treatment targeting IL-6 is a promising therapeutic option for the treatment of kidney diseases associated with RA.

Keywords AA amyloidosis · Glomerulonephritis · Interleukin-6 · Nephrotic syndrome · Rheumatoid arthritis · Tocilizumab

Introduction

Rheumatoid arthritis (RA) is a collagen vascular disorder characterized by persistent synovitis, systemic inflammation and the development of autoantibodies and often manifests as joint pain [1]. RA is often accompanied by various organ disorders, including kidney disease [2]. Previous histological analyses have identified a wide variety of glomerular and tubulointerstitial lesions related to RA, including renal amyloidosis and membranous nephropathy [3, 4].

Recent significant advances in the development of biological agents have drastically altered the management of RA [5–7]. These drugs include anti-human interleukin-6 (IL-6) receptor and tumor necrosis factor- α (TNF- α) inhibitors. Clinical studies have reported that treatment with biological agents can reduce the level of proteinuria and improve the decreased kidney function observed in patients with autoimmune-mediated disorders [8–14].

S. Yamada · A. Tsuchimoto · Y. Kaizu · M. Taniguchi ·
K. Masutani · K. Tsuruya · T. Kitazono
Department of Medicine and Clinical Science, Graduate School
of Medical Sciences, Kyushu University, Fukuoka, Japan

S. Yamada · H. Ooboshi
Department of Internal Medicine, Fukuoka Dental College,
Fukuoka, Japan

H. Tsukamoto
Department of Medicine and Biosystem Science, Graduate
School of Medical Sciences, Kyushu University, Fukuoka, Japan

K. Tsuruya (✉)
Department of Integrated Therapy for Chronic Kidney Disease,
Graduate School of Medical Sciences, Kyushu University, 3-1-1
Maidashi, Higashi-ku, Fukuoka 812-8582, Japan
e-mail: tsuruya@intmed2.med.kyushu-u.ac.jp

We herein describe the case of a RA patient with glomerulonephritis and renal amyloidosis whose nephrotic-range proteinuria rapidly and completely disappeared 1 month after treatment with tocilizumab, a monoclonal antibody against IL-6 receptor, which has recently become available for the treatment of RA [7].

Case

A 71-year-old female was hospitalized for the evaluation and treatment of nephrotic syndrome. At 56 years of age, she was diagnosed to have chronic hepatitis caused by the hepatitis C virus. At age 66, she had been diagnosed with RA in the wake of joint pain in the right wrist and bilateral knees, which was treated with prednisolone and bucillamine (100 mg/day) for 4 years. She had never received anti-TNF- α treatment before. Bucillamine was discontinued 6 months before admission, because the arthralgia and serum inflammatory response were very mild. Although the patient stopped bucillamine treatment, she continued the oral prednisolone treatment (3 mg/day). Four months prior to admission, the patient developed progressive pitting edema in the bilateral lower extremities, followed by a low serum albumin level (2.0 g/dL), severe proteinuria (>3.5 g/dL) and increased serum creatinine level (0.87 mg/dL).

Upon hospitalization, the patient was alert. Her physical conditions were as follows: height 141 cm, body weight 49.5 kg, blood pressure 144/72 mmHg, heart rate 70 beats per min, her body temperature 35.8 °C, and respiratory rate 12 breaths/min. A physical examination revealed severe pretibial pitting edema bilaterally. No skin lesion was observed. Joint deformities were mild. Biochemical studies showed a white blood cell count of 6,430/ μ L with 80.4 % neutrophils and 13.2 % lymphocyte (848/ μ L), a hemoglobin level of 11.5 g/dL and a platelet count of 17.4×10^5 / μ L. The blood urea nitrogen level was 30 mg/dL, the serum creatinine level was 0.89 mg/dL, the serum albumin level was 2.0 g/dL, the total protein level was 5.6 g/dL, the serum sodium level was 139 mmol/L, the potassium level was 4.6 mmol/L, the chloride level was 106 mmol/L and the C-reactive protein level was 1.18 mg/dL. The serum total cholesterol level was 194 mg/dL, high-density lipoprotein level was 37 mg/dL, and the triglyceride level was 100 mg/dL. The complement (C) 3 level was 63 mg/dL (N; 71–135), the C4 level was 11 mg/dL (N; 11–36), the CH50 level was 36 U/mL (N; 20–50) and the rheumatoid factor level was 358 U/L, anti-nuclear antibodies were negative, PR3-antineutrophilic cytoplasmic antibodies (ANCA) were negative, MPO-ANCA were negative, the serum amyloid A (SAA) level was 36.7 μ g/mL, the double-strand DNA level was 16.4 U/mL (N; <10.0), the immunoglobulin (Ig) G level was 1,056 mg/dL, the IgA level was 495 mg/dL

and the IgM level was 198 mg/dL. Serum cryoglobulin was negative. The serum matrix metalloproteinase-3 level was 223 ng/mL. The serum thyroid-stimulating hormone level was 2.64 μ U/mL and the serum-free T4 level was 1.26 ng/dL. A tuberculin test was negative; however, an interferon-gamma releasing test was positive. A dipstick test for urine showed 3+ positive for proteinuria and 3+ positive for hematuria. Urinary sediment revealed red blood cells (30–40 cells/high power field, HPF), white blood cells (20–30 cells/HPF), epithelial cells (5–6 cells/HPF) and granular casts (2–3 cells/HPF). The total urinary protein excretion over 24 h was 4.3 g/day, and the selectivity index was 0.17. A radiographic examination revealed slight joint destruction. Meanwhile, echocardiography demonstrated no granular sparkling signs, and an endoscopic biopsy of the duodenum revealed no amyloid deposition.

A percutaneous kidney biopsy was performed to determine the histological diagnosis of nephrotic syndrome and decline in the renal function. Periodic acid–Schiff staining of the specimen included 19 glomeruli, five of which exhibited global sclerosis. A moderate level of mesangial expansion with proliferation was observed in eight glomeruli, with endocapillary proliferation in two glomeruli (Fig. 1a, b). Four glomeruli showed segmental sclerosis with fibrocellular crescents (Fig. 1b, c). Amorphous structures stained slightly with periodic acid–Schiff staining were observed in the mesangial area of the glomeruli (Fig. 1a, b). The amorphous substances were positively stained according to the Dylon method (Fig. 1d), indicating the presence of amyloid fibril deposition. No wire loop lesions were observed. A moderate degree of cellular infiltration, interstitial fibrosis and tubular atrophy were observed. Some of the interlobular arteries demonstrated severe intimal fibrous thickening with mild hyaline degeneration. An immunofluorescence study showed granular deposition of C1q (1+), C3 (1+), IgG (1+), IgA ($\pm$), IgM (1+), kappa light chain ($\pm$) and lambda light chain (1+) in the mesangial lesion (Fig. 2). Immunohistochemistry disclosed positivity for SAA proteins in the mesangial area and the walls of small arteries (Fig. 1e). Electron microscopy revealed microfilament deposition, ranging from 10 to 20 nm in width, primarily in the mesangial area, as well as diffuse foot process effacement and enlargement of endothelial cells (Fig. 3a, b). However, electron dense deposits, including subepithelial deposits, a finding suggestive of membranous nephropathy, were not observed. The final diagnosis was renal AA amyloidosis and glomerulonephritis with crescent formation.

A summary of the patient's clinical course is shown in Fig. 4. After hospitalization, treatment with losartan (25 mg/day) was initiated, leading to decreases in the blood pressure (around 120/60) and proteinuria (2 g/day). To further control the activity of RA and the RA-related

Fig. 1 Histology of the renal biopsy specimen. **a** A representative photomicrograph of a periodic acid–Schiff-stained section showing deposits of an amorphous substance in the mesangial lesion with endocapillary and mesangial proliferation (original magnification, $\times 200$). **b** A photomicrograph of periodic acid–Schiff staining showing deposition of an amorphous substance in the vascular pole as well as mesangial hypercellularity with small crescents (original magnification, $\times 200$). **c** A photomicrographs of periodic acid–methenamine silver staining showing fibrocellular crescent formation (original magnification, $\times 200$). **d** A photomicrograph of Dylon staining showing the presence of amyloid fibrils in the mesangial lesion (original magnification, $\times 200$). **e** A photomicrograph of immunohistochemical staining for serum amyloid A proteins. Note that amyloid A proteins were observed in the mesangial lesion and small vessel walls (original magnification, $\times 200$)

proteinuria, the administration of tocilizumab (8 mg/kg, 385 mg/body) every 4 weeks was initiated. One month after starting treatment with tocilizumab, the patient's proteinuria decreased to 0.3 g/g creatinine, then completely disappeared 2 months later, although RA-related joint symptoms remained very mild before and after tocilizumab treatment. The SAA protein level also decreased over 1 month, reaching a stable level after 3 months. As for urinary sediments, both red blood cells and white blood cells decreased to 1–4/HPF at 2 months after tocilizumab treatment, indicating that glomerulonephritis improved significantly. Furthermore, the serum creatinine level decreased from 1.43 to 0.82 mg/dL at 3 months, then to 0.70 mg/dL at 10 months. The tocilizumab treatment was continued for 18 months at an interval of every 4 weeks. Following the cessation of tocilizumab therapy, the patient's proteinuria did not recur, and her serum creatinine level remained unchanged for over 1 year.

Discussion

Renal involvement is a common complication often observed during the course of RA [2, 3]. Previous histological examinations revealed that glomerulonephritis, renal amyloidosis and membranous nephropathy are common histological types in patients with RA [3]. In the present case, histopathology revealed several characteristic lesions, including AA amyloid deposition in the glomeruli and small arteries, mesangial and endocapillary proliferation, segmental lesions, including segmental sclerosis and fibrocellular crescents, and tubulointerstitial lesions (interstitial fibrosis, cellular infiltration and tubular atrophy). Electron microscopy showed deposition of amyloid fibrils in the mesangial lesions. However, no features indicative of membranous nephropathy, such as bubbling or thickening of the capillary walls or subepithelial electron dense deposition, were observed, although the patient had a

Fig. 2 Photomicrographs of the immunofluorescence findings of the kidney specimen. C1q (1+), C3 (1+), IgG (1+), IgA (±), IgM (1+), kappa light chain (±) and lambda light chain (1+) are positively

stained in the mesangial patterns (original magnification, ×200). C complement, Ig immunoglobulin

Fig. 3 Photomicrographs of the electron microscopic findings of the kidney specimen. **a** A photomicrograph in low magnification (original magnification, ×5,000). **b** A photomicrograph in high magnification (original magnification, ×5,000). Note the presence of amyloid fibrils (10–20 μm in width) in a haphazard arrangement in the mesangial lesion

history of bucillamine use before the onset of nephrotic syndrome. Consequently, the proteinuria observed in the present case can be attributed to AA amyloidosis and glomerulonephritis related to RA.

Renal amyloidosis is often observed in RA patients [3]. In the present case, a microstructure, which is considered to reflect the deposition of SAA, was observed in the mesangial lesions and vascular walls in a haphazard arrangement. The overproduction of SAA proteins in the liver results in the accumulation of amyloid fibrils in the kidneys in patients with various chronic inflammatory diseases

[15]. Because increased production of IL-6 plays an important role in the synthesis of SAA proteins [16], it is reasonable to consider that the active control of the serum IL-6 concentration at a lower level is a promising treatment strategy for preventing the progression of amyloidosis secondary to RA. Indeed, previous studies have reported that treatment with anti-IL-6 receptor antibodies decreases the SAA level and mitigates RA-related amyloidosis [10, 11]. These results indicate that in the present case, from an ethical point of view, we did not perform the additional renal biopsy to confirm the reduction or disappearance of

Fig. 4 Clinical course before and after tocilizumab therapy. BP blood pressure, Cr creatinine, SAA serum amyloid A, Up/Ucr urinary protein–creatinine ratio. The black bar shows the duration of hospitalization. The black arrows indicate the intravenous administration of tocilizumab every 4 weeks

amyloid deposition in the glomeruli. Interestingly, the time to remission after tocilizumab treatment was only 1 month. Indeed, the SAA protein level reached its baseline value at 3 months after tocilizumab treatment, 2 months after the remission of nephrotic syndrome. Given that the development of nephrotic-range proteinuria related to amyloidosis often requires a much longer duration [11], these results suggest that the effects of tocilizumab on nephrotic-range proteinuria can be partly directed toward another pathophysiology, as observed in the present case.

Another potential mechanism underlying the remission of proteinuria is the involvement of RA-related glomerulonephritis. Previous studies have shown that proliferative glomerulonephritis is a common histological type in patients with RA [3]. In addition, several cytokine networks, including IL-6, play critical roles in the pathogenesis of RA and RA-related glomerulonephritis [17, 18]. In fact, Brandt et al. [19] reported glomerular enlargement and mesangial proliferation in a mouse model of IL-6 overproduction. With regard to the clinical settings, Castleman's disease, which is a state of IL-6 overproduction, presents various types of renal involvement, including membranoproliferative glomerulonephritis, membranous nephropathy, mesangial proliferative glomerulonephritis and crescentic glomerulonephropathy [20]. Furthermore, electron microscopy of the kidneys in patients with Castleman's disease showed foot process effacement, endothelial proliferation, endothelial swelling, subendothelial widening and a wrinkled GBM; some of these findings are compatible with our case, indicating the direct role of IL-6 in the pathogenesis of RA-related glomerulonephritis. However, because platelet-derived growth factor also plays

a central role in the pathogenesis of Castleman's disease, all of the histological findings described above could not be explained by IL-6 overproduction. In addition, because a complex cytokine network might be involved in the pathogenesis of RA-related glomerulonephritis, further studies are needed to clearly demonstrate the causal relationship between IL-6 and RA-related histological findings.

There are other potential diseases that could explain the histological findings in the present case; lupus nephritis, IgA nephropathy, and cryoglobulinemic glomerulonephritis. The present case might have been complicated with systemic lupus erythematosus (SLE), namely overlap syndrome, because she fulfilled the criteria for SLE set by the American Society for Rheumatology (arthritis, proteinuria, lymphocytopenia and positive for double-stranded DNA). In this regard, tocilizumab could have ameliorated the lupus nephritis in the present case. IL-6 plays critical roles in the pathogenesis of SLE [21]. However, because the patient had been suffering from chronic liver dysfunction, and showed incompatible findings (negativity for anti-nuclear antibodies, absence of wire-loop lesions and electron dense deposit by histology, absence of other SLE-related clinical symptoms, relatively low coincidence of lupus nephritis and AA amyloidosis) [22], we believe that even if SLE was present, the glomerulonephritis and renal amyloidosis were related to RA, although we could not completely rule out the possibility of the coincidental development of SLE. With regard to IgA nephropathy, because IgA was not dominant in the immunofluorescence study, we do not think that IgA nephropathy was the cause of the present renal manifestation. Lastly, serum cryoglobulin was negative, and light microscopic findings were not typical presentation of

cryoglobulinemic glomerulonephritis. Besides, the size and shape of electron dense deposit were not compatible with cryoglobulinemic glomerulonephritis. Accordingly, we believe that AA amyloidosis and RA-related glomerulonephritis were the primary cause of renal histology in the present case.

Our case raises an important issue whether crescent formation in patients with AA amyloidosis reflects the secondary lesions accompanied by AA amyloid deposition or the distinct lesion of glomerulonephritis related to RA. We previously reported 13 cases of renal AA amyloidosis associated with crescent formation, where 12 of the 13 patients were affected by RA [23], indicating that crescent formation in RA patients may be caused by abnormal immunological features of RA, not by amyloid deposition. We speculated that presence of amyloid deposition aggravates crescent formation by unknown mechanisms. However, several lines of evidence have highlighted the co-existence of AA amyloid deposition and crescent formation in various underlying diseases for renal amyloidosis other than RA, indicating that crescent formation may be secondary to amyloid deposition independent of RA [24, 25]. Therefore, further studies are needed to clarify whether the marked reduction of proteinuria observed after tocilizumab treatment can be attributable to the amelioration of AA amyloidosis or of non-AA amyloid-related glomerulonephritis.

Based on the pathogenesis of RA [16, 17], several types of biological agents are available for the treatment of RA, including anti-TNF- α and anti-IL-6 receptor antibodies. In the present case, we selected tocilizumab for the treatment of RA-related nephrotic syndrome. There are some reasons to select anti-IL-6 receptor antibodies. First, IL-6 has been shown to be more important than TNF- α in the pathogenesis of RA [26, 27]. Second, the synthesis of SAA is primarily regulated by IL-6 [15]. To prevent further progression of secondary amyloidosis related to RA, blocking IL-6 signaling is most important. However, importantly, some patients develop de novo glomerulonephritis induced by treatment with biological agents, including anti-IL-6 antibodies [28, 29]. Hence, further studies are needed to confirm which biological agent is more useful and safe for the treatment of renal involvement in patients with RA.

In summary, we herein presented the case of an RA patient with AA amyloidosis and RA-related glomerulonephritis whose nephrotic-range proteinuria disappeared completely following the administration of tocilizumab therapy. Treatment with biological agents, including tocilizumab, has the potential to safely improve RA-related glomerulonephritis and ameliorate proteinuria and may be promising therapeutic strategy for treating RA-related renal involvement in patients with RA.

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