Renal Replacement Therapy

CASE REPORT

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Importance of multidisciplinary collaboration for smooth kidney transplantation in HIV-infected patients with chronic kidney disease: a case report

Tetsuya Abe[1*], Daisuke Ishii[2], Yuki Imura[2], Ayano Noguchi[2], Kazuki Kitajima[2], Yasuo Takeuchi[1], Tatsuhiko Wada[3] and Kazunari Yoshida[2]

Abstract

Background: Antiretroviral therapy (ART) has reduced mortality caused by AIDS resulting from HIV infection. Meanwhile, the prevalence of chronic kidney disease, a chronic HIV complication, is increasing. Antiretroviral therapy has improved the life expectancy of HIV-infected kidney transplant recipients. In Japan, discrimination and prejudice against HIV persist, and few kidney transplants are performed. We report three cases in which kidney transplantation was smoothly performed with multidisciplinary collaboration.

Case presentation: The first case involved a 29-year-old male urgently hospitalized due to severe kidney dysfunction, diagnosed with HIV-associated nephropathy (HIVAN), and placed on maintenance dialysis. The patient was administered oral lamivudine, abacavir, and raltegravir as ART and underwent blood group-matched living donor kidney transplantation at age 32. The second case involved a 49-year-old male diagnosed as HIV-positive at age 33 and placed on maintenance dialysis for HIVAN at age 47. Darunavir, ritonavir, and dolutegravir (DTG) were initially administered. However, the ART was switched to rilpivirine (RPV) and DTG prior to kidney transplantation because of potential ART interactions with calcineurin inhibitors. The patient underwent blood group-matched living donor kidney transplantation. The third case involved a 41-year-old male diagnosed as HIV-positive at 23 years old and treated with RPV and DTG. Due to autosomal dominant polycystic kidney disease (ADPKD), his kidney function gradually worsened, and he was started on hemodialysis. He underwent hemodialysis, followed by blood type-matched living donor kidney transplantation. In all cases, transplant physicians, nephrologists, infectious disease physicians, hepatologists, nurses, pharmacists, nutritionists, and clinical psychologists collaborated to discuss and share medical problems and sociopsychological backgrounds of the patients. There was no rejection, CD4+ lymphocyte counts were maintained, and there was no increase in viral load post-surgery. Information sharing among various departments has continued post-surgery, kidney function has improved, and no increase in viral load has been identified on follow-up.

Conclusions: Kidney transplantation is the kidney replacement therapy of choice for HIV-infected patients with CKD. Specialized support is required for kidney transplantation, including coordinating immunosuppressive therapy to

*Correspondence: tetsuyaa@med.kitasato-u.ac.jp

[1] Department of Nephrology, Kitasato University School of Medicine, 1-15-1 Kitasato, Minami, Sagamihara, Kanagawa 252-0375, Japan
Full list of author information is available at the end of the article

avoid rejection, learning about drug interactions, and providing sociopsychological support. Multidisciplinary collaboration is important to ensure safe and smooth kidney transplantation care for HIV-infected patients.

Keywords: HIV, Kidney transplantation, Multidisciplinary cooperation

Background

HIV is a single-stranded RNA virus that infects CD4-positive T lymphocytes, and opportunistic infections are likely to occur when CD4-positive T lymphocytes fall below 200/μL. Before introducing antiretroviral therapy (ART), the prognosis of patients who developed AIDS was extremely poor; ART has dramatically improved the prognosis of Japanese patients [1, 2].

Chronic kidney disease (CKD) is a chronic complication of HIV infection [3]. HIV-related kidney disorders include HIV-related nephropathies such as focal glomerulosclerosis, drug-induced nephropathy due to ART, and diabetes and hypertension as side effects of ART [4]. The risk of end-stage kidney failure in HIV-positive patients is approximately four times that in HIV-negative patients, and the risk of kidney dysfunction is also high [5]. Although ART has improved the prognosis of HIV-positive dialysis patients and kidney transplant recipients [2, 6], discrimination and prejudice persist in HIV care in Japan, and medical personnel are uncomfortable providing care for patients with HIV. Against this background, kidney transplantation in HIV-infected patients with CKD in Japan is underreported. Multidisciplinary collaboration and comprehensive medical care that includes the patient as a treatment team member is important in HIV treatment and kidney transplantation. Our team for HIV-infected kidney transplantation consists of transplant physicians, nephrologists, infectious disease specialists, hepatologists, nurses, pharmacists, nutritionists, and clinical psychologists (Fig. 1). This multidisciplinary team can share information about medical issues, such as renal transplant surgery, managing drug interactions, and controlling HIV and hepatitis viruses. In addition, HIV care can include sociopsychological support for patient psychological concerns and worries and social discrimination and prejudice. We report three cases of kidney transplantation at our hospital, in which the procedure was performed safely and smoothly with multidisciplinary collaboration for HIV-infected patients with CKD.

Case presentation

Case 1

A 32-year-old male with a history of homosexual intercourse at the age of 16 presented to our clinic at the age of 29 with a fever and decreased appetite. The patient

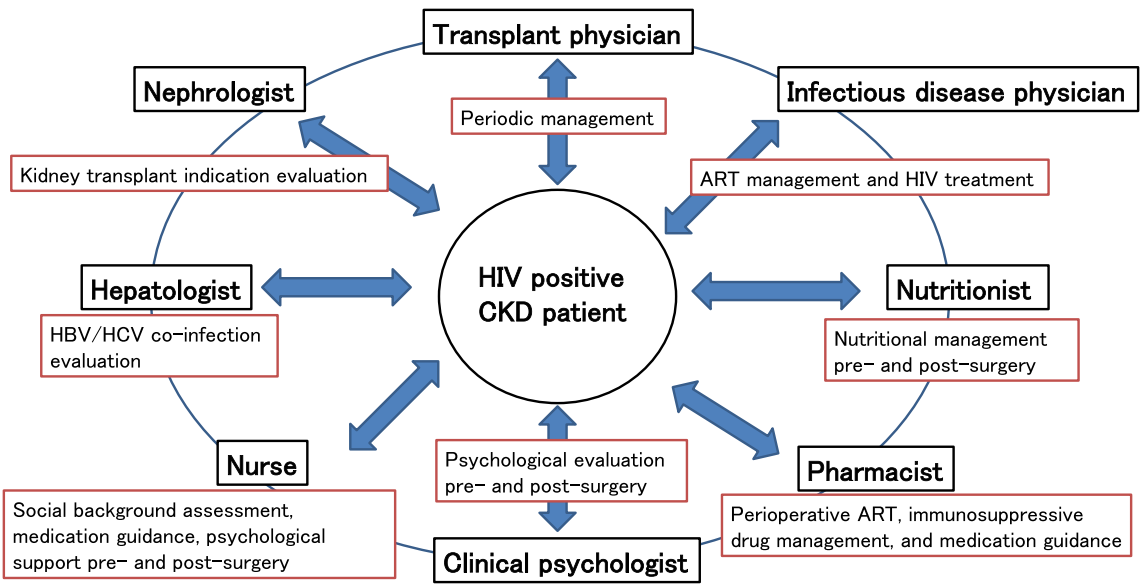

Fig. 1 Multidisciplinary cooperation in our hospital. Transplant physicians, nephrologists, infectious disease physicians, hepatologists, nurses, pharmacists, nutritionists, and clinical psychologists collaborated to discuss and share medical problems and sociopsychological backgrounds of patients

was found to be HIV-positive (CD4+ 261 cells/μL, CD4/CD8 0.33, HIV RNA 9.5×10^3 copy/mL) and had severe kidney dysfunction (serum creatinine [sCr] 26.7 mg/dL, eGFR 2.0 mL/min/1.73 m^2). Emergency hemodialysis was performed. Antiretroviral therapy was initiated with two nucleoside reverse transcriptase inhibitors (NRTIs), lamivudine (3TC) and abacavir (ABC), and raltegravir (RAL), an integrase strand transfer inhibitor (INSTI). The patient was HLA-B5701 negative. When he was 30 years old, he visited our hospital as he wished to undergo living donor kidney transplantation with his mother as donor. When he came to our hospital, his ART included 3TC, ABC, and RAL, two of which were NRTIs, and tests showed CD4+ 806 cells/μL, CD4/CD8 0.54, and HIV RNA < 20 copies/mL. A preoperative multidisciplinary meeting confirmed that the HIV treatment course was good and family members understood and agreed to the procedures. ART was continued as no interactions with immunosuppressive drugs for kidney transplantation were observed. Blood group-matched living donor kidney transplantation (O⇒A) was performed using the mother as the donor (HLA: 2 mismatches, FCXM: class 1 negative (0.08%), class 2 negative (7.59%)). Flow PRA: class 1 negative (0.74%), class 2 negative (0.50%), warm ischemic time (WIT) 5 min 5 s, cold ischemic time (CIT) 89 min, and first urine was 11 min. Postoperative kidney function rapidly improved, and the sCr level was 2.62 mg/dL at discharge (Fig. 2). The lamivudine dose was increased as renal function improved.

Case 2

The patient was a 49-year-old male who was diagnosed with HIV at 33 years old and commenced ART at 37 years old. He placed on maintenance dialysis for HIVAN at age 47. The patient was referred to our hospital at 48 years of age for kidney transplantation, with his mother as donor. At the time of presentation, ART included protease inhibitors (PIs) (darunavir and ritonavir), and the INSTI

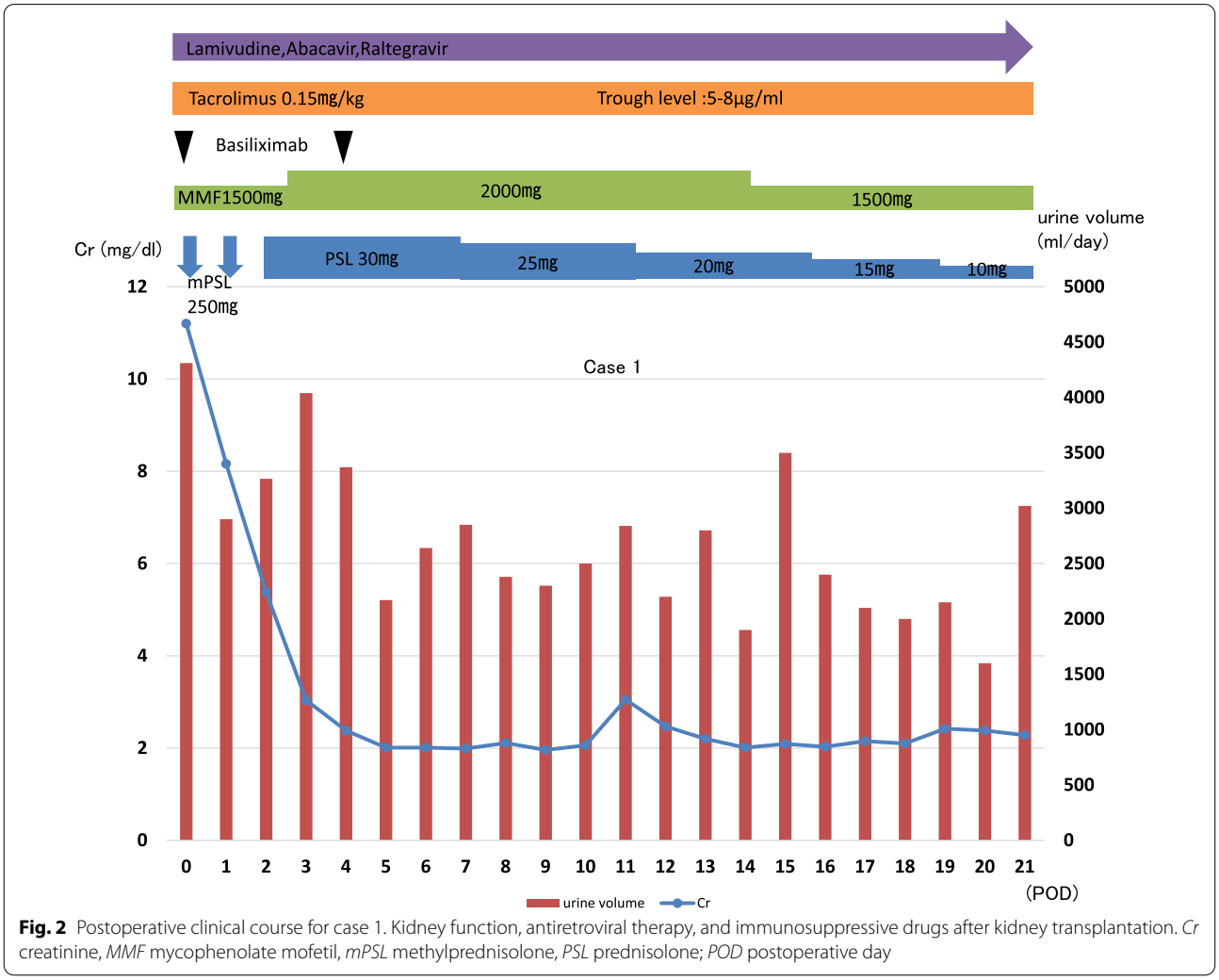

Fig. 2 Postoperative clinical course for case 1. Kidney function, antiretroviral therapy, and immunosuppressive drugs after kidney transplantation. *Cr* creatinine, *MMF* mycophenolate mofetil, *mPSL* methylprednisolone, *PSL* prednisolone; *POD* postoperative day

dolutegravir (DTG). Test results showed CD4+1168 cells/μL, CD4/CD8 1.81, and HIV RNA < 20 copies/mL. Additional tests showed HBVAg−, HBVAb+, HBcAb+, and HBV-DNA < 2.1 logcopy/mL. During a multidisciplinary team meeting, the ART regime was changed, due to interactions of PIs with calcineurin inhibitors, to RPV, a non-nucleoside reverse transcriptase inhibitor (NNRTI), and DTG, an INSTI. PRV and DTG were selected because these drugs can be used as a fixed-dose combination and are expected to improve medication adherence in the outpatient setting as a single-tablet regimen. It was determined that hepatitis B virus (HBV) infection was preexisting, and no treatment was necessary prior to transplantation. Psychologically, there were no problems with understanding the treatment among family members. Blood group-compatible living donor kidney transplantation (O⇒B) was performed with the mother as donor (HLA 1 mismatch, FCXM class 1 negative (1.0%), class 2 positive (3.8%), donor specific antibody negative by the anti-HLA antigen single antigen identification test). The WIT was 6 min, CIT was 111 min, and first urine was 12 min. Postoperative kidney function improved quickly, and sCr was 2.83 mg/dL at discharge (Fig. 3).

Case 3

A 41-year-old male, diagnosed as HIV-positive at the age of 23, commenced ART at the age of 26 and was treated with tolvaptan for ADPKD, however, his kidney function worsened, and he was placed on hemodialysis at the age of 41. He visited our hospital because he wanted to undergo living donor kidney transplantation with his father as donor. On presentation, ART comprised RPV and DTG. Test results revealed CD4+360 cells/μL, CD4+/CD8 1.10, and HIV RNA < 20 copies/mL, HBV-DNA 2.1 log copy/mL. During a multidisciplinary team meeting, it was determined that ART would be continued, HBV infection was already present, and no

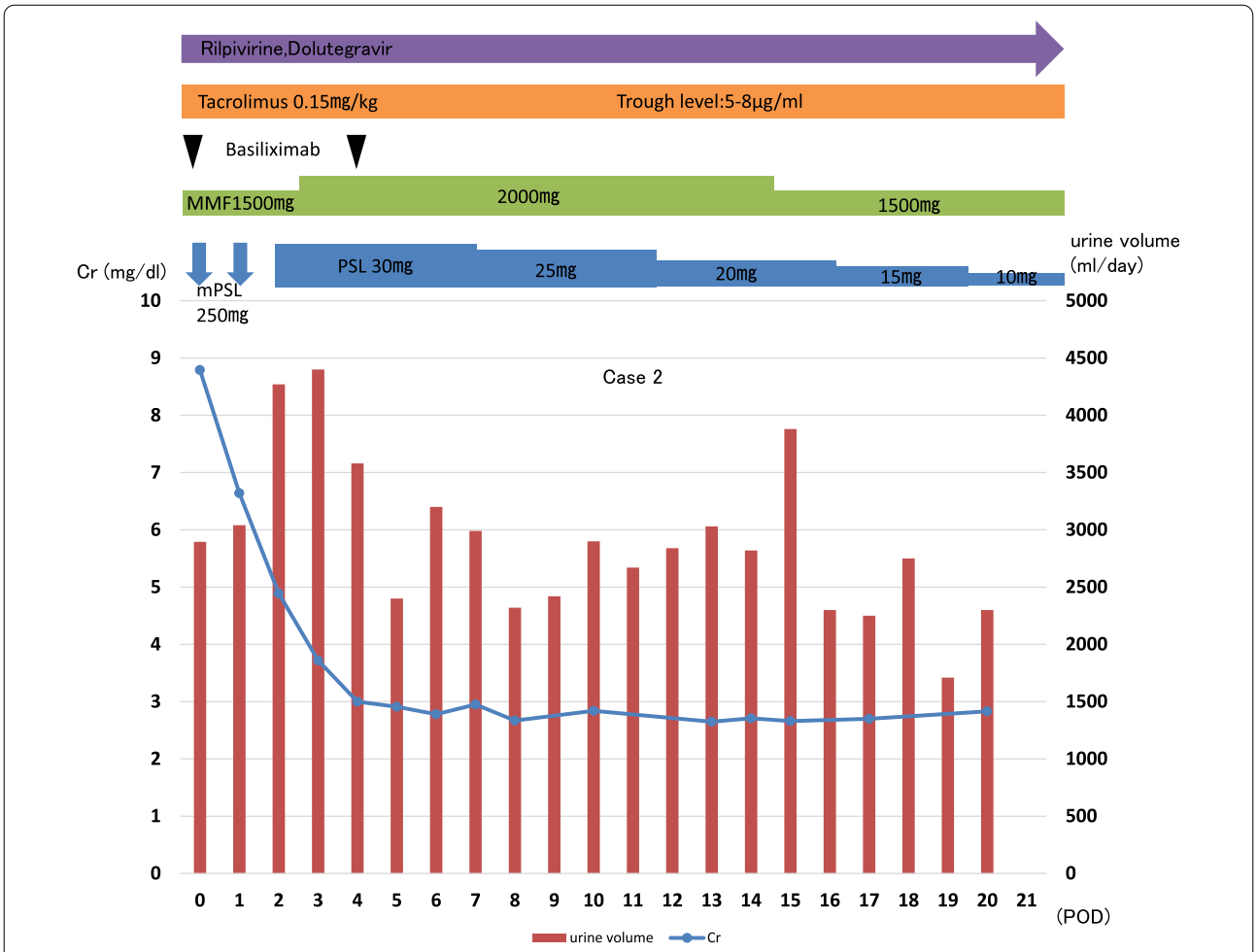

Fig. 3 Postoperative clinical course for case 2. Kidney function, antiretroviral therapy, and immunosuppressive drugs after kidney transplantation. *Cr* creatinine, *MMF* mycophenolate mofetil, *mPSL* methylprednisolone; *PSL* prednisolone; *POD* postoperative day

pretransplant treatment was needed. The patient had no psychological or familial problems. Blood type-matched living donor kidney transplantation (B⇒AB) was performed with the father as donor (HLA3 mismatch, FCXM class I negative [0.96%], class II negative [0.96%]), WIT 4 min, CIT 112 min, first urine 24 min. The sCr level at discharge was 2.44 mg/dL (Fig. 4).

The final observation period was 5 years 2 months for case 1, 3 years 7 months for case 2, and 9 months for case 3. All patients were treated without apparent rejection, CD4+lymphocyte counts were maintained, and there was no increase in the viral load for HIV or HBV post-surgery.

Immunosuppression

Standard maintenance immunosuppressants used in the blood group matched transplants included steroids, calcineurin inhibitors (tacrolimus [TAC]), and metabolic antagonists (mycophenolate mofetil). In all three cases, steroids (methylprednisolone, 250 mg intravenously) were administered first, intraoperatively, then on the following day. Basiliximab was also administered in all cases. The target levels of immunosuppressive drugs used in our hospital during the study period were as follows: TAC extended-release target trough level was 8–10 ng/mL; then, maintenance dose was reduced to achieve 5–7 ng/mL; Mycophenolate mofetil was adjusted to achieve a target area under the concentration–time curve during the first 4 h after administration of 40–80 μg·h/mL.

Prednisolone was started at a dose of 30 mg/day and was subsequently reduced to 5 mg/day 3 weeks after surgery.

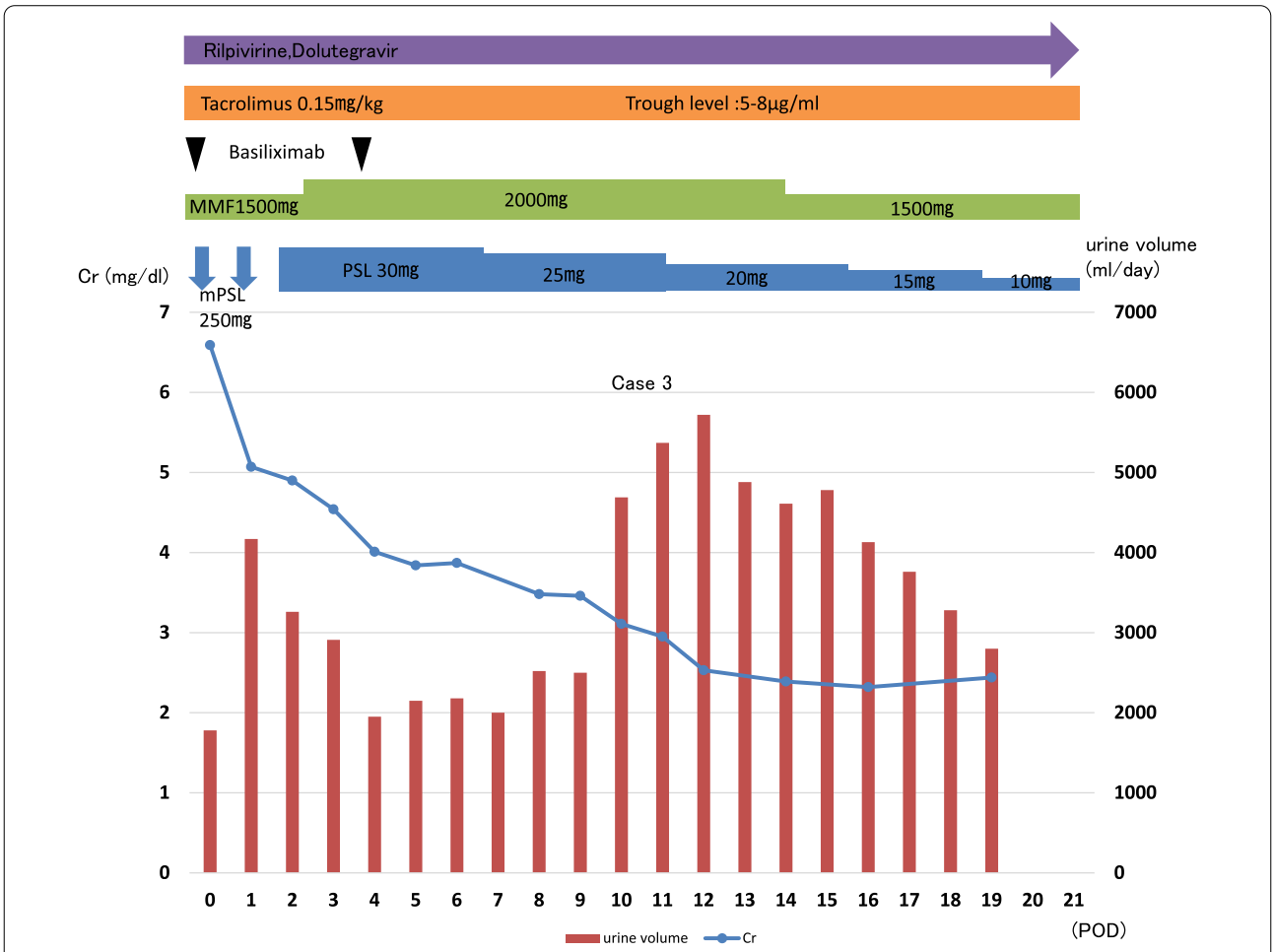

Fig. 4 Postoperative clinical course for case 3. Kidney function, antiretroviral therapy, and immunosuppressive drugs after kidney transplantation. *Cr* creatinine, *MMF* mycophenolate mofetil, *mPSL* methylprednisolone, *PSL* prednisolone, *POD* postoperative day

Discussion and conclusions

Multidisciplinary cooperation and protection from prejudice

Multidisciplinary collaboration is an important aspect of HIV-infected kidney transplantation. In the present report, the kidney transplant team consisted of transplant physicians, nephrologists, nurses, pharmacists, nutritionists, and clinical psychologists (Fig. 1). The first HIV-infected kidney transplant began with establishing a partnership with an infectious disease specialist. If viral hepatitis was a complication, a hepatologist was also asked to join the team. Pharmacists provided perioperative medication management and drug selection, while dietitians provided nutritional management after kidney transplantation. Before kidney transplantation, multidisciplinary consultations were held to share patient information and ensure a seamless continuation of treatment after the transplant. Patients with HIV infection also had psychological anxieties, worries, and experienced social discrimination and prejudice.

Since all patients underwent living donor kidney transplantation, it was extremely important to understand the relationship between the patient, the donor, and other family members. It was necessary for nurses and clinical psychologists to listen to this information and assess to whom and to what extent the patient's personal information could be communicated. Antiretroviral therapy and immunosuppressive medications in kidney transplantation require long-term oral use, and patients with HIV infection may be nonadherent to medication due to depression [7]. Team advanced information sharing was thought to improve postoperative medication adherence, maintain transplant kidney function, and protect patients from the discriminatory prejudice persisting in Japan.

Postoperative outpatient care was managed jointly by a transplant physician and a nephrologist. Patients were treated as outpatients once a week until one month postoperatively, once every two weeks from two to six months postoperatively, and once every three to four weeks until the first year postoperatively. Outpatient services included confirmation of infection, management of immunosuppressive medications, and transplant kidney biopsy at 3 months and 1 year postoperatively. Infectious disease physicians monitored HIV-RNA level and prescribed anti-HIV medications. Pharmacists monitored adherence to medications, responded to forgotten medications, and reminded the patients of food with drug interactions. The dietitian assessed the dietary intake and diet of the patients, advised on weight management, and consulted with partners.

HIV complication screening and treatment

Prior to ART, the mortality rate for HIV-infected kidney transplant recipients was 50%, with 30% of patients dying of AIDS [8]. Therefore, kidney transplantation was contraindicated in patients with HIV. Antiretroviral therapy markedly reduces mortality in AIDS patients and increases the viability of kidney transplantation in HIV-infected patients [8]. According to overseas data, the graft survival rate of HIV-infected kidney transplant recipients after ART is 90.4% and 73.7% at 1 and 3 years, respectively, with survival rates of 94.6 and 88.2% at 1 and 3 years, respectively [9]. These data are similar to the prognosis for HIV-negative kidney transplant patients [2]; however, we could not find data for Japan. Acute kidney injury associated with HIV includes the direct nephrotoxicity of indinavir and tenofovir used for ART [10]. Chronic kidney injury includes reports of focal glomerulosclerosis, thrombotic microangiopathy, and complex immune nephritis [11].

ART has changed the major cause of mortality in HIV-infected patients from AIDS index disease to CKD, malignancy, and ischemic heart disease, which are chronic phase complications. Patients with HIV have a higher incidence and increasing prevalence of CKD than HIV-negative patients [12]. The prevalence of CKD in HIV-infected patients in Japan was 15.4% among 732 patients, and 9.7% had grade 3 CKD or higher [13].

Prejudice and discrimination against HIV infection persist in Japan, and HIV clinicians are highly concerned about their risk of infection [14]. Therefore, while the number of HIV-infected patients with CKD is increasing in Japan, the number of facilities that accept HIV-infected dialysis patients is low. In 2015, HIV-infected dialysis patients in Japan accounted for 0.49% of all dialysis patients [15], but the number could be higher, given that only 8.5% of hemodialysis facilities accepted HIV-infected hemodialysis patients in 2017 [16]. This indicates that medical professionals avoid HIV care in Japan. This may mean that appropriate information is not available for HIV-positive patients with CKD who should undergo kidney transplantation. It is hoped that medical personnel treating CKD will also have accurate knowledge of HIV infection and be able to provide information that kidney transplantation is possible even for HIV-infected patients.

The indications for kidney transplantation in HIV-positive patients include (i) CD4-positive T cells > 200 / μL, (ii) HIV-RNA less than detection sensitivity, (iii) treatment for HBV or hepatitis C virus (HCV) co-infection, (iv) screening for TB and syphilis, (v) opportunistic infections in patients not receiving ART, (vi) no malignancy, and (vii) extensive experience in transplant management in HIV-infected patients [2]. After confirming

patient willingness for transplantation, the clinic requests an infectious disease specialist to check the CD4-positive cell count and HIV-RNA and begin coordinating the ART. Upper endoscopy, fecal occult blood test, and whole-body CT scan are performed, in addition to close examinations for flow cytometry lymphocyte crossmatch and malignancy.

Coordination of HIV medications and immunosuppressive medications

It is important to understand the interaction between ART and immunosuppressive drugs used in kidney transplantation during the perioperative period. Calcineurin inhibitors, mammalian target of rapamycin inhibitors, mycophenolate mofetil, steroids, and immunosuppressive drugs used in kidney transplantation can also be used in HIV-infected patients. Non-nucleoside reverse transcriptase inhibitors and PIs, which are key drugs in ART, interact with calcineurin inhibitors. Protease inhibitors inhibit cytochrome P450-3A4, so care should be taken to avoid elevated calcineurin inhibitor levels. Non-nucleoside reverse transcriptase inhibitors also decrease the concentration of calcineurin inhibitors via cytochrome P450-3A4 inducers. Therefore, calcineurin inhibitors should be increased when an NNRTI is used and decreased when a PI is used [2]. Integrase strand transfer inhibitors can be used in kidney transplantation because they do not interact with calcineurin inhibitors [17]. Rilpivirine, which is an NNRTI, was used in two of the three cases in this study. Since RPV does not interact with cytochrome P450-3A4, it was continued in the perioperative period after consultation with an infectious disease specialist and a pharmacist [18].

Treatment and precautions after kidney transplantation

HIV-infected kidney transplant recipients had higher rejection rates than HIV-negative kidney transplant recipients. Drug interactions affecting cytochrome P450-3A4, chronic immune activation, and inflammatory responses due to chronic HIV exposure are influential [2, 19]. Although the three patients in the present study progressed without apparent rejection to date, we need to carefully monitor future changes in rejection. According to previous reports, approximately half of patients respond to glucocorticoid therapy when rejection occurs [20]. However, caution should be exercised with thymoglobulin use, as it may decrease CD4-positive T cells and cause serious infections in HIV-infected kidney transplant recipients [20]. The use of TAC may also be considered, as it may decrease the risk of rejection compared to cyclosporine. Additionally, the risk of rejection has been reported to be higher in cadaveric kidney transplantation for HIV-infected CKD patients than in living donor kidney transplants, and caution is warranted [9].

Measures in hepatitis virus co-infection

HIV-positive patients may be co-infected with HBV and HCV. Two of the three patients in this report were already co-infected with HBV. Although there is a fivefold increased risk of liver failure in HBV-positive recipients, there is no difference in the 5-year and graft survival compared to HBV-negative recipients [21, 22]. Kidney transplantation for patients with HBV infection requires antiviral therapy before transplantation and lifelong treatment after surgery. Lamivudine use is expected to be effective for both HBV and HIV, but resistance is likely. HBV reactivation after transplantation should be carefully monitored. Collaboration with hepatologists is important.

Prospects for kidney transplantation in HIV patients

Thus, kidney transplantation is a viable option for kidney replacement therapy in HIV-positive end-stage kidney failure patients. While the medical aspects of HIV infection and kidney transplantation, such as rejection, drug interactions, co-infection with HBV, and HCV reactivation, are important, social and psychological support are equally important. Collaboration with multiple intra-institutional professionals is a factor in the safe and smooth implementation of kidney transplantation care in HIV-positive CKD patients.

Abbreviations

ART: Antiretroviral therapy; HIVAN: Human immunodeficiency virus-associated nephropathy; 3TC: Lamivudine; ABC: Abacavir; RAL: Raltegravir; DTG: Dolutegravir; RPV: Rilpivirine; ADPKD: Autosomal dominant polycystic kidney disease; CKD: Chronic kidney disease; sCr: Serum creatinine; NRTI: Nucleoside reverse transcriptase inhibitor; INSTI: Integrase strand transfer inhibitor; PI: Protease inhibitor; NNRTI: Non-nucleoside reverse transcriptase inhibitor; WIT: Warm ischemic time; CIT: Cold ischemic time; TAC: Tacrolimus; HBV: Hepatitis B virus; HCV: Hepatitis C virus.

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Author contributions

AT, KK, ID, IY, NA, WT, and YK treated the patients. AT and YK drafted the manuscript. KK, ID, and TY discussed the case. ID and YK critiqued and revised the manuscript. All authors read and approved the final manuscript.

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Declarations

Ethics approval and consent to participate

Written informed consent was obtained from the patient. For case reports, a formal approval from a local ethics committee was not required.

Consent for publication

Written informed consent was obtained from the patients or their families for publication of this case report.

Competing interests

The authors declare that they have no competing interests.

Author details

[1]Department of Nephrology, Kitasato University School of Medicine, 1-15-1 Kitasato, Minami, Sagamihara, Kanagawa 252-0375, Japan. [2]Department of Urology, Kitasato University School of Medicine, 1-15-1 Kitasato, Minami, Sagamihara, Kanagawa 252-0375, Japan. [3]Department of Rheumatology and Infectious Disease, Kitasato University School of Medicine, 1-15-1 Kitasato, Minami, Sagamihara, Kanagawa 252-0375, Japan.

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