How Should We Treat Early Post-Transplant Lymphoproliferative Disease After Heart Transplantation?

A Case Report

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Summary

Although post-transplant lymphoproliferative disease (PTLD) is one of the major fatal complications encountered several years after heart transplant (HTx), little is known about early-PTLD emerging within the first year. We here describe the rare case of a 24-year-old female patient who suffered from early-PTLD (DLBCL: diffuse large B-cell lymphoma) associated with an Epstein-Barr virus (EBV) infection, that developed around the jejunum at 7 months after HTx. She suffered from acute abdominal peritonitis due to perforation of the jejunum soon after the first chemotherapy. She was treated successfully by emergent partial resection of the jejunum and colostomy after the discontinuation of everolimus (EVL) and successive low-dose chemotherapy under careful monitoring and adjustment of intravenous immunosuppressant including cyclosporine (CyA) and prednisolone to avoid a rejection reaction. Prophylactic strategies for early-PTLD in HTx recipients should be undertaken with caution. (Int Heart J 2015; 56: 676-678)

Key words: Malignancy after heart transplantation, Epstein-Barr virus, Everolimus

Although the short-term prognosis in heart transplantation (HTx) recipients has improved recently owing to sophisticated perioperative procedures and the establishment of an optimal immunosuppressant strategy, post-transplant lymphoproliferative disease (PTLD), one of the major post-HTx malignant diseases, remains a major threat because of its high mortality and morbidity. Generally speaking, such a complication emerges several years after HTx because long-term continuous immunosuppression triggers the development and spread of malignant tissue. In contrast, little is known about early-PTLD which occurs 1-year after transplantation. Early-PTLD is sometimes clinically challenging because relatively strong immunosuppression is still necessary during this period. We describe here a HTx recipient who suffered from a diffuse large B-cell lymphoma (DLBCL) at 7 months after the operation.

Case Report

A 24-year-old female patient received HTx in May 2013 after 3-year extracorporeal ventricular assist device support. The donor was a female in her 40s who had cerebrovascular disease and was Epstein-Barr Virus immunoglobulin G (EBV-IgG) sero-positive. The recipient was sero-negative preoperatively. After HTx, she was treated with tacrolimus (TCR), prednisolone, and mycophenolate mofetil (MMF), which was then switched to everolimus (EVL) due to the development of neutropenia.

She had been followed mainly as an outpatient without any complications, until she was admitted to our hospital complaining of epigastric distress due to unknown causes in December 2013 (post-HTx 7 months). Although the first computed tomography (CT) along with a general blood test performed on admission did not reveal any abnormalities including negative assay of cytomegalovirus (CMV) antigenemia, the second CT performed at day-10 showed significant swelling of the mesenteric lymph nodes and diffuse edema of the jejunum. EBV-IgG became positive (80-fold higher) in September 2013 before admission, and on admission was still positive (40-fold) and the EBV-DNA level was elevated (2.0 × 10^4 copies). Double-balloon endoscopy detected multiple ulcers in the jejunum. Pathophysiological analysis of the jejunum demonstrated diffuse infiltration of atypical large lymphocytes into the mucosa, and an immunohistological assay demonstrated that they were CD3 (-), CD20 (+), and CD30 (+), which was compatible with diffuse large B-cell lymphoma (DLBCL). Considering the positive assay of EBV-encoded RNA in situ hybridization, she was diagnosed as DLBCL associated with an EBV infection. Systemic CT and bone marrow aspiration demon-
After conversion from TCR to cyclosporine (CyA), first course chemotherapy that included adriamycin (50 mg/m^2), cyclophosphamide (750 mg/m^2), and prednisolone (60 mg/m^2) without anti-CD20 antibody (rituximab) and vincristine was executed at day-28. At 5 days after the chemotherapy, she complained of abdominal pain and melena, and was diagnosed with perforation of the jejunum by emergent CT. After the discontinuation of EVL, she underwent emergent partial resection of the jejunum and a colostomy. During fasting with intravenous hyperalimentation, intravenous CyA and predonisolone were administered as immuno-suppressants at a concentration of 150-250 ng/mL and 10 mg/day, respectively. After 7 courses of CP therapy including a 50% dose of cyclophosphamide and prednisolone along with 6 courses of standard dose rituximab, complete remission was demonstrated by positron emission tomography and gastro-endoscopy. After the conversion to oral administration of immuno-suppressant, she was discharged without any complications on day-284 (Figure 2).

**DISCUSSION**

PTLD is one of the major fatal complications that typically emerges several years after HTx. Although the precise mechanism has not yet been fully determined, cumulative long-term immunosuppression would permit the malignant transformation of lymphocytes. Therefore, the incidence of PTLD has been increasing owing to the recent improvement of strong immunosuppression strategies, especially those with TCR. The known risk factors for PTLD are a previous history of induction therapy, pediatric recipients, and recent EBV infection. EBV infection triggers the malignant transformation of lymphocytes. An immature immune system and strong immunosuppression under transformed malignant cells with marked proliferating ability in pediatric recipients may facilitate the occurrence of PTLD.

PTLD emerged at 7 months after HTx in the present patient, however, little is known about such early-PTLD developing within the first year. Schober, et al proposed young recipient age, EBV infection, or the usage of TCR or MMF as risk factors of early-PTLD, and Khedmat, et al reported that early-PTLD often involves the respiratory tract. Considering the disadvantages of TCR in suppressing the occurrence of malignancy, we converted TCR to CyA soon after the diagnosis of PTLD.

In the present case, the early diagnosis of early-PTLD was very difficult, because of its low incidence and occurrence at an atypical lesion accompanied by almost normal data except for the nonspecific digestive symptom. We initially suspected CMV enteritis because of its high incidence and previous history of positive assay of CMV antigenemia. The most important key for the early diagnosis in the present patient was the EBV sero-conversion from sero-negative to sero-positive after HTx. The donor was EBV sero-positive, whereas the recipient was sero-negative preoperatively. Routine confirmation of EBV sero-conversion in such EBV-mismatch cases would be helpful for the screening of patients at high risk of PTLD.

In contrast, a disadvantage of EVL is its delayed healing of wounds because of its anti-proliferative effect. Perforation of the digestive tract sometimes occurs during chemotherapy because of acute collapse of the surrounding tumor. We were able to perform the surgery successfully without any complications at the anastomosed site partly due to the early discontinuation of EVL before the initiation of chemotherapy. In PTLD patients who are at high risk of digestive tract perfo-
ration, it may be preferable to discontinue EVL before chemotherapy.

Although there is no recommended blood concentration for managing the intravenous continuous infusion of immunosuppressant, we adjusted the blood concentration of CyA during the 9 months of fasting considering the target concentration of the trough level, 150-250 ng/dL, recommended in a guideline, and avoided a rejection reaction and wound infection. Determination of an optimal target concentration during continuous intravenous infusion of immunosuppressant should be attempted in the future.

REFERENCES