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Tocilizumab improves obesity-related glomerulopathy associated with rheumatoid arthritis

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ABSTRACT

Background: The incidence of obesity-related glomerulopathy (ORG), often progressing to end-stage kidney disease, has been increasing in developed countries. Thus, establishing successful treatment for ORG is critical. ORG is associated with inflammation; however, to date, no successful treatment for this condition has been reported. Tocilizumab, a humanised monoclonal antibody against the interleukin-6 (IL-6) receptor, has not yet been reported to be effective in treating glomerulopathy. Here we report the first case of ORG associated with rheumatoid arthritis (RA) that favourably responded to tocilizumab.

Case Presentation: A 69-year-old Japanese woman presented with pain in her left knee. She was diagnosed as having RA following a biopsy using an arthroscope, and seropositivity for RA was indicated by high RA hemagglutination levels. Treatment with methotrexate (4 mg/d) and prednisolone (10 mg/d) was initiated. After 4 months, the patient presented with proteinuria of 4.7 g/d. Following her admission to the hospital, a kidney biopsy was performed, which revealed that glomerular size >250 µm. However, the glomeruli did not demonstrate obvious membranous changes, and cell proliferation was not noticeable. Immunofluorescence assessment did not demonstrate negative staining. Furthermore, Congo red staining results were negative. The apparent histological characteristics included glomerular hypertrophy only. According to marked obesity (body mass index [BMI]; 35.1 kg/m^2), we diagnosed the condition as ORG. Following this, when RA activity increased, we added infliximab to her therapeutic regime. It was effective for treating RA but had no effect on proteinuria. During this time, the body weight of the patient had increased from 76.8 kg to 92 kg. Although RA activity had ceased, we attempted a switch from infliximab to tocilizumab since proteinuria was still unresolved. After the treatment, nephrotic-range proteinuria improved significantly.

Conclusions: This case suggests that tocilizumab may be a new therapeutic option in cases of ORG that have a strong inflammatory component.

Case Report

Implication for health policy/practice/research/medical education:
This case suggests that tocilizumab may be a new therapeutic option in cases of obesity-related glomerulopathy which have a strong inflammatory component.

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1. Background

Obesity is a growing concern among developed nations, with approximately 30% of the Japanese adult men classified as obese in the 2010s. Furthermore, a high body mass index (BMI) increases the risk for developing end-stage kidney disease (1). Therefore, conducting research on kidney injuries associated with obesity is important. Kambham et al (2) first reported on obesity-related glomerulopathy

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(ORG). The characteristics of ORG are adiposity with BMI of >30 kg/m^2, proteinuria without oedema, and normal serum albumin levels, if nephrosclerosis and diabetic nephropathy are excluded. The pathophysiology of ORG has been described as glomerular hyperfiltration because of hypertension, hyperinsulinemia, and nephron mass-body size mismatch (2-4). However, its mechanism has not been completely understood. The standard treatment for ORG complicated with sleep apnoea syndrome is reduction in weight and improvement of oxygenation (5). However, Wu et al (6) reported that the association between ORG and inflammation was intriguing and that a therapeutic treatment that reduces inflammation is not currently established for ORG.

Tocilizumab, a humanised monoclonal antibody against the interleukin-6 (IL-6) receptor, is a biological agent approved for treating rheumatoid arthritis (RA) and is effective for treating nephritis, as observed in cases of kidney injury due to Castleman's disease, ANCA-associated glomerulonephritis in RA patients, crescentic glomerulonephritis in RA patients, and AA amyloidosis complicated by familial Mediterranean fever (7-10). However, there appear to be no reports on the effectiveness of tocilizumab in treating glomerulopathy.

Here we report the first case of ORG associated with RA that favourably responded to tocilizumab.

2. Case Presentation

A 69-year-old Japanese woman presented with pain in her left knee in 2003 and was initially diagnosed as having RA following a biopsy using an arthroscope in a previous hospital. She was diagnosed with seropositive RA since the measured RA hemagglutination levels were 1280-fold higher than the normal values. Treatment with methotrexate (4 mg/d) and prednisolone (10 mg/d) was initiated. After 4 months, the patient presented with proteinuria (4.7 g/d) and was consequently admitted to Chiba-east National hospital for kidney biopsy. Patient had no medical history except RA and no family history of hypertension or diabetes mellitus. She was a non-smoker. On admission, her physical examination results were as follows; height, 160.5 cm, body weight (BW); 76.8 kg, BMI; 35.1 kg/m^2 (very high), and blood pressure (BP); 121/80 mm Hg (normal). Possibly because of prednisolone, her BW had increased by 10 kg prior to admission. She demonstrated considerable abdominal distension. There was no oedema in the lower extremities. Swelling and tenderness in the elbow joint were observed. The laboratory test results were: haemoglobin, 12.3 g/dL (normal); serum albumin, 3.3 g/dL (slightly low); serum creatinine, 0.50 mg/dL; total cholesterol, 207 mg/dL (normal); and C-reactive protein, 3.7 mg/dL (high). A urine test revealed that proteinuria (0.45 g/d) reduced after admission. Serological testing revealed a matrix metalloproteinase-3 level of 715 ng/mL, serum amyloid A, level of 94.4 μg/mL, and anti-galactose-deficient immunoglobulin (Ig) G antibody level of 481 AU/nL. Kidney sizes were within the normal range, as measured using ultrasonography.

We also performed a kidney biopsy; however, we could not use only one specimen because of the patient's marked obesity. Kidney biopsy results are shown in Figure 1. Six glomeruli were obtained, one of them was glomerular sclerosis. The glomerular size was >250 μm (Figure 1A). Furthermore, there was a conspicuous dilatation of the glomerular capillary. The glomeruli did not demonstrate obvious membranous changes, cell proliferation, or adhesion, and tubulointerstitial and vascular lesions were not noticeable. Immunofluorescence assessment demonstrated negative staining for IgG, IgA, IgM, C3 and C1q. Congo red staining and amyloid A staining results were both negative (Figures 1B and 1C). A specimen for electron microscopy (EM) could not be obtained. The only apparent histological characteristic was glomerular hypertrophy. Based on BW, we diagnosed the condition as ORG.

Following this, the patient could not lose BW because of the RA-induced activity limitation and use of prednisolone. Her proteinuria was 2+ using urine qualitative (The proteinuria was not evaluated using g/gCr during a period of 3.5 years from 2004 to 2007). In 2007, when the RA activity increased, infliximab was added to the therapeutic regimen. It was effective for treating RA but did not affect proteinuria. During this time, the body weight of the patient had increased to 92 kg in 2008. Therefore, we considered performing a second biopsy of the kidneys. Although RA was inactive, we attempted a switch

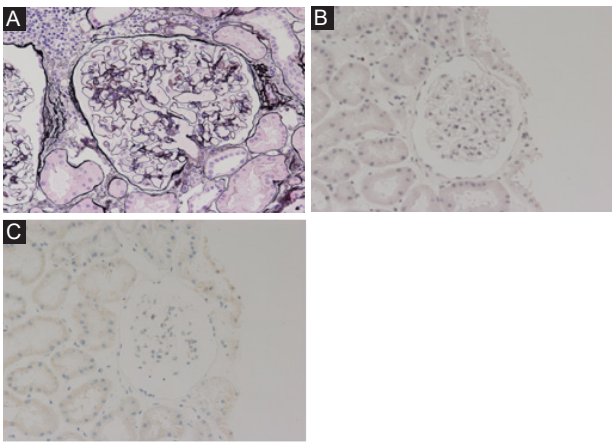

Figure 1.

from infliximab to tocilizumab in 2010 as proteinuria continued. One month after initiating tocilizumab treatment, proteinuria was resolved. However, neither the RA activity nor BW changed (Figure 2). Following this intervention, no adverse drug events occurred, and a complete remission of proteinuria was maintained for 30 months. In addition, the estimated glomerular filtration rate reduced moderately. Subsequently, she died of an unknown cause.

3. Discussion

The mechanism of ORG has not been completely understood previously, and it was generally believed that the main mechanism underlying ORG was glomerular hyperfiltration. However, ORG has been associated with glomerular hyperfiltration and inflammation, with the typical inflammatory cytokines being IL-6 and tumour necrosis factor-alpha (TNF-α). As mentioned earlier, there were several previous reports regarding tocilizumab efficacy (7-10). However, this efficacy may have been mediated by its ability to suppress IL-6. In the experimental studies, IL-6 receptor blockage ameliorated murine lupus nephritis (11) and also exacerbated crescentic glomerulonephritis (12). To date, the role of IL-6 in kidney diseases has been controversial, with IL-6 contributing to various kidney diseases. Conversely, with respect to TNF-α, anti-TNF-α therapy was effective in treating renal ischaemia perfusion injury in mice (13). Bitzan et al (14) also reported that a patient with recurrent focal segmental glomerulosclerosis after kidney transplantation achieved sustained partial remission of proteinuria after anti-TNF-α therapy. However, anti-TNF-α therapy was not effective in our case. When the RA activity, BW, and BP were stable, proteinuria improved after we switched the treatment from infliximab to tocilizumab. Thus, we can conclude that ORG in this patient had improved because of the therapeutic efficacy of tocilizumab. We propose two possible underlying mechanisms to explain this result.

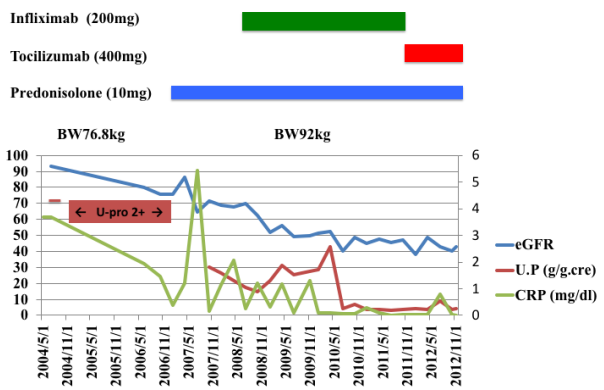

Figure 2.

The first mechanism is the improvement of glomerular hypertension. Podocyte depletion that results from glomerular hypertension and hyperinsulinemia was considered a cause of secondary focal segmental glomerulosclerosis because of ORG (15). In mice, IL-6 deficiency blunted the increases in BP, which was induced by angiotensin II (16). In this case, the patient's blood pressure was normal, but glomerular blood pressure could have been high as the glomeruli were markedly dilated. Glomerular hypertension is associated with mechanical stress in podocytes. Tocilizumab could ameliorate the injury to podocytes because of glomerular hypertension by suppressing the general inflammation and angiotensin II production. This is consistent with the finding that the patient experienced complete remission immediately after the treatment was changed. The second possible mechanism is the improvement in metabolism. In our case, we considered that the abnormal glucose tolerance combined with obesity and the use of steroids contributed to podocyte damage. Obesity induces production of abnormal adipokines such as IL-6 and adiponectin (17). Sharma et al (18) reported that adiponectin replacement attenuated albuminuria. Furthermore, tocilizumab improved the insulin resistance and serum adiponectin levels (19). IL-6 is associated with inflammation and insulin sensitivity. Therefore, IL-6 blockage could attenuate ORG. However, this case has few limitations. First, we did not measure serum IL-6 and TNF-α levels. Although the RA activity, when we switched from infliximab to tocilizumab, was low, we considered that tocilizumab had improved ORG. However, we may have observed not only a specific effect of tocilizumab but also a general improvement in inflammation because of tocilizumab-mediated serum IL-6 suppression. Second, there is a direct association between podocytes and IL-6. IL-6 secreted by podocytes in response to inflammatory agents, such as TNF-α and lipopolysaccharide (LPS), can protect against the renal injury (20,21). Moreover, the mice deficient for gp130, the common signal-transducing receptor subunit of the IL-6 family of cytokines, in podocytes showed no histological differences stimulated by LPS and nephrotoxic serum compared with the control mice (22). Podocytes play an important role in proteinuria resulting from ORG. However, we could not explain the efficacy of tocilizumab by its effect on podocytes alone. Third, we could not obtain the EM images. We could have diagnosed ORG correctly had we observed the degree of foot process effacement. The patient might have minimal change disease with spontaneous revision. However, the patient's proteinuria improved when she rested and was administered dietary therapy during her hospital stay. In addition, although she had nephrotic-range proteinuria, she did not have nephrotic syndrome. Thus, the proteinuria could have resulted due to her haemodynamic state. Therefore, we

believe that the pathological diagnosis was ORG and that proteinuria was resolved due to tocilizumab.

4. Conclusions

We have reported the first case of successful treatment of ORG associated with RA using tocilizumab. Thus, tocilizumab may be useful in cases of ORG with a strong inflammatory component.

Author' contribution

TS and YS designed the manuscript. RM participated in the interpretation of patient data. HK made the pathological diagnosis. EO examined additional information of the patient. All authors have approved the final manuscript.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors. Informed consent was obtained from the patient for report.

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