Bortezomib Eliminates Plasma Cells From a Renal Graft in Plasma Cell–Rich Acute Rejection

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ABSTRACT

Plasma cell–rich acute rejection (PCAR) and antibody-mediated rejection (ABMR), for which a standard treatment has not yet been established, are associated with poor graft survival after kidney transplantation. Here, we report a case series of 3 Japanese patients diagnosed with PCAR accompanied by ABMR. Steroid pulse therapy and rabbit antithymocyte globulin, plasma exchange, intravenous immunoglobulin, and rituximab therapies were sequentially performed in the first case. A graft biopsy after each treatment showed that plasma cell infiltration persisted. Five months after the initiation of rejection therapy, the patient was subjected to bortezomib therapy, which led to the partial elimination of plasma cells from the graft. However, the graft function gradually deteriorated, and hemodialysis treatment was warranted. In the other 2 cases, the patients received the same combination of therapy including bortezomib within a short period. Graft biopsies performed subsequently showed a marked decrease in the number of infiltrated plasma cells, and stabilization of renal graft function was achieved in both cases. Bortezomib, which targets plasma cells, is a potent drug that eliminates infiltrated plasma cells from the graft in PCAR. Thus, in addition to conventional therapy comprising plasma exchange, intravenous immunoglobulin, and rituximab against ABMR, bortezomib may be necessary to administer without any delay to control PCAR.

PLASMA cell–rich acute rejection (PCAR), in which plasma cells constitute 10% to 20% of the inflammatory cells infiltrating a renal graft [1], is associated with poor graft survival after kidney transplantation (KTx) [2–4]. Although great progress has been made in treating rejection and prolonging graft survival with potent immunosuppressive drugs, standard therapeutic options for the treatment of PCAR are yet to be established. Antibody-mediated rejection (ABMR) is also being recognized as a major cause of renal allograft injury, contributing to significant morbidity and graft loss. Several studies have shown that PCAR is associated with ABMR; is resistant to standard antirejection therapy such as plasma exchange (PEX), intravenous immunoglobulin (IVIG), rituximab, antithymocyte globulin (ATG), or steroid pulse; and may portend poor graft outcome [2–6]. In contrast, a few studies have suggested that the combination of these antirejection therapies was effective in reducing the number of plasma cells in the graft followed by the stabilization of the graft function [7,8]. Recently, bortezomib, a proteasome inhibitor that induces apoptosis of plasma cells, was used in attempts to treat PCAR and decreased the number of plasma cells in the graft [9]. However, the effect of bortezomib on plasma cells was quite similar to findings reported in a previous study that did not include a specific anti–plasma cell agent [8]. The necessity of bortezomib in the treatment of PCAR

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remains unclear, and evidence for the treatment of PCAR accompanied by ABMR is still lacking.

We report here a series of 3 cases of PCAR accompanied by ABMR in which bortezomib in combination with ABMR treatment might have been necessary for the elimination of infiltrated plasma cells from renal grafts and stabilization of renal graft function. In one of these cases, delay of treatment with bortezomib might be related to the failure of plasma cell elimination in PCAR.

MATERIALS AND METHODS

Three KTx recipients diagnosed with PCAR accompanied by ABMR between 2014 and 2017 were included in our study. The Ethics Committee of the Faculty of Medicine of Niigata University approved the study (NH27-001), which was performed in accordance with the principles stated in the Declaration of Helsinki. Informed consent was obtained from all patients before participation in the study. The patients received renal graft biopsies because of elevated serum creatinine levels. ABMR was diagnosed using Banff 2015 classification. Plasma cells were identified by their characteristic morphology (eosinophilic cytoplasm, eccentrically placed nucleus, and clock-face nuclear chromatin). Periodic acid-Schiff stain was used for plasma cell counting. Biopsy findings were defined as "plasma cell rich" if plasma cells, manually counted from the interstitium of the biopsy specimen, accounted for at least 10% of the infiltrating cell population. We calculated the area of the biopsy specimens using Adobe Photoshop CS5 extended Ver. 12 and compared the number of infiltrating plasma cells per unit area before and after treatment. The plasma cells were counted independently by 3 persons, and the average number of infiltrating plasma cells counted was used. Immunohistochemistry was performed for CD20 (BD Biosciences) and CD138 (Beckman Coulter, Marseille, France) and for kappa and lambda light chains (Dako, Carpinteria, Calif, United States) by using monoclonal antibodies. C4d staining was performed by immunofluorescence on frozen sections by using monoclonal antibody against complement protein C4d (Quidel, San Diego, Calif, United States). C4d positivity was interpreted and reported according to Banff 2015 criteria. SV40 (Calbiochem, Darmstadt, Germany) was used routinely for the diagnosis of BK virus nephropathy. In situ hybridization for Epstein-Barr virus–encoded RNAs (EBERs) was performed to confirm Epstein-Barr virus infection in the renal grafts.

Human leukocyte antigen (HLA) antibody testing was performed using a bead-based fluorometric Luminex assay (Luminex Corporation, Austin, Texas). Mean fluorescence intensity (MFI) >1000 was considered positive.

RESULTS

Case Presentation

Case 1. A 21-year-old man was admitted to our hospital because of an elevated serum creatinine level. He had been diagnosed with Alport syndrome at 3 years of age and received a KTx from a deceased donor at 14 years of age. The ABO blood type was matched and HLA alleles were mismatched at 5 loci: A2, A11, B46, B48, and DR9. The complement-dependent cytotoxicity (CDC) test and the flow cytometric crossmatch (FCXM) test were negative before KTx. Maintenance immunosuppressive therapy consisted of tacrolimus (FK: trough levels of 5–8 ng/mL); mycophenolate mofetil (MMF), 750 mg/d; and methylprednisolone (MP), 4 mg/d. His serum creatinine level was stable after KTx (1.4 mg/dL 6 weeks before admission) but rapidly increased to 3.07 mg/dL on admission. Steroid pulse therapy, 500 mg for 2 days and tapered, was initiated, but the serum creatinine level remained at 3.3 mg/dL 8 days later (Fig 1A). Renal graft biopsy showed T-cell-mediated rejection (TCMR) and PCAR with 14.4% of plasma cell infiltration accompanied by ABMR (Fig 1B, Bx1). SV40 staining was negative. In situ hybridization for EBERs was negative. HLA antibody testing by Luminex showed the development of donor-specific antibodies (DSAs, HLA-A2); MFI was 1639 (Fig 1A). We administered an additional 7 doses of rabbit antithymocyte globulin (rATG), 1.5 mg/kg/d. Serum creatinine and DSA levels slightly decreased to 3.06 mg/dL and an MFI value of 345, respectively. Renal graft biopsy 1 month after rATG treatment showed slight improvement in TCMR and ABMR and no change in PCAR (Fig 1B, Bx2). After 3 months, 3 sessions of PEX were performed, followed by the administration of IVIG (0.1 g/kg) and rituximab (100 mg). The serum creatinine level decreased to 2.76 mg/dL 2 weeks after therapy with PEX, IVIG, and rituximab was initiated but gradually increased to 3.25 mg/dL. In recognition of the persistence of infiltrated plasma cells in renal graft biopsy at this point (Fig 1B, Bx3), 4 doses of bortezomib (1.3 mg/m^2/dose) were administered. The serum creatinine level slowly increased thereafter; however, biopsy showed partial elimination of infiltrated plasma cells in some area 3 months after bortezomib treatment (Fig 1B, Bx4), although the number of plasma cells per unit area was relatively unchanged (Fig 1C). Unfortunately, the patient's renal function deteriorated, and hemodialysis was necessary 17 months after the diagnosis of PCAR accompanied by ABMR.

Case 2. A girl who was born as the donor of twin-to-twin transfusion syndrome had acute renal failure due to renal thrombosis and required peritoneal dialysis thereafter. She received a kidney from a living-related donor (mother) at 4 years of age. The ABO blood types were mismatched (O→A), and the HLA alleles were mismatched at 2 loci, B39 and DR15. She had received blood transfusion previously, and the CDC test was negative for T-cell and B-cell warm antibodies but positive for B-cell cold antibodies before KTx. The FCXM test and DSAs investigated using the Luminex assay were negative before KTx. Immunosuppression therapy consisted of basiliximab induction (10 mg on days 0 and 4), cyclosporine A (CyA: trough levels, 100–150 ng/mL for 1 month, then tapered to 50–100 ng/mL), MMF (250 mg, twice daily), and MP (125 mg/d, tapered to a maintenance dose of 4 mg/d). Protocol biopsy on day 56 showed mild nephrotoxicity caused by a calcineurin inhibitor (CNI), and the dose of CyA was reduced (trough level, 50 ng/mL). The post-transplant baseline serum creatinine level ranged from 0.3 to 0.5 mg/dL (Fig 2A). Because of the elevated serum creatinine level, she admitted to our hospital and a renal graft biopsy was performed on post-transplant day 336, which showed acute TCMR and PCAR with 12.2% of

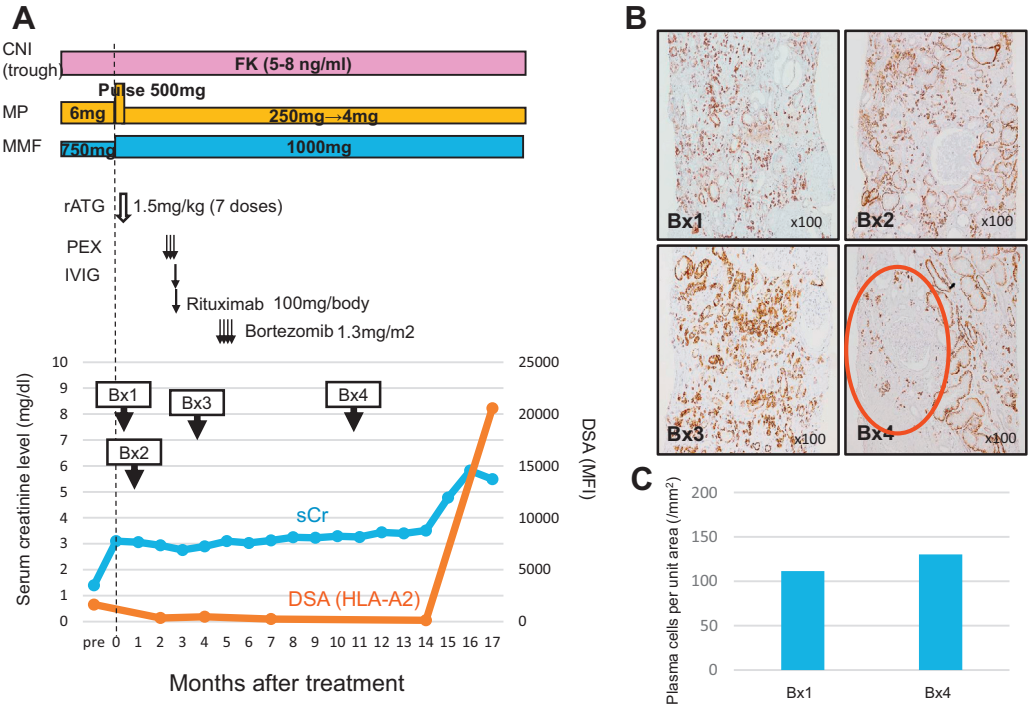

Fig 1. **(A)** Clinical course in case 1. Blue line and orange line show serum creatinine and DSA levels, respectively. CNI, calcineurin inhibitor; FK, tacrolimus; MP, methylprednisolone; MMF, mycophenolate mofetil; rATG, rabbit antithymocyte globulin; PEX, plasma exchange; IVIG, intravenous immunoglobulin; Bx, biopsy; DSA, donor specific antibody; MFI, mean fluorescence intensity. **(B)** Immunohistochemistry of renal graft biopsy. Plasma cells and part of the tubular cells were stained with anti-CD138 antibody. Plasma cells were infiltrated in the grafts after steroid pulse therapy (Bx1). Infiltrated plasma cells were not changed after treatment with rATG (Bx2) and after treatment with PEX, IVIG, and rituximab (Bx3). The number of plasma cells decreased in part of area after bortezomib administration (Bx4, red circle). **(C)** The number of infiltrated plasma cells in the biopsy specimen per unit area (/mm^2).

plasma cell infiltration accompanied by ABMR (Fig 2B, Bx1). SV40 staining was negative. In situ hybridization for EBERs was negative. HLA antibody testing by the Luminex assay showed the development of DSAs (HLA-DR15, MFI: 5564) (Fig 2A). Steroid pulse therapy (250 mg for 2 days and tapered) was initiated, and CyA was switched to FK. The dose of MMF was increased from 250 mg/d to 500 mg/d (trough level, 3–5 ng/mL). Three sessions of PEX and IVIG administration (total dose, 1 g/kg) were performed. The serum creatinine level decreased from 1.14 to 0.62 mg/dL and then increased to 0.72 mg/dL; DSAs persisted (MFI: 4163) (Fig 2A). For the treatment of ABMR, another 3 sessions of PEX were performed, and IVIG (total dose, 1 g/kg) and rituximab (375 mg/m^2) were administered. In addition, 4 doses of bortezomib (1.3 mg/m^2/dose) were administered because infiltrated plasma cells were found in the renal graft. Renal graft biopsy performed 4 months after the treatment for rejection showed a marked improvement in PCAR (Fig 2B, Bx2). However, TCMR persisted, although it was improved compared to that before treatment, and therefore 7 doses of rATG (1.5 mg/kg/d) were administered. The patient's serum creatinine level was stable, and a level of DSAs was maintained negative thereafter (Fig 2A). Renal graft biopsy performed subsequently showed improvement in TCMR (Fig 2B, Bx3), and the latest graft biopsy showed no worsening of PCAR (Fig 2B, Bx4). The number of plasma cells per unit area markedly decreased after bortezomib administration (Fig 2C).

Case 3. A 15-year-old woman had been diagnosed with type 1 diabetes and developed end-stage renal disease due to diabetic nephropathy, for which she required hemodialysis since 29 years of age. She received a simultaneous pancreas-kidney transplantation from a deceased donor at the age of 30 years. The ABO blood type was matched, and the HLA alleles were mismatched at 5 loci: A24, A26, B54, B62, and DR7. The CDC and FCXM tests were negative before transplantation. MP, MMF, FK, and rATG were used to induce immunosuppression. Maintenance immunosuppressive therapy consisted of FK (trough levels, 4–5 ng/mL) and azathioprine (50 mg/d). Her serum creatinine levels were stable for 6 years after transplantation but she admitted to our hospital because her creatinin level increased to 1.47 mg/dL from 1.0 mg/dL thereafter (Fig 3A). Her blood sugar and C-peptide levels were fortunately stable without any insulin use. She showed drug nonadherence, and renal graft biopsy demonstrated PCAR with 14.4% of plasma cell infiltration accompanied by ABMR (Fig 3B, Bx1). HLA antibody testing by the Luminex assay showed

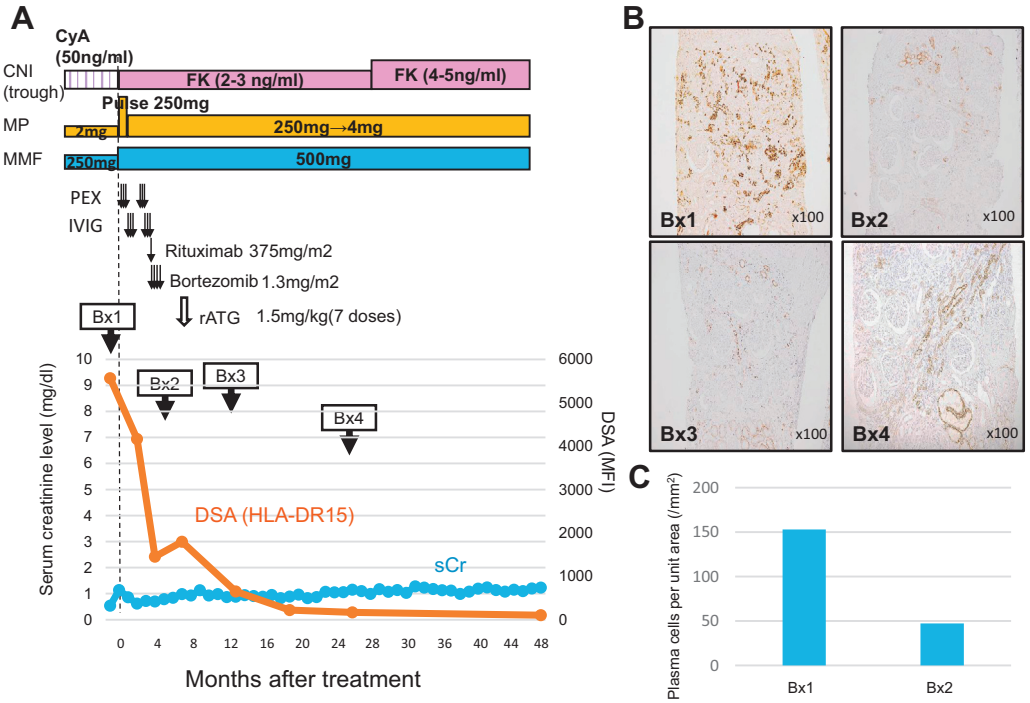

Fig 2. **(A)** Clinical course in case 2. Blue line and orange line show serum creatinine and DSA levels, respectively. CNI, calcineurin inhibitor; CyA, cyclosporine A; FK, tacrolimus; MP, methylprednisolone; MMF, mycophenolate mofetil; rATG, rabbit antithymocyte globulin; PEX, plasma exchange; IVIG, intravenous immunoglobulin; Bx, biopsy; DSA, donor specific antibody; MFI, mean fluorescence intensity. **(B)** Immunohistochemistry of renal graft biopsy. Plasma cells and part of the tubular cells were stained with anti-CD138 antibody. Plasma cells were infiltrated in the grafts before treatment (Bx1). Plasma cells were eliminated after bortezomib administration (Bx2). No plasma cell infiltration was noted thereafter (Bx3 and Bx4). **(C)** The number of infiltrated plasma cells in the biopsy specimen per unit area (/mm^2).

the development of DSAs (HLA-DR7, MFI: 26141) (Fig 3A). Therefore, combination therapy consisting of steroid pulse therapy, 3 sessions of PEX, low dose of IVIG (0.1 g/kg), and rituximab (100 mg) was performed; however, plasma cell infiltration persisted in the graft (Fig 3B, Bx2). We decided to administer 4 doses of bortezomib (1.3 mg/m^2/dose) just after the second biopsy. Six months after the treatment for rejection, renal graft biopsy showed elimination of many of the infiltrated plasma cells from the graft (Fig 3B, Bx3). The patient's serum creatinine levels were stable, and DSAs markedly decreased (MFI: 7329) (Fig 3A). The number of plasma cells per unit area markedly decreased after bortezomib administration (Fig 3C).

Histologic and Immunohistochemical Assessment

Table 1 shows the results of renal graft biopsies assessed based on the 2015 Banff classification. Combination therapy for mixed rejection (TCMR, ABMR, and PCAR) resulted in improvements in acute changes, such as tubulitis in 2 patients and interstitial mononuclear infiltration and peritubular capillaritis in all 3 patients. However, chronic changes, such as interstitial fibrosis and tubular atrophy, persisted. Even though serum DSA levels decreased in all patients after treatment, glomerulitis worsened in case 2. C4d depositions were noted after treatment in cases 1 and 3. Figure 4 shows immunofluorescence microscopy findings in case 2, when the patient was diagnosed with PCAR. The figure shows CD138-positive cells clustered with CD20-positive cells in the renal graft.

Adverse Events

Cytomegalovirus (CMV) viremia, determined using the CMV antigenemia assay, was seen after rATG administration in case 1, although oral ganciclovir prophylaxis (200 mg 2 times per day twice a week) was used concurrently, and intravenous ganciclovir treatment was required. Valganciclovir was used for CMV prophylaxis (450 mg 1 time per day twice a week) in cases 2 and 3, and the results of testing for CMV antigens were continuously negative during follow-up. In case 1, pancytopenia was noted 7 days after bortezomib administration. White blood cell, red blood cell, and platelet counts decreased from 4390/μL, 303 × 10^4/μL, and 17.9 × 10^4/μL to 1870/μL, 257 × 10^4/μL, and 11.4 × 10^4/μL, respectively. White blood cell and red blood cell counts recovered after injections of granulocyte-colony stimulating factor and erythropoietin. Platelet count decreased to 8.9 × 10^4/μL 15 days after bortezomib administration and spontaneously recovered thereafter. Serum immunoglobulin

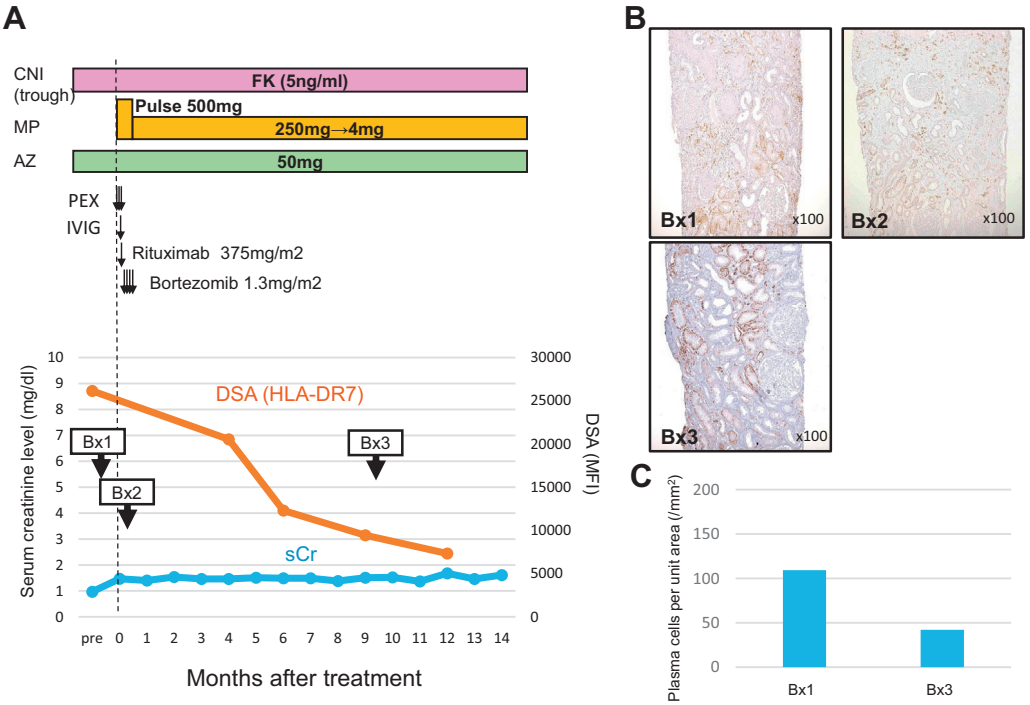

Fig 3. **(A)** Clinical course in case 3. Blue line and orange line show serum creatinine and DSA levels, respectively. CNI, calcineurin inhibitor; FK, tacrolimus; MP, methylprednisolone; AZ, azathioprine; rATG, rabbit antithymocyte globulin; PEX, plasma exchange; IVIG, intravenous immunoglobulin; Bx, biopsy; DSA, donor specific antibody; MFI, mean fluorescence intensity. **(B)** Immunohistochemistry of renal graft biopsy. Plasma cells and part of the tubular cells were stained with anti-CD138 antibody. Plasma cells were infiltrated in the grafts before treatment (Bx1 and Bx2). Plasma cells were eliminated after bortezomib administration (Bx3). **(C)** The number of infiltrated plasma cells in the biopsy specimen per unit area (/mm^2).

levels were unchanged from pretreatment levels in all patients. Serum titers of antibodies to measles and rubella did not decrease in any patient after combination therapy for PCAR. Patient 1 had general fatigue during bortezomib treatment, which spontaneously resolved. None of the patients showed other opportunistic infections or peripheral neuropathy.

Table 1. Banff 2015 Classification

Case	Bx	t	i	g	v	ptc	ct	ci	cg	cv	ptcbm	C4d
Case 1	Bx 1	2	2	2	0	3	2	1	1b	1	1	0
	Bx 2	2	2	0	0	0	1	1	1b	1	2	0
	Bx 3	0	0	0	0	0	3	3	0	2	0	0
	Bx 4	0	0	1	0	0	3	3	0	2	1	3
Case 2	Bx 1	3	2	1	0	3	0	0	0	0	1	3
	Bx 2	1	2	1	0	3	2	1	0	0	2	1
	Bx 3	0	0	3	0	2	1	1	0	0	1	0
	Bx 4	2	0	3	0	2	3	2	0	0	1	0
Case 3	Bx 1	1	1	0	0	3	1	1	0	0	1	3
	Bx 2	1	0	0	0	2	1	1	1	0	1	0
	Bx 3	3	0	0	0	0	1	0	0	0	0	3

Abbreviation: Bx, biopsy. t, tubulitis. i, interstitial inflammation. g, glomerular inflammation. v, arterial inflammation. ptc, peritubular capillaritis. ct, tubular atrophy. ci,interstitial fibrosis. cg, transplant glomerulopathy. cv, arterial fibrointimal thickness. ptcbm, peritubular capillary basement membrane thickness. C4d, complement 4d deposition on peritubular capillary.

DISCUSSION

Herein, we have reported 3 cases in which bortezomib was used for the treatment of PCAR accompanied by TCMR or ABMR. Early reports showed that half of the patients with PCAR lost their allografts within 6 months [2,4] and that antirejection therapy such as steroids, deoxyspergualin, and OKT3 was not effective for the treatment of PCAR [10–12]. Although recent immunosuppressive therapies targeting ABMR have been developed, the evidence for effective PCAR treatment is inadequate. Furuya et al reported a marked reduction in plasma cell infiltration after rituximab treatment in addition to PEX and high-dose IVIG [7]. Abbas et al demonstrated that treatment consisting of ATG, rituximab, and PEX was effective in reducing the number of plasma cells [8]. However, rituximab is a chimeric monoclonal antibody that binds specifically to the CD20 antigen, which is not expressed on plasma cells. Rituximab as well as ATG failed to cause the apoptosis of plasma cells in vitro [13] and did not reduce the number of splenic plasma cells in vivo [14]. IVIG also had no effect on plasma cells in PCAR [1]. Most recently, Abbas et al reported the results of bortezomib administration [9], in addition to their previous findings for treatment with ATG, rituximab, and PEX, in PCAR with ABMR [8]. Plasma cells reduced from 30.59%

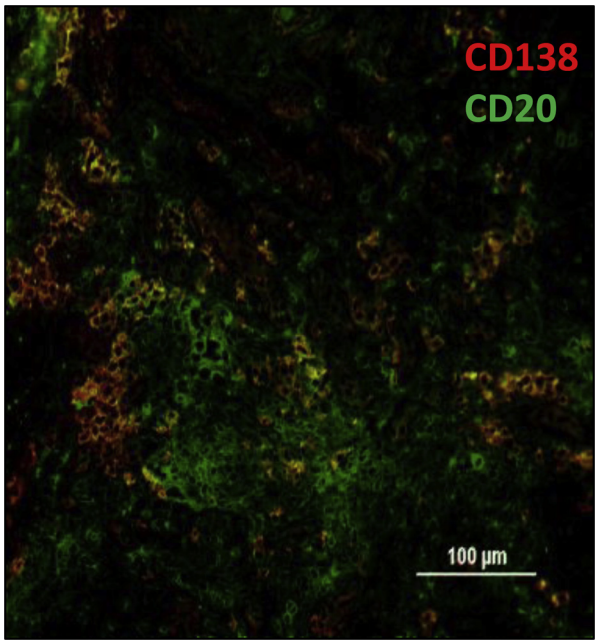

Fig 4. Immunofluorescence microscopy at diagnosis of plasma cell–rich acute rejection (PCAR). CD138-positive cells (red) clustered with CD20-positive cells (green) at the diagnosis of PCAR (case 2).

± 8.99% to 8.82% ± 8.68% in the absence of bortezomib treatment [8] and from 33.40% ± 11.55% to <14.00% ± 6.99% with bortezomib treatment [9]. The findings were rather similar, and the effect of bortezomib in terms of plasma cell elimination from the graft was unclear. Sun et al reported a case in which PCAR was treated with ATG followed by bortezomib [15]. In that case, the number of plasma cells was unchanged after ATG treatment but decreased after bortezomib administration.

In our cases, steroid pulse therapy and administration of rATG were performed for TCMR and steroid-resistant TCMR, respectively. PEX, IVIG, and rituximab were used for ABMR treatment. In case 1, we confirmed the effect of treatments with steroid, rATG, IVIG/rituximab, and bortezomib on plasma cells by biopsies after each treatment, and we noted that the biopsies showed no change in the number of infiltrated plasma cells after treatment. However, partial elimination of the cells could be seen in some part of the graft after bortezomib administration. In case 3, the number of plasma cells did not decrease after treatment with PEX, IVIG, and rituximab but markedly decreased after bortezomib administration. Bortezomib has been shown to directly affect the function and integrity of nonmalignant plasma cells [13,16,17] and to cause apoptosis of plasma cells in vitro [13]. In the present study, bortezomib was confirmed to reduce the number of the infiltrated plasma cells from the graft in vivo. Because case 1 was followed up in a different clinic, PCAR treatment was delayed. Furthermore, to avoid over-immunosuppression, there was some interval from the start of treatment to bortezomib administration . In contrast, in cases 2 and 3, bortezomib was administered after a short interval following conventional therapy consisting of PEX, IVIG, and rituximab for ABMR. The results in case 1 might have been affected by the delay in treatment.

The pathogenesis of PCAR is unknown. Several studies have suggested that PCAR is a variant of ABMR [3,6]. Plasma cells are terminally differentiated from B cells as final effectors of the humoral immune response. As antibody-secreting elements, plasma cells play a key role in ABMR. However, the causes of the infiltration of plasma cells into grafts remain unknown. In case 2, immunofluorescence microscopy showed CD138-positive cells clustered together with CD20-positive cells in PCAR (Fig 4), suggesting that B cells locally differentiated into mature plasma cells in the renal graft in PCAR accompanied by ABMR. The use of bortezomib in addition to rituximab may be necessary to achieve the elimination of plasma cells in PCAR.

This study has some limitations. The sample size was small, and the study was retrospective in nature. Furthermore, there were no control cases. The optimal number of bortezomib courses remains unclear, and multiple courses of bortezomib could be the best option for PCAR treatment.

CONCLUSIONS

We presented a series of 3 cases of PCAR accompanied by ABMR in which bortezomib was successful in decreasing the number of infiltrated plasma cells. PCAR accompanied by ABMR carries a high risk of graft loss. Careful follow-up and prompt diagnosis followed by treatment including bortezomib, PEX, IVIG, and rituximab without any delay may be important in controlling these types of rejection.

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