Primary Central Nervous System Post-Transplant Lymphoproliferative Disorder Following Kidney Transplantation: A Multi-Institution Study in Japan Over 30 years

Primary central nervous system post-transplant lymphoproliferative disorder following kidney transplantation: A multi-institution study in Japan over 30 years

Hiroki Ishihara, *Masayoshi Okumi and Kazunari Tanabe and the Japan Academic Consortium of Kidney Transplantation (JACK)

[1]Department of Urology, Tokyo Women's Medical University

Correspondence:

Masayoshi Okumi, MD, PhD

Department of Urology, Tokyo Women's Medical University

8-1 Kawada-cho, Shinjuku, Tokyo 162-8666

Japan

Telephone: +81- 3-3353-8111

Fax: +81-3-5269-7353

Email: okumi@twmu.ac.jp

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Dear Editor,

Post-transplant lymphoproliferative disorder (PTLD) with central nervous system (CNS) involvement is associated with poor outcomes (1, 2). Patients undergoing kidney transplantation (KTx) have the highest risk of primary CNS (PCNS)-PTLD development, and the development rate is reportedly increasing (1). However, clinical information about PCNS-PTLD has been limited, especially in Asian populations, because of its rarity. Herein, we reviewed the records of patients with PCNS-PTLD by using data from a multicenter observational cohort study of patients undergoing KTx (The Japan Academic Consortium of KTx; JACK: UMIN00001832). We included 2020 consecutive patients undergoing KTx at 3 transplant centers (Tokyo Women's Medical University, Toda-Chuo General Hospital, and Okubo Hospital) between 1986 and 2016. To the best of our knowledge, the present study is the first to highlight PCNS-PTLD following KTx in Asian population.

PTLD developed in 16 patients, including 6 cases of PCNS-PTLD. The clinicopathological characteristics are shown in Table 1. The study revealed several interesting findings, including a higher rate of PCNS-PTLD development among the PTLD cases than was expected (6 of 16 patients, 37.5%), and very

late-onset development (mean time from transplantation to diagnosis, 116.5 months in 3 of 6 patients, 50.0%) compared to a previous study (2). We speculated that this tendency might be caused by an unidentified genome type that is specific to the Japanese population with regard to Epstein-Barr virus (EBV) infection and the mechanism of EBV-associated carcinogenesis. We found that 60% of PCNS-PTLD cases (3 of 5 patients; patient No.1 was not considered) were associated with EBV. Lustberg et al. (3) reported that specific human leukocyte antigen types display novel susceptibility factors for PTLD in EBV-seropositive and EBV-seronegative individuals. Moreover, PCNS-PTLD was commonly diagnosed as EBV-associated lymphoma or B-cell lymphoma (including diffuse large B-cell lymphoma)(1, 2). Indeed, in this study, such cases were observed in 5 of 6 patients (83.3%). Fink et al. (4) suggested that EBV has a major impact on cellular microRNA expression in PTLD, and that EBV-associated PCNS-PTLD could possibly have a different mechanism for the activation of tumor cell growth and inhibition of apoptosis than systematic PTLD did, resulting in a higher frequency of EBV-association in PCNS-PTLD compared to that of systematic PTLD. Thus, there might be a genomic association specific to Japanese people, considering PCNS-PTLD development.

Finally, the immunosuppressive regimen administered at diagnosis was homogeneous, and included mycophenolate mofetil (MMF). MMF use has been previously suggested as a risk factor for PCNS-PTLD development, as the deep immunosuppressive effect is suspected to influence the carcinogenic mechanism (1). Indeed, in an international report on PCNS-PTLD, MMF usage was frequently observed (82%)(2). In this study, unfortunately, we could not find the association between MMF and carcinogenesis because the trough level of MMF was missing. Meanwhile, we found that trough level of calcineurin inhibitor did not affect PCNS-PTLD development (data not shown); however, these data were strongly limited due to the small number of patients.

In summary, PCNS-PTLD can develop long after KTx, even after ≥10 years, and the development rate may be higher than expected. Thus, we should monitor disease development for a long time, especially when MMF is used in the immunosuppressive regimen. We believe that the present data from a large multicenter Japanese database can provide new information for physicians.

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analysis.

Conflicts of interest

The authors declare that they have no conflict of interest.

References

1. Crane GM, Powell H, Kostadinov R, et al. Primary CNS lymphoproliferative disease, mycophenolate and calcineurin inhibitor usage. *Oncotarget* 2015;**6**(32):33849-33866.
2. Evens AM, Choquet S, Kroll-Desrosiers AR, et al. Primary CNS posttransplant lymphoproliferative disease (PTLD): an international report of 84 cases in the modern era. *American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons* 2013;**13**(6):1512-1522.
3. Lustberg ME, Pelletier RP, Porcu P, et al. Human leukocyte antigen type and posttransplant lymphoproliferative disorder. *Transplantation* 2015;**99**(6):1220-1225.
4. Fink SE, Gandhi MK, Nourse JP, et al. A comprehensive analysis of the cellular and EBV-specific microRNAome in primary CNS PTLD identifies different patterns among EBV-associated tumors. *American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons* 2014;**14**(11):2577-2587.

Table 1: Clinicopathological characteristics

Pt.	Sex	Age at Dx (y)	Tx to Dx (mo)	Year at Dx	Donor	Initial IS	IS at Dx	Pre-Tx EBV IgG	Pathology	EBV-associated tumor	Treatment	Patient outcome	Patient survival (mo)	Graft outcome	Graft survival (mo)
1	M	27	7.76	1989	Living	CYA/AZ/MP/ ALG/DSG	CYA/AZ/ MP	Positive	ML	N/A	RI, radiotherapy	Died	1	Function	1
2	M	55	250.8	2011	Deceased	CYA/MZ/MP	FK/MMF/ MP	N/A	Polymorphic B-cell lymphoma	Yes	RI, CYVE	CR	44.4	Loss	2.89
3	M	65	131.6	2011	Deceased	FK/MMF/MP	FK/MMF/ MP	Positive	DLBCL	Yes	RI, R-CHOP, HD-MTX	CR	58.4	Function	58.4
4	M	67	38.3	2013	Deceased	FK/MMF/MP/ RTX	FK/MMF/ MP	Positive	DLBCL	Yes	RI, surgery, radiotherapy	Alive with brain damage	34.1	Function	34.1
5	M	79	45.0	2015	Living	FK/MMF/MP/ RTX	FK/MMF/ MP	Positive	DLBCL	No	RI, R-CHOP	Died	6.8	Function	6.8
6	F	50	225.6	2015	Living	FK/AZ/MP	FK/MMF/ MP	Positive	DLBCL	No	RI, MTX	Alive with brain damage	8.71	Function	8.71

Pt, patient; Dx, diagnosis; Tx, Transplantation; IS, immunosuppression; EBV, Epstein-Barr virus; IgG, immunoglobulin; CYA, cyclosporine; AZ, azathioprine; MP, methylprednisolone; ALG, antilymphocyte globulin; DSG, deoxyspergualine; MZ, mizoribine; FK, tacrolimus; MMF, mycophenolate mofetil; RTX, rituximab; N/A, not applicable; ML, malignant lymphoma; DLBCL, diffuse large B-cell lymphoma; RI, reduced immunosuppression; CYVE, cytarabine-etoposide; R-CHOP, rituximab-cyclophosphamide-doxorubicin-vincristine-predonisolone; HD-MTX, high-dose methotrexate; MTX, methotrexate; CR, complete response