

Case Study

# Epstein-Barr Virus-Negative, CD5-Positive Diffuse Large B-Cell Lymphoma Developing after Treatment with Oral Tacrolimus for Mixed Connective Tissue Disease : A Case Report and Review of the Literature

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A 69-year-old woman, who had been diagnosed as having Sjögren's syndrome at 37 years old and mixed connective tissue disease at 42 years old, was under treatment with oral prednisolone. In 2009, she was diagnosed as having active systemic lupus erythematosus, and started on treatment with tacrolimus at 3 mg/day. In 2010, para-aortic lymphadenopathy and superficial multiple lymphadenopathy were detected. Tacrolimus was discontinued. Axillary lymph node biopsy revealed Epstein-Barr (EB) virus-negative CD5-positive diffuse large B-cell lymphoma (DLBCL). The patient was classified into clinical stage IIIA and as being at high risk according to the international prognostic index. After the discontinuation of tacrolimus, the lymph nodes reduced temporarily in size. In January 2011, the lymphadenopathy increased again, and the patient received a total of 8 courses of therapy with rituximab, pirarubicin, vincristine, cyclophosphamide and prednisolone, followed by intrathecal injection to prevent central nervous system infiltration, which was followed by complete remission. In February 2012, fluorodeoxyglucose positron emission tomography showed relapse in multiple lymph nodes and central nervous system infiltration. The patient was considered to have iatrogenic lymphoproliferative disorder classified as "other iatrogenic immunodeficiency-associated lymphoproliferative disorders" by the WHO, and this is the first reported case of CD5-positive DLBCL and central nervous system infiltration following administration of the drug. The patient was considered to have a poor prognosis as EB virus was negative, discontinuation of tacrolimus was ineffective and there was evidence of central nervous system infiltration. [*J Clin Exp Hematopathol* 52(3) : 211-218, 2012]

**Keywords:** mixed connective tissue disease (MCTD), tacrolimus, other iatrogenic immunodeficiency-associated lymphoproliferative disorders, CD5-positive, diffuse large B-cell lymphoma (DLBCL)

## INTRODUCTION

Iatrogenic lymphoproliferative disorders (LPD), classified as immunodeficiency-associated LPD, are known to occur following treatment with immunosuppressive agents, such as methotrexate. In the present case, LPD developed after treatment with tacrolimus for mixed connective tissue disease (MCTD). The patient showed transient recovery following

discontinuation of tacrolimus; however, early relapse of Epstein-Barr (EB) virus-negative CD5-positive diffuse large B-cell lymphoma (DLBCL) occurred. The patient was diagnosed as having tacrolimus-associated LPD, a type of iatrogenic immunodeficiency-associated LPD. Only three cases of LPD occurring in the absence of transplantation or topical tacrolimus treatment have been reported, including the present case. However, CD5-positive DLBCL as a complication of iatrogenic immunodeficiency-associated LPD has not been reported, even after treatment with methotrexate, so this is the first reported case of its kind. In the future, it is considered necessary to accumulate further cases, and to conduct a large-scale study with long-term monitoring for EB virus infection, the dose, administration period and blood levels of tacrolimus, and CD5 expression status in order to elucidate the pathogenesis and prognosis of LPDs developing in association with oral or intravenous tacrolimus treatment.

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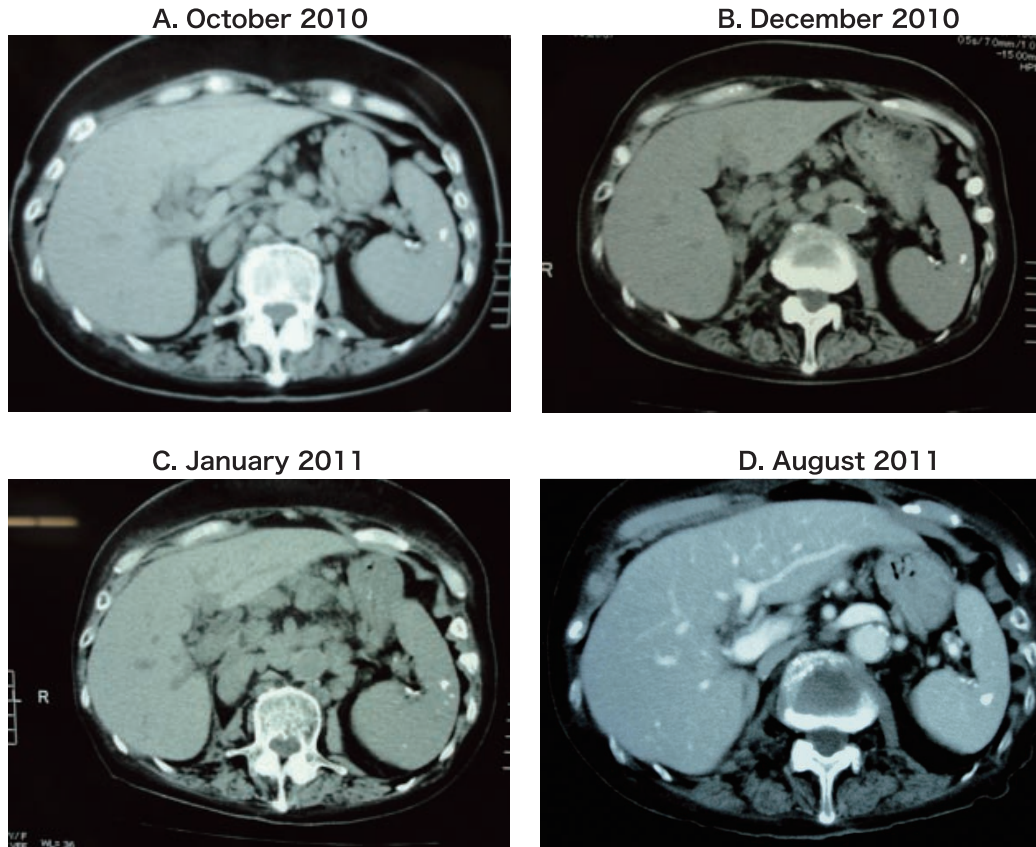
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**Fig. 1.** Plain abdominal CT. (*IA*) Abdominal para-aortic and mesenteric lymphadenopathy was detected in October 2010, approximately 1 year after the start of oral tacrolimus administration, and tacrolimus was discontinued. (*IB*) In December 2010, the abdominal para-aortic and mesenteric lymph nodes reduced in size. (*IC*) In January 2011, the abdominal para-aortic and mesenteric lymphadenopathy exacerbated again, and chemotherapy was started. (*ID*) In August 2011, the abdominal para-aortic and mesenteric lymphadenopathy disappeared altogether, and complete remission was confirmed.

## CASE REPORT

A 69-year-old woman presented with multiple superficial and deep lymphadenopathies and reduced renal function. Her medical history included right nephrectomy for nephrolithiasis at 25 years of age, diagnosis of Sjögren's syndrome (SjS) at 37 years of age, diagnosis of MCTD at 42 years of age and diagnosis of hypertrophic obstructive cardiomyopathy at 68 years of age.

With regard to the history of her present illness, the patient had been diagnosed as having SjS at a hospital in her neighborhood in 1978, but was kept under observation without treatment. In 1984, she was diagnosed as having MCTD at the same hospital and was started on treatment with oral prednisolone at a dose of 10 mg/day. Her clinical course was favorable, and the prednisolone dose was reduced to a maintenance dose of 5 mg/day. In 2001, the patient developed lupus nephritis and was treated with intravenous drip infusion of cyclophosphamide (500 mg/dose). Thereafter, she was con-

tinued on maintenance prednisolone at a dose of 10 mg/day and her clinical course appeared to be favorable. In 2006, the patient began to receive treatment at the Division of Rheumatology of our hospital. The prednisolone dose was gradually reduced to a maintenance dose of 5 mg/day, and the patient's medical course was favorable. In October 2009, the serum anti-dsDNA antibody level increased, along with a reduction of the serum complement activity. The patient was diagnosed as having active systemic lupus erythematosus. The prednisolone dose was increased to 10 mg/day, and concomitant treatment with tacrolimus was started, at a dose of 3 mg/day. Following this treatment, the anti-dsDNA antibody level and complement activity improved to the normal ranges.

In February 2010, follow-up computed tomography (CT) revealed para-aortic lymphadenopathy, and the patient was kept under observation. In October 2010, multiple bilateral cervical and axillary lymphadenopathy developed, along with reduced renal function. Drug-induced renal dysfunction was suspected, and the tacrolimus was discontinued. At the same

time, a repeat CT showed an increase in the sizes of the bilateral cervical, axillary, mediastinal, abdominal para-aortic and mesenteric lymph nodes (Fig. 1A). In November 2010, a right axillary lymph node biopsy revealed the diagnosis of DLBCL, and the patient was referred to the Division of Hematology. Clinical examination revealed a reduction in the superficial lymphadenopathy following discontinuation of tacrolimus. In December 2010, CT showed improvement of the abdominal para-aortic and other lymphadenopathy (Fig. 1B), and the patient was kept under observation. In January 2011, CT again revealed exacerbation of the lymphadenopathy (Fig. 1C), and the patient was diagnosed as having relapse of the DLBCL. In February 2011, the patient was admitted to hospital.

Examination at admission revealed a few palpable lymph nodes measuring a few cm in size each in both axillae.

The laboratory findings at admission are shown in Table 1. Histopathological examination of hematoxylin-eosin-stained sections of the lymph node biopsy specimen from the right axilla showed tumor cells consisting of large centroblasts with faint nuclei and 2-4 nucleoli, and immunoblasts with a single nucleolus (Fig. 2A). On immunostaining, the large tumor cells were strongly positive for CD20 and MIB-1 (Ki-67) (Fig. 2B & 2D) and weakly positive for CD5, and the medium-sized reactive T cells were strongly positive for CD5 (Fig. 2C). All the cells showed negative staining for cyclin D1 and EB virus-encoded ribonucleic acid (Fig. 2E & 2F).

Two-color flow cytometry showed  $\kappa$  positivity,  $\lambda$  negativity (Fig. 3A), double positivity for CD5 (weakly positive) and CD20 (Fig. 3B), CD10 negativity (Fig. 3C) and CD19 positivity (Fig. 3D). As chromosome G-band patterns, each of 46, XX, t(2;14) (q31;q32) and 46, XX, t(5;14) (q15;q32) was observed in 1 out of the 6 cells analyzed. Four out of the 6 cells had a normal karyotype. Southern blot analysis revealed rearrangement of the *immunoglobulin heavy chain joining region (IgHJH)*, but not of *T-cell receptor  $\beta 1$  (TCR $\beta 1$ )*. Fluorescence *in situ* hybridization analysis showed a negative result for the *immunoglobulin heavy chain-B-cell lymphoma 2 (IgH-BCL2)* fusion gene.

The clinical course after admission is shown in Fig. 4. The clinical stage was IIIA, and the patient was classified as being at high risk according to the international prognostic index. The lymph nodes showed a transient decrease in size following one course of treatment with rituximab, pirarubicin, vincristine, cyclophosphamide and prednisolone (R-THP-COP). The patient's clinical course was favorable, and she was discharged in March 2011.

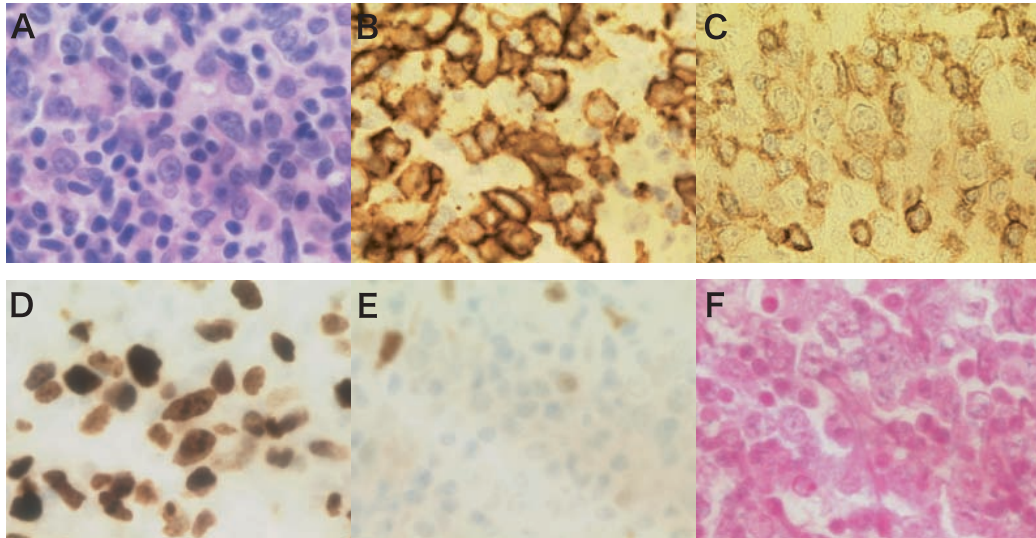
After completion of 8 courses of R-THP-COP therapy, a CT (Fig. 1D) obtained in August 2011 confirmed complete remission (CR). Despite the absence of any evidence of infiltration of the central nervous system, one course of intrathecal anticancer drug injection was administered to prevent central nervous system infiltration. However, no further intrathecal treatment was performed, as the patient refused con-

**Table 1.** Laboratory findings on admission

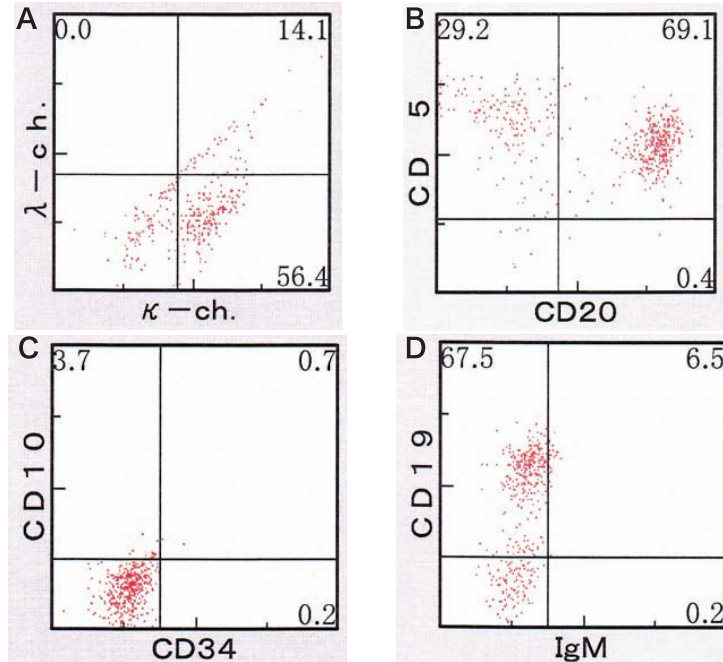
Complete blood count		Coagulation	
White blood cell	5,900/ $\mu$ L	Prothrombin time	$\geq 100\%$
Neutrophil	80.6%	Activated partial thromboplastin	26.6 sec
Lymphocyte	16.6%	Fibrin fibrinogen degradation	$\leq 5.0 \mu\text{g/mL}$
Monocyte	2.2%	Urinalysis	No abnormalities
Eosinophil	0.1%	Serum tacrolimus level (trough level)	2.2 ng/mL
Basophil	0.1%	Immuno-serological findings	
Red blood cell	$527 \times 10^3/\mu\text{L}$	Immunoglobulin G	762 mg/dL
Hemoglobin	13.2 g/dL	Immunoglobulin A	251 mg/dL
Hematocrit	40.2%	Immunoglobulin M	19 mg/dL
Platelet	$17.4 \times 10^4/\mu\text{L}$	Antinuclear antibodies	$\times 40$
Biochemistry		Anti-ds-DNA IgG antibody	$< \times 10$
Total protein	6.2 g/dL	Anti-CL $\beta$ 2GP1 antibody	$\leq 1.2 \text{ U/mL}$
Albumin	3.5 g/dL	Anti-RNP antibody	7.8 U/mL
AST	22 IU/L	Anti-Sm antibody	$\leq 7.0 \text{ U/mL}$
ALT	16 IU/L	Anti-SSA antibody	$\leq 7.0 \text{ U/mL}$
LDH	378 IU/L (119-229)	Anti-SSB antibody	$\leq 7.0 \text{ U/mL}$
ALP	264 IU/L	CH50	17 U/mL
Total bilirubin	0.6 mg/dL	C3	69 mg/dL
BUN	56 mg/dL	C4	3 mg/dL
Creatinine	2.15 mg/dL	Soluble interleukin-2 receptor	3,900 U/mL
Uric acid	11.7 mg/dL	HTLV-1 antibodies	Negative
Corrected Ca	12.9 mg/dL	HIV antibodies	Negative
CRP	$\leq 0.3 \text{ mg/dL}$		

The normal range is shown in parentheses. Ly, lymphoid cell; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; ALP, alkaline phosphatase; BUN, blood urea nitrogen; Ca, calcium; CRP, C-reactive protein; HTLV-1, human T-cell leukemia virus-1; HIV, human immunodeficiency virus

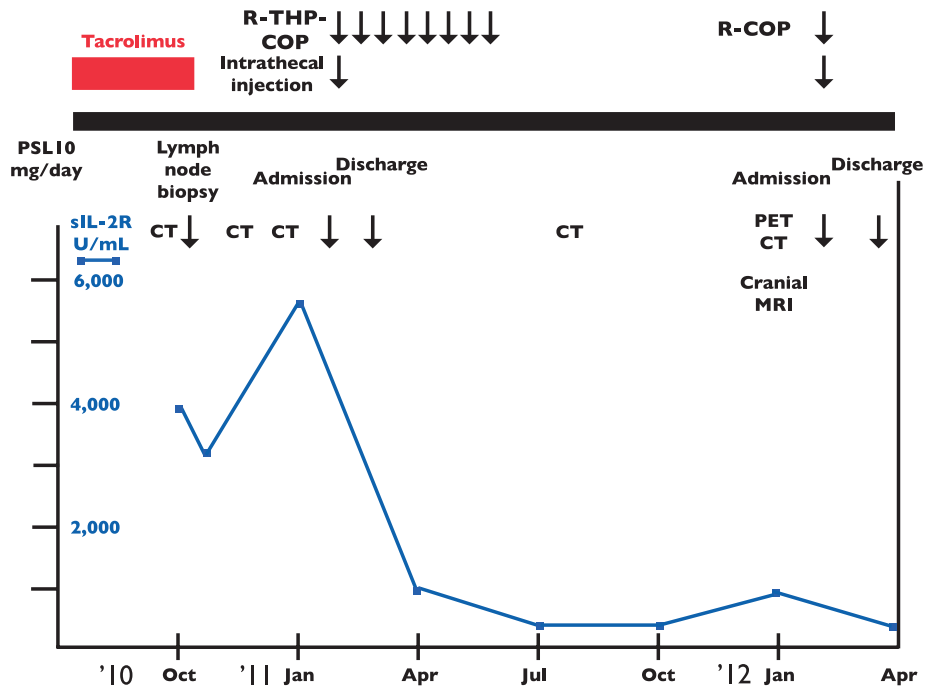




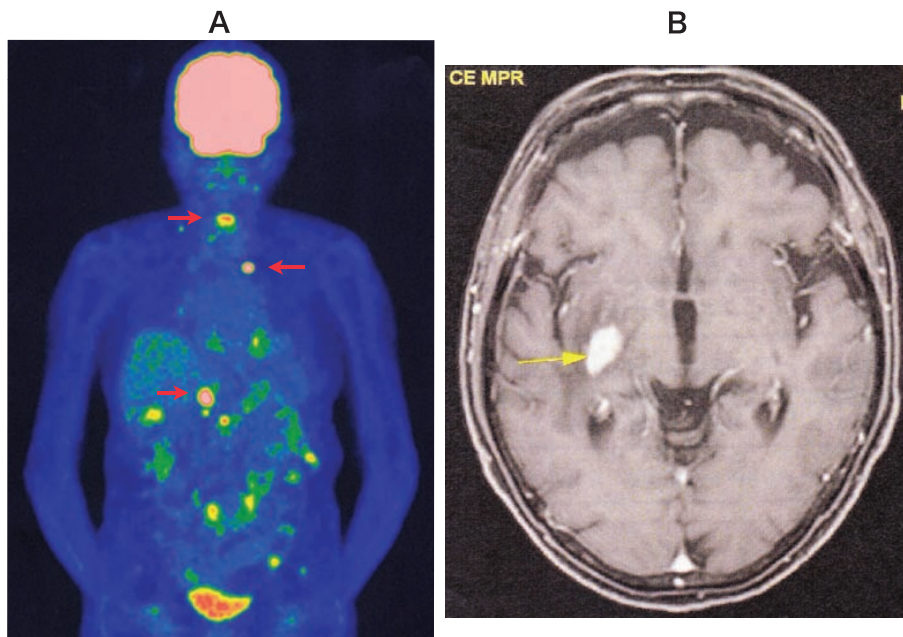
**Fig. 2.** Histopathological findings of the right axillary lymph node. (2A) Lymph node biopsy sections stained with hematoxylin and eosin revealed disruption of the lymph node architecture, with loss of the follicles, and diffuse proliferation of medium- to large-sized atypical cells with numerous mitoses. (2B) Large tumor cells showed positive staining for CD20. (2C) The large tumor B cells were weakly positive for CD5, and the small reactive T cells were strongly positive for CD5. (2D) The large tumor B cells showed a high rate of positivity for Ki-67. (2E) The tumor cells were negative for cyclin D1. (2F) The tumor cells were negative for EB virus-encoded ribonucleic acid. (2a)-(2E) :  $\times 600$ .



**Fig. 3.** Flow cytometry of the right axillary lymph node. (3A)  $\kappa$ -positivity and  $\lambda$ -negativity indicated B-cell neoplasms. (3B) Tumor cells were double positive for CD5 and CD20. (3C) Tumor cells were negative for CD10. (3D) Tumor cells were positive for CD19.



**Fig. 4.** Clinical course. R-THP-COP, rituximab-pirarubicin, cyclophosphamide, vincristine, prednisolone; R-COP, rituximab-cyclophosphamide, vincristine, prednisolone; PSL, prednisolone; sIL-2R, soluble interleukin-2 receptor; CT, computed tomography; PET, positron emission tomography; MRI, magnetic resonance imaging



**Fig. 5.** Imaging findings at the time of relapse. (5A) Fluorodeoxyglucose (FDG) positron emission tomography showing FDG accumulation in the left superior internal jugular lymph node (SUV max 13.9), thoracic para-aortic lymph nodes (SUV max 6.3) and lymph nodes between the inferior vena cava and portal vein (SUV max 12.0). (5B) Cranial magnetic resonance imaging showing lymphomatous infiltration of the right basal ganglia and left trigeminal nerve.

sent for the injections.

In February 2012, fluorodeoxyglucose positron emission tomography (FDG-PET-CT) showed accumulation of FDG in multiple superficial and deep lymph nodes (Fig. 5A). A right cervical lymph node biopsy was performed, which revealed a relapse of the B-cell lymphoma. The cell surface marker expressions showed the same pattern as at the initial diagnosis. Chromosome G-banding could not be performed due to the poor growth. However, Southern blot analysis revealed a rearrangement of *IgH/JH*, but not of *TCR $\beta$ 1*. Fluorescence *in situ* hybridization analysis showed a negative result for the *IgH-BCL2* fusion gene. At about this time, the patient developed left facial sensory disturbance and diplopia, and magnetic resonance imaging showed tumor infiltration in the right basal ganglia and left trigeminal nerve (Fig. 5B). Cerebrospinal fluid examination showed no abnormal findings.

In March 2012, the patient was readmitted to the hospital (Fig. 4). One course of treatment with rituximab, cyclophosphamide, vincristine and prednisolone (R-COP) and one course of intrathecal anticancer drug therapy were administered. Since the superficial lymph nodes became smaller in size, and the central nervous symptoms improved, the patient was discharged in April 2012. The patient was under follow-up at our outpatient clinic. Because the central nervous system manifestations became more severe in September of the same year, R-COP therapy was performed, but no improvement was seen, and at present the patient is unable to walk.

## DISCUSSION

The present patient, who had no primary immunodeficiency and no history of human immunodeficiency virus infection or organ transplantation, developed lymphoma after tacrolimus treatment of MCTD, and recovered transiently after discontinuation of tacrolimus. Thus, the patient was diagnosed as having iatrogenic LPD, classified as “other iatrogenic immunodeficiency-associated lymphoproliferative disorders” by the WHO.<sup>1</sup>

A total of 25 such cases after topical treatment with immunosuppressive drugs, including 8 cases of cutaneous T-cell lymphoma and 17 cases of lymphoma in sites other than the skin, have been reported, although there are not many reports of such cases after oral tacrolimus treatment.<sup>2</sup> In the present case, transient improvement of the DLBCL was noted by 1 month after the discontinuation of tacrolimus, suggesting that the immunosuppression with tacrolimus may have caused the disease. However, relapse occurred three months after discontinuation of tacrolimus. The present patient developed DLBCL after four months of treatment with tacrolimus, consistent with the mean of 150 (21-790) days reported by the U.S. Food & Drug Administration (FDA).<sup>3</sup> Although many immunodeficient patients show evidence of infection with EB

virus,<sup>1</sup> the present patient was negative for EB virus-encoded ribonucleic acid, suggesting the involvement of factors other than the EB virus in the pathogenesis of DLBCL.

Although there have been no reports of CD5-positive DLBCL in cases of “other iatrogenic immunodeficiency-associated lymphoproliferative disorders,” it is expected that the present patient may have a poor prognosis given the central nervous system infiltration.

Oral and intravenous tacrolimus administration has been reported as a risk factor for post-transplantation lymphoproliferative disorder after kidney or liver transplantation in children,<sup>4,7</sup> but not in adults,<sup>8</sup> and further accumulation of adult cases with a history of transplantation is considered to be necessary for more detailed analysis.

In one previous case report, topical tacrolimus could not be excluded as the cause of lymphoma.<sup>9</sup> Another report suggested that topical tacrolimus increased the risk of T-cell lymphoma.<sup>10</sup> However, many large-scale analyses have indicated that topical tacrolimus does not increase the risk of malignant lymphoma.<sup>11-15</sup> In addition, topical tacrolimus was effective for the treatment of cutaneous T-cell lymphoma in one case<sup>16</sup> and in the treatment of cutaneous lesions of angioimmunoblastic T-cell lymphoma in another case.<sup>17</sup> These cases are of great interest in terms of the relationship between tacrolimus and lymphoma.

To the best of our knowledge, the association of oral tacrolimus, rather than topical tacrolimus, with LPD in the absence of a history of transplantation has been suggested in only 3 cases, including the present case (Table 2).<sup>18,19</sup> All the 3 cases have been reported from Japan. The mean age of these patients was 72 (69-74) years, the male : female ratio was 1 : 2 and the primary disease was SjS/MCTD in 1 case, rheumatoid arthritis in 1 case and myasthenia gravis in 1 case. The tacrolimus dose used in all these cases remains unknown, except in the present case (3 mg/day). The mean administration period before the diagnosis of iatrogenic LPD was approximately 18.7 months (10 months to 2 years 8 months), which is longer than the mean of 150 days reported by the FDA. The EB virus infection status was unknown for the other cases, and was negative in the present case. In all cases, the type of LPD was B-cell lymphoma, including DLBCL in 1 case, Burkitt lymphoma in 1 case and lymphoplasmacytic lymphoma in 1 case. For treatment, chemotherapy was administered in 2 cases and radiotherapy in 1 case. CR was achieved in all three patients. After initially showing CR, the present case relapsed, while the outcomes of the other 2 cases remain unknown. It has been reported that 30-50% of patients with LPDs developing after topical tacrolimus treatment show spontaneous remission after the discontinuation of tacrolimus, without further intervention, similar to the case of the patients developing such disorders after treatment with methotrexate.<sup>2</sup> However, none of the 3 patients who developed LPD after oral tacrolimus showed spontaneous remis-

**Table 2.** Reports of suspected cases of LPD, without a history of transplantation, associated with oral tacrolimus treatment

Case	Age/sex	Primary disease	Pretreatment	TAC dose	TAC administration period	EBV	Type of LPD	CD5	Treatment of LPD	Effect	Outcome	Reference
1	69/F	SjS/ MCTD	PSL/CPA	3 mg/day	14 Mo	Negative	DLBCL	Positive	Discontinuation of tacrolimus	PR	Survival for 22 Mo	This case
									R-THP-COP	CR		
									R-COP	PR		
2	74/F	RA	DMARD	N.A.	32 Mo	N.A.	BL	N.A.	DA-EPOCH-R	CR	N.A.	18
3	73/M	MG	PSL	N.A.	10 Mo	N.A.	LPL	N.A.	Radiation	CR	N.A.	19

LPD, lymphoproliferative disorders ; M, male ; F, female ; SjS, Sjögren's syndrome ; MCTD, mixed connective tissue disease ; RA, rheumatoid arthritis ; MG, myasthenia gravis ; PSL, prednisolone ; CPA, cyclophosphamide ; DMARD, disease-modifying antirheumatic drugs ; TAC, tacrolimus ; N.A., not available ; Mo, month ; EBV, Epstein-Barr virus ; DLBCL, diffuse large B-cell lymphoma ; BL, Burkitt lymphoma ; LPL, lymphoplasmacytic lymphoma ; R, rituximab ; THP-COP, pirarubicin, cyclophosphamide, vincristine, prednisolone ; COP, cyclophosphamide, vincristine, prednisolone ; DA-EPOCH, etoposide, vincristine, doxorubicin, cyclophosphamide, prednisolone ; PR, partial remission ; CR, complete remission

sion, necessitating chemotherapy. Thus, in patients developing LPDs after oral tacrolimus treatment, spontaneous remission with only discontinuation of tacrolimus, with no further intervention, may be unlikely. Central nervous system infiltration is known to be common in CD5-positive DLBCL,<sup>20,21</sup> but whether there is any association between tacrolimus and central nervous system infiltration is unknown.

### CONSENT

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

### COMPETING INTERESTS

The authors declare that they have no competing interests.

### AUTHORS' CONTRIBUTIONS

YS treated the patient, collected and analyzed the data, and wrote the manuscript. AS, HI, MW and KS treated the patient and collected the data. NN and TS analyzed the data. NK and MN provided guidance to YS for preparation of this manuscript. All authors read and approved the final manuscript.

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