Splenectomy for ABO-Incompatible Kidney Transplantation and Very Late-Onset Cytomegalovirus Disease

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Abstract

Introduction: Splenectomy had been previously performed in ABO-incompatible kidney transplantation to reduce the B cell pool. However, studies have shown that patients undergoing splenectomy may have a lifelong susceptibility to infection and mortality. Splenectomy may affect the incidence of cytomegalovirus (CMV) disease even at a very late stage after transplantation in ABO-incompatible recipients. **Patients and Methods:** Seven patients received their graft from an ABO-incompatible living donor at our institution and underwent splenectomy for B cell reduction. Among them, 3 recipients experienced very late-onset CMV disease approximately 10 years after their transplant and were enrolled in this study. **Results:** Very late-onset CMV disease occurred at 9 years and 9 months, 15 years, and 13 years and 5 months after transplantation, respectively. Two recipients suffered from CMV retinitis, while one experienced colitis. The age of the patients at onset of CMV disease was 69 years, 42 years, and 71 years, respectively. **Conclusion:** This may be the first report on very late-onset CMV disease after splenectomy in ABO-incompatible kidney transplantation. We should be aware that these recipients can experience very late-onset CMV disease even approximately 10 years after their transplant.

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Introduction

In Japan, ABO-incompatible kidney transplantation has become a popular alternative to deceased kidney transplantation due to the shortage of deceased donors [1, 2]. Splenectomy had been performed to reduce the B cell pool in ABO-incompatible kidney transplant recipients but is now being replaced by the administration of rituximab, an anti-CD20 antibody [3–5]. During the early era of ABO-incompatible kidney transplantation in Japan, splenectomy had been performed in ABO-incompatible kidney transplant recipients because Japanese insurance had not covered administration of rituximab for kidney transplantation. As a result, nowadays, there is a certain

Table 1. Patient characteristics at transplantation

Case	1	2	3
Age, years	59	28	57
Sex	male	female	male
Cause of kidney disease	chronic glomerulonephritis	IgA nephropathy	chronic glomerulonephritis
Hemodialysis duration, months	32	24	53
Donor relation	wife	father	wife
ABO blood type (donor/recipient)	A/O	AB/A	AB/A
HLA mismatches (-A, -B, -DR)	5/6	3/6	5/6
Initial anti-A/B antibody titers (IgG/IgM)	1:256/1:16	1:16/1:16	1:8/1:8
Initial flow cytometry crossmatch with (T/B cells)	–/–	–/–	–/–
Desensitization	DFPP ×5	DFPP ×3	DFPP ×3
	PE ×1	PE ×1	PE ×1
	splenectomy	splenectomy	splenectomy
Induction immunosuppressive therapy	BAS, MP, MMF, Tac	ALG, Pr, AZ, Tac	BAS, MP, MMF, CsA
Acute rejection within 1 year after Tx (treatment)	+ (steroid pulse)	+ (steroid pulse)	–
CMV serostatus before Tx	+	+	+
CMV viremia within 1 year after Tx	+	+	+

HLA, human leukocyte antigen; DFPP, double filtration plasmapheresis; PE, plasma exchange; BAS, basiliximab; MP, methylprednisolone; MMF, mycophenolate mofetil; Pr, prednisolone; Tac, tacrolimus; CsA, cyclosporine A; ALG, antilymphocyte globulin; AZ, azathioprine; Tx, transplantation; CMV, cytomegalovirus.

number of long-term graft recipients who survive without spleen.

A previous study had reported on the benefits of splenectomy not only for graft survival but also for patient survival in kidney transplant recipients [6]. However, splenectomy has been reported to be associated with a lifelong increased susceptibility to infection and mortality [7]. Although the risk of infection after splenectomy varies with age, reason for surgery, and length of time after surgery, the extent and magnitude of this risk in these patients have not been well defined. In fact, the relationship between splenectomy and infectious disease in ABO-incompatible kidney transplant recipients undergoing immunosuppressive therapy remains unclear.

Cytomegalovirus (CMV) is the most dangerous viral pathogen after kidney transplants, and CMV disease usually occurs during the first 3 months of transplantation [8]. Reports have been made on very late-onset CMV disease that developed appropriately 10 years after transplantation [9]. Splenectomy may therefore affect the incidence of CMV disease at a very late stage in ABO-incompatible kidney transplant recipients. In this study, we summarized our results on very late-onset CMV disease in recipients who had undergone splenectomy as desensitization for ABO-incompatible kidney transplantation at our institution.

Materials and Methods

Seven patients received their graft from an ABO-incompatible living donor at the Osaka City University Hospital; Osaka, Japan, and underwent splenectomy as B cell reduction between January 1999 and May 2006. Among them, 3 recipients experienced very late-onset CMV disease approximately 10 years after their transplant and were enrolled in this study. All 3 patients were followed until March 2019. The age at transplant was 59, 28, and 57 years, respectively. The patients had initial anti-A/B antibody titers ranging from 1:8 to 1:256. Patient data are given in Table 1.

Immunosuppressive Protocol
To remove the anti-A/B antibodies, the patients underwent 4–6 sessions of double-filtration plasmapheresis and plasma exchange prior to kidney transplantation until the anti-A/B titers were less than 1:16. Splenectomy was performed at the time of kidney transplantation. The protocol for ABO-incompatible kidney transplantation with splenectomy is shown in Figure 1 [4]. The pretransplant immunosuppressive protocol included B-lymphocyte suppression with 1 week on an antimetabolite. For postoperative immunosuppression, the same regimen as for ABO-compatible cases was followed, in which calcineurin inhibitors were initiated 3 days before transplantation combined with two doses of basiliximab. Calcineurin inhibitors (tacrolimus or cyclosporin) were administered at a dose level that resulted in a blood trough level of 13–18 ng/mL (tacrolimus) or 250–300 mg/dL (cyclosporin). Basiliximab or anti-lymphocyte globulin was administered for induction immunosuppressive therapy. Maintenance immunosuppression included a calcineurin inhibitor (target

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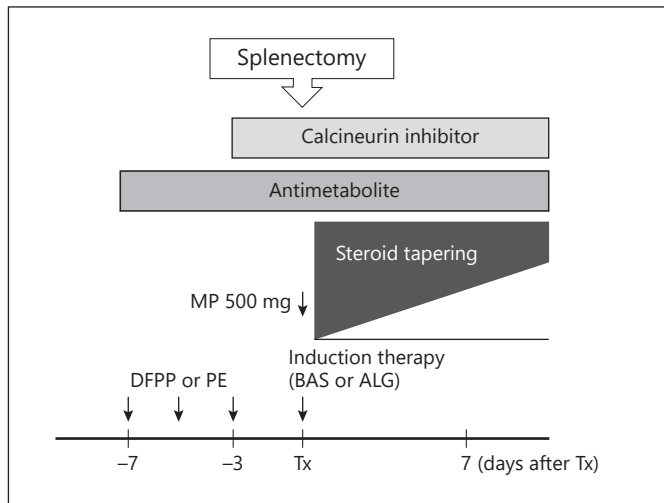
Fig. 1. Immunosuppressive protocol for ABO-incompatible kidney transplantation with splenectomy. ALG, antilymphocyte globulin; BAS, basiliximab; DFPP, double filtration plasmapheresis; MP, methylprednisolone; PE, plasma exchange; Tx, transplantation.

trough level of tacrolimus or cyclosporin; 3–5 ng/mL or 50–100 mg/dL, respectively), mycophenolate mofetil, and methylprednisolone.

For treatment of acute cellular rejection episodes, methylprednisolone was administered at a dose of 500 mg/day for 3 days alone or in combination with deoxyspergualin (5 mg/kg/day: 5–7 days). When resistance to these drugs was confirmed, OKT-3 was administered. Acute cellular rejection and antibody-mediated rejection were histologically diagnosed by light microscopy of graft biopsy specimens according to the Banff criteria.

Diagnosis of CMV Infection

CMV infection was routinely diagnosed and monitored using the C7HRP antigenemia assay once a month until 1 year after kidney transplantation. Recipients were diagnosed with CMV infection in the presence of 5 or more infected cells/5×10^4 leukocytes. CMV disease was diagnosed in patients with at least one of the following: CMV infection and one or more of the following: fever (>38.0 °C), new-onset malaise, leukopenia, atypical lymphocytosis, thrombocytopenia, elevation of hepatic transaminases, or localized CMV infection in a biopsy. These definitions of CMV infection and disease are consistent with the American Society of Transplantation guidelines [10].

Results

Baseline Characteristics

Two patients had received a graft from their spouses, and the other patient had received it from her father. Two patients underwent biopsy-proven acute cellular rejection within 1 year of transplantation. All patients were

CMV-seropositive before transplantation. They all had experienced CMV infection as CMV viremia and had been treated with administration of ganciclovir within 1 year of transplantation. Patient characteristics are shown in Table 1.

Very Late-Onset CMV Disease

Very late-onset CMV disease occurred at 9 years and 9 months, 15 years, and 13 years and 5 months after transplantation, respectively. Two recipients suffered from CMV retinitis, while one experienced colitis. Patient 1 had nephelopsia, patient 2 suffered from intractable diarrhea and melena, and patient 3 had nephelopsia and reduced visual acuity. The age of the patients at onset of CMV disease was 69 years, 42 years, and 71 years, respectively, and C7HRP levels at onset of CMV disease were 72, 2, and 16 infected cells/50,000 leukocytes, respectively. One was accompanied by pneumocystis pneumonitis due to pneumocystis jirovecii with CMV retinitis, and another had ulcerative colitis with CMV colitis. Two patients received tacrolimus, mycophenolate mofetil, and steroid, and one received cyclosporine, mycophenolate mofetil, and steroid (Table 2).

Treatment of Very Late-Onset CMV Disease

All 3 recipients who experienced CMV disease were treated with administration of ganciclovir at a dose of 5 mg/kg weight. Patient 1 and 2 underwent additional granulocyte and monocyte adsorptive apheresis to reduce pro-inflammatory cytokines reactivating CMV and to remove CMV-permissive cells. All recipients were successfully treated with administration of ganciclovir in combination with granulocyte and monocyte adsorptive apheresis or only administration of ganciclovir. Patient 1 who had pneumocystis pneumonia was treated with additional administration of sulfamethoxazole/trimethoprim. Patient 2 received salazosulfapyridine for treatment of ulcerative colitis (Table 3).

Outcome

One recipient who suffered from CMV colitis was re-introduced to hemodialysis therapy. The other 2 patients did not experience graft loss or death after transplantation and have maintained good graft functions. However, 2 patients experienced recurrence of CMV disease, and the current serum creatinine level was 1.2 and 1.3 mg/dL, respectively. The observation period after very late-onset CMV disease was 5 years and 1 month, 3 years and 6 months, and 1 year and 4 months, respectively (Table 3).

Table 2. Characteristics at very late-onset CMV disease

Case	1	2	3
Age at onset, years	69	42	71
Symptoms	nephelopsia	diarrhea, melena	nephelopsia, reduced visual acuity
CMV disease	CMV retinitis	CMV colitis	CMV retinitis
Period from transplantation to onset	9 years and 9 months	15 years	13 years and 5 months
C7HRP (infected cells /5×10^4 leukocytes)	72	2	16
Immunosuppressive therapy at onset	MP, MMF, Tac	Pr, MMF, Tac	MP, MMF, CsA
Comorbidity	PCP	IgA nephropathy recurrence ulcerative colitis	diabetes mellitus

CMV, cytomegalovirus; MP, methylprednisolone; MMF, mycophenolate mofetil; Pr, prednisolone; Tac, tacrolimus; CsA, cyclosporine A; PCP, pneumocystis pneumonia.

Table 3. Treatments of very late-onset CMV disease and outcomes

Case	1	2	3
Treatment of CMV disease	GCV GCAP	GCV GCAP	GCV
Recurrence of CMV disease	once (after half month)	twice (after 3 and 5 months)	–
Patient survival	+	+	+
S-Cr at onset (mg/dL)	1.5	3.8	1.3
S-Cr at remission (mg/dL)	1.2	10.3 (graft loss)	1.3
Observation period after CMV disease	5 years and 1 month	3 years and 6 months	1 year and 4 months

CMV, cytomegalovirus; GCV, ganciclovir; GCAP, granulocytapheresis; S-Cr, serum creatinine levels.

Discussion/Conclusion

The present study reported on very late-onset CMV disease after splenectomy in ABO-incompatible kidney transplantation. Splenectomy had been performed to reduce B cells in recipients of ABO-incompatible kidney transplantation. However, approximately 10 years after their transplant, 3 of our 7 patients who had received splenectomy suffered from very late-onset CMV disease including retinitis and colitis. Although the sample size of this study was small, our results suggested that splenectomy may be involved in the pathogenesis of very late-onset CMV disease after kidney transplantation. Even to this day, splenectomy may be performed in patients who cannot receive rituximab due to allergy to rituximab in ABO-incompatible kidney transplantation. This may be the first demonstration of very late-onset CMV disease after splenectomy in ABO-incompatible kidney transplantation. We should be aware that very late-onset CMV disease can occur in recipients of ABO-incompatible kidney transplantation with splenectomy even approximately 10 years after their transplant.

CMV infection is associated with significantly decreased kidney transplant patient and graft survivals [8, 11]. The direct effects of CMV may present as a viral syndrome or tissue-invasive disease [12], and the indirect effects may result in opportunistic infection, acute and chronic graft rejection, graft loss, and decreased recipient survival [13]. The risk is highest in the first few months after transplantation, which is increased by treatment of an acute rejection episode [14]. While antiviral prophylaxis for 3 to 6 months after transplantation has effectively prevented early-onset CMV, it has been reported that approximately 18–31% of kidney transplant recipients develop late-onset CMV infection or disease after prophylaxis cessation. Late-onset CMV infection at 6 months to 1 year after transplant is most frequently observed in high-risk CMV-seronegative recipients of an organ from a CMV-seropositive donor [15]. However,

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very late-onset CMV infection at more than 3.5 years following transplantation is not significantly associated with traditional risk factors such as donor seropositive/recipient seronegative status, rejection, induction therapy, and mycophenolate mofetil. Moreover, very late-onset CMV disease is not associated with antiviral prophylaxis [16]. The risk factors of very late-onset CMV disease remain unestablished, but immunosuppressive therapy after ABO-incompatible kidney transplantation with splenectomy may be a risk for very late-onset CMV disease.

During the early era of ABO-incompatible kidney transplantation, the higher trough concentrations of calcineurin inhibitors for this procedure had been applied because of the possible high-risk procedure for rejection compared with ABO-compatible kidney transplantation. Although ABO-incompatible kidney transplantation is an immunological high-risk procedure due to anti-A/B antibodies, a previous study showed no significant differences in frequency of CMV infection between ABO-incompatible and ABO-compatible kidney transplant recipients [2]. However, the risk of CMV infection after ABO-incompatible kidney transplantation was significantly higher than that after ABO-compatible kidney transplantation in patients who received a non-rituximab-based desensitization protocol [17]. In our study, 3 of 7 patients who had received ABO-incompatible kidney transplantation with splenectomy and without administration of rituximab as a desensitization protocol developed very late-onset CMV disease. ABO-incompatible kidney transplantation with a non-rituximab-based desensitization protocol may therefore be high risk not only for usual CMV infection but also for very late-onset CMV disease, which has not been previously reported.

It appears that a relatively higher proportion of very late-onset CMV disease is tissue-invasive. Gastrointestinal disease and retinitis are also more commonly observed with very late-onset CMV disease [18, 19]. Delayed diagnosis of CMV disease is one potential explanation for the more severe manifestations of very late-onset CMV disease. CMV as a direct cause of death may be more commonly observed in very late-onset CMV disease, because of lack of clinical suspicion or delayed diagnosis [16]. A previous report demonstrated that 3 of 5 cases of very late-onset CMV disease that occurred 3–8 years after transplantation died because of lack of early clinical recognition [20]. If signs of very late-onset CMV disease such as fever, diarrhea, or nephelopsia are recognized, elective further examination, such as C7HRP antigenemia assay or biopsy of the target organ, for diagnosis of CMV infection may be needed for early detection of CMV infection.

The mechanism of CMV reactivation is generally believed to involve local expression of a wide variety of pro-inflammatory cytokines that play a crucial role in recruiting immune cells, including monocytes, to inflammatory organs. Pro-inflammatory cytokines, such as interferon-γ and tumor necrosis factor-α, promote reactivation of CMV in monocytes and dendritic cells. Stimulated by the release of these cytokines and chemokines from inflammatory organs, latently infected circulating monocytes and dendric cells likely migrate to these sites and differentiate into permissive cells, supporting active replication of CMV [21]. Granulocyte and monocyte adsorptive apheresis is a widely used treatment for inflammatory bowel disease in Japan [22], which may reduce pro-inflammatory cytokine production and decrease the number of monocytes positive for CD14, CD16, and DR subsets. Our previous study suggested that a combination of granulocyte and monocyte adsorptive apheresis with ganciclovir can shorten the therapeutic duration of CMV disease in kidney transplant recipients without any adverse effects [23]. Currently, intravenous administration of ganciclovir is the recommended standard treatment for CMV disease following solid organ transplantation. In recipients with no evidence of ganciclovir resistance, intravenous administration of ganciclovir has been used successfully to reduce the viral burden [24]. Granulocyte and monocyte adsorptive apheresis with ganciclovir may be an effective therapy for very late-onset CMV disease.

There might be several limitations in this study because of the small number of cases and the fact that is a retrospective study. However, there has been no report on very late-onset CMV disease after splenectomy in ABO-incompatible kidney transplantation. This study may be the first demonstration that splenectomy may be involved in the pathogenesis of very late-onset CMV disease after transplantation. To confirm these findings, further prospective cohort trials with a larger number of patients are needed in the future.

In conclusion, the present study reported on very late-onset CMV disease after splenectomy for ABO-incompatible kidney transplantation. We should be aware that very late-onset CMV disease can occur in recipients of ABO-incompatible kidney transplantation with splenectomy even approximately 10 years after their transplant.

Statement of Ethics

This study was approved by the Ethics Committee of Osaka City University Graduate School of Medicine (No. 3957). Opt-out consent was obtained instead of written informed consent. The patients received information explaining the proposed research plan (the purpose, required individual data, and duration of research) by means of an information website of our hospital and gave them the opportunity to opt out. All procedures were in accordance with the Helsinki Declaration of 2000 and the Declaration of Istanbul of 2008.

Disclosure Statement

The authors have no conflicts of interest to declare.

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