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[Review]

REINFECTION OF CYTOMEGALOVIRUS IN RENAL TRANSPLANTATION

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Abstract : Cytomegalovirus (CMV) is the most important pathogen affecting the outcome of renal transplantation. Reinfection of CMV can occur in CMV-seropositive donors and CMV seropositive recipients (D+/R+) settings because the protection against CMV conferred by preexisting immunity is limited due to its strain-dependent immune responses. To analyze the influence of CMV reinfection in renal transplantation, ELISA using fusion proteins encompassing epitope of glycoprotein H(gH) from both AD169 and Towne strains was employed before transplantation. The CMV-gH seropositive rate increased with increases in age and the rate of samples which contained antibodies against both AD169 and Towne were significantly high in the age of 50 years or over. Antibodies from HLA-DR10 and DR11 were associated with a significantly lower response rate against CMV-gH. In renal transplantation, the high degrees of antigenemia and high incidences of CMV disease are more prevalent in the CMV gH antibody-mismatched group in D+/R+ setting. The nucleotide sequence of the region of the gH epitope in the CMV-DNA extracted from the transplant recipients who showed high degree of antigenemia revealed the CMV reinfection from the donors. As a CMV indirect effect, the incidence of acute rejection in the mismatched gH antibody group was higher than that observed in the matched and D+/R- groups. The adverse events were more likely to occur in cases of D+/R+ renal transplantation with mismatched strain-specific antibodies which would indicate the risk of CMV reinfection after transplantation.

Key words : cytomegalovirus, renal transplantation, glycoprotein H, reinfection

INTRODUCTION

Renal transplantation is a most valuable treatment for patients with chronic renal failure. However, despite significant advances in the field of renal transplantation, long-term graft survival has not markedly increased¹⁾. Among the varied reasons of this, cytomegalovirus (CMV) infection continues to be a potential contributor to graft failure, and a cause of severe mortality and morbidity. Several studies have suggested that CMV infection can lead to allograft rejection¹⁻⁵⁾ and an episode of acute transplant rejection can lead to allograft loss and can affect the recipient's survival.

Historically, CMV serostatus influences clinical outcome in renal transplantation. The combination

of CMV-seronegative transplant recipients with CMV-seropositive transplant donors (D+/R-) leads to the highest risk of CMV infection. However, the analyzed data from United States Renal Data System and United Network of Organ Sharing revealed that the D+/R+ group, not the D+/R-, had the worst graft and patient survival by 3 years^{6,7)}. The reason for this has not been clear. However, it may reflect the prevalence of multiple CMV virotypes and the D+/R+ recipients may have a double CMV exposure with different CMV strain. Studies of CMV reinfection will provide clues for future strategies in prevention and treatment of CMV disease and acute rejection in renal transplantation.

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CYTOMEGALOVIRUS VIROLOGY

CMV, a member of the beta herpes virus family, one of the DNA viruses and is a widespread opportunistic pathogen. Primary CMV infection usually occurs during the first decades of life and lead to a latent infection that can persist throughout the entire life of the host. The principal reservoirs of latent CMV are white blood cells and CD13-positive cells⁸⁾ and the latent virus has been detected in most tissues in the body. CMV is transmitted via saliva, body fluid, cells and tissues⁹⁾.

The envelope of CMV contains lipoproteins and structural proteins some of which are glycoproteins. To date, at least 57 potential glycoproteins are encoded by laboratory strain of CMV AD169 and several glycoproteins have been characterized¹⁰⁾. They are used for cellular entry of the virus, are the targets of virus-neutralizing antibody. Among the CMV glycoproteins, the genes encoding the glycoprotein H and B often show genetic polymorphism.

Glycoprotein H

Glycoprotein H (gH) is one of the immunologically dominant envelope glycoproteins of CMV. CMV-gH has been proposed to mediate viral/host cell membrane fusion in the initial step of infectivity¹¹⁾ and is essential for virus replication in cell culture¹²⁾. Anti-CMV gH antibodies exhibit virus neutralizing activity and the gH is considered a major antigen for the humoral immune response¹³⁾.

There is sequence heterogeneity which was found in the first 37aa of gH between two laboratory strains of CMV, AD169 and Towne¹⁴⁾. This region is recognized by virus-neutralizing antibodies as strain-specific epitope. This heterogeneity influences CMV susceptibility to host neutralizing antibodies. A recent report on congenital CMV infection provided clear evidence that exposure to CMV with a different genotype caused congenital infection, even in seropositive mothers¹⁵⁾.

Glycoprotein B

Glycoprotein B (gB) is one of the most abundant envelope components. Serological responses to the CMV gB are detected in individuals with past CMV infection. The antigenicity of gB is well studied. Linear and conformation-dependent epitopes of neutralizing and non-neutralizing antibodies have been defined on gB^{16,17)}. Of the epitopes, antigen domain 1 (AD1) is located between aa positions 560 and 640 of gB¹⁸⁾. The AD1 is one of the most highly conserved regions of gB and recognized as a target

of virus-neutralizing antibodies.

The second antibody binding site on gB is the antigen domain 2 (AD2), which is located between aa 28 and 84 of gB¹⁶⁾. Two antibody binding sites, AD2 site I and site II, have been identified within the AD2 domain. Site I is located between aa 68 and 77 in the AD2 of the AD169 strain. This region is conserved between CMV isolates and is the target of neutralizing antibodies. Site II is located between aa 50 and 54. Site II binds non-neutralizing antibodies and is strain specific¹⁶⁾.

CYTOMEGALOVIRUS STRAIN-SPECIFIC SEROEPIDEMIOLOGY

Glycoprotein-specific antibody responses

There are several reports on the rate of women positive for CMV antibodies which had usually analyzed at the time of pregnancy. According to these reports, the percentage of women who are CMV seropositive varies from 82.5% in the United States¹⁹⁾, to 93.8% in Japan and 86.7% in Chile²⁰⁾. It has been reported that symptomatic congenital infection is rare in the infants of women with pre-conceptual immunity to CMV. However, the protection conferred by pre-conceptual immunity is limited because of its strain-dependent immune responses¹⁵⁾. Reinfection can occur during organ transplantation from a donor with preexisting immunity against one strain of CMV to a recipient with antibodies against another strain, resulting in CMV transmission²¹⁾. Thus, it is crucial to obtain information about preexisting strain-specific immunity and the glycoproteins have been used to determine preexisting strain-specific antibodies to CMV^{15,21-23)}. The preexisting strain-specific immunity can be estimated by the presence of antibodies against glycoproteins of CMV. In our seroepidemiological analysis, which was approved by the institutional ethics committee, we employed the ELISA using GST-fusion proteins containing the strain-specific gH epitopes from AD169 and Towne strains (Figure 1) to detect strain-specific antibodies in transplant recipients. The antibodies against strain-specific gB AD2 site II epitopes and the strain-common AD2 site I epitope were also investigated. The distributions of antibody response against glycoproteins in Japan are summarized in Figure 2A. The ELISA using these fusion proteins was evaluated by a panel of sera obtained from 352 blood donors whose serostatus had been diagnosed using a conventional commercial ELISA kit. Among the

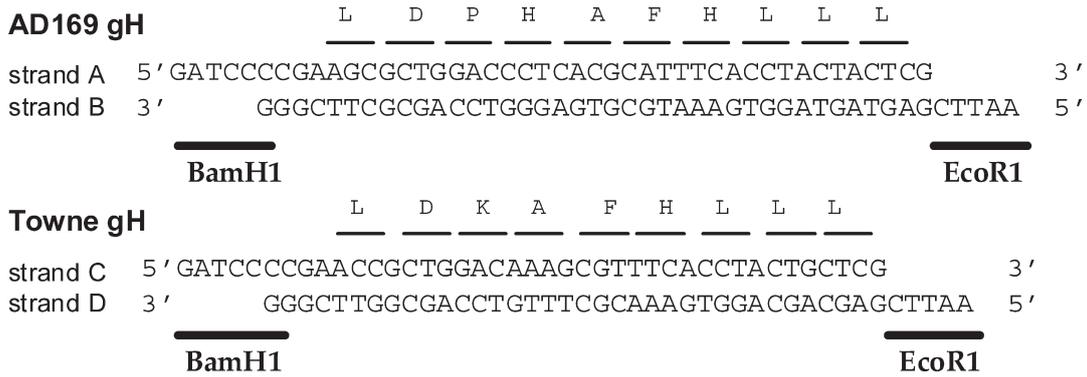


Fig. 1. Oligonucleotides containing CMV gH epitopes from AD169 and Towne strains used for the expression of gH epitopes (shown at the top of the oligonucleotides) as GST fusion proteins. Each cassette has BamHI and EcoRI sites at the ends for cloning. (Ref. 21)

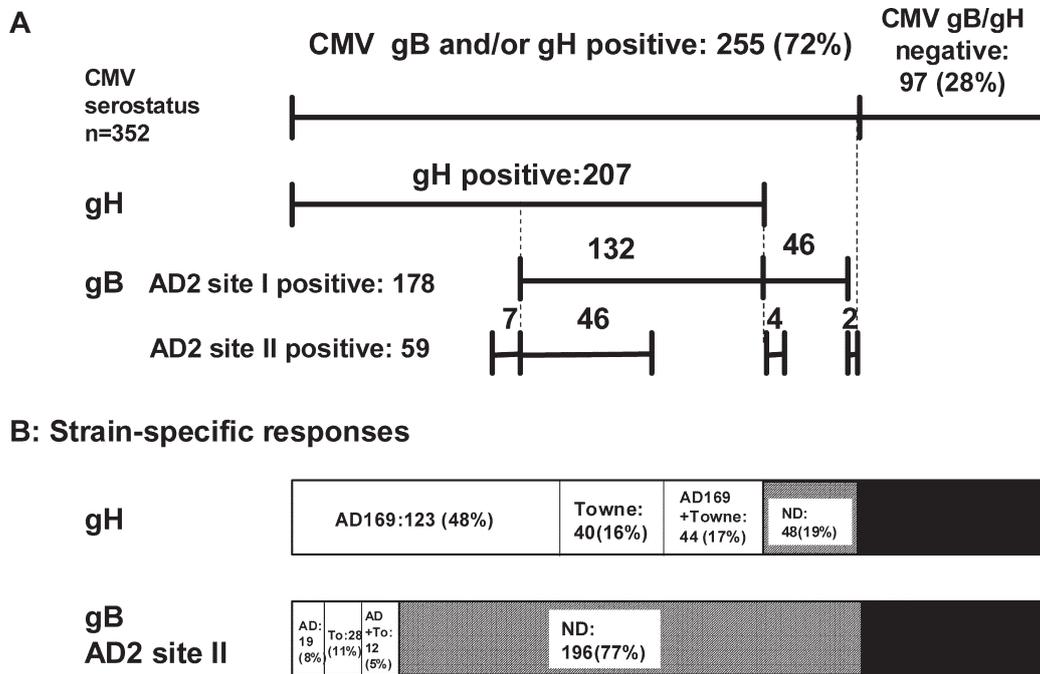


Fig. 2. A : Summary of number and distribution of samples according to antibody responses against strain-specific gH epitopes, and gB AD2. B : Number and percentage of samples from subjects that reacted with strain-specific antibodies against gH and gB AD2 siteII. (Ref. 23)

255 serum samples with antibodies against gH and/or gB, 178(69.8%) were reactive with the gB AD2 site I ELISA and 207(81.2%) with the gH ELISA, with 132 samples reactive with both gB and gH. Strain-specific antibody responses among the 207 gH seropositive samples showed 44 samples were reactive with the gH of both AD169 and Towne (Figure 2B). Figure 3 shows the correlation between CMV serostatus and age. The CMV seropositive rate was lower in subjects aged in their teens (50%) and 20's (62%) than in the other age groups, and the rate increased significantly with increases in age, reaching 80-90% in subjects aged 30 years or

over. Of the 44 donors whose serum contained antibodies against both AD169 and Towne, 27 (61%) were aged 50 years or over (Figure 3 : closed columns). This dual-positive rate was significantly higher than that for donors under 50 years ($p < 0.01$). It will indicate that organ transplantation from older donors to younger recipients ; for example, from father or mother to one of their children as is common in living related transplantation, can increase the risk of reinfection with CMV.

Association between gH antibodies and HLA-DR

In the age-related distribution of strain-specific

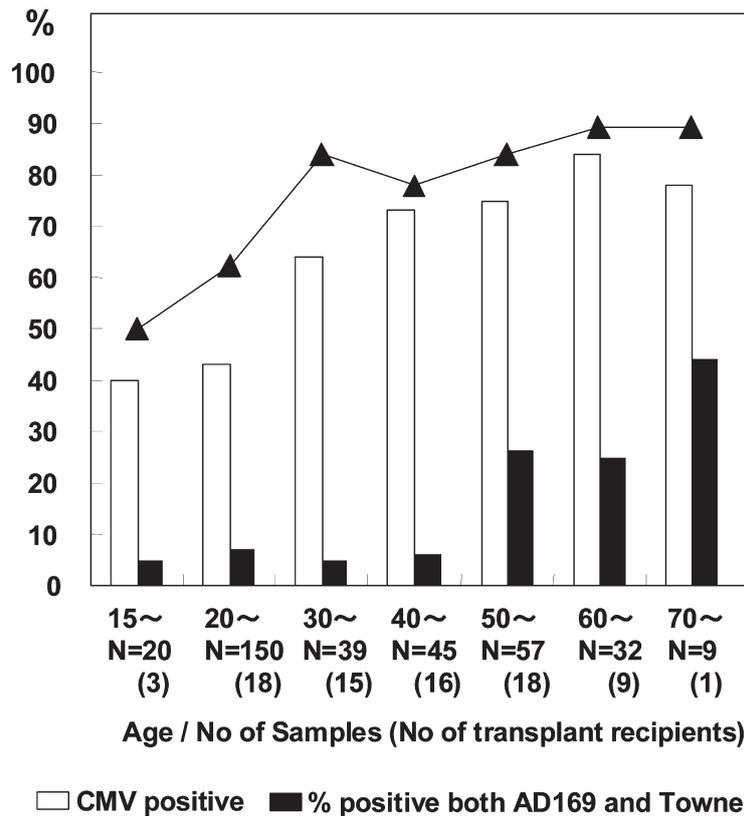


Fig. 3. Seroprevalence of CMV. Closed triangles indicate CMV serostatus analyzed using a conventional ELISA kit. Rate of positive antibodies against gH (open columns) and rate of positive strain-specific antibodies against both AD169 and Towne strains (closed columns) according to age. Age group and number of serum samples are shown on the horizontal axis. (Ref. 23)

antibodies against CMV gH, we found that some population of CMV-seropositive individuals did not have strain-specific gH antibodies. There reported that certain HLA alleles may be associated with antibody responses against CMV glycoprotein B²⁴. HLA allele distribution and positive antibodies against CMV gH ELISA in the total of 471 subjects are listed in Table 1. Positive rates were over 80% in most HLA subpopulations. HLA-DR9 showed the highest positivity rate against CMV gH ELISA, and on the contrary, HLA-DR10 and DR11 were found to be associated with a significantly lower response rate against CMV gH ELISA compared with other groups (Figure 4)²⁵. Because immune responses against CMV are so complex, the mechanisms underlying the relationship between HLA-DR10 or DR11 and anti-CMV gH antibodies are indefinite. However, in the case of lack of strain-specific antibodies against a donor's CMV strain, CMV disease can be caused in recipients after renal transplantation²¹. Besides, carriers of HLA-DR11 alleles are more susceptible to active CMV infection in the case of solid organ transplanta-

tion^{26,27}. An attractive hypothesis to explain this is that organ transplant recipients with HLA-DR11 are unlikely to have strain-specific antibodies against CMV gH. Further studies with larger numbers are needed.

INFLUENCE OF CYTOMEGALOVIRUS REINFECTION IN RENAL TRANSPLANTATION

CMV infections in solid organ transplant recipients induce serious direct and indirect consequences. The direct clinical effects of CMV include CMV infection, CMV disease and end-organ diseases *i.e.* gastrointestinal disease, hepatitis, retinitis, nephritis, cystitis, myocarditis, pancreatitis and the like. In addition to the directly effects, CMV is associated with graft rejection, accelerated atherosclerosis, and fungal or bacterial superinfection, which are known as the "indirect effects" of CMV²⁸. All of these effects increase the cost of care after transplantation.

Classically, because of its high rate of CMV primary infection, concern was mainly focused in CMV

Table 1. Distribution of subjects carrying at least one given HLA allele in the whole population and response against CMV gH ELISA (Ref. 25)

HLA-DR	Whole population (N=471) No.(%)	Response against gH ELISA No.(%)		Odds ratio	95% C.I.
		positive (N=404)	Negative (N=67)		
1	50(10.6)	45(11.1)	5(7.5)	1.51	0.59-3.88
4	226(48.0)	193(47.8)	33(49.3)	0.95	0.61-1.46
8	91(19.3)	79(19.6)	12(17.9)	1.09	0.57-2.07
9	95(20.2)	87(21.5)	8(11.9)	1.89	0.89-4.01
10	11(2.3)	5(1.2)	6(9.0)	0.13	0.04-0.44
11	24(5.1)	17(4.2)	5(7.5)	0.38	0.15-0.95
12	48(10.2)	41(10.1)	7(10.4)	0.96	0.42-2.19
13	58(12.3)	48(11.9)	10(14.9)	0.77	0.38-1.57
14	100(21.2)	88(21.8)	12(17.9)	1.23	0.65-2.33
15	148(31.4)	127(31.4)	21(31.3)	0.99	0.60-1.65
16	9(1.9)	7(1.7)	2(3.0)	0.57	0.12-2.78

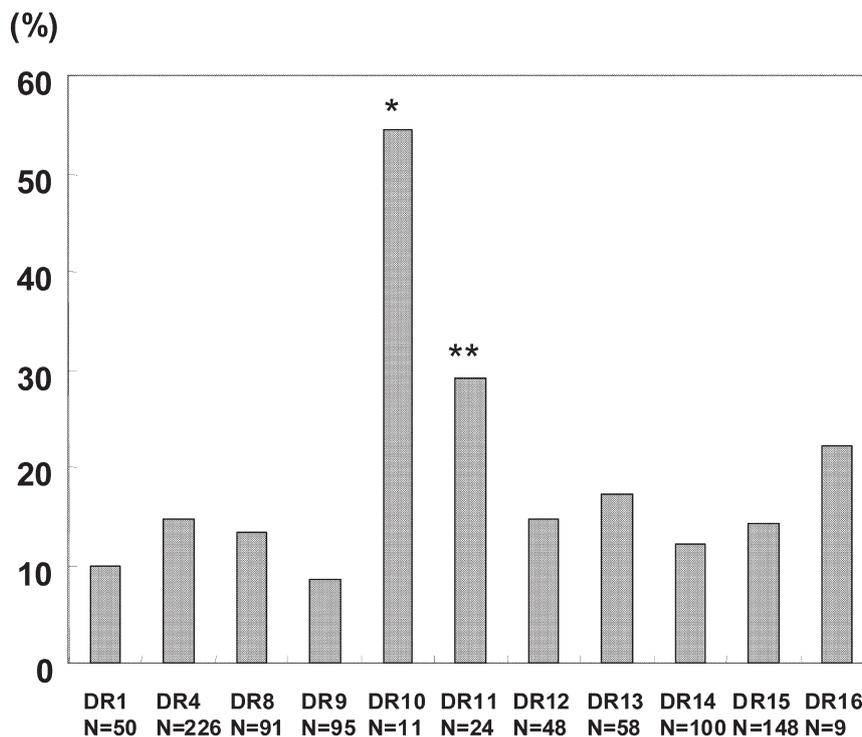


Fig. 4. Percentages of serum samples which had no response against CMV gH ELISA in each HLA type subpopulation. *Subjects with HLA-DR10 showed significantly lower response rate against gH ELISA compared with subjects with HLA-DR1, DR4, DR8, DR9, DR12, DR13, DR14 and DR15. **Subjects with HLA-DR11 showed significantly lower response rate compared with subjects with HLA-DR1, DR9 and DR14. (Ref. 25).

D+/R- transplantation. However, in the D+/R+ transplantation, the presence of antibodies against matched CMV gH epitopes had influences to the outcome of transplantation. More adverse event was observed in the case of reinfection of different

CMV strain.

Classification of patients according to CMV gH antibody responses

On the basis of the combinations of antibody

responses against the strain-specific gH epitopes, the conventional CMV D+/R+ pairings are classified into two groups. When a recipient received an organ graft from a donor who has the same strain-specific gH antibody of CMV as the recipient, the pairing classified as 'matched gH' pairing. The pairings that the recipients do not have the strain-specific gH antibodies which matched to their donor's are classified as 'mismatched gH' pairings. Our data which analysed 101 pairings of renal transplantation showed the differences among the D+/R-, matched gH and mismatched gH pairings in the clinical course after renal transplantation.

CMV disease and antigenemia

The data which analyzed consecutive 77 D+/R+ transplant recipients showed that the recipients in the gH-matched group were more likely to be protected from CMV disease compared with those in the gH-mismatched group or D+/R- group (Table 2). Although statistical differences in the incidence of CMV infection were not observed, CMV disease was significantly more prevalent in the mismatched group than in the matched group. The proportion of cases of CMV infection that progressed to CMV disease in the strain-specific antibody-mismatched and antibody-matched groups were 64% and 17%, respectively ($P=0.0038$). Among the D+/R- pairs, 67% of recipients had CMV infection, and 54% of them developed CMV disease.

The maximum numbers of pp65-positive cells obtained during the follow up antigenemia assay after renal transplantation are plotted in Figure 5. The difference in the maximum positive cell numbers in the gH antibody-matched group was statistically significant compared with gH antibody-mismatched group and D+/R- group. These findings indicate the relationship between the degree of neutralization and outcome of transplantation in the D+/R+ setting. In addition to the gH antibody, the absence of antibody responses against gB AD2 can

be a good indicator for CMV disease²⁹.

CMV strain-specific ELISA can reveal the strain-specific sero-status and it also allow us to estimate the type of CMV glycoprotein H persisting in the subject. The nucleotide sequence of the region of the glycoprotein H epitope in the CMV-DNA extracted from the transplant recipients who showed high degree of antigenemia during the follow up revealed that CMV strains causing infection were of donor origin (Table 3).

The combination of strain-specific CMV-gH antibody responses in transplant donors and recipient can predict the possibility of CMV reinfection after transplantation. The high degrees of antigenemia and high incidences of CMV disease are more prevalent in the case of reinfection of CMV after transplantation.

Acute rejection and CMV serostatus

The indirect CMV effects result in organ injury and damage. Several studies have implicated CMV in acute rejection after renal transplantation. A large retrospective study of renal and pancreas-renal transplantation found that the risk of renal allograft loss was increased in the presence of CMV disease⁵. A prospective study of 106 renal transplant recipients concluded that CMV disease, but not asymptomatic CMV infection, was independently associated with biopsy-proven acute allograft rejection³⁰.

Classically, renal allografts in D+/R- settings were considered to be at higher risk of acute rejection and graft loss³¹. However, some of the recipients in the conventionally classified D+/R+ pairings experience different outcomes after transplantation than was expected according to CMV gH strain-specific antibody matching. The occurrence of acute rejection after transplantation are prevalent in the cases of D+/R+ transplantation with mismatched gH antibodies (Figure 6)²¹. The reason why the incidence of acute rejection in the mismatched gH

Table 2. CMV infection and CMV disease after renal transplantation (Ref. 21)

CMV status/ strain-specific Ab status	D+/R+		D+/R-	total
	matched	mismatched		
No. of patients	45	32	24	101
Mean weeks (range) of the initial antigenemia detection	7(1-20)	7(4-13)	8(1-20)	7(1-20)
No.(%) of positive antigenemia	23(51)	14(44)	16(67)	53(52)
No.(%) of CMV disease	4(9)	9(28) ^a	13(54) ^b	26(26)

^a $p=0.026$ vs. matched, ^b $p=0.0008$ vs. matched

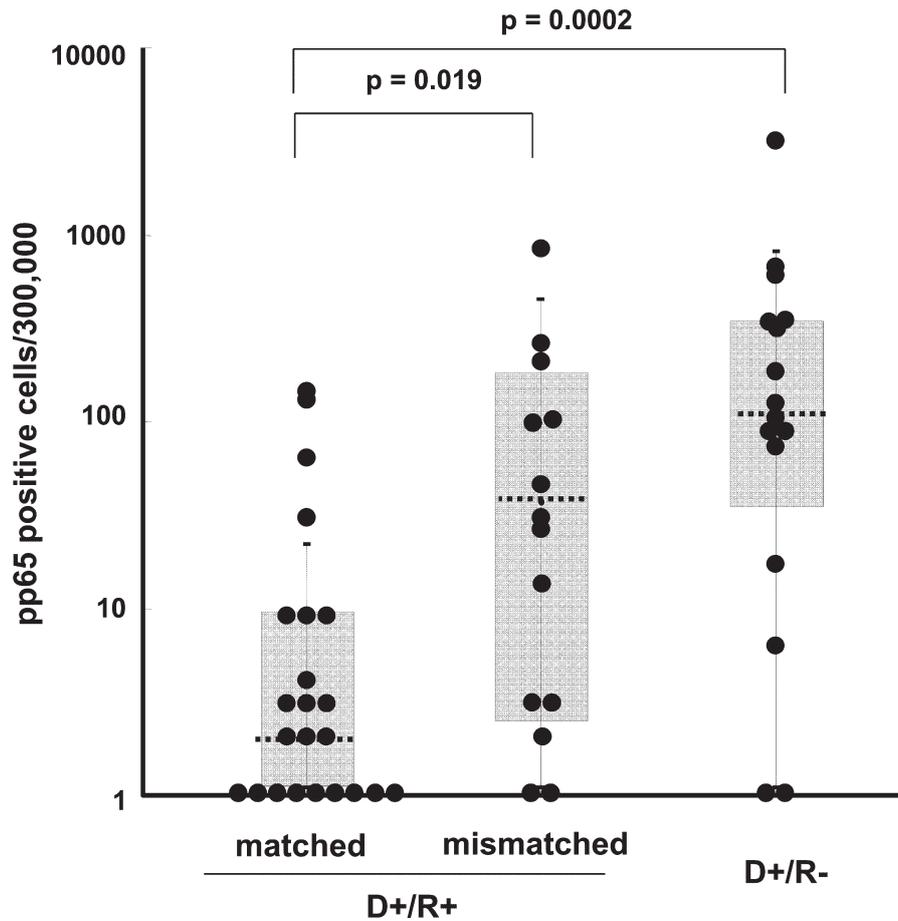


Fig. 5. Antigenemia in the transplant recipients. Maximum number of pp65-positive cells during the monitoring period (6 months) for each recipient with CMV infection was plotted. The broken bars in the box plot indicate the median of the pp65-positive cells. (Ref. 21)

Table 3. Strain-specific antibody responses and amino acid sequences of CMV glycoprotein H (Ref. 23)

Patient No.	ELISA against CMV gH before transplantation		Strain-specific antibodies of recipients 6M after transplantation	Weeks of the CMV viremia after transplantation	A.A sequence of PCR product from peripheral blood samples, type of gH and number of TA clone (%)			Acquired CMV strain after transplantation
	Donor	Recipient						
1	AD169	negative	AD169	6-7	SEALDPHAFHLLL	AD169	11(100)	AD169
2	Towne	negative	Towne	7-8	SEPLD*KAFHLLL	Towne	10(100)	Towne
3	AD169	Towne	AD169 and Towne	8-10	SEALDPHAFHLLL	AD169	17(100)	AD169
4	AD169	Towne	AD169 and Towne	7-8	SEALDPHAFHLLL	AD169	10(67)	AD169
					SEPLD*KAFHLLL	Towne	5(33)	
5	AD169 and Towne	AD169	AD169 and Towne	10	SEALDPHAFHLLL	AD169	11(69)	Towne
					SEPLD*KAFHLLL	Towne	5(31)	

antibody group has been higher than that observed in the matched group is not entirely clear. It is possible that acute rejection is the consequence of strong recipient-derived cytotoxic T lymphocyte

responses against ongoing CMV activities that had escaped humoral responses. Lack of CMV specific memory T cells may contribute to the lower rate of acute rejection in D+/R- setting.

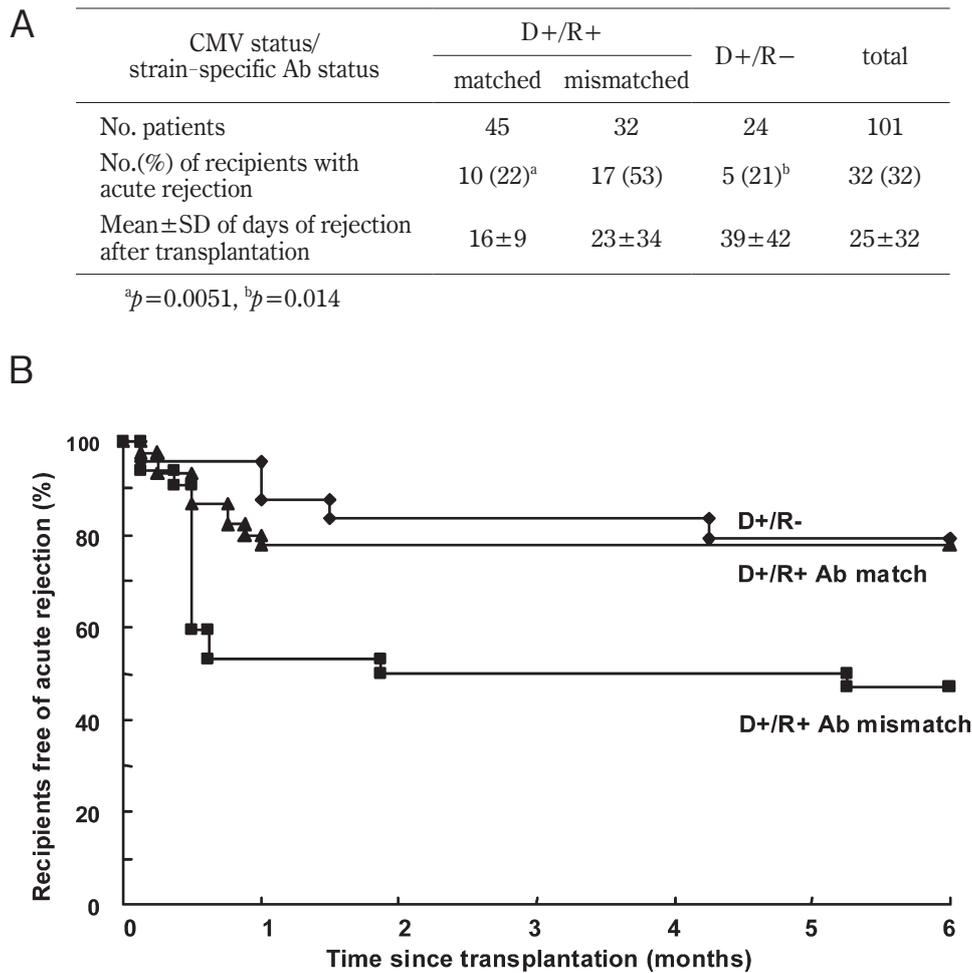


Fig. 6. (A) Summary of incidences of acute rejection. ^a $p=0.014$ vs. mismatched, ^b $p=0.0051$ vs. mismatched (B) Kaplan-Meier curves for the cumulative probability of freedom from biopsy-proven acute rejection. The incidence of acute rejection in the CMV strain-specific antibody mismatched group was significantly higher than those in the D+/R- and strain-specific antibody matched group ($p=0.002$). (Ref.21)

Prophylaxis strategies, rather than preemptive therapies, can have efficacy on preventing CMV indirect effect. Kleim *et al.*³²⁾ reported that universal CMV prophylaxis with oral gancyclovir improved long-term renal graft survival compared with preemptive therapy. The most significant effect was observed in D+/R+ subgroup. The recipients of the D+/R+ group with gH mismatch antibodies are most likely to have benefits of CMV prophylaxis strategy.

CONCLUSION

Among the CMV D+/R+ renal transplant recipients, more adverse events were observed when the CMV gH antibodies were mismatched, indicating that reinfection with a different CMV strain may increase complications. The ELISA using the antigens of recombinant gH and gB will provide useful

information regarding antibody responses against CMV, predicting CMV reinfection.

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CONFLICT OF INTEREST STATEMENT

No authors have any conflicts of interest to declare.

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