Short-term outcome and quality of life in kidney transplant recipient with monoclonal gammopathy

Masaaki Yanishi¹ · Hiroyasu Tsukaguchi² · Takashi Yoshida¹ · Hisanori Taniguchi¹ · Kenji Yoshida¹ · Takao Mishima¹ · Yoshihiro Komai¹ · Kaneki Yasuda¹ · Masato Watanabe¹ · Motohiko Sugi¹ · Hidefumi Kinoshita¹ · Tadashi Matsuda¹

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Abstract Monoclonal gammopathy of undetermined significance (MGUS) is the common pre-malignant B cell disorders with a general prevalence of 3–5 % at age over 50. Because of the potential malignant transformation and immune insufficiency, pre-transplant MGUS recipient should be carefully followed after allograft transplantation. The post-transplant prognosis and quality of life (QOL) in patient with MGUS have not yet been fully determined. The aim of this study is to evaluate function and pathology of the renal allograft and self-assessment QOL changes during 2 years after transplantation in our case of MGUS-bearing recipient. We here studied the clinical course and QOL improvement before and 20 months after transplant in a 56-year-old woman, who had pre-existing MGUS and underwent living donor kidney transplantation. After the

renal allograft transplant, the patients maintained normal GFR and had neither acute rejections nor histologic evidence of renal injuries related to the monoclonal gammopathy on the protocol biopsy of 1 year post-transplant. During further 20 months follow-up, the pre-transplant MGUS remained uneventful without any hematologic abnormalities and other medical complications, i.e., infection. Evaluation of QOL using a self-assessment questionnaire showed significant improvement for physical and mental items on both 6 and 18 months post-transplant. The renal transplant thus successfully provided a greater satisfaction for the recipient on both physical and mental health aspects. Our observations suggest that renal transplantation is beneficial even in those who had pre-existing

✉ Masaaki Yanishi
masaaki.yanishi@gmail.com

Hiroyasu Tsukaguchi
tsukaguh@takii.kmu.ac.jp

Takashi Yoshida
yoshidtk@hirakata.kmu.ac.jp

Hisanori Taniguchi
taniguhi@hirakata.kmu.ac.jp

Kenji Yoshida
yoshiken@hirakata.kmu.ac.jp

Takao Mishima
mishimat@hirakata.kmu.ac.jp

Yoshihiro Komai
komaiky@takii.kmu.ac.jp

Kaneki Yasuda
yasudaka@takii.kmu.ac.jp

Masato Watanabe
watanmas@hirakata.kmu.ac.jp

Motohiko Sugi
sugim@hirakata.kmu.ac.jp

Hidefumi Kinoshita
kinoshih@hirakata.kmu.ac.jp

Tadashi Matsuda
matsudat@hirakata.kmu.ac.jp

- ¹ Department of Urology and Andrology, Kansai Medical University, Hirakata, Osaka, Japan
- ² Division of Nephrology, 2nd Department of Internal Medicine, Graduate School of Medicine, Kansai Medical University, 2-5-1 Shinmachi, Hirakata, Osaka 573-1010, Japan

MGUS if managed and followed carefully, which ultimately could significantly improve the patient QOL.

Keywords Kidney transplantation · Monoclonal gammopathy · QOL

Introduction

Monoclonal gammopathy of undetermined significance (MGUS) is regarded as a pre-malignant condition of B cell lymphoproliferative disease, especially multiple myeloma. MGUS is characterized by the presence of a serum monoclonal M-protein <3 g/dL, absence of overt multiple myeloma/B cell proliferation (<10 % plasma cells in the bone marrow) and the absence of end organ complications, including hypercalcemia, renal failure, anemia, and lytic bone lesions [1, 2]. The general prevalence of MGUS is 3.2 % in individuals aged over 50 years and 5.3 % in persons aged over 75 years [3]. As the average age of kidney graft recipients is over 50 years [4], MGUS may become an important medical complication in transplant candidates. Moreover, MGUS progresses to myeloma multiple or B cell malignant lymphoproliferative disorders at a rate of 1 % per year [5]. Despite the prevalence of this hematologic disorder and its potential risk for later malignancy, few reports have assessed the prognosis and quality of life (QOL) of MGUS patients following renal transplantation. This study prospectively evaluated graft function, histology, medical complications, and physical and mental QOL in a kidney graft recipient with preexisting MGUS over 20 months following transplantation.

Case report

A 56-year-old woman who developed end-stage renal disease (ESRD), mainly due to diabetic nephropathy, was referred to our hospital for living donor kidney transplantation. Preoperative examination showed elevated creatinine (5.2 mg/dL) and anemia (Hb 9.5 g/dL), and she was incidentally found to have serum M protein (1.2 g/dL) on protein electrophoresis. The isotype of the paraproteins was immunoglobulin G (IgG) with lambda light chains; the free light chain (FLC) ratio was 1.15:1. Bone marrow aspiration showed the presence of 1.3 % plasma cells, and simple X-rays and computed tomography showed no bone lesions in the spine or skull (Table 1). These findings led to the diagnosis of MGUS. Epstein-Barr virus (EBV) IgG was positive, whereas EBV IgM and Epstein-Barr virus nuclear antigen (EBNA) were negative pre-transplant.

In February 2014, she received a preemptive living donor kidney transplant from her 46-year-old husband. The

initial immunosuppressive regimen consisted of tacrolimus, mycophenolate mofetil, anti-CD25, and prednisone. A protocol biopsy of the graft 1 year later showed neither acute rejection nor histologic evidence of renal injuries related to the monoclonal gammopathy (Fig. 1). There was no evidence of de novo deposition of free light chains in glomerular and tubular epithelia. She had no medical complications, including infection and hematologic abnormalities, and was free of malignant B cell transformation for 20 months.

Her physical and mental QOL were assessed before and 6 and 18 months after transplantation using the Kidney Disease Quality of Life KDQOL-SF™ version 1.3, a widely used measure of QOL in patients with end stage kidney disease [6]. This instrument consists of 79 items, divided into eight scales. Thirty-six items are questions about general health-related QOL (HRQOL; the Medical Outcomes Study SF-36), whereas 43 items are questions about kidney-disease related QOL before and after transplant. Relative to her pre-transplant scores, the patient showed significant improvements in QOL scores on all items 6 months after kidney transplantation, with these improvements maintained for 18 months (Fig. 2). These results indicated that kidney transplantation enhanced patient satisfaction with daily social and physical activities and her emotional well-being compared with her scores before transplantation.

Discussion

Clinical management of transplanted patients with MGUS is of increasing importance, as the age of kidney recipients is increasing. All recipients, especially those aged ≥50 years, should be regularly screened for serum M protein, both before and after transplantation [2]. Studies of the natural history of MGUS in 1384 non-transplanted patients showed that 115 (8.3 %) had progressed to multiple myeloma, IgM lymphoma, primary amyloidosis, macroglobulinemia, chronic lymphocytic leukemia, or plasmacytoma [7]. At 10, 20, and 25 years, the cumulative probabilities of malignant progression in patients with MGUS were found to be 12, 25, and 30 %, respectively, whereas the general probabilities of non-MGUS associated deaths were 53, 72, and 76 %, respectively, indicating that the risks of non-MGUS associated deaths far exceed the risks of MUGS related deaths. Other studies also support the benign and stable nature of MGUS, finding that 75–90 % of patients with MGUS do not progress to multiple myeloma or other related malignancies.

Several studies have attempted to address whether pre-existing MGUS has any detrimental effects on post-transplant clinical course and graft survival. The possible

Table 1 Laboratory examination

	Pre-transplant	Post-transplant after 6 months	Post-transplant after 18 months
Hb (g/dL)	9.5	13.7	13.5
Ht (%)	29.8	42.4	41.2
Cr (mg/dL)	5.2	0.75	0.77
Ca (mg/dL)	8.6	9.7	9.5
Alb (g/dL)	3.5	4.4	4.1
ALP (U/L)	247	223	253
IgG (mg/dL)	1509	1412	1509
IgM (mg/dL)	143	150	138
IgA (mg/dL)	221	243	242
IgD (mg/dL)	1.9	1.5	1.5
HbA1c (%)	7.8	7.7	7.9
β2 microglobulin (mg/L)	5.9	1.6	1.4
Ratio of FIC	0.401	0.431	0.387

malignant transformation of B cells is important when caring for patients with post-transplant MGUS. Malignant B cell proliferation significantly worsens patient prognosis, as malignant transformation can cause serious immunologic insufficiency, skeletal bone lesions, and injuries in the renal allograft. Patients with the IgG isotype paraprotein have a better prognosis than those with the IgM and IgA isotypes [2]. Higher M protein levels at the time of diagnosis have been associated with higher risks of progression to myeloma or a related malignancy. Other factors independently associated with progression to myeloma include the percentage of bone marrow plasma cells [8] and FLC ratio [9]. Determination of risk factors in our patient showed an IgG type paraprotein, an abnormal FLC ratio, and an M protein concentration >1.5 g/dL. The estimated rates of progression to myeloma or related malignancy over 20 years in MGUS patients with 0, 1, 2, and 3 cumulative risk factors have been reported to be 5, 21, 37, and 58 %, respectively. In this context, our patient can be classified into the lowest risk group, and is therefore likely to have a risk of progression below 5 %.

The risk of progression of MGUS to myeloma or a related malignancy has been estimated at ~1 % per year. A comparison of patient survival from initial diagnosis in nine transplanted and 25 non-transplanted individuals with MGUS showed no difference [2]. However, the mean age of the transplanted group was greater than that of the non-transplanted group, suggesting that general medical risks, such as cardiovascular diseases, were more frequent in the former. In contrast, a long-term follow-up of five transplant recipients with MGUS showed that two had developed

Fig. 1 The first year of the protocol biopsy (PAS staining)

smoldering myeloma, six and 10 years after the initial diagnosis, respectively [10]. A recent large cohort study of MGUS patients with or without solid organ transplant showed that transplantation did not significantly affect the risks of malignant progression, infection and thrombosis [11]. Furthermore, although B cell is suppressed by immunosuppression including steroid, these might prevent abnormal B cell proliferation and myeloma. However, it is unknown in this point.

Post-transplant MGUS patients are regarded as a highly immunocompromised, as B cell proliferation may be over-suppressed due to the administration of immunosuppressive agents. A study of 16 transplant recipients with pre-transplant MGUS, showed that two developed post-transplantation lymphoproliferative disorder (PTLD) [12]. As organ recipients with MGUS are at risk of PTLD, they should be regularly monitored for antibodies against Epstein-Barr virus (EBV) and cytomegalovirus (CMV). As the effect of decreasing their infection risk is immunosuppressive regimens containing everolimus with dose reduction or without tacrolimus/mycophenolate. The immunosuppressive regimens containing everolimus have been reported that the rate of infection (BK, CMV, or EBV) decreased [13, 14]. Not using everolimus in this case, but we think that it is preferable to conversion in the near future.

We did not find any histological changes in protocol biopsied renal grafts 1 year after transplantation. Various renal pathologies have been reported in patients with MGUS and related B cell disorders, including glomerulonephritis, AL amyloidosis, and tubule-interstitial injuries, a condition called monoclonal gammopathy of renal significance (MGRS) [15]. The pathogenic mechanisms underlying MGRS are mostly ascribed to primary abnormal deposition of monoclonal light chains into renal tissues

Fig. 2 Change in QOL evaluation

and/or subsequent secondary inflammatory responses. Early recognition is crucial, as suppression of IgM secretion by chemotherapy often improves outcomes. Careful follow-up is necessary, due to the nephrotoxicity of over-produced monoclonal immunoglobulins.

Recipient outcomes, including medical condition, socioeconomic status, and health-related QOL, should be carefully monitored. Self-assessment questionnaires are important tools in determining how kidney transplantation improves patient QOL [16, 17]. The KDQOL-SF assesses general QOL during activities of daily life, using the short form health survey SF-36, as well as assessing kidney-disease specific issue (symptoms/problems, effect of kidney disease, burden of kidney disease, work status, cognitive function, quality of social interaction, sexual function, and sleep). Compared with her pre-transplant QOL, our patient showed improved QOL 6 months after transplantation, with the improved QOL maintained for 18 months. Preemptive transplant allowed the patient to circumvent a time-consuming daily dialysis therapy, thereby greatly improving her social and economic QOL. Larger prospective studies are needed to better understand the long-term effects of kidney transplantation in patients with pre-existing MGUS. It is necessary to determine whether transplantation affects MGUS disease progression and whether it has life-time survival benefits for both graft and patient health.

Conclusion

This study showed that kidney transplantation into a patient with pre-existing MGUS had favorable post-transplant outcomes for 20 months. There was no evidence of histological recurrence of MGUS-related kidney disorders in the biopsied renal allograft, hematologic B cell malignant transformation, or immune insufficiencies. Transplantation significantly improved the physical and mental QOL of the MGUS-bearing kidney recipient. MGUS, the most frequently reported plasma cell-related disorder, is an important medical complication for transplant recipients. Further studies are needed to evaluate long-term outcomes. Particular attention should be paid to potential post-transplant malignant transformation and immune deficiency in allograft recipients with pre-transplant MGUS.

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Compliance with ethical standards

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

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