Successful Treatment of Hemodynamic Compromise Caused by Antibody-Mediated and Cellular Rejection in a Recipient 12 years After Heart Transplantation

Teruhiko Imamura, MD, Koichiro Kinugawa, MD, Naoko Kato, PhD, Yukie Kagami, RN, Miyoko Endo, RN, Nobuyuki Kaneko, Shun Minatsuki, MD, Hironori Muraoka, MD, Toshiro Inaba, MD, Hisataka Makisawa, MD, Masaru Hatano, MD, Kent Doi, MD, Atushi Yao, MD, Yutaka Takazawa, MD, Minoru Ono, MD, Shunei Kyo, MD, and Issei Komuro, MD

Summary

Heart transplantation (HTx) is an established therapy for stage D heart failure due to recent advances in immunosuppressive regimens. However, antibody-mediated rejection remains an unsolved problem because of its refractoriness to standard immunosuppressive therapy with high mortality and graft loss. We experienced a 16-year old patient with hemodynamic compromise caused by both cellular and antibody-mediated rejection 12 years after HTx. The rejection was refractory to repeated steroid pulse treatment, intravenous immunoglobulin administration, and intensifying immunosuppression including addition of everolimus. Eventually, she was successfully treated with repeated plasma exchange accompanied by a single administration of the anti-CD20 monoclonal antibody rituximab. (Int Heart J 2013; 54: 328-331)

Key words: Rituximab, Plasma exchange, Teenager, Adherence

Recent advances in immunosuppressive therapy have greatly improved the outcome of heart transplantation (HTx) in stage D heart failure (HF) patients. Cellular rejection (CR), which is mainly mediated by T-cells, accounts for the majority of allograft rejection episodes after HTx. CR has become controlled to a considerable extent by current immunosuppressive regimens that are designed to target T-cell immune function. On the other hand, antibody-mediated rejection (AMR) after HTx has long been an unsolved problem because few schemes for the treatment of B cell-driven AMR have been established. Circulating antibodies mediate rejection through complement activation and fixation on graft endothelium, thereby contributing to both early and late graft loss, cardiac allograft vasculopathy, and higher mortality. Recently, rituximab, a chimeric anti-CD20 monoclonal antibody that binds to the antigen expressed on B-cells, has been effective for AMR in several case reports though it is still off-label. AMR usually occurs early after HTx, and reports of it occurring a long time after HTx are rare. We experienced a patient with acute decompensated HF caused by CR and AMR simultaneously 12 years after HTx, which might be attributable to poor adherence to medication. The rejection was successfully treated by plasma exchange (PE) and a single administration of rituximab.

In August 2000, a 4-year old Japanese female with dilated cardiomyopathy underwent HTx in the United States. Her postoperative course was uneventful, and she was followed at other hospitals near Tokyo. Her last endomyocardial biopsy in 2010 showed no rejection and echocardiography revealed preserved ejection fraction. Eventually, she was successfully treated with repeated plasma exchange accompanied by a single administration of the anti-CD20 monoclonal antibody rituximab.
Pressure was 16 mmHg, pulmonary capillary wedge pressure was 29 mmHg, and cardiac index was 1.49 L/minute/m^2 (Table). Coronary angiography did not show any evidence of cardiac allograft vasculopathy. An endomyocardial biopsy at day 1 showed CR at ISHLT grade 3R and positive staining of complement component C4d on the endothelium of capillaries (Figure 2).

After several manipulations aimed at overcoming the rejection, including initiation of everolimus, methylprednisolone pulse therapy (twice), and the administration of intravenous immunoglobulin (IVIg), myocardial injury with lymphocyte invasion gradually recovered, but her hemodynamic status had worsened on day 8 (Table). Because of severe lung congestion and renal dysfunction, she eventually needed continuous hemodiafiltration under respiratory ventilatory support on day 14. After determining that the serum level of panel reactive antibody (PRA) was 52.1%, we performed 8 consecutive sessions of plasma exchange (PE), accompanied by a single administration of rituximab at a dose of 500 mg (equivalent to 375 mg/m^2) on day 22. Her %B-cell and %PRA levels decreased dramatically by day 25 and remained at low levels without any need for additional PE and rituximab administration. No side effects such as hypotension, anaphylactic reactions, or infections occurred after rituximab treatment.

Her cardiac function and hemodynamic status had improved remarkably by day 38 (Table). Repeated endomyocardial biopsy showed recovery of CR and C4d stain turned negative. With significant recovery of her exercise tolerance, she was discharged on day 130.

**Discussion**

Antibody-mediated rejection (AMR) remains an unsolved clinical problem because of the difficulties in diagnosis and treatment. A consensus conference in 2010 defined AMR as a pathologic entity, ie, histologic findings including endothelial cell swelling, accumulation of intravascular macrophages, interstitial edema or hemorrhage, and presence of neutrophils around capillaries. Immunofluorescent or immunohistochemical findings include deposition of immunoglobulin, complement, and identification of macrophages within capillaries. Using these criteria, a current recommendation categorizes AMR on a scale from 0 to 3. The present case was assigned to pAMR 3 considering immunopathologic and histopathologic evidence for severe AMR.

Another diagnosis regarding clinical features is based on a triad of the following, (1) clinical evidence of allograft dysfunction, (2) serological evidence of donor specific antibodies (DSA) or high %PRA level, and (3) aforementioned endomyocardial biopsy features. Unfortunately, donor information about human leukocyte antigen (HLA) was not available because she had received HTx abroad several years previously, but the high titer of %PRA might represent the existence of DSA.

AMR has generally been considered to occur early after
HTx, typically within a few months after the implantation.\textsuperscript{12} Therefore, our case had an unusual onset. A recent study reported that late AMR occurring more than 1 year after HTx due to newly-developed DSA was uncommon but a serious problem with 46% of persistent cardiac dysfunction and 1.3 years of mean survival after diagnosis of AMR.\textsuperscript{11} Though distinct risk factors for late AMR have remained unknown thus far, her adherence to immunosuppressive medicine was probably poor considering the very low level of tacrolimus at the time of admission. Poor adherence to medication is common among recipients when they become a teenager.\textsuperscript{13} Furthermore, a biopsy-free period of more than 2 years might have resulted in overlooking rejection until hemodynamic compromise emerged. A high %PRA level at the time of HTx is obviously one of the risk factors for AMR,\textsuperscript{3} but %PRA had not been assayed before the admission to our hospital.

At present, the management of AMR is not standardized, or the optimal surveillance, treatment, and timing of intervention are undefined.\textsuperscript{1} Current options for treatment of AMR include steroid pulse therapy, PE, IVIg administration, and intensifying immunosuppression.\textsuperscript{12} Desensitization or reduction of circulating HLA antibody is the essence of the above-mentioned treatment. In the present case, the first 3 sessions of PE were effective at achieving a considerable reduction of %PRA, but %PRA soon became elevated again so we decided to administer rituximab together with successive PE sessions. Rituximab is a chimeraic humanized monoclonal antibody directed against the pan B-cell surface molecule CD20, and enhances lysis of CD20-positive B-cells, deleting them from peripheral circulation, lymph nodes, and bone marrow.\textsuperscript{5} It has been approved for the treatment of lymphoma. Recently, there have been several case reports in which rituximab was found to be effective for the treatment of AMR, though still off-label.\textsuperscript{5-7,11} T-cells are unaffected by rituximab, and as a consequence opportunistic infection rarely occurs in association with its administration.\textsuperscript{7} A single administration of rituximab was enough to manage %PRA and %B-cell count at low levels in our case, and histological findings for rejection immediately disappeared along with marked improvement in cardiac function.

In the present case, we prioritized the treatment for CR because the histological finding of CR was so apparent in the first endomyocardial biopsy, and therefore the treatment for AMR was belated after confirming the refractoriness to the treatment for CR. Her hemodynamics collapsed during the treatment for CR, and she eventually needed continuous hemodiafiltration under respiratory ventilatory support. We were confronted with difficulty constructing an optimal therapeutic strategy because there were virtually no reports indicating that AMR emerged together with CR at a point in time long after HTx, but her cardiac function might have recovered much sooner if the treatment for AMR including PE and rituximab was initiated together with the treatment for CR. Therefore, we believe the case was worth reporting in order to make informed decisions.

| Table. Echocardiography and Hemodynamic Parameters |
|-----------------------------------------------|---|---|---|---|
|                                           | On Admission | Post PSL + IVIg | Post PE | Post Rituximab |
|                                           | Day 1        | Day 8         | Day 18  | Day 38         |
| Left ventricular diastolic diameter, mm    | 47           | 45            | 46      | 42             |
| Ejection fraction, %                      | 13           | 22            | 24      | 58             |
| E/e' ratio                             | 36.8         | 34.4          | 28.6    | 10.1           |
| E/A ratio                               | 3.24         | 3.04          | 3.18    | 3.60           |
| Deceleration time, sec                   | 86           | 49            | 120     | 140            |
| eRVsP, mmHg                              | 26           | 40            | 48      | 28             |

PSL indicates prednisolone; IVIg, intravenous immunoglobulin; PE, plasma exchange; E/e', ratio of early diastolic filling velocity to early mitral lateral annulus velocity; E/A, ratio of early to late diastolic filling velocity; and eRVsP, estimated right ventricular systolic pressure.

![Figure 2. Endomyocardial biopsy at day 1 showed cellular rejection at ISHLT grade 3R (A). Immunofluorescence staining showed moderate deposition of C4d in the capillary endothelium (B) (A, hematoxylin and eosin, ×40; B, anti-C4 FITC conjugate, ×100).](image-url)
decisions in patients with such severe rejection. Finally, we cannot emphasize enough about the risk of poor adherence to medication among teen recipients.

REFERENCES