Recurrent IgA nephropathy complicated with Crohn's disease after renal transplantation

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Abstract A 27-year-old man was diagnosed with IgA nephropathy and Crohn's disease. He had been diagnosed with proteinuria and hematuria since he was 20 years old. Diarrhea had been a continuing problem during the past 5 months. Neither corticosteroid therapy nor tonsillectomy was performed. Hemodialysis was required at age of 30, while the symptoms of Crohn's disease were ameliorated by an elemental diet. He received a renal transplant from his mother 4 months after starting dialysis therapy. The initial immunosuppression therapy consisted of methylprednisolone, mycophenolate mofetil, cyclosporine, and basiliximab. Eight months after transplantation, proteinuria and hematuria appeared and serum creatinine was 1.4 mg/dL. Relapse of IgA nephropathy was confirmed by the one-year protocol biopsy. He had suffered from tonsillitis at 32 months after the transplantation. Urinary protein increased to 3 g/day and serum creatinine was elevated to 2.04 mg/dL. Renal biopsy was performed 2 weeks after the urinary findings were aggravated. The cellular crescents constituted 36 % of the glomeruli. The findings of rejection were not confirmed in both biopsies. Tonsillectomy was performed thereafter. No additional immunosuppressive

therapy was added. Proteinuria and hematuria disappeared at 4 and 20 months, respectively, after tonsillectomy, even when the symptoms of Crohn's disease worsened 69 months and 89 months after transplantation. A renal biopsy was performed 101 months after transplantation. Although IgA in the mesangium area was confirmed by immunohistochemical staining, no active lesion was seen. Tonsillectomy along with immunosuppressants for the graft might be an effective treatment for some patients with active recurrent IgA nephropathy.

Keywords Recurrent IgA nephropathy · Tonsillectomy · Crohn's disease

Introduction

The frequency of recurrence for IgA nephropathy is 20–60 % [1, 2]. Several studies of renal transplant recipients have established that approximately 13 % of the patients will exhibit some recurrence-related renal graft dysfunction after a mean follow-up of 5 years, and approximately 5 % will have lost their graft as a result of recurrent IgA nephropathy [3]. Here, we describe a case of recurrent IgA nephropathy and aggravated Crohn's disease after renal transplantation. IgA nephropathy was successfully treated by tonsillectomy alone and Crohn's disease ameliorated by infliximab.

Case report

A 27-year-old man was admitted to our hospital complaining of diarrhea, fever, and body weight loss. He had been diagnosed with proteinuria and hematuria since he

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was 20 years old. Diarrhea had been a continuing problem for the past 5 months. Laboratory studies revealed the following data: WBC 16500/ μ L, Hb 11.2 g/dL, platelets $48 \times 10^4/\mu$ L, TP 7.1 g/dL, Alb 2.8 g/dL, BUN 10 mg/dL, Cr 2.0 mg/dL, CRP 10.7 mg/dL, IgG 1670 mg/dL, IgA 777 mg/dL, and IgM 104 mg/dL. Urinalysis revealed urinary protein 3 g/day, occult blood (3+), sediment RBC 5–10/hpf, granular cast 2/apf, WBC cast 1/apf, fatty cast 4/apf, and waxy cast 9/apf. After admission, a perianal abscess was found and body temperature decreased after antibiotics therapy. Colonoscopy showed active colitis with aphthous and longitudinal ulcers. A non-caseating epitheloid granuloma was demonstrated by the biopsy. Small intestine enema revealed a longitudinal ulcer. Crohn's disease involving the large and small intestine was diagnosed. Diarrhea was ameliorated by an elemental diet. Renal biopsy revealed IgA nephropathy. There were 17 glomeruli with 9 sclerosed glomeruli and 1 cellular crescent. Histological score was classified as M1, S0, E1, T2 by the Oxford criteria [4] and histological grade (HG) 3 in the classification by the special IgA nephropathy study group [5]. Immunofluorescence staining showed granular staining for IgA and C3 in the mesangial area. Electron microscopy revealed mesangial and paramesangial electron dense deposits. The patient was treated with temocapril. Neither corticosteroid therapy nor tonsillectomy was performed. He required hemodialysis 41 months after the biopsy.

The patient received a living-related renal transplant from his mother 4 months after the initiation of dialysis

therapy. The ABO blood type and three HLA typings were identical. The initial immunosuppression therapy consisted of methylprednisolone, mycophenolate mofetil, cyclosporine, and basiliximab. Clinical course after renal transplantation is depicted in Fig. 1. Nine days after the operation, serum creatinine increased from 1.8 to 2.4 mg/dL. Angiography detected a stenosis and thrombus in the graft. The renal artery of the graft was anastomosed to the right internal iliac artery. After the operation, serum creatinine decreased to 1.4 mg/dL. Three graft biopsies (1-hour protocol biopsy, 9-day episode biopsy, and 3-month protocol biopsy) were conducted within 3 months. In 1-hour protocol biopsy, 21 glomeruli were included with no sclerotic glomerulus, and pathological findings were not evident. The scores by the Banff classification [6] were t0, i0, g0, and vo. In 9-day episode biopsy, 22 glomeruli were included with no sclerotic glomerulus. Thrombus-like lesion in the vascular pole was found in one glomerulus. The scores by the Banff classification were t0, i0, g0, and vo. In 3-month protocol biopsy, 9 glomeruli including one sclerosed glomerulus were found. Segmental double contour was found in one glomerulus. The effect of a stenosis and thrombus in the graft soon after operation was suspected. Evidence of sub-clinical rejection and recurrent original disease were not found. The scores by the Banff classification were t0, i0, g0, vo, ci0, ct0, cg0, mm0, cv0, and ah0. Eight months after transplantation, urine dipstick was positive twice for protein and erythrocytes, sediment RBC 2–4/hpf, and 24-h proteinuria was 0.9 g. BUN was

Fig. 1 Clinical course of recurrent IgA nephropathy complicated with Crohn's disease. *SCr* serum creatinine, *MMF* mycophenolate mofetil, *Cs* cyclosporine, *mPSL* methylprednisolone, *5-ASA* 5-aminosalicylic acid, *CDAI* Crohn's disease activity index, *UP* urinary protein, *OB* urinary occult blood, *Bx* kidney biopsy

Fig. 2 Light microscopy findings. **a** One-year protocol biopsy showed focal segmental necrosis (PAM stain). **b** Thirty three-month episode biopsy was performed when serum creatinine exacerbated. The figure shows cellular crescent (PAM stain)

17 mg/dL and creatinine was 1.4 mg/dL. The protocol biopsy was performed 1 year after the transplantation. At the protocol biopsy, immunosuppressant consisted of 1.0 g mycophenolate mofetil, 180 mg cyclosporine, and 4 mg methylprednisolone. There were 32 glomeruli including one sclerosed glomerulus. In the remaining glomeruli, focal segmental mesangial expansion was observed. Tuft adhesion was seen in one glomerulus. Tuft necrosis was seen in one glomerulus (Fig. 2a). There was no crescent. Evidence of sub-clinical rejection was not found. The scores by the Banff classification were t0, i0, g0, vo, ci0, ct0, cg0, mm1, cv0, and ah0. IgA was positive by immune staining. Histological score was M0, S1, E0, T0 and HG 1. Laboratory findings at the protocol biopsy were: urinary protein (+), occult blood (2+), BUN 12 mg/dL, Cr 1.6 mg/dL, IgG 929 mg/dL, IgA 470 mg/dL, and IgM 80 mg/dL. Thereafter, urinary protein stayed between 0.3 and 0.9 g/day and urinary occult blood remained at every testing at the outpatient clinic. Serum creatinine remained at 1.6–1.8 mg/dL. He had suffered from tonsillitis 32 months after the transplantation. On laboratory data, serum creatinine was elevated to 2.04 mg/dL, urinary protein increased to 3.01 g/day and red blood cell casts were present in the urinary sediment. Renal biopsy was performed 2 weeks after urinary findings were aggravated. There were 23 glomeruli including 5 sclerosed glomeruli. In the remaining glomeruli, diffuse mild mesangial expansion was observed. Tuft necrosis was observed in two glomeruli and cellular crescent was observed in 8 glomeruli. Histological score was M0, S1, E1, T1 and HG 3 (Fig. 2b). The findings of rejection were not confirmed. The scores were t0, i1, g0, vo, ci2, ct1, cg0, mm3, cv0, and

ah3. Cyclosporine-associated arteriopathy was evident. Tonsillectomy was performed 39 months after the transplantation. No additional immunosuppressive therapy was added. Urinary protein has been negative by dipstick from 4 months and occult blood has been negative from 21 months after tonsillectomy until now (109 months after transplantation).

From 48 months after transplantation, the patient experienced occasional diarrhea and high fever. At 69 months, colonoscopy revealed cobblestone appearance and bleeding at the terminal ileum. Crohn's disease activity index (CDAI) was 196. Thus, 5-aminosalicylic acid (5-ASA) was started. Eighty-nine months after transplantation, he was admitted due to melena. Colonoscopy findings revealed longitudinal ulcers and exposed blood vessels in the ascending colon and descending colon. Anal fistula was evident. By a small bowel series, a fistula from the appendix to terminal ileum was observed. CDAI was now 164. Infliximab (5 mg/kg) was started. After the first infusion, the diarrhea improved. A renal biopsy was performed 101 months after transplantation. Ten glomeruli including 4 sclerosed glomeruli were seen. In the remaining glomeruli, diffuse increased mesangial matrix and focal segmental increased mesangial cells were observed. No active lesion such as tuft necrosis, crescent, or endocapillary hypercellularity was seen. Adhesion or focal sclerosis was not observed. The scores by Banff classification were t0, i0, g0, v0, ci2, ct1, cg0, mm3, cv0, and ah3. Histological score was M0, S0, E0, T1 and HG 2. IgA in the mesangium area was confirmed by immunohistochemical staining and electron microscopy revealed electron dense deposits in the mesangial and paramesangial areas.

Discussion

Emerging evidence indicates that B cells in mucosal infections, particularly in tonsillitis, may produce the nephritogenic IgA [7]. Tonsillectomy may affect upstream of the pathogenic mechanism by eliminating antigenic stimuli from the tonsillar mucosa. Some Japanese studies have recently reported that tonsillectomy in combination with steroid-pulse therapy can be a more effective therapy for IgA nephropathy than steroid-pulse monotherapy alone [8] or tonsillectomy alone [9, 10]. Steroid-pulse therapy can affect downstream of the immunological mechanism by suppressing the abnormal immune response in bone marrow, leading to subsequent inflammation in renal glomeruli [11]. In recurrent IgA nephropathy, some reports demonstrated that tonsillectomy alone could be an effective treatment [12, 13]. Maintenance of a regimen containing steroid after renal transplantation may contribute to reducing downstream inflammation signals and immune complex deposition. The effect of tonsillectomy was reported to be especially marked in the patients with mild mesangial changes, such as minor glomerular abnormalities when compared to patients with severe mesangial changes [12]. Akagi et al. [14] proposed that tonsillectomy is indicated for patients who have renal pathology scores of HG 1 to HG 3 and a serum creatinine level of 2.0 mg/dL or less. Our case fulfilled these criteria. Proteinuria and hematuria disappeared 4 and 20 months after tonsillectomy, respectively. As for histopathology, focal necrosis was found in the 4th biopsy and the proportion of the glomeruli constituted by the crescent was 36 % in the 5th biopsy. These acute lesions had diminished in the 6th biopsy, although electron dense deposits were still present. Conceivably, his tonsil was the immunological stimulus causing acute lesions and receiving immunosuppressive therapy suppressed the abnormal immune response leading to subsequent inflammation in glomeruli. On the other hand, Sakai et al. [15] reported a case of recurrent IgA nephropathy which went into remission clinically after tonsillectomy but progressed pathologically. Further investigations are needed to distinguish which cases of recurrent IgA nephropathy can be treated by tonsillectomy alone.

Crohn's disease complicated with IgA nephropathy has been reported [16–21]. In most cases, onset or aggravation of IgA nephropathy coincided with the worsening of Crohn disease. In several cases, the nephropathy subsided with improvement of the intestinal disease [16–19]. It is speculated that mucosal inflammation in the intestine promotes exposure of immune cells to various antigens in food or bacteria, which provokes increases of polymeric IgA, leading to the development of immune complexes that accumulate in the glomerulus [16–19]. On the contrary,

cases in which the aggravation of urinary findings and digestive exacerbation did not coincide have also been reported [20, 21]. In the present case, aggravation of IgA nephropathy coincided with Crohn's disease at the time of the first visit to our hospital. However, the activity of IgA nephropathy did not link with that of Crohn's disease after renal transplantation. Heterogeneous pathogenesis may exist to cause IgA nephropathy associated with Crohn's disease, a property that is also a characteristic of secondary IgA nephropathy. There is no evidence supporting the effectiveness of tonsillectomy in the case of IgA nephropathy complicated with Crohn's disease. The relationship between Crohn's disease and tonsillectomy is controversial. Among Danish patients with Crohn's disease belonging to an unselected cohort, undergoing tonsillectomy decreased the odds for Crohn's disease [22]. On the other hand, tonsillectomy was a risk for developing Crohn's disease in a Greek case-control study [23]. Other reports demonstrated that tonsillectomy was not associated with any increase or decrease of risk of Crohn's disease [24, 25]. In the present study, the patient's digestive condition worsened 9 months after tonsillectomy. At least tonsillectomy had no protective effect for aggravation of Crohn's disease. A Japanese epidemiologic study is needed to clarify the relation of tonsillectomy with Crohn's disease.

In conclusion, we report a case wherein tonsillectomy had a favorable effect on recurrent IgA nephropathy complicated with Crohn's disease. Tonsillectomy along with immunosuppressants for the graft might be an effective treatment for some patients with active recurrent IgA nephropathy.

Conflict of interest We declare that no conflict of interest exists.

References

1. Ponticelli C, Traversi L, Banfi G. Renal transplantation in patients with IgA mesangial glomerulonephritis. *Pediatr Transplant*. 2004;8:334–8.
2. Ponticelli C, Traversi L, Feliciani A, et al. Kidney transplantation in patients with IgA mesangial glomerulonephritis. *Kidney Int*. 2001;60:1948–54.
3. Floege J. Recurrent IgA nephropathy after renal transplantation. *Semin Nephrol*. 2004;24:287–91.
4. Working Group of the International IgA Nephropathy Network and the Renal Pathology Society, Roberts IS, Cook HT, et al. The Oxford classification of IgA nephropathy: pathology definitions, correlations, and reproducibility. *Kidney Int*. 2009;76:546–56.
5. Kawamura T, Joh K, Okonogi H, et al. A histologic classification of IgA nephropathy for predicting long-term prognosis: emphasis on end-stage renal disease. *J Nephrol*. 2013;26:350–7.
6. Racusen LC, Solez K, Colvin RB, et al. The Banff 97 working classification of renal allograft pathology. *Kidney Int*. 1999;55:713–23.

7. Suzuki Y, Suzuki H, Nakata J, et al. Pathological role of tonsillar B cells in IgA nephropathy. *Clin Dev Immunol*. 2011;2011: 639074.
8. Komatsu H, Fujimoto S, Hara S, et al. Effect of tonsillectomy plus steroid pulse therapy on clinical remission of IgA nephropathy: a controlled study. *Clin J Am Soc Nephrol*. 2008;3:1301–7.
9. Nakagawa N, Kabara M, Matsuki M, et al. Retrospective comparison of the efficacy of tonsillectomy with and without steroid-pulse therapy in IgA nephropathy patients. *Intern Med*. 2012;51: 1323–8.
10. Yamamoto Y, Hiki Y, Nakai S, et al. Comparison of effective impact among tonsillectomy alone, tonsillectomy combined with oral steroid and with steroid pulse therapy on long-term outcome of immunoglobulin A nephropathy. *Clin Exp Nephrol*. 2013;17: 218–24.
11. Hotta O. Use of corticosteroids, other immunosuppressive therapies, and tonsillectomy in the treatment of IgA nephropathy. *Semin Nephrol*. 2004;24:244–55.
12. Kennoki T, Ishida H, Yamaguchi Y, Tanabe K. Proteinuria-reducing effects of tonsillectomy alone in IgA nephropathy recurring after kidney transplantation. *Transplantation*. 2009;88: 935–41.
13. Ushigome H, Suzuki T, Fujiki M, et al. Efficacy of tonsillectomy for patients with recurrence of IgA nephropathy after kidney transplantation. *Clin Transplant*. 2009;Suppl 20:17–22.
14. Akagi H, Doi A, Kosaka M, et al. Indication criteria for tonsillectomy in IgA nephropathy patients. *Adv Otorhinolaryngol*. 2011;72:50–2.
15. Sakai K, Saneshige M, Takasu J, et al. Clinical remission and pathological progression after tonsillectomy in a renal transplant patient with recurrent IgA nephropathy. *Clin Transplant*. 2009;23(Suppl 20):44–8.
16. Filiopoulos V, Trompouki S, Hadjiyannakos D, et al. IgA nephropathy in association with Crohn's disease: a case report and brief review of the literature. *Renal Fail*. 2010;32:523–7.
17. Takemura T, Okada M, Yagi K, Kuwajima H, Yanagida H. An adolescent with IgA nephropathy and Crohn disease: pathogenic implications. *Pediatr Nephrol*. 2002;17:863–6.
18. Forshaw MJ, Guirguis O, Hennigan TW. IgA nephropathy in association with Crohn's disease. *Int J Colorectal Dis*. 2005;20: 463–5.
19. Ueno Y, Tanaka S, Toshiko T, et al. Infliximab treatment for Crohn's disease in a patient with IgA nephropathy. *Clin J Gastroenterol*. 2009;2:380–3.
20. Dabadie A, Gié S, Taque S, Babut JM, Roussey M. Glomerular nephropathy with IgA mesangium deposits and Crohn disease. *Arch Pediatr*. 1996;3:884–7.
21. Lee JM, Lee KM, Kim HW, et al. Crohn's disease in association with IgA nephropathy. *Korean J Gastroenterol*. 2008;52:115–9.
22. Hansen TS, Jess T, Vind I, et al. Environmental factors in inflammatory bowel disease: a case-control study based on a Danish inception cohort. *J Crohns Colitis*. 2011;5:577–84.
23. Koutroubakis IE, Vlachonikolis IG, Kapsoritakis A, et al. Appendectomy, tonsillectomy, and risk of inflammatory bowel disease: case-controlled study in Crete. *Dis Colon Rectum*. 1999;42:225–30.
24. Kurina LM, Goldacre MJ, Yeates D, Seagroatt V. Appendicectomy, tonsillectomy, and inflammatory bowel disease: a case-control record linkage study. *J Epidemiol Community Health*. 2002;56:551–4.
25. López Ramos D, Gabriel R, Cantero Perona J, et al. Association of MALTectomy (appendectomy and tonsillectomy) and inflammatory bowel disease: a familial case-control study. *Rev Esp Enferm Dig*. 2001;93:303–14.