Single low-dose rituximab for the treatment of steroid-resistant nephrotic syndrome with acute kidney injury

Eijin Ashikaga¹ · Susumu Uda¹ · Kazuhisa Kamata^{1,2} · Yasuto Shikida¹ · Takashi Inoue¹ · Yoshihiro Kuno¹ · Atsushi Yao¹ · Mari Nakamura¹ · Keiko Kai¹

Received: 31 May 2014 / Accepted: 30 July 2015 / Published online: 25 March 2016
© Japanese Society of Nephrology 2016

Abstract The efficacy of rituximab for kidney disease, such as frequent relapsing nephrotic syndrome, has been reported recently. Herein, we report a case of a patient with acute kidney injury that was steroid-resistant nephrotic syndrome who responded to a single administration of low-dose rituximab. An 86-year-old Japanese woman with hypertension presented with severe peripheral edema within several days after onset. Due to the patient's age, renal biopsy was not performed, nephrotic syndrome was diagnosed and prednisolone was administered at 40 mg/day on the day after admission. However, anuria developed and hemodialysis was inevitably initiated on the 5th hospital day. The renal function did not recover, and the general condition gradually became aggravated. On the 50th hospital day, 100 mg rituximab was administered, which led to immediate depletion of CD20-positive cells. The urine volume gradually increased from 2–3 weeks after the rituximab administration, and the renal function recovered slightly. After 5 weeks, it became possible to wean the patient from dialysis, which had been applied for 3 months. Rituximab might be an option for the treatment of acute kidney injury due to steroid-resistant nephrotic syndrome.

Keywords Rituximab · Steroid-resistant nephrotic syndrome · Acute kidney injury

Introduction

Rituximab is a therapeutic drug that was recently developed for non-Hodgkin's B cell lymphoma, and its efficacy against other autoimmune diseases, such as rheumatoid arthritis and vasculitis, has been confirmed. Thus, this drug is now used as a new treatment for these diseases. With respect to the efficacy against glomerular disease, rituximab has been reported to be effective for pediatric frequently relapsing and steroid-dependent nephrotic syndromes [1].

We encountered an adult patient with steroid-resistant nephrotic syndrome who underwent 3 months of hemodialysis for acute kidney injury (AKI). Single administration of low-dose rituximab improved the renal function in this patient and led to weaning from hemodialysis.

Case report

An 86-year-old woman developed severe bilateral peripheral edema within several days in mid-May 2012, and she was admitted to our hospital in late May. She had been treated at an outpatient clinic for hypertension since she was 77 years old and a thoracic aortic aneurysm was discovered at 79 years of age.

Upon admission, the height was 141 cm; body weight, 44 kg (40 kg prior to the development of edema); body temperature, 35.5 °C; blood pressure, 131/61 mmHg; and pulse, 48/min. Upon physical examination, no cardiac murmur was heard, the lung sound was clear, the abdomen was flat and soft, and no skin eruption or neurological abnormality was noted. Marked edema was noted in the bilateral legs, and no superficial lymph nodes were palpated.

✉ Susumu Uda
suda9682@yahoo.co.jp

¹ Division of Nephrology, Kanto Rosai Hospital, 1-1 Kizukisumiyoshi-cho, Nakahara-ku, Kawasaki 211-8510, Japan

² Tanaka Medical Clinic, Kawasaki, Japan

In laboratory tests upon admission, the serum total protein level was 5.2 g/dL; serum albumin, 2.0 g/dL; total cholesterol, 334 mg/dL; and serum creatinine, 2.45 mg/dL (0.5 mg/dL 3 months ago), indicating renal dysfunction (Ccr 15.6 mL/min). Anti-nuclear antibody was negative, and there was no sign of hypocomplementemia. M-protein and free light chain were not detected. No hematuria was observed, and urinary protein was 10.0 g/day (Table 1). Based on these findings, the patient was diagnosed with nephrotic syndrome. The urinary selectivity index was 0.18, showing high selectivity, and Bence Jones protein was negative. Both urine sodium and chloride levels were below 20 mEq/L, and the fractional excretion of urea was 12.2 %. Urine *N*-acetyl- β -D-glucosaminidase (NAG) and α 1 microglobulin (MG) levels were increased to 85.2 U/L and 32.9 mg/L, respectively (Table 1). On abdominal CT and ultrasonography, no atrophy was noted in either kidney. These findings suggested that the renal dysfunction was due to AKI, rather than chronic kidney disease.

Since the patient was elderly, renal biopsy was considered a high risk and was not performed. However, we generally assumed her case to be minimal change nephrotic syndrome (MCNS), because the disease development was acute, no hematuria was observed, and urinary protein was highly selective. For treatment of the nephrotic syndrome, prednisolone was administered at 40 mg/day on the day after admission. A diuretic was administered for the edema,

but no diuresis was achieved, and the edema gradually became exacerbated. The renal dysfunction progressed and nearly reached anuria, for which hemodialysis was initiated on the 5th hospital day, and was repeated 3 times per week. However, the anuria persisted and D-dimer increased to 11.9 μ g/mL. Since renal arterial embolism derived from the mural thrombus in the thoracic aortic aneurysm and renal venous thrombosis were also considered as potential causes of the anuria, contrast thoracoabdominal pelvic CT was performed on the 23rd hospital day. The thoracic aortic aneurysm was mostly thrombosed. No thrombus was detected in the renal artery or vein, and the cortical blood flow was retained, ruling out the influence of a thrombus as the cause of anuria (Fig. 1).

While steroid administration with prednisolone was continued at 40 mg/day for 4 weeks, including pulse therapy (500 mg of methylprednisolone for 3 days), the anuria persisted. Based on this, the disease was diagnosed as steroid-resistant nephrotic syndrome, and prednisolone treatment was tapered from the 33rd hospital day and discontinued at the 64th hospital day in consideration of the potential for adverse effects. Meanwhile, the complications of small cerebellar infarction and duodenal ulcer had developed. Total parenteral nutrition was initiated on the 20th hospital day, because oral ingestion, including the administration of oral medication, became virtually impossible. We were unable to select an oral

Table 1 Laboratory data on admission

Complete blood count		Blood chemistry				Urinalysis/renal function	
WBC	4700/ μ L	TP	5.2 g/dL	T-Cho	334 mg/dL	Gravity	1.031
Neutro	63.4 %	Alb	2.0 g/dL	TG	254 mg/dL	pH	6.5
Lym	23.7 %	Cr	2.45 mg/dL	LDL-C	236 mg/dL	Protein	10.0 g/day
Mono	8.7 %	UN	57 mg/dL	HDL-C	61 mg/dL	Selectivity index	0.18
Eosino	3.8 %	UA	8.6 mg/dL	CK	104 IU/L	RBC	<1/HPF
Baso	0.4 %	T-bil	0.4 mg/dL	HbA1c	5.9 % (NGSP)	WBC	10–19/HPF
RBC	$407 \times 10^4/\mu$ L	AST	22 IU/L	IgG	1104 mg/dL	Granular cast	1–9/LPF
Hb	13 g/dL	ALT	12 IU/L	IgA	324 mg/dL	Hyaline cast	10–99/LPF
Ht	38.1 %	LDH	292 IU/L	IgM	134 mg/dL	Na	<20 mEq/L
Plt	$17.5 \times 10^4/\mu$ L	ALP	228 IU/L	IgE	507 IU/mL	Cl	<20 mEq/L
Coagulation		γ GTP	25 IU/L	C3	110 mg/dL	FEUN	12.2 %
		Na	127 mEq/L	C4	33 mg/dL	NAG	85.2 U/L
		K	5.9 mEq/L	CH50	>60.0 CH50/mL	α 1MG	32.9 mg/L
		Cl	97 mEq/L	ANA	<40 $\times$	Bence Jones protein	(–)
		Ca	8.1 mg/dL	RF	<7.0 IU/mL	Ccr	15.6 mL/min
		P	6.4 mg/dL	TSH	2.241 μ IU/mL		
		Glu	102 mg/dL	RPR	(–)		
		CRP	0.12 mg/dL	HBsAg	(–)		
		BNP	50 pg/mL	HCV	(–)		
		CEA	4.6 ng/mL	HIV	(–)		
		CA19-9	34.9 U/mL

Fig. 1 Abdominal CT: no thrombus was detected in the renal artery or vein, the contrast effect on the cortex was retained, and no atrophy of the kidney was observed. Severe subdermal edema was evident around the trunk

anticoagulation therapy for prevention of thrombosis, and we were only able to administer intravenous drugs for her nephrotic syndrome. One and half months had passed since the initial admission, but the anuria still persisted. The serum albumin level remained at about 1.5 g/dL, malnutrition was severe, and the patient gradually became weak and bedridden. Despite the administration of albumin during dialysis, maintenance of the blood pressure became difficult, and continuation of the dialysis became difficult.

On the 50th hospital day, a single infusion of 100 mg rituximab was administered with 20 mg prednisolone, after obtaining written informed consent from the family, because use of this agent for nephrotic syndrome is off-label in our country. This protocol and the consent documents were approved by the ethics committee of Kanto Rosai Hospital. CD20-positive cells were depleted rapidly thereafter. The urine volume started to increase gradually from 2–3 weeks after administration, and reached a sufficient volume at 5 weeks after administration. Withdrawal of dialysis, which had been ongoing for about 3 months,

then became possible. The food intake increased, and the patient was able to actively participate in rehabilitation. She was discharged in a wheelchair to home on the 133rd hospital day. Five months after rituximab administration, the urinary protein decreased to 0.3 g/day, and serum albumin improved to 2.9 g/dL (Fig. 2). Furthermore, she maintained a partial remission (urinary protein 0.3–0.6 g/gCr) 32 months after rituximab administration, although her B cell number was fully restored.

Discussion

The nephrotic syndrome in this patient was likely due to MCNS based on the course. However, the possibility of focal segmental glomerulosclerosis or membranous nephropathy remains, because we did not perform a renal biopsy to diagnose this precisely. Nephrotic syndrome is classified into steroid-sensitive nephrotic syndrome, which responds favorably to steroids, and steroid-resistant nephrotic syndrome, for which 4-week administration of steroid at a normally sufficient dose is ineffective. Therefore, the disease was diagnosed as steroid-resistant nephrotic syndrome in this case.

Some cases of nephrotic syndrome, in particular MCNS, progress to AKI, and may advance to renal dysfunction requiring renal replacement therapy in adults, compared to the more benign course with pediatric cases [2–5]. Higher risks have been reported in men with lower serum albumin and proteinuria, the elderly, and in hypertensive patients [5]. The cause of AKI in nephrotic syndrome remains unclear, but influences include decreases in glomerular permeability [6, 7], ischemia-associated tubular injury [3–5, 8], diuretic administration [9, 10], and renal venous thrombosis [11]. In this patient, the presence of an underlying prerenal factor was considered as a potential cause

Fig. 2 Clinical course: since the disease was steroid-resistant and anuria persisted, hemodialysis was continued. CD20-positive cells were rapidly depleted by rituximab administration. The urine volume increased and the renal function recovered, which led to weaning from dialysis. *mPSL* methylprednisolone, *PSL* prednisolone, *HD* hemodialysis

based on the urinary Na and Cl levels and the fractional excretion of urea. In addition, increases in urine NAG and α 1MG levels suggested the presence of interstitial injury.

We administered a single low dose of rituximab to this patient with steroid-resistant nephrotic syndrome, who developed AKI and had been treated with dialysis for about 3 months, and achieved weaning from dialysis. In this case, we considered using another immunosuppressant such as mizoribine, cyclosporine and cyclophosphamide before administration of rituximab. However, we were able to administer only intravenous drugs to her, because this patient had developed an active duodenal ulcer as a complication, along with worsened general condition. Intravenous administration of cyclosporine and cyclophosphamide is used off-label for nephrotic syndrome in our country. In addition, with cyclophosphamide it is difficult to determine an appropriate dose in conditions with renal dysfunction. Therefore, we attempted rituximab administration to avoid the need for a dose adjustment due to these conditions.

It seems that steroids were effective in reducing urinary protein before administration of rituximab as shown in Fig. 2. However, we recognized that it did not reflect an accurate amount of urinary protein, because the urine volume was only 10–50 mL/day during that period. On the other hand, the urine volume gradually increased from 2–3 weeks after rituximab administration, while steroids were tapering. Therefore, we are convinced that the most effective agent of this steroid-resistant nephrotic syndrome was rituximab.

Rituximab is an antibody against the differentiation antigen CD20, which is expressed on the surface of B cells. It is a chimeric antibody comprised of the variable region of mouse anti-human CD20 monoclonal antibody IgG1 and the constant region of human IgG1 κ . Efficacy in the treatment of adult MCNS was initially reported in 2007 [12], and the efficacy for frequently relapsing and steroid-resistant MCNS has since been reported in Japan and other countries. However, the dose and administration methods were inconsistent in these reports. In many studies, the dose (375 mg/m²) and dosing frequency (once a week, 1–4 cycles) established for the treatment of non-Hodgkin's lymphoma have been adopted [13–15]. Single administration of rituximab to dialysis patients at doses of 50, 150, and 375 mg/m² has been reported to result in no differences in the level of B cell depletion or persistence [16]. In our patient, rituximab was administered as a single low dose, and showed efficacy in decreasing CD20-positive cells similar to that achieved at high doses in the previous reports.

Since disease has been reported to recur several months after remission in response to rituximab in many patients in previous reports, additional administration may be necessary for our patient; however, the appropriate timing of

such additional administration remains unclear. Indeed, in some reports disease recurred when the number of CD20-positive cells increased, whereas no recurrence occurred and remission was maintained even after the number of CD20-positive cells increased in others [17].

At present, there is no established evidence to support rituximab administration in the treatment of steroid-resistant nephrotic syndrome, including safety and administration profiles. However, it may become a new option for patients with protracted AKI and elderly patients, such as this patient.

Conclusion

In a patient with steroid-resistant nephrotic syndrome in whom AKI developed and inevitably required 3 months of dialysis, weaning from dialysis was achieved following a single administration of low-dose rituximab. For patients who manifest steroid-resistant nephrotic syndrome, rituximab may be a treatment option.

Compliance with ethical standards

Conflict of interest The authors have declared that no conflict of interest exists.

References

- Iijima K, Sako M, Nozu K, Mori R, Tuchida N, Kamei K, et al. Rituximab for childhood-onset, complicated, frequently relapsing nephrotic syndrome or steroid-dependent nephrotic syndrome: a multicentre, double-blind, randomised, placebo-controlled trial. *Lancet*. 2014;384:1273–81.
- Nolasco F, Cameron JS, Heywood EF, Hicks J, Ogg C, Williams DG. Adult-onset minimal change nephrotic syndrome: a long-term follow-up. *Kidney Int*. 1986;29:1215–23.
- Smith JD, Hayslett JP. Reversible renal failure in the nephrotic syndrome. *Am J Kidney Dis*. 1992;19:201–13.
- Jennette JC, Falk RJ. Adult minimal change glomerulopathy with acute renal failure. *Am J Kidney Dis*. 1990;16:432–7.
- Waldman M, Crew RJ, Valeri A, Busch J, Stokes B, Markowitz G, et al. Adult minimal-change disease: clinical characteristics, treatment, and outcomes. *Clin J Am Soc Nephrol*. 2007;2:445–53.
- Vande Walle J, Mauel R, Raes A, Vandekerckhove K, Donckerswolcke R. ARF in children with minimal change nephrotic syndrome may be related to functional changes of the glomerular basal membrane. *Am J Kidney Dis*. 2004;43:399–404.
- Cameron MA, Peri U, Rogers TE, Moe OW. Minimal change disease with acute renal failure: a case against the nephrosarcoma hypothesis. *Nephrol Dial Transplant*. 2004;19:2642–6.
- Chen CL, Fang HC, Chou KJ, Lee JC, Lee PT, Chung HM, et al. Increased endothelin 1 expression in adult-onset minimal change nephropathy with acute renal failure. *Am J Kidney Dis*. 2005;45:818–25.
- Meltzer JI, Keim HJ, Laragh JH, Sealey JE, Jan KM, Chien S. Nephrotic syndrome: vasoconstriction and hypervolemic types indicated by renin-sodium profiling. *Ann Intern Med*. 1979;91:688–96.

10. Geers AB, Koomans HA, Roos JC, Dorhout Mees EJ. Preservation of blood volume during edema removal in nephrotic subjects. *Kidney Int.* 1985;28:652–7.
11. Llach F. Hypercoagulability, renal vein thrombosis, and other thrombotic complications of nephrotic syndrome. *Kidney Int.* 1985;28:429–39.
12. Francois H, Daugas E, Bensman A, Ronco P. Unexpected efficacy of rituximab in multirelapsing minimal change nephrotic syndrome in the adult: first case report and pathophysiological considerations. *Am J Kidney Dis.* 2007;49:158–61.
13. Sawara Y, Itabashi M, Kojima C, Tabata H, Kamei D, Kawanishi K, et al. Successful therapeutic use of a single-dose of rituximab on relapse in adults with minimal change nephrotic syndrome. *Clin Nephrol.* 2009;72:69–72.
14. Kurosu N, Sugiura H, Iwasaki C, Asamiya Y, Kojima C, Moriyama T, et al. Successful use of single-dose rituximab for the maintenance of remission in a patient with steroid-resistant nephrotic syndrome. *Intern Med.* 2009;48:1901–4.
15. Yang T, Nast CC, Vo A, Jordan SC. Rapid remission of steroid and mycophenolate mofetil (mmf)-resistant minimal change nephrotic syndrome after rituximab therapy. *Nephrol Dial Transplant.* 2008;23:377–80.
16. Vieira CA, Agarwal A, Book BK, Sidner RA, Bearden CM, Gebel HM, et al. Rituximab for reduction of anti-HLA antibodies in patients awaiting renal transplantation: 1. Safety, pharmacodynamics, and pharmacokinetics. *Transplantation.* 2004;77:542–8.
17. Munyentwali H, Bouachi K, Audard V, Remy P, Lang P, Mojaat R, et al. Rituximab is an efficient and safe treatment in adults with steroid-dependent minimal change disease. *Kidney Int.* 2013;83:511–6.