RESEARCH

Clinical characteristics of renal transplant recipients who developed de novo donor-specific antigen in Kyoto University Hospital: a case series

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Abstract

Background: The clinical significance of de novo donor-specific antigen (DSA) in renal transplant recipients is not yet fully understood. This study aimed to report the prevalence of de novo DSA detected in antihuman leukocyte antigen (HLA) antibody testing and to evaluate the association between de novo DSA and renal transplant prognosis in living-donor renal transplant recipients at our hospital.

Methods: Of the 110 patients who underwent living-donor renal transplantation from 1980 to 2019, 80 patients who underwent anti-HLA antibody screening tests were retrospectively reviewed for the development of de novo DSA and outcomes regarding graft function.

Results: The mean age at transplantation was 43.2 ± 14.6 years. Of the 80 patients, 43 (53.8%) were men and 68 (85.0%) underwent ABO-compatible transplantation. Anti-HLA antibody was detected in 14 patients (17.5%), including eight (10.0%) with de novo DSA. Graft loss occurred in two (25%) of the eight patients with de novo DSA, none of the six patients with non-DSA anti-HLA antibody and no anti-HLA antibody ($P = 0.0419$, log-rank test). The mean estimated glomerular filtration rate at the time of the anti-HLA antibody test was 45.1 ± 14.4 mL/min/1.73m^2 in the 66 patients with no anti-HLA antibody, while it was 35.0 ± 11.5 mL/min/1.73m^2 in the eight patients with de novo DSA ($P = 0.0702$) and 39.3 ± 15.3 mL/min/1.73m^2 in the six patients with non-DSA anti-HLA antibody ($P = 0.3921$). The mean monthly cyclosporin A trough concentration for the past year from the anti-HLA antibody test was 59.2 ± 24.8 ng/ml in the seven patients with no anti-HLA antibody, while it was 61.9 ± 12.5 ng/ml in the five patients with de novo DSA ($P = 0.5670$) and 36.3 ± 9.0 ng/ml in a patient with non-DSA anti-HLA antibody ($P = 0.3921$). The mean monthly tacrolimus trough concentration for the past year from the anti-HLA antibody test was 4.62 ± 1.20 ng/ml in the 55 patients with no anti-HLA antibody, while it was 4.09 ± 1.10 ng/ml in the three patients with de novo DSA ($P = 0.0027$) and 4.21 ± 1.14 ng/ml in the four patients with non-DSA anti-HLA antibody ($P = 0.0722$).

Conclusions: The optimal treatment for patients with de novo DSA has not been established, and immunosuppressive management that suppresses the development of de novo DSA is essential.

Keywords: De novo DSA, ABMR, Renal transplantation

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Background

Advances in immunosuppressive drugs have improved the incidence of acute rejection and the prognosis of transplanted kidneys, but antibody-mediated rejection (ABMR) caused by de novo donor-specific antibody (DSA) to human leukocyte antigen (HLA) remains difficult to treat and is a major cause of transplant renal dysfunction [1–6]. However, the association between the development of de novo DSA and ABMR is unclear, as not all DSA-positive patients develop ABMR. Additionally, no standard treatment for ABMR due to de novo DSA has been established.

In 2018, annual anti-HLA antibody screening tests were approved for renal transplant recipients in Japan. Herein, we report the prevalence of de novo DSA and evaluate the association of de novo DSA with functional graft outcomes in living-donor renal transplant recipients at our hospital.

Methods

Study design and participants

The present study was performed in accordance with the guidelines of the Declaration of Helsinki and was approved by the research ethics committee of Kyoto University (#R2485-1).

Of the 110 patients who underwent living-donor renal transplantation from 1980 to 2019, 80 patients who were screened for anti-HLA antibody were retrospectively reviewed. One patient who had preformed DSA was excluded. The other patient was excluded because he had a myocardial infarction soon after surgery and died early. Patient characteristics such as age, sex, ABO-compatibility, cause of renal dysfunction, and history of liver transplantation were investigated based on the clinical records. The patient characteristics are shown in Table 1. The mean age at transplantation was 43.2 ± 14.6 years. There were 43 men (53.8%) and 68 ABO-compatible cases (85.0%). IgA nephropathy was the most common cause of renal dysfunction (n = 20, 25.0%). There were one secondary renal transplant cases, and five patients had a history of liver transplantation. The median follow-up period was 101 months (range 17–487 months).
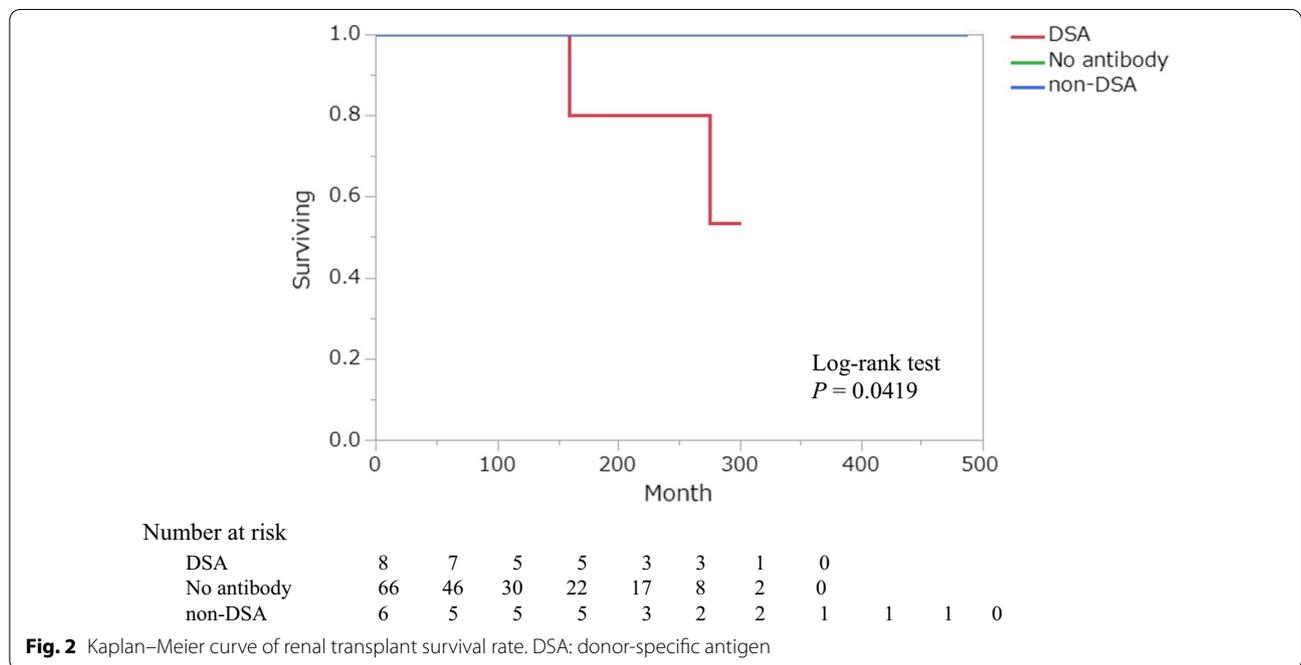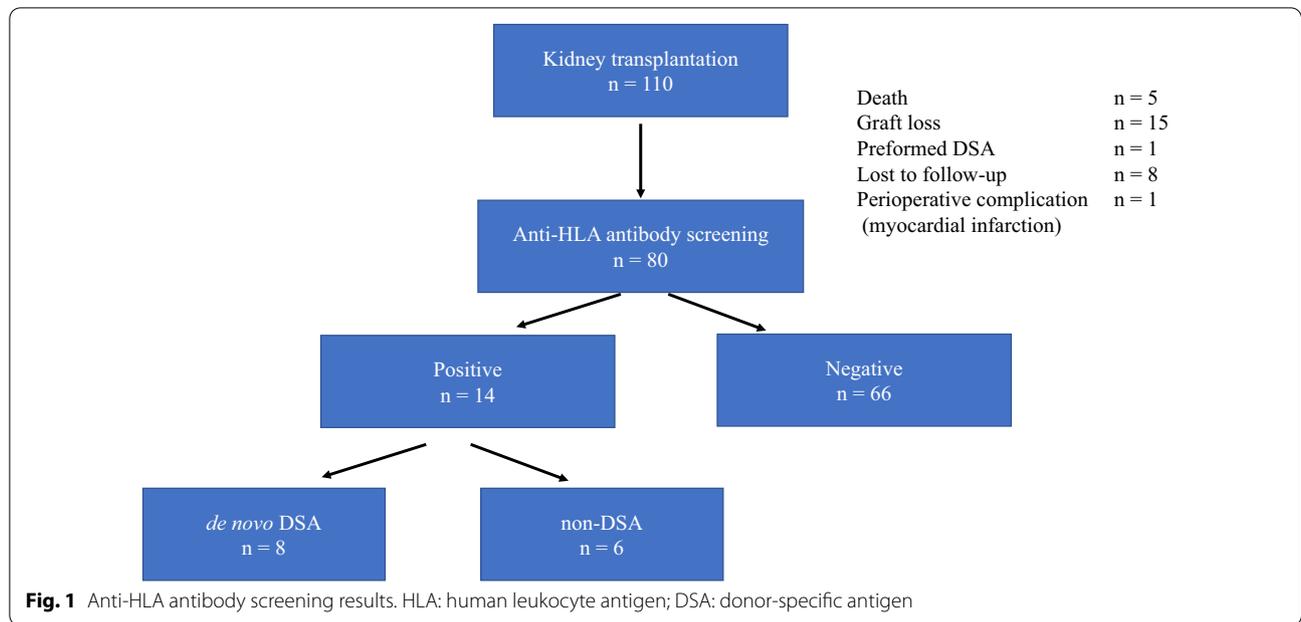
The estimated glomerular filtration rate and the monthly trough concentration of cyclosporin A and tacrolimus were compared using the Mann–Whitney U test. The functional graft survival was estimated by the Kaplan–Meier method and compared by the log-rank test. Statistical significance was set at $P < 0.05$. All analyses were completed using JMP® software (JMP pro version 15; SAS Institute Inc., Cary, NC, USA).

Table 1 Characteristics of renal transplantation recipients

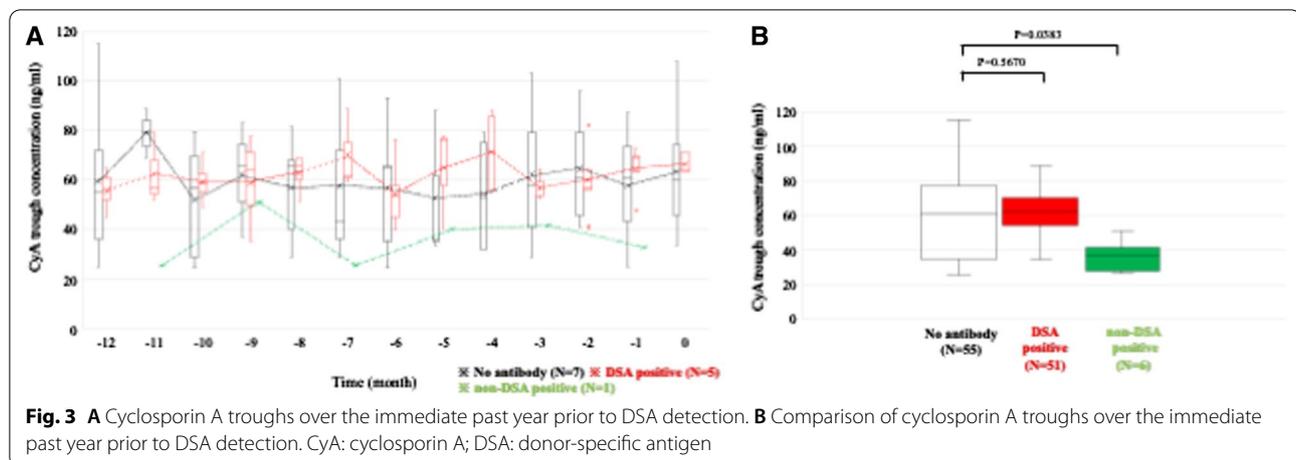| Recipient characteristic	n = 80
Age in years, mean ± SD	43.2 ± 14.6
Sex	
Male, n (%)	43 (53.8%)
Female, n (%)	37 (46.2%)
ABO	
Compatible, n (%)	68 (85.0%)
Incompatible, n (%)	12 (15.0%)
Primary disease	
IgA nephropathy, n (%)	20 (25.0%)
Diabetic nephropathy, n (%)	7 (8.8%)
Chronic glomerulonephritis, n (%)	10 (12.5%)
Reflux nephropathy, n (%)	4 (5.0%)
Drug nephropathy, n (%)	5 (6.3%)
Nephrosclerosis, n (%)	2 (2.5%)
Henoch-Schönlein purpura nephritis, n (%)	2 (2.5%)
Autosomal dominant polycystic kidney disease, n (%)	5 (6.3%)
Membranoproliferative glomerulonephritis, n (%)	5 (6.3%)
Rapidly progressive glomerulonephritis, n (%)	2 (2.5%)
Others, n (%)	18 (30.0%)
History of liver transplantation, n (%)	5 (6.3%)
Follow-up duration in months, median (range)	101 (17–487)

Results

Anti-HLA antibody was detected in 14 patients (17.5%), comprising DSA in eight patients (10.0%) (Fig. 1). Functional graft loss occurred in two (25%) of the eight patients who were positive for DSA, none of the six patients who were positive for non-DSA anti-HLA antibody, and none of the 66 patients who were negative for anti-HLA antibody ($P = 0.0419$, log-rank test, Fig. 2). The mean estimated glomerular filtration rate at the time of the anti-HLA antibody test was 45.1 ± 14.4 mL/min/1.73m^2 in the 66 patients with no anti-HLA antibody, while it was 35.0 ± 11.5 mL/min/1.73m^2 in the eight patients with de novo DSA ($P = 0.0702$) and 39.3 ± 15.3 mL/min/1.73m^2 in the six patients with non-DSA anti-HLA antibody ($P = 0.3921$). The mean monthly cyclosporin A trough concentration for the past year from the anti-HLA antibody test was 59.2 ± 24.8 ng/ml in the seven patients with no anti-HLA antibody, while it was 61.9 ± 12.5 ng/ml in the five patients with de novo DSA ($P = 0.5670$) and 36.3 ± 9.0 ng/ml in a patient with non-DSA anti-HLA antibody ($P = 0.3921$) (Fig. 3). The mean monthly tacrolimus trough concentration for the past year from the anti-HLA antibody test was 4.62 ± 1.20 ng/ml in the 55 patients with no anti-HLA antibody, while it was 4.09 ± 1.10 ng/ml in the three patients with de novo DSA ($P = 0.0027$) and

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Fig. 1 Anti-HLA antibody screening results. HLA: human leukocyte antigen; DSA: donor-specific antigen

Fig. 2 Kaplan–Meier curve of renal transplant survival rate. DSA: donor-specific antigen

4.21 ± 1.14 ng/ml in the four patients with non-DSA anti-HLA antibody ($P = 0.0722$) (Fig. 4).

Table 2 summarizes the characteristics of the eight patients who were positive for de novo DSA. All eight patients received an ABO-compatible renal transplant. Delayed graft function occurred in two patients. De novo DSA was detected at a median of 141.5 months (range 18–275 months) after transplantation. In all cases, the de novo DSA was HLA class II (DQ only in three patients, DR only in three, and DQ+DR in two). Six patients (75%) had a mean fluorescence intensity (MFI) of 10,000 or more. The transplanted renal function was lost in two patients (25%). Four patients (50%) did not show any signs of rejection, while the remaining four were screened for anti-HLA antibody due to elevated serum creatinine levels. Renal biopsy was performed in all eight

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Fig. 3 **A** Cyclosporin A troughs over the immediate past year prior to DSA detection. **B** Comparison of cyclosporin A troughs over the immediate past year prior to DSA detection. CyA: cyclosporin A; DSA: donor-specific antigen

patients, and five (62.5%) were pathologically diagnosed with ABMR (subclinical ABMR in two patients, and clinical ABMR in three). Table 3 shows the pathological findings (Banff classification). Immunosuppression was enhanced using steroid pulse therapy, plasmapheresis, rituximab, intravenous immunoglobulin, and dose increase in maintenance immunosuppressants.

Two patients with loss of transplanted renal function are described below.

Case 3 was a 27-year-old man (body weight 80 kg) with chronic glomerulonephritis who received a living-donor renal transplant from her mother (Fig. 5). The maintenance immunosuppressant therapy was a combination of cyclosporin A (1.5 mg/kg), prednisolone (5 mg/body), and azathioprine (0.9 mg/kg). Twenty years after the renal transplantation, his serum creatinine was stable at 1.5–1.6 mg/dl. A graft kidney biopsy was performed because DSA was detected on blood sampling. Pathological findings indicated ABMR. The azathioprine was changed to mycophenolate mofetil (MMF) (2000 mg/body), and his MFI was halved 1 year later, but his serum creatinine increased after that. His serum creatinine level decreased temporarily with steroid pulse therapy (methylprednisolone 500 mg/body for 3 days). At that time, the patient did not want additional treatment. However, his serum creatinine increased again 4 months later, and hemodialysis was reintroduced at 23 years after the kidney transplantation.

Case 4 was a 49-year-old woman (body weight 40 kg) with an unknown primary disease who received a living-donor renal transplantation from her husband (Fig. 6). Maintenance immunotherapy was a combination of cyclosporin A (2 mg/kg), prednisolone (5 mg/body), and MMF (1000 mg/body). Her serum creatinine was stable at about 1.0 mg/dl for 11 years after renal transplantation, but then gradually increased. The MMF was changed to
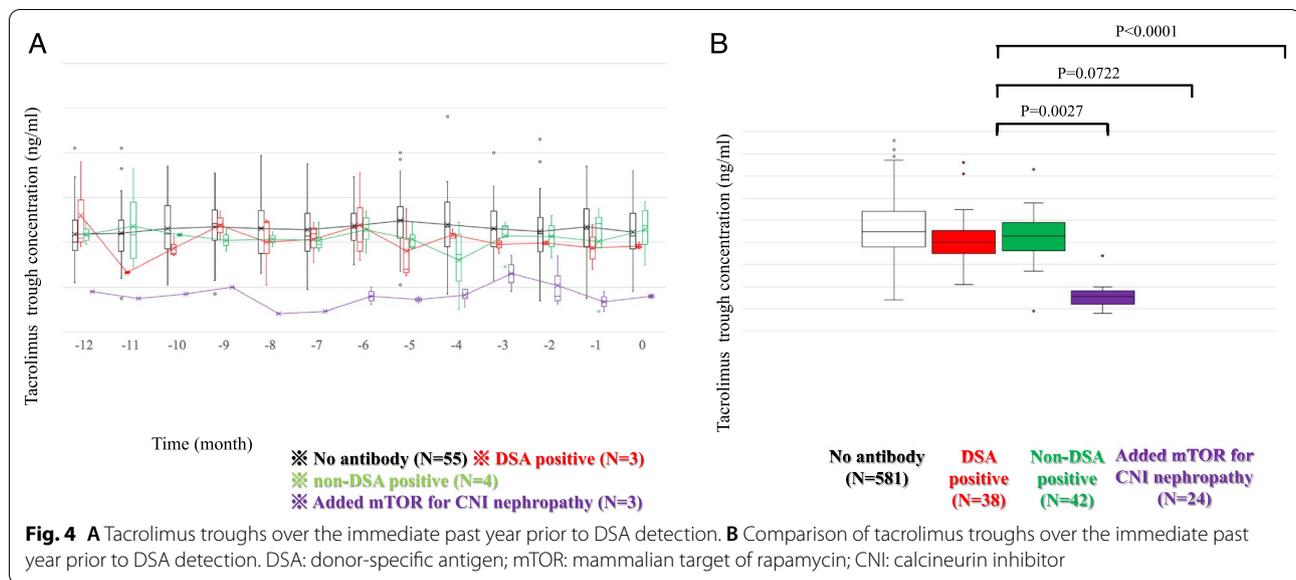
mizoribine (2.5 mg/kg) when she developed herpes zoster. After that, she had an elevated serum creatinine level and proteinuria of 3 g/day. DSA was detected and renal biopsy revealed ABMR. The patient did not respond to any immunosuppression enhancement including steroid pulse therapy (methylprednisolone 250 mg/body on the first day, 100 mg/body on the second day, 100 mg/body on the third day), two sessions of plasmapheresis, rituximab administration (250 mg/body), intravenous immunoglobulin (2 g/kg), and everolimus (1.5 g/body) administration. Hemodialysis was restarted at 13 years after the renal transplant.

Discussion

The pathophysiology of ABMR is that the produced DSA attacks the vascular endothelium of the transplanted kidney, resulting in tissue damage [7]. ABMR is still one of the main causes of renal transplant loss, but it is often difficult to treat at the time of diagnosis because it develops subclinically and tissue damage progresses.

DSA is broadly divided into preformed DSA that exists in serum before transplantation and de novo DSA that is newly produced after transplantation [8, 9]. Preformed DSA is caused by pregnancy, past blood transfusions, and organ transplants. Patients with preformed DSA are at high risk of acute ABMR; even if desensitization therapy is performed before transplantation, the incidence of ABMR is 1–10% [10]. Patients with de novo DSA develop ABMR later than patients with preformed DSA [8, 9] and have a reduced long-term survival rate [11].

The reported incidence of de novo DSA varies, but is about 2–10% at 1 year after renal transplantation, increases by 2% per year and reaches about 10–40% at 4–5 years after transplantation [11–15]. The average time of de novo DSA appearance is reportedly 3.8–68 months after transplantation [12, 15, 16]. In the present study, de

Fig. 4 **A** Tacrolimus troughs over the immediate past year prior to DSA detection. **B** Comparison of tacrolimus troughs over the immediate past year prior to DSA detection. DSA: donor-specific antigen; mTOR: mammalian target of rapamycin; CNI: calcineurin inhibitor

novo DSA was detected at a median time of 141.5 months after transplantation (range 18–275 months), which is longer than previously reported, but we consider that DSA was probably present before it was detected. In addition, the de novo DSA is reportedly predominantly class II antibody [11, 12, 16], which is a risk factor for ABMR [11, 17]. Similarly in the present study, the de novo DSA comprised class II antibodies in all eight patients.

It has been reported that the occurrence of de novo DSA is more common when the blood concentration of tacrolimus fluctuates greatly [18] and when the trough value of tacrolimus is 8 ng/ml or less [19]; thus, such patients should be monitored for the appearance of DSA. This may lead to the early detection of patients at risk of rejection due to inadequate immunosuppression. In addition, monitoring for DSA may improve the prognosis of the transplanted kidney through early diagnosis and treatment at the subclinical ABMR stage before the clinical appearance of renal damage [5, 20, 21]. In the present study, subclinical ABMR was diagnosed in case 3, but as 20 years had passed since the renal transplantation and the MFI had a markedly high value of 21,566, it is considered that DSA was present earlier. In addition, although cyclosporine A was used for CNI in many cases in the past, tacrolimus was used in many cases in recent years, and de novo DSA was frequently observed in patients using cyclosporine A. The target trough for cyclosporine A was less than 100 ng/ml, and the target trough for tacrolimus was 4–6 ng/ml, but the tacrolimus trough concentration was significantly lower in patients with de novo DSA than in patients with no anti-HLA antibody. $(4.09 \pm 1.10$ ng/ml vs. 4.62 ± 1.20 $P = 0.0027)$ (Fig. 4).

Therefore, more stringent control of blood levels may be necessary to reduce the occurrence of de novo DSA.

Although there is no established treatment for ABMR, the treatment options include steroid pulse therapy, rabbit antithymocyte globulin administration, antibody removal using plasma exchange, rituximab administration, immunoglobulin therapy, bortezomib administration, and eculizumab administration [22]. Steroid pulse therapy alone has a low therapeutic effect for ABMR and should be used in combination with other drugs [23]. Plasma exchange and combined therapy comprising plasma exchange and immunoglobulin administration are reportedly effective treatments for ABMR [22, 24]. ABMR with de novo DNA is considered more resistant to treatment than ABMR with preformed DSA [25]. Our treatment strategy for ABMR is steroid pulses followed by plasmapheresis, rituximab, intravenous immunoglobulin, and intensified maintenance immunotherapy. In the present study, two of the eight patients with ABMR did not respond to treatment and eventually lost the transplanted renal function.

The present study had several limitations. This was a retrospective study with a small sample size, the timing of renal transplantation varied, and patients who had already lost transplanted renal function were not included. In addition, the follow-up period after anti-HLA antibody screening was short. It is necessary to accumulate more cases and continue with long-term follow-up to determine whether early intervention for ABMR improves the prognosis of the transplanted kidney.
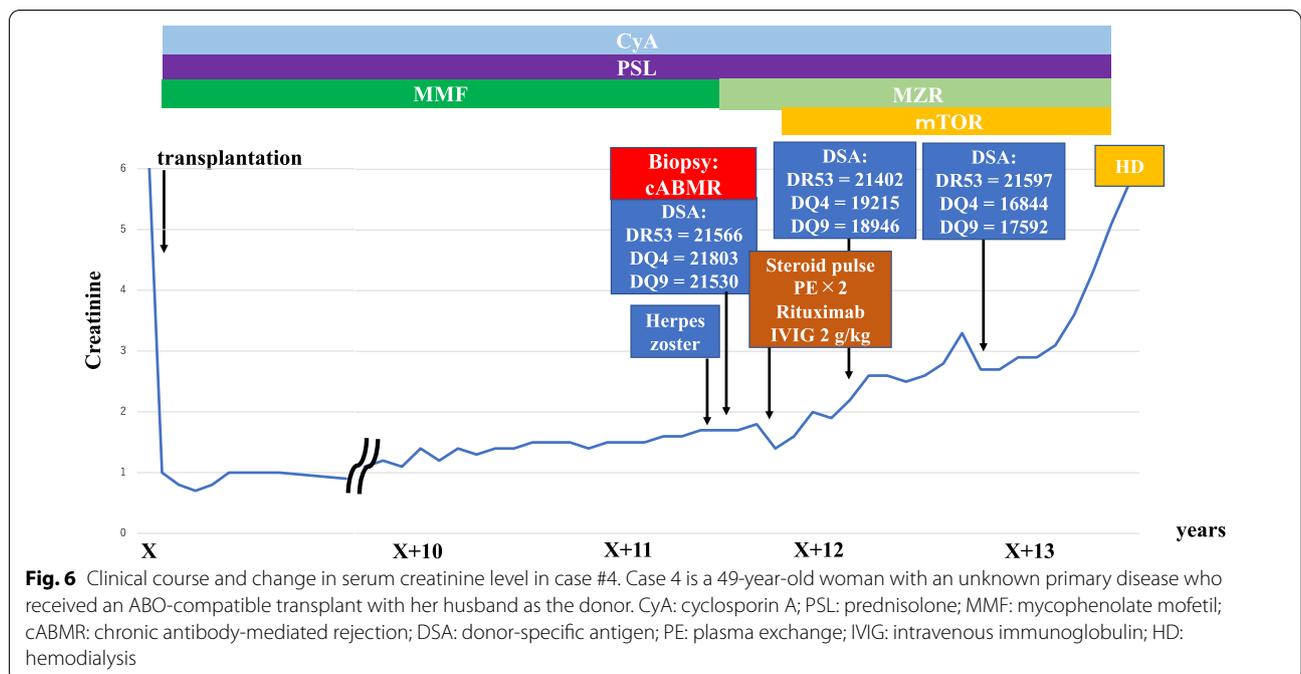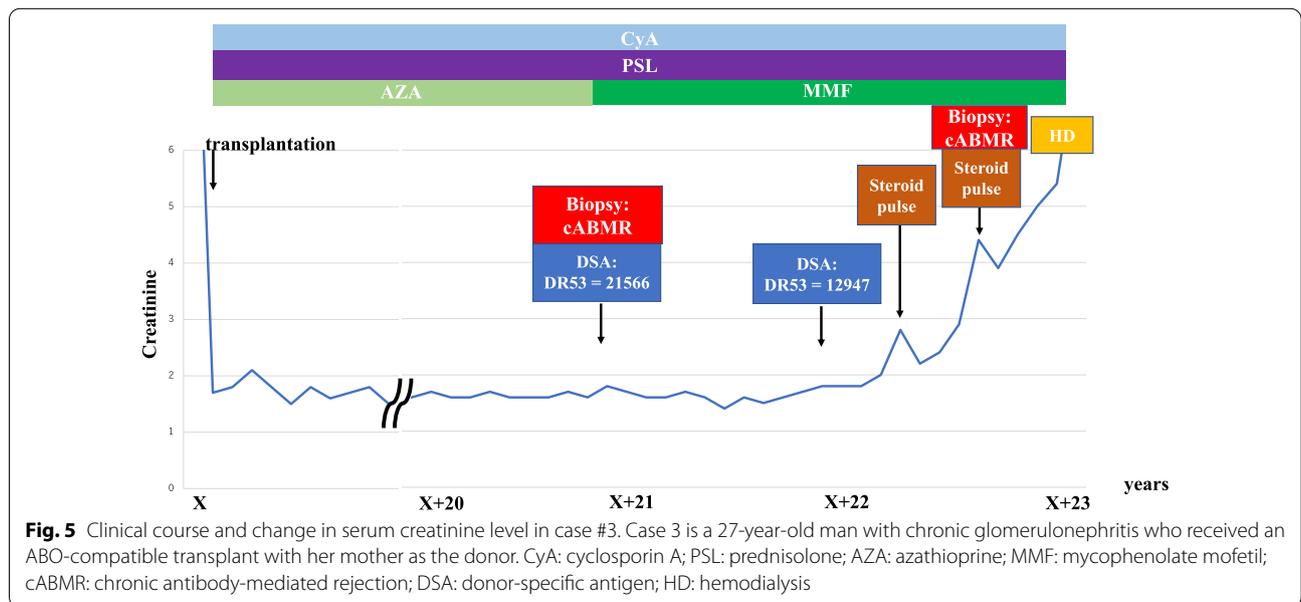
Table 2 Clinical characteristics of DSA-positive recipients

Case no	Age	Sex	Primary disease	ABO	Delayed graft function	Time of DSA detection (post—Tx)	HLA	MFI	Reason for HLA screening	Biopsy	Treatment	Outcome
1	44	Male	IgA nephropathy	Compatible	With	275 months	DR13 DQ6	11226 19056	Protocol	cABMR	AZA→MMF	Alive with graft function
2	43	Male	Chronic glomerulonephritis	Compatible	Without	252 months	DQ6	20866	Serum Cr↑	cABMR+CNI	Steroid pulse, PE, IVIG, Rit, mTOR	Alive with graft function
3	48	Male	Chronic glomerulonephritis	Compatible	Without	251 months	DR53	21566	Protocol	cABMR	AZA→MMF, steroid pulse	Alive with graft loss
4	61	Female	Unknown disease	Compatible	With	142 months	DR53 DQ4 DQ9	22850 21803 21530	Serum Cr↑	cABMR	Steroid pulse, PE, IVIG, Rit, mTOR	Alive with graft loss
5	54	Female	ADPKD	Compatible	Without	141 months	DQ7	7246	Protocol	Not definition for cABMR	Steroid pulse, PE, IVIG	Alive with graft function
6	53	Male	Sarcoidosis	Compatible	Without	88 months	DR53	3326	Protocol	nothing particular	–	Alive with graft function
7	44	Male	IgA nephropathy	Compatible	Without	52 months	DR51	15056	Serum Cr↑ Proteinuria↑	IgA+ cABMR	Steroid pulse, PE, IVIG, Rit	Alive with graft function
8	77	Male	IgA nephropathy	Compatible	Without	18 months	DQ7	14915	Serum Cr↑	Borderline change	rATG, steroid pulse, PE, IVIG	Alive with graft function

ADPKD: Autosomal dominant polycystic kidney disease; DSA: donor-specific antigen; Tx: treatment; HLA: human leukocyte antigen; MFI: mean fluorescence intensity; Cr: creatinine; cABMR: chronic antibody-mediated rejection.; CNI: calcineurin inhibitor; TCMR: T-cell-mediated rejection; AZA: azathioprine; MMF: mycophenolate mofetil; cABMR: chronic antibody-mediated rejection; DSA: donor-specific antigen; PE: plasma exchange; IVIG: intravenous immunoglobulin; Rit: rituximab; mTOR: mammalian target of rapamycin; rATG: rabbit antithymocyte globulin

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Table 3 Banff classification of DSA-positive recipients

Case no	i	t	v	g	ptc	cg	mm	cv	ci	ct	ti	i−IFTA	ah	aah	C4d	Diagnosis
1	0	0	0	0	1	3	0	0	2	2	1	1	0	0	1	cABMR
2	1	0	0	0	2	1b	0	1	2	1	1	1	2	3	0	cABMR+CNI
3	2	1	0	1	0	1b	1	1	2	1	1	1	1	0	1	cABMR
4	1	0	0	0	3	2	1	2	2	2	1	0	2	0	1	cABMR
5	0	0	0	0	0	0	0	1	1	1	0	0	1	0	0	Not definition for cABMR
6	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	Nothing particular
7	1	0	0	2	2	1b	1	1	0	1	0	0	1	0	1	IgA+cABMR
8	3	1	0	0	2	0	0	0	1	1	3	3	0	0	1	Boderline change

Fig. 5 Clinical course and change in serum creatinine level in case #3. Case 3 is a 27-year-old man with chronic glomerulonephritis who received an ABO-compatible transplant with her mother as the donor. CyA: cyclosporin A; PSL: prednisolone; AZA: azathioprine; MMF: mycophenolate mofetil; cABMR: chronic antibody-mediated rejection; DSA: donor-specific antigen; HD: hemodialysis

Fig. 6 Clinical course and change in serum creatinine level in case #4. Case 4 is a 49-year-old woman with an unknown primary disease who received an ABO-compatible transplant with her husband as the donor. CyA: cyclosporin A; PSL: prednisolone; MMF: mycophenolate mofetil; cABMR: chronic antibody-mediated rejection; DSA: donor-specific antigen; PE: plasma exchange; IVIG: intravenous immunoglobulin; HD: hemodialysis

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Conclusions

In the present study, the incidence of anti-HLA antibody development was 17.5%, including the development of DSA in 10.0%. Two (25%) of the eight patients with de novo DSA eventually had graft loss. Most immunosuppressive enhancement therapies were not effective in decreasing the DSA levels. As there is no effective treatment established for the reduction of DSA, careful immunosuppressive management is essential to prevent the development of de novo DSA.

Abbreviations
DSA: Donor-specific antigen; HLA: Human leukocyte antigen; ABMR: Antibody-mediated rejection; MMF: Mycophenolate mofetil.

Authors' contributions
KN and TK contributed to the overall concept and study design; KN, AS, YK, JK, KM, TS, TG, SA, OO, and TK contributed to the intellectual discussion regarding the drafting, revision, and final approval of the manuscript. All authors read and approved the final manuscript.

Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study was approved by the research ethics committee of Kyoto University (#R2485-1). Clinical information and materials related to patients will be anonymized and stored separately at our facility. When the results of the analysis are presented, the anonymized aggregate results will be used so that no individual is identified. This was a retrospective epidemiological study of the medical records. Therefore, there was no need to obtain individual written consent. All patients agreed to the use of their data in retrospective research.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

References
1. Wiebe C, Gibson IW, Blydt-Hansen TD, et al. Evolution and clinical pathologic correlations of *de novo* donor-specific HLA antibody post kidney transplant. Am J Transpl. 2012;12:1157–67.
2. Montgometry RA, Loupy A, Segev DL. Antibody-mediated rejection: new approaches in prevention and management. Am J Transpl. 2018;18(Suppl 3):3–17.
3. Fehr T, Gaspert A. Antibody-mediated kidney allograft rejection: therapeutic options and their experimental rationale. Transpl Int. 2012;25:623–32.
4. Einecke G, Sis B, Reeve J, et al. Antibody-mediated microcirculation injury is the major cause of late kidney transplant failure. Am J Transplant. 2009;9:2520–31.
5. Orandi BJ, Chow EH, Hsu A, et al. Quantifying renal allograft loss following early antibody-mediated rejection. Am J Transpl. 2015;15:489–98.
6. Gaston RS, Cecka JM, Kasiske BL, et al. Evidence for antibody-mediated injury as a major determinant of late kidney allograft failure. Transplantation. 2010;90:68–74.
7. Farkash EA, Colvin RB. Diagnostic challenges in chronic antibody-mediated rejection. Nat Rev Nephrol. 2012;8:255–7.
8. Aubert O, Loupy A, Hidalgo L, et al. Antibody-mediated rejection due to preexisting versus *de novo* donor-specific antibodies in kidney allograft recipients. J Am Soc Nephrol. 2017;28:1912–23.
9. Haas M, Mirocha J, Reinsmoen NL, et al. Differences in pathologic features and graft outcomes in antibodies. Kidney Int. 2017;91:729–37.
10. Chehade H, Pascual M. The challenge of acute antibody-mediated rejection in kidney transplantation. Transplantation. 2016;100:264–5.
11. Wiebe C, Gibson IW, Blydt-Hansen TD, et al. Rates and determinants of progression to graft failure in kidney allograft recipients with *de novo* donor-specific antibody. Am J Transplant. 2015;15:2921–30.
12. Konvalinka A, Tinckam K. Utility of HLA antibody testing in kidney transplantation. J Am Soc Nephrol. 2015;26:1489–502.
13. Heilman RL, Nijim A, Desemarteau YM, et al. *De novo* donor-specific human leukocyte antigen antibodies early after kidney transplantation. Transplantation. 2014;98:1310–5.
14. Everly MJ, Rebellato LM, Haisch CE, et al. Incidence and impact of *de novo* donor-specific alloantibody in primary renal allografts. Transplantation. 2013;95:410–7.
15. Fotheringham J, Angel C, Goodwin J, et al. Natural history of proteinuria in renal transplant recipients developing *de novo* human leukocyte antigen antibodies. Transplantation. 2011;91:991–6.
16. de Kort H, Willicombe M, Brookes P, et al. Microcirculation inflammation associates with outcome in renal transplant patients with *de novo* donor-specific antibodies. Am J Transplant. 2013;13:485–92.
17. Devos JM, Gaber AO, Teeter LD, et al. Intermediate-term graft loss after renal transplantation is associated with both donor-specific antibody and acute rejection. Transplantation. 2014;97:534–40.
18. Rodrigo E, Segundo DS, Fernadez-Fresnedo G, et al. Within-patient variability in tacrolimus blood levels predicts kidney graft loss and donor-specific antibody development. Transplantation. 2016;100:2479–85.
19. Davis S, Gralla J, Klem P, et al. Lower tacrolimus exposure and time in therapeutic range increase the risk of *de novo* donor-specific antibodies in the first year of kidney transplantation. Am J Transplant. 2018;18:907–15.
20. Parajuli S, Joachim E, Alagusundaramoorthy S, et al. Subclinical antibody-mediated rejection after kidney transplantation: treatment outcomes. Transplantation. 2019;103:1722–9.
21. Loupy A, Vernerey D, Tinel C, et al. Subclinical rejection phenotypes at 1 year post-transplant and outcome of kidney allografts. J Am Soc Nephrol. 2015;26:1721–31.
22. Wan SS, Ying TD, Wyburn K, et al. The treatment of antibody-mediated rejection in kidney transplantation: an updated systematic review and meta-analysis. Transplantation. 2018;102:557–68.
23. Crespo M, Pascual M, Tolkoff-Rubin N, et al. Acute humoral rejection in renal allograft recipients: I. Incidence, serology and clinical characteristics. Transplantation. 2001;71:652–8.
24. Lee Y, Lin WC, Wu MS, et al. Repeated cycles of high-dose intravenous immunoglobulin and plasmapheresis for treatment of late antibody-mediated rejection of renal transplants. J Formos Med Assoc. 2016;115:845–52.
25. Velidedeoglu E, Cavaillé-Coll MW, Bala S, et al. Summary of 2017 FDA public workshop: antibody-mediated rejection in kidney transplantation. Transplantation. 2018;102:e257–64.

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