De novo myeloperoxidase-antineutrophil cytoplasmic antibody (MPO-ANCA)-associated glomerulonephritis 31 years after living-donor kidney transplantation

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Abstract A 61-year-old woman was admitted to our hospital because of an unexpected rise in serum creatinine (sCr) level with proteinuria and microhematuria. She had undergone living-donor kidney transplantation 31 years before for end-stage renal disease caused by chronic glomerulonephritis (GN). On admission, her sCr was 1.27 mg/dL which was increased from 0.6 mg/dL, urinary protein/creatinine ratio was 1.39 g/gCr, and urinary red blood cell count was more than 100 per high power field. The allograft biopsy revealed crescentic glomerulonephritis with moderate to severe tubulointerstitial inflammation. Immunofluorescence staining yielded only a minimal staining for immunoglobulin A, and negative C4d in peritubular capillary. Since increased myeloperoxidase-antineutrophil cytoplasmic antibody (MPO-ANCA) titer of 45.5 U/mL was detected, we made the diagnosis of post-transplant MPO-ANCA-associated GN. She was treated with three doses of bolus methylprednisolone (500 mg) followed by oral prednisolone therapy. Her sCr was stable at 1.20 mg/dL thereafter. ANCA-associated GN should be considered in older kidney transplant patients with new-onset urinary abnormalities because typical systemic symptoms and

vasculitis in other organs might be masked by maintenance immunosuppression.

Keywords De novo MPO-ANCA-associated glomerulonephritis · Crescentic glomerulonephritis · Renal transplantation · Allograft biopsy

Introduction

Anti-neutrophil cytoplasmic antibody (ANCA)-associated glomerulonephritis (GN) is characterized by pauci-immune necrotizing GN accompanied by vasculitis of small- and medium-sized arteries. ANCA reacts with myeloperoxidase (MPO) and proteinase 3 (PR3), and can be a specific disease marker [1]. MPO-ANCA-associated disease is common in Japan, whereas PR3-ANCA-associated disease is much more common in western countries [2]. The mean age of onset of MPO-ANCA-associated GN in Japan is reported to be 66.6 years old [3] and the annual incidence of ANCA-associated vasculitis is 22.6 per million adults [4]. Since severe extra-renal complications such as pulmonary hemorrhage (25–55 %), interstitial pneumonia (10 %), and gastro-intestinal bleeding (10 %) are observed [5–7], early diagnosis and treatment are quite important.

Kidney transplantation is one of the therapeutic options in end-stage renal disease caused by ANCA-associated GN. The mortality and recurrence rates were reported to be lower in patients who underwent kidney transplantation compared with the patients on dialysis, possibly because of immunosuppressive therapy [8]. ANCA titers are carefully monitored in patients who undergo kidney transplantation due to ANCA-associated GN. However, it is difficult to detect de novo ANCA-associated GN in patients with other primary kidney diseases, because this condition is quite

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rare, and the latent period is longer than in patients with recurrent ANCA-associated GN [9].

We report here the case of de novo MPO-ANCA-associated GN which was diagnosed 31 years after living-donor kidney transplantation, and was successfully treated with bolus methylprednisolone.

Case report

A 61-year-old woman was admitted to our hospital because of an unexpected rise in sCr level and new onset of proteinuria and microhematuria since more than 6 months before. She had received living-donor kidney transplantation from a younger brother when she was 30 years old. Since then, her sCr level had been stable at 0.6 mg/dL. She was on maintenance immunosuppressive therapy with prednisolone 5 mg/day and mizoribine 50 mg/day. She was also taking propranolol, hydralazine, and nifedipine for hypertension, and her blood pressure had been maintained at 110–140/70–90 mmHg.

Proteinuria and microhematuria were firstly detected when the patient was 26 years old. Two years later, she had developed severe gestational hypertension during the fourth week of pregnancy. Because of her poorly controlled blood pressure, massive proteinuria, and severe edema, she decided to have an abortion, but even after the termination of pregnancy, she had persistent hypertension and proteinuria. Her renal function progressively deteriorated, and she was started on hemodialysis when she was 30 years old.

On the latest admission to our hospital, her blood pressure was 152/80 mmHg and body temperature was 37.0 °C. Both legs were slightly edematous, but there was no purpura or eruptions. Her respiratory and heart sounds were normal, and her conjunctival palpebrae showed no evidence of anemia. She did not have shortness of breath or hemoptysis and did not complain of any lethargy or arthralgia. Urinalysis revealed 2+ proteinuria on dipstick, urinary protein/creatinine ratio was 1.39 g/gCr, and urinary red blood cell count was more than 100 per high power field. Blood tests revealed sCr level of 1.27 mg/dL, blood urea nitrogen 24 mg/dL, hemoglobin 11.7 g/dL, and C-reactive protein 0.06 mg/dL. Positive anti-hepatitis C antibody was noted and the titer was high (more than 57.4 cut-off index value), but serum transaminase and complement levels were also normal. Abdominal ultrasonography did not show liver abnormalities, nor allograft kidney hydronephrosis. The allograft kidney size was 10.4 cm × 5.2 cm.

Allograft biopsy was performed 4 days after admission (Fig. 1). The specimens contained 38 glomeruli: 5 had global glomerulosclerosis, and glomerular crescents were

detected in 17 glomeruli (5 cellular, 6 fibro-cellular, and 6 fibrous). There was moderate interstitial inflammatory cell infiltration, mild tubular atrophy, and mild interstitial fibrosis. Some tubules showed moderate to severe tubulitis. Immunofluorescent staining revealed only minimal glomerular immunoglobulin A deposition in mesangial area, and negative for other immunoglobulin or complement. C4d deposition in peritubular capillary was also negative. On electron microscopy, mild mesangial matrix increase and foot process effacement were found. But, no electron dense deposit was found in glomeruli (Fig. 2a). In both glomerular and peritubular capillaries, we did not confirm the swelling of endothelial cells, disappearance of fenestration, or basement membrane multilayering suggestive of acute/active and chronic active antibody-mediated rejection (Fig. 2b). Based on these findings, we histologically diagnosed as pauci-immune crescentic glomerulonephritis. Additionally, we found the increased MPO-ANCA of 45.5 U/mL (normal range <10 U/mL) with negative for PR3-ANCA. The diagnosis of MPO-ANCA-associated GN was confirmed. Further systemic screening revealed no pulmonary hemorrhage or interstitial lung disease on chest computed tomography, and gastrointestinal endoscopy also showed normal. Therefore, this case's vasculitis was considered to be renal-limited.

The patient was treated with three doses of bolus methylprednisolone (500 mg) followed by a steroid recycle (starting with prednisolone 30 mg/day). Her clinical course is shown in Fig. 3. At discharge, sCr level was 1.48 mg/dL, urinary protein/creatinine ratio 0.22 g/gCr, and the MPO-ANCA titer had decreased to 19.7 U/mL. There was no adverse effect of steroid and no infectious event in the whole clinical course. The activity of hepatitis C virus infection did not become exacerbated during the treatment. Three months after discharge, her sCr level was maintained at 1.2 mg/dL, urinary protein/urinary creatinine ratio was <0.3 g/gCr, and MPO-ANCA titer was below 10 U/mL, under immunosuppressive treatment with prednisolone 20 mg/day and mizoribine 50 mg/day.

Discussion

We described here a case of de novo MPO-ANCA-associated GN occurring 31 years after kidney transplantation. This disease typically develops in older patients, and is characterized by rapidly progressive GN. Systemic symptoms, such as fever, general malaise, weight loss, and polyarthralgia are common. Blood tests often show severe anemia and elevated C-reactive protein level. In our case, the patient showed insidious onset of graft dysfunction and urinary abnormalities for more than 6 months. This may

Fig. 1 Allograft biopsy findings. **a** Allograft biopsy showing moderate interstitial inflammation, mild tubular atrophy, and mild interstitial fibrosis. Glomeruli partially show crescent formation. **b** Some tubuli show moderate to severe tubulitis. **c** Glomerulus

showing tuft necrosis (*arrow*), cellular crescent, segmental endocapillary proliferation and segmental sclerosis. **a** PAS stain ($\times 200$), **b** and **c** PAM stain ($\times 400$)

Fig. 2 Electron microscopic findings. **a** Glomerulus showing mild mesangial matrix increase and foot process effacement. No electron dense deposit was found in mesangial, subepithelial, and

subendothelial area. **b** Peritubular capillary without evidence of endothelial injury and basement membrane multilayering suggestive of acute/active or chronic active antibody-mediated rejection

have been caused by her maintenance immunosuppressive therapy.

We made the diagnosis of “de novo” ANCA-associated GN for several reasons. First, the latent period was too long for her deterioration to be due to recurrent disease. Nachman et al. [10] reported that the recurrence rate of ANCA-

associated GN was 17.3 %, and the mean latent period was just 31 months (range 5 days–89 months). Briganti et al. [11] experienced two cases of graft loss due to recurrent pauci-immune GN, and both of the cases were diagnosed end-stage renal disease within 10 years after transplantation. Second, the clinical course of original renal disease

Fig. 3 Clinical course after admission. *mPSL* methylprednisolone, *MZR* mizoribine, *PSL* prednisolone, *sCr* serum creatinine, *MPO-ANCA* myeloperoxidase-antineutrophil cytoplasmic antibody

Table 1 Reported cases of de novo ANCA-associated glomerulonephritis after kidney transplantation

References	Asif [12]	Tabata [13]	Present case
Age (years), Gender	38, female	34, female	61, female
Type of vasculitis	Granulomatosis with polyangiitis	Microscopic polyangiitis	Microscopic polyangiitis
Causes of ESRD	Unknown (ANCA negative)	IgA nephropathy	CGN
Latency period after KTx	14 years	14 years and 10 months	31 years
Immunosuppressants at diagnosis (daily doses)	mPSL 4–6 mg (alternatively), CsA 225 mg	mPSL 2 mg, MZR 100 mg, Tac 4 mg	PSL 5 mg, MZR 50 mg
ANCA titer	PR3-ANCA 1:320, MPO-ANCA >100 U/mL	MPO-ANCA 12 U/mL	MPO-ANCA 45.5 U/mL
Baseline sCr (mg/dL)	2.4	1.0	0.6
sCr at diagnosis (mg/dL)	2.6	2.4	1.27
Urinary abnormalities	UP 3+, RBC 50–100/HPF	UP 1+, RBC 10–19/HPF	UP 2+, RBC >100/HPF
Allograft biopsy findings	Crescentic glomerulonephritis with necrotizing arteritis	Crescentic glomerulonephritis	Crescentic glomerulonephritis
Extra-renal manifestation	Subarachnoid hemorrhage	None	None
Treatment	Intravenous mPSL (1000 mg × 3 days), CP 125 mg/day	Intravenous mPSL (500 mg × 3 days)	Intravenous mPSL (500 mg × 3 days)
Follow-up period	6 months	5 years	2 years
Graft outcome	sCr 4.0 mg/dL at the last observation	Graft loss	sCr 1.1 mg/dL at the last observation

AZA azathioprine, CGN chronic glomerulonephritis, CP cyclophosphamide, CsA cyclosporine A, ESRD end-stage renal disease, HPF high power field, KTx kidney transplantation, mPSL methylprednisolone, MZR mizoribine, PSL prednisolone, RBC red blood cell, sCr serum creatinine, Tac tacrolimus, UP urinary protein

was quite different from that of ANCA-associated GN, even we did not measure ANCA at that time. She had originally presented with proteinuria and microhematuria, without extra-renal symptoms and inflammatory response on blood tests. In addition, her renal function subsequently deteriorated due to gestational hypertension and severe nephrotic syndrome. Thus, we concluded that her original disease was more compatible with chronic glomerulonephritis which was exacerbated by pregnancy.

Table 1 shows the characteristics of two previously reported cases of de novo ANCA-associated GN after kidney transplantation [12, 13] and our case. In both of the previously reported cases, the onset of vasculitis was about 14 years after transplantation and the initial findings were urinary abnormalities and impaired graft function. In patients with primary ANCA-associated GN, ANCA titers are monitored regularly, but in both these cases with de novo disease, ANCA titers were not measured before clinical deterioration. Both cases had severe graft dysfunction even after treatment, and in one case the graft function was lost 5 years later.

In ANCA-associated glomerulonephritis, inflammatory tubular injury could be observed as the “t3” grade in the criteria of the Banff’s Conference. In this case, T cell mediated acute rejection had possibility to co-exist with the glomerulonephritis. Furthermore, ANCA-associated glomerulonephritis sometimes involves perivascular capillaritis. In a while, according to Banff 2013 meeting report, antibody-mediated rejection could occur despite of the negativity of C4d stain [14]. In this case, the specimen also revealed severe peritubular capillaritis, but we did not identify the other changes found in acute/active and chronic active antibody-mediated rejection. Therefore, the lesions of peritubular capillaries are not considered as the result of the antibody-mediated allograft rejection.

The optimal treatment of de novo ANCA-associated glomerulonephritis after kidney transplantation has not been established. In patients with the recurrent disease, re-introduction of cyclophosphamide has been the main therapeutic strategy [15]. Plasma exchange and rituximab were also used in some cases [16, 17], especially with pulmonary involvement and high ANCA titers. However, cyclophosphamide treatment carries a substantial risk of toxicity including malignancy [18]. Deegens et al. [19] reported an increased incidence of malignancy in 43 patients with ANCA-associated vasculitis after renal transplantation. In addition, plasma exchange and rituximab are not approved for the treatment of this disease in Japan. Therefore, we treated the patient with steroid only. The initiation of therapy was effective, and graft function was preserved. However, the long-term effect of therapy without cyclophosphamide is not clear and further observation is needed.

In conclusion, we report a case of de novo MPO-ANCA-associated GN that occurred 31 years after kidney transplantation. The patient was successfully treated with bolus methylprednisolone, and graft function was preserved. When an older kidney transplant patient shows progressive graft dysfunction and new-onset urinary abnormalities, we need to keep in mind the possibility of ANCA-associated GN.

Conflict of interest Honoraria: Kazuhiko Tsuruya (Kyowa Hakko Kirin Co., Chugai Pharmaceutical Co.), Research funding: Kazuhiko Tsuruya (Kyowa Hakko Kirin Co., Chugai Pharmaceutical Co., Fuso Pharmaceutical Industries, MSD K.K., Takeda Pharmaceutical Co.), Endowed department: Kazuhiko Tsuruya (Baxter).

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