Clinicopathological analysis in PTCL-NOS with CADM1 expression

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<Abstract>

Peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS) is a heterogeneous disease with respect to clinicopathological features. Cell adhesion molecule 1 (CADM1) has been reported to be ectopically expressed in adult T-cell leukaemia/lymphoma (ATLL). However, the frequency of CADM1 expression remains unknown in peripheral T-cell lymphomas. In the current study, CADM1 expression was analysed in 88 PTCL-NOS patients. CADM1 was expressed in 14 of 88 (15.9%) PTCL-NOS cases, and its expression was associated with C-C chemokine receptor type 4 (CCR4) expression and nuclear atypia. CADM1-positive PTCL-NOS cases (10/74) had a significantly poorer prognosis than CADM1-negative cases (64/74) (P=0.001). Multivariate analysis confirmed that CADM1 expression was an independent prognostic factor in PTCL-NOS. These findings suggest that CADM1 expression is a novel prognostic factor for PTCL-NOS.

Keyword: *Peripheral T-cell lymphoma, not otherwise specified, CADM1, clinicopathological analysis, prognosis*

<*Introduction*>

Peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS), which is one of the non-Hodgkin lymphoma entities referenced in the World Health Organization (WHO) classification, is currently estimated to represent 50% of all peripheral T-cell lymphoma (PTCL) cases and has heterogeneous clinicopathological features. PTCL-NOS generally follows an aggressive clinical course with a poor outcome[1].

Cell adhesion molecule 1 (CADM1/TSLC1/IgSF4) was initially identified as a tumour suppressor gene in malignant epithelial tumours[2]. *CADM1* encodes an immunoglobulin superfamily cell adhesion molecule that mediates intercellular adhesion through calcium-independent homophilic trans-interaction[3]. Reduced CADM1 expression in various cancers by promoter methylation has been reported to enhance invasion and/or metastasis and to be associated with a poor prognosis[4-8]. Aberrant expression of CADM1 has been observed among some malignant epithelial tumours. For example, in a patient with breast cancer, aberrant CADM1 expression in the cytoplasm was reported to be associated with progression, particularly with invasion into the stroma and subsequent metastasis[9]. In addition, CADM1 overexpression in small-cell lung cancer enhances spheroid-like cell growth and tumorigenicity[10]. Therefore, changes in CADM1 expression appear to influence clinicopathologic features and prognosis in a variety of tumours.

Among T-cell malignancies, CADM1 was reported to be ectopically expressed in adult T-cell leukaemia/lymphoma (ATLL), and its expression was suggested to play a significant role in oncogenesis[11,12]. With respect to PTCLs other than ATLL, a previous report of a small number of clinical samples revealed that some of them were positive for CADM1 protein expression[13]. A previous study using an in vivo xenograft mice model revealed that CADM1 expression was also associated with development and progression of T-cell lymphoma[14]. However, the association between CADM1 expression and clinical manifestations in PTCL-NOS has not been fully evaluated.

In the current study, we evaluated the expression of CADM1 in PTCL-NOS and analysed the

clinicopathological characteristics associated with CADM1 expression in PTCL-NOS.

<*Patients and methods*>

・*Patient selection*

We studied 88 PTCL-NOS cases, including 78 cases previously submitted to the international PTCL project[15] and 10 cases submitted for diagnosis to the Department of Pathology, Kurume University, Kurume, Japan between 2005 and 2012. Paraffin-embedded tissues were available. To compare the CADM1 expression of PTCL-NOS and other peripheral T-cell lymphoma, we also enrolled 68 patients with ATLL, 13 with ALK negative anaplastic large cell lymphoma (ALCL), and 52 with angioimmunoblastic T-cell lymphoma (AITL) who were diagnosed between 2005 and 2012 at the Department of Pathology, Kurume University School of Medicine, or submitted to the international PTCL project[15]. Pathological diagnoses were made by two expert haematopathologists (H.M. and K.O.) in accordance with the WHO criteria. PTCL-NOS cases enrolled in this study were serologically negative for human T-lymphotropic virus type I (HTLV-1) or were determined to be negative for monoclonal integration of HTLV-1 proviral DNA in tumour cells as determined by Southern blot analysis. Clinical information was obtained by reviewing patient medical charts. Materials and clinical information were approved by the Research Ethics Committee of Kurume University and were in accordance with the Declaration of Helsinki.

・*Morphological and immunohistochemical analysis*

Paraffin sections from each sample were evaluated for their morphologic characteristics, including cell size and nuclear atypia. In reference to the evaluation of nuclear atypia[16], the group of nuclear atypia are defined as follows: (1) nuclear atypia-positive: pleomorphic nuclei of varying sizes showing hyperchromatism with coarse and irregular distribution often associated with large nucleoli; (2) nuclear

atypia-negative: nuclei of uniform size and shape, which are not hyperchromatic or may be hyperchromatic with evenly dispersed chromatin or with finely granular chromatin without clumping (Figure 1).

In addition, sections were immunostained with monoclonal antibodies against CADM1 (1:1000, Clone 3E1, anti-chicken IgY [Immuno Bio Science]), CD3 (1:50, Clone F7.2.38; Dako Japan, Tokyo, Japan), CD4 (1:30, Clone SP35; Roche Diagnostics, Tokyo, Japan), CD8 (1:50, Clone 4B11; Leica Biosystems, Tokyo, Japan), T-cell–restricted intracellular antigen-1 (TIA-1) (1:200, Clone IM 2550; Beckman Coulter, Hialeah, FL), C-C chemokine receptor type 4 (CCR4) (ready to use, POTELIGEO TEST: Kyowa Medex, Tokyo, Japan), CD30 (1:100, Clone Ber-H2; Dako Japan), forkhead box P3 (FOXP3) (1:100, Clone SP97; Abcam, Tokyo, Japan), GATA binding protein 3 (GATA3) (1:200, Clone D13C9; Cell Signaling Technology), and T-bet/Tbx21 (1:100, Clone 4B10; abcam). Tissue samples were considered positive if >20% of the lymphoma cells were positive for CADM1, CD3, CD4, CD8, TIA-1, CD30, CCR4, FOXP3, GATA3, and T-bet/Tbx21.

・Statistical analysis

The following clinicopathological features were analysed: age, sex, performance status (PS), clinical stage, B symptoms, elevated serum lactate dehydrogenase level (LDH), hypercalcemia, extranodal involvement, bone marrow involvement, peripheral blood involvement, skin involvement, international prognostic index (IPI) score, prognosis index of PTCL-unspecified (PIT) score, treatment, therapeutic effect, morphological findings, and immunophenotypic findings.

The significance of differences between the CADM1-positive and -negative groups was examined with Fisher's exact test or chi-square test. Patient survival data were analysed by the Kaplan-Meier method and were compared using log-rank tests. Univariate and multivariate analyses were performed with a Cox proportional hazards regression model. In this study, $P<0.05$ was considered to be significant.

All statistical analyses were performed using JMP, version 11 software (SAS Institute, Tokyo, Japan).

<*Results*>

CADM1 expression in PTCL-NOS

CADM1 was positive in 14 of 88 (15.9%) PTCL-NOS patients. Immunohistochemical staining showed membranous and granular cytoplasmic CADM1 expression patterns in CADM1-positive neoplastic cells[13] (Fig. 2).

Comparison of clinicopathological characteristics by CADM1 expression in PTCL-NOS patients

We compared the clinical characteristics of CADM1-positive versus CADM1-negative PTCL-NOS cases (Table 1). Among the 88 PTCL-NOS patients, there were 57 males (64.7%) and 31 females (35.3%) who ranged in age from 4 to 86 years (mean, 66 years). The percentage of patients >60 years was relatively larger among CADM1-positive cases (86%) than among CADM1-negative cases (60%) (*P*=0.074). However, other factors (sex, PS, clinical stage, presence of B symptoms, elevated serum LDH, hypercalcemia, extranodal site involvement including peripheral blood, bone marrow, and skin, IPI score, PIT score, treatment, and therapeutic effect) were not significantly different between CADM1-positive and CADM1-negative patients.

Pathological features are described in Table 2. CADM1 expression was significantly associated with nuclear atypia (p=0.036), CCR4 expression (p<0.001) and GATA3 expression (p=0.002). CD30 was relatively more frequently expressed in CADM1-positive cases than in CADM1-negative cases, although the difference did not reach significance (*P*=0.052). The other pathological factors, including cell size and CD3, CD4, CD8, TIA-1, FOXP3, and T-bet/Tbx21 expression, were not significantly associated with CADM1 expression.

Prognostic factors

Overall survival (OS) according to CADM1 status is shown in Fig. 3. CADM1 expression was significantly associated with poor outcome in PTCL-NOS patients (P=0.001, log-rank method). Univariate analyses revealed that PS 2-4 (hazard ratio [HR], 3.263; 95% confidence interval [CI], 1.436-7.197), >1 extranodal site (HR, 3.333; 95% CI, 1.403-7.660), IPI (HR, 3.179; 95%CI, 1.406-7.186), CCR4 positivity (HR, 2.039; 95% CI, 1.660-3.937), and CADM1 positivity (HR, 3.224; 95% CI, 1.423-6.642) were significantly associated with poor OS. Multivariate analyses with PS, extranodal disease, and CCR4 revealed CADM1 expression (HR, 4.405; 95% CI, 1.075-16.39) and PS (HR, 2.921; 95% CI, 1.004-8.035) to be significantly associated with OS. On the other hand, multivariate analysis with IPI also showed the same significance in CADM1 expression (HR, 3.167; 95% CI, 1.188-8.440) and IPI (HR, 2.167; 95% CI, 1.110-6.134) (Table 3).

<*Discussion*>

In this study, we used immunohistochemistry to demonstrate that CADM1 is expressed in approximately 16% of PTCL-NOS cases, and this expression is associated with nuclear atypia and CCR4 expression. CADM1 positivity had independent prognostic significance among PTCL-NOS patients.

Among haematological tumours, CADM1 has been reported to be highly and ectopically expressed in ATLL, while no expression was detected in normal CD4+ T cells or in leukaemia cells without HTLV-1 infection[11, 12, 17]. In a previous study, Nakahata et al. evaluated the expression of CADM1 in 36 ATLL and 54 non-ATLL lymphomas, including 15 T- or NK-cell lymphomas, by immunohistochemical staining,

although the diagnostic details of these T-/NK-cell lymphomas were not clearly described[13]. The present immunohistochemical data revealed that 14 of 88 (15.9%) PTCL-NOS cases expressed CADM1 protein. CADM1 expression was also observed in 54 of 68 (79.4%) ATLL cases, 4 of 13 (30.8%) ALK-negative anaplastic large cell lymphoma (ALCL) cases, and 2 of 52 (3.8%) angioimmunoblastic T-cell lymphoma (AITL) cases (supplemental Fig. 1). In addition, by using datasets from the GEO database (accession numbers: GSE6338 and GSE19069), *CADM1* mRNA expression levels were higher not only in ATLL but also in other PTCLs compared to normal T cells (supplemental Fig. 2). In particular, ATLL cases and PTCL-NOS cases had high level expression population of CADM1 mRNA in this data. We also detected expression of CADM1 in PTCLs other than ATLL in clinical samples. Further studies to characterize the significance of CADM1 expression in various types of PTCL are required.

In this study, CADM1 expression was found to be an unfavourable prognostic factor for PTCL-NOS patients, and multivariate analysis clarified its independence from several other prognostic factors. Many factors, including age, PS, clinical stage, LDH level, >1 extranodal site, bone marrow involvement, response to chemotherapy, IPI score, PIT score, and several biologic markers, such as CCR4 expression, have been reported to have prognostic significance in univariate analysis and/or multivariate analyses of PTCL-NOS cases[18-24]. The present study revealed that CADM1 expression had a higher HR and a lower *P*-value compared to PS, >1 extranodal site, and CCR4 expression in multivariate analysis for OS. Additionaly, multivariate analysis with CADM1 expression and IPI showed that CADM1 an independent prognostic factor from IPI score although CADM1 expression was not statistically associated with IPI score. CADM1 is therefore thought to be an important prognostic factor for PTCL-NOS patients and might play important function in disease progression in PTCL-NOS.

In PTCL-NOS, gene expression profile(GEP) analysis identified a GATA3-overexpressing subgroup and TBX21-overexpressiong subgroup, which were characterized to Th2 profile and Th1 profile as hypothetical cell-of-origin model[25]. These reports also showed that each representative case in GATA3 and TBX21 overexpressing subgroup in GEP analysis had also high protein expression by immunohistochemistry(IHC). And PTCL-NOS with GATA3 overexpression by GEP or IHC was reported to be associated with worse prognosis than PTCL-NOS without GATA3 overexpression[25-27]. Our study revealed that CADM1 positive PTCL-NOS had a significant inverse association with GATA3 protein expression and had no significant association with TBX-21 protein expression. Indeed, it was also suggested by GEP analysis that more than 20% PTCL-NOS did not meet criteria for GATA3 subgroup and TBX21 subgroup[25]. CADM1 positive PTCL-NOS might have a prognostic significance through different mechanism from GATA3 positive group.

The reason why CADM1-positive PTCL-NOS is significantly associated with poor outcome remains unclear. The pathogenesis of CADM1 expression has been reported to be partially derived from activation of NF-kB pathway in cell line models[28, 29]. Dewan et al. reported that transplantation of EL4 T-cell lymphoma cells expressing CADM1 promoted the development of leukaemia and shortened the life span of syngeneic mice compared to those not expressing CADM1[14]. These mechanisms could be related to the pathogenesis of CADM1 expression in PTCL-NOS.

CADM1-positive PTCL-NOS was strongly associated with CCR4 positivity, nuclear atypia, and significantly poor prognosis. These characteristics were also reported by Nakagawa et al. to be common in PTCL-NOS cases with genomic imbalance[30,31]. These researchers reported that PTCL-NOS with genomic imbalances and lymphoma-type ATLL had similar clinicopathological and molecular features, including nuclear size, nuclear atypia, and CCR4 expression, as well as similar genetic alteration patterns[30]. Therefore, these findings suggest that PTCL-NOS with CADM1 expression and lymphoma-type ATLL partially share some common clinicopathological features. However, it should be

noted that further elucidation of the molecular aspects in CADM1-positive PTCL-NOS cases is required in the future to precisely describe the similarity between PTCL-NOS and lymphoma-type ATLL.

There are some limitations in this study. Firstly, this is a retrospective study of small number of cases lacking therapeutic information. Further retrospective studies with larger cohort or prospective studies with

more detailed information are warranted to validate our results. Secondly, the role of CADM1 in PTCL-NOS remains unknown. Future molecular analyses are needed to determine the function of CADM1 expression for PTCL patients other than ATLL.

In conclusion, CADM1 expression might be an important prognostic factor in PTCL-NOS. Further analyses of additional biologic markers, including genetic features, in a larger series will certainly increase our understanding of the role of CADM1 in PTCL-NOS.

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TK and HM performed research; KO designed research; TK, HM and KO performed data analysis; TK, HM, NY, MS and KO wrote the manuscript; SK, NY, YI, MS, KU and YM supported research; HM and KO supervised research. All authors read and approved the final manuscript.

Figure Legends

Fig. 1 Histopathologic profiles of PTCL-NOS cases (haematoxylin/eosin [H&E] staining). (a) (c) (e) neoplastic cells with nuclear atypia show pleomorphic large cell morphology with irregular nuclei. (b) (d) (f) neoplastic cells without nuclear atypia show dispersed chromatin without irregular nuclei.

Fig. 2 Representative immunohistochemical findings of CADM1 expression in PTCL-NOS. (a)(b) CADM1-positive PTCL-NOS. The cytoplasm and membranes of neoplastic cells were positive for CADM1. (c)(d) CADM1-negative PTCL-NOS. CADM1 was negative for neoplastic cells. Original magnification ×600 for all panels.

Fig. 3 Overall survival (OS) of PTCL-NOS patients. CADM1-positive PTCL-NOS patients (n=75) had a significantly poorer prognosis compared to CADM1-negative patients (P=0.001).

Supplemental Figure 1. CADM1 expression among PTCLs. CADM1 was expressed in 14 of 88 (15.9%) PTCL-NOS cases, 54 of 68 (79.4%) ATLL cases, 4 of 13 (30.8%) ALK-negative ALCL cases, and 2 of 52 (3.8%) AITL cases.

Abbreviations: PTCL-NOS, peripheral T-cell lymphoma, not otherwise specified; ATLL, adult T-cell leukaemia/lymphoma, ALCL, anaplastic large cell lymphoma; AITL, angioimmunoblastic T-cell lymphoma

Supplemental Figure 2. *CADM1* gene expression levels were determined using published data (GSE6338 and GSE19069). *CADM1* expression was observed not only in ATLL, but also in some PTCLs.

Abbreviations: PTCL-NOS, peripheral T-cell lymphoma, not otherwise specified; ATLL, adult T-cell leukaemia/lymphoma, ALCL, anaplastic large cell lymphoma; AITL, angioimmunoblastic T-cell lymphoma

Compliance with Ethical Standards

Conflict of Interest

The authors have no financial conflicts of interest to disclose with regard to this study.

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Figure

Fig. 1

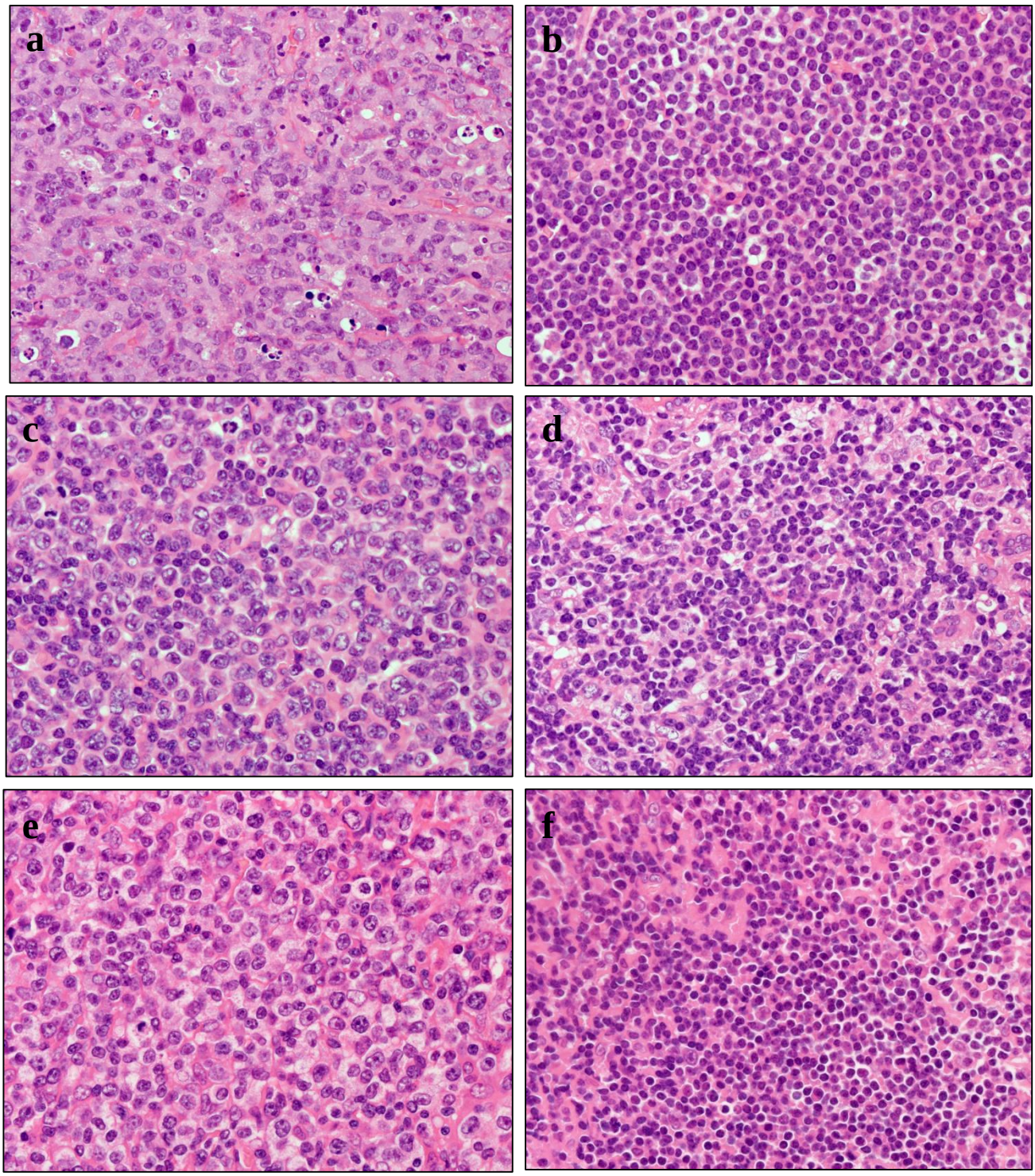


Fig. 2

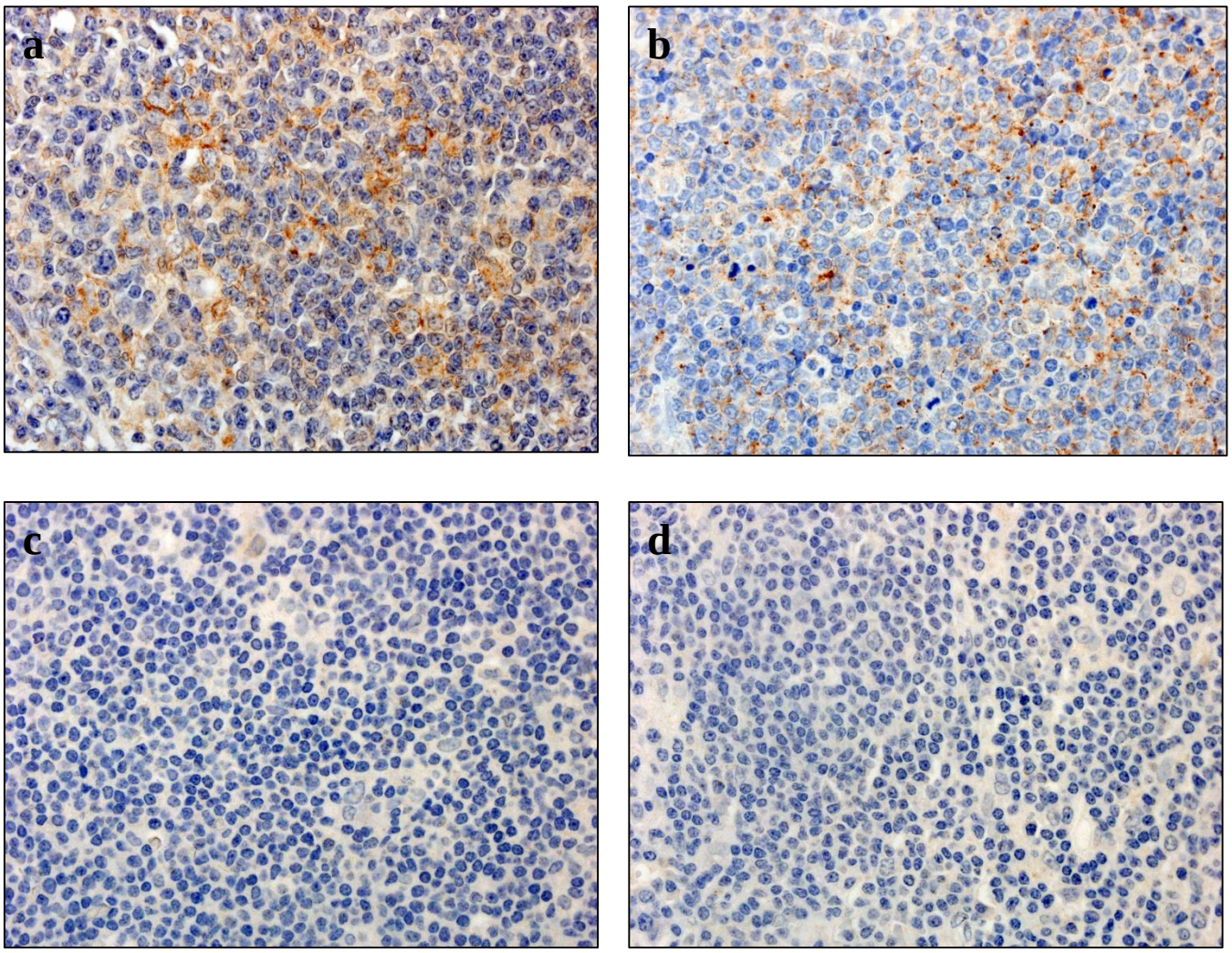
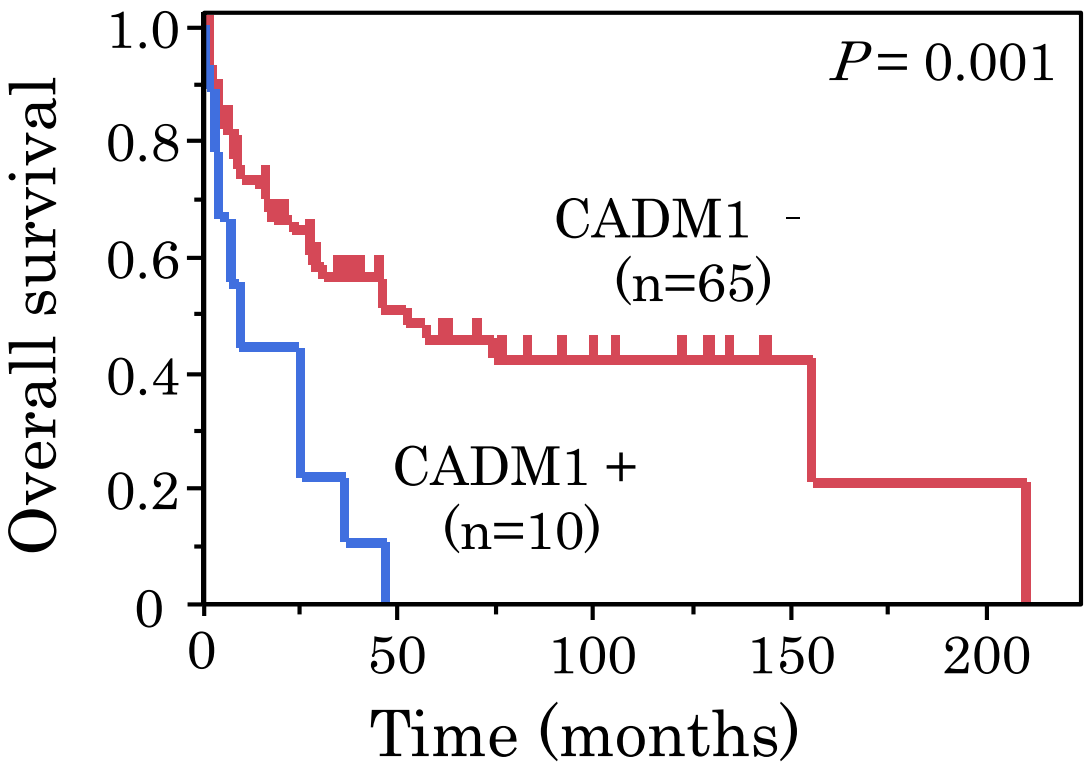


Fig. 3



Median overall survival
(95% CI) - months

CADM1 + : 8.8 (0.1-35.6)
CADM1 - : 51.1 (26.4-209.1)

Table

Table 1. Clinical characteristics of PTCL-NOS patients with or without CADM1 expression

	Total, % (n=88)	CADM1(+), % (n=14)	CADM1(-), % (n=74)	*P*-value (Fisher)
Clinical characteristics				
Age, years				0.074
≥60	64% (56/88)	86% (12/14)	60% (44/74)	
<60	34% (32/88)	14% (2/14)	40% (30/74)	
Sex				0.966
Male	65% (57/88)	64% (9/14)	65% (48/74)	
Female	45% (31/88)	36% (5/14)	35% (26/74)	
Performance status				1.000
0-1	70% (35/50)	67% (4/6)	70% (31/44)	
2-4	30% (15/50)	33% (2/6)	30% (13/44)	
Clinical stage				0.643
I-II	26% (13/50)	33% (2/6)	25% (11/44)	
III-IV	74% (37/50)	67% (4/6)	75% (33/44)	
B symptoms				0.211
Present	44% (22/50)	17% (1/6)	48% (21/44)	
Absent	56% (28/50)	83% (5/6)	52% (23/44)	
LDH level				1.000
Elevated	46% (23/50)	50% (3/6)	45% (20/44)	
Normal	54% (27/50)	50% (3/6)	55% (24/44)	
Hypercalcemia				0.330
Present	6% (3/46)	17% (1/6)	5% (2/43)	
Absent	94% (46/49)	83% (5/6)	95% (41/43)	
Extranodal involvement				0.297
>1 site	30% (13/43)	0% (0/4)	33% (13/39)	
≤1 site	70% (30/43)	100% (4/4)	67% (26/39)	
Bone marrow involvement				0.571
Involved	17% (8/47)	0% (0/5)	19% (8/42)	
Not involved	83% (39/47)	100% (5/5)	81% (34/42)	
Peripheral blood involvement				1.000
Involved	22% (11/50)	17% (1/6)	23% (10/44)	
Not involved	78% (39/50)	83% (5/6)	77% (34/44)	
Skin involvement				1.000

Involved	14% (7/50)	17% (1/6)	14% (6/44)	
Not involved	86% (43/50)	83% (5/6)	86% (38/44)	
IPI score				0.323
Low/Low-intermediate	53% (23/43)	25% (1/4)	56% (22/39)	
High-intermediate/High	47% (20/43)	75% (3/4)	44% (17/39)	
PIT score				0.146
Group 1/Group 2	58% (28/48)	20% (1/5)	63% (27/43)	
Group 3/Group 4	42% (20/48)	80% (4/5)	37% (16/43)	
Treatment				0.742*
CHOP/CHOP-like	76% (38/50)	83% (5/6)	75% (33/44)	
Other regimens	16% (8/50)	17% (1/6)	16% (7/44)	
No therapy	8% (4/50)	0% (0/6)	9% (4/44)	
Therapeutic efficacy				0.665
CR	46% (23/50)	33% (2/6)	53% (21/40)	
Non-CR	54% (23/50)	67% (4/6)	47% (19/40)	

*Chi-square test

Abbreviations: PTCL-NOS, peripheral T-cell lymphoma, not otherwise specified; CADM1, cell adhesion molecule 1; LDH, lactate dehydrogenase; IPI, international prognostic index; PIT, prognosis index of peripheral T-cell lymphoma, unspecified; CHOP, cyclophosphamide, doxorubicin, vincristine and prednisolone; CR, complete response

Table 2. Pathological characteristics of PTCL-NOS patients with or without CADM1 expression

	Total, % (n=88)	CADM1(+), % (n=14)	CADM1(-), % (n=74)	*P*-value (Fisher)
Morphology				
Cell size				0.513*
Medium	58% (51/88)	50% (7/14)	59% (44/74)	
Large	42% (37/88)	50% (7/14)	41% (30/74)	
Nuclear atypia				0.036
Positive	58% (51/88)	85% (12/14)	51% (39/74)	
Negative	42% (37/88)	15% (2/14)	49% (35/74)	
Immunohistochemistry				
CD3				0.308
Positive	92% (81/88)	86% (12/14)	93% (69/74)	
Negative	8% (7/88)	14% (2/14)	7% (5/74)	
CD4				0.371
Positive	87% (77/88)	79% (11/14)	89% (66/74)	
Negative	13% (11/88)	21% (3/14)	11% (8/74)	
CD8				0.689
Positive	16% (14/88)	21% (3/14)	15% (11/74)	
Negative	84% (74/88)	79% (11/14)	85% (63/74)	
TIA-1				0.734
Positive	24% (21/88)	29% (4/14)	23% (17/74)	
Negative	76% (67/88)	71% (10/14)	77% (57/74)	
CCR4				<0.001
Positive	40% (34/85)	86% (12/14)	31% (22/71)	
Negative	60% (51/85)	14% (2/14)	69% (49/71)	
CD30				0.053
Positive	8% (6/79)	23% (3/13)	5% (3/66)	
Negative	92% (73/79)	77% (10/13)	95% (63/66)	
FOXP3				1.000
Positive	6% (5/88)	7% (1/14)	5% (4/74)	
Negative	94% (83/88)	92% (13/14)	95% (70/74)	
GATA3				0.002
Positive	86% (76/88)	64% (9/14)	91% (67/74)	
Negative	14% (12/88)	36% (5/14)	9% (7/74)	

T-bet/Tbx21				0.1427
Positive	39% (34/88)	57% (8/14)	35% (26/74)	
Negative	61% (54/88)	43% (6/14)	65% (48/74)	

*Chi-square test

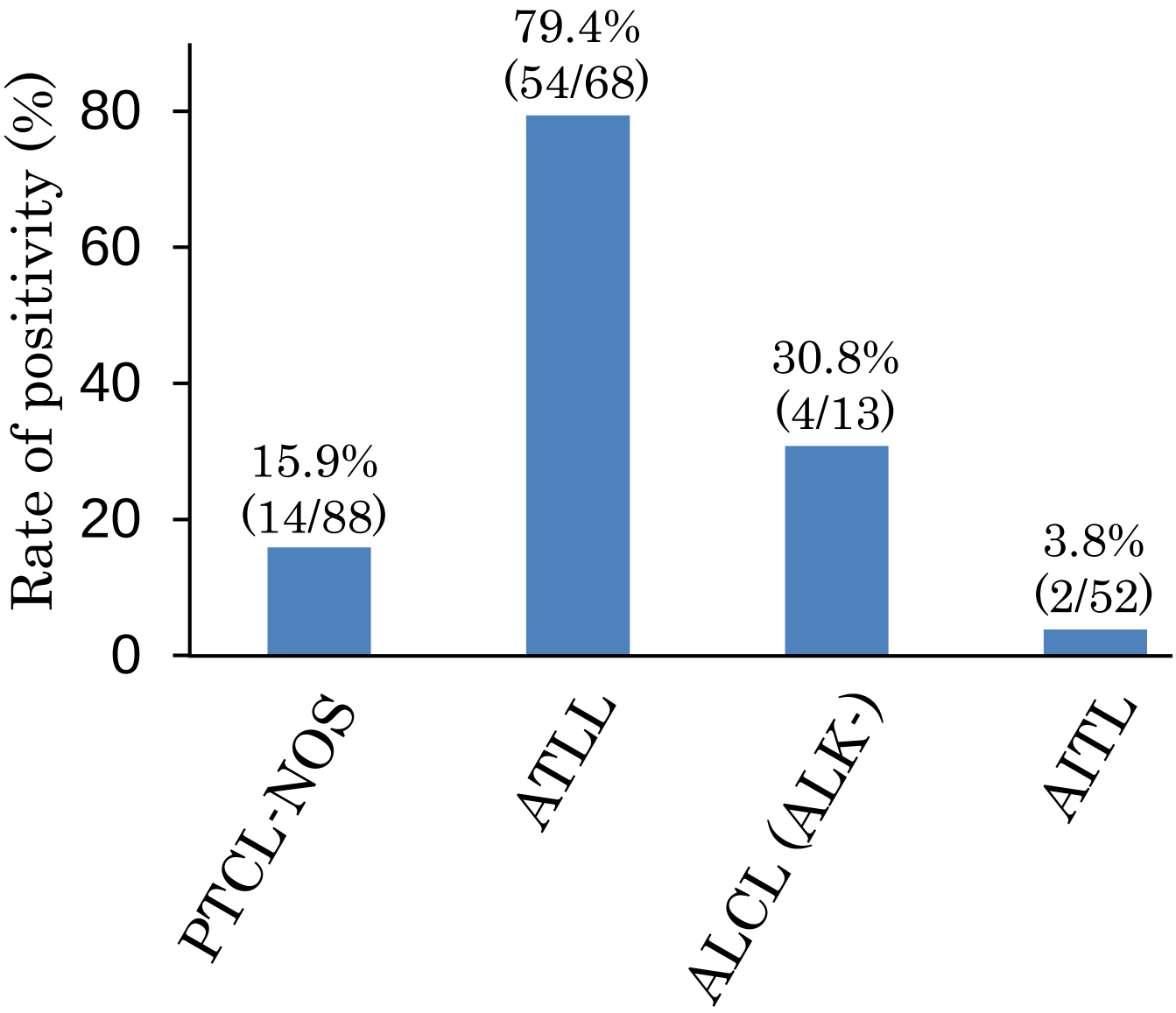
Abbreviations: PTCL-NOS, peripheral T-cell lymphoma, not otherwise specified; CADM1, cell adhesion molecule 1; TIA-1, T-cell–restricted intracellular antigen-1; CCR4, C-C chemokine receptor type 4; FOXP3, forkhead box P3; GATA3, GATA binding protein 3; Tbx21, T-box 21

Table 3. Prognostic factors affecting overall survival

Variable	Univariate analysis		Multivariate analysis 1		Multivariate analysis 2	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age, >60	1.332 (0.695-2.689)	0.394	-			
PS, 2-4	3.263 (1.436-7.197)	0.006	2.921 (1.004-8.035)	0.049		
Stage, III, IV	1.159 (0.503-3.002)	0.739	-			
LDH, >Normal	0.518 (0.228-1.117)	0.094	-			
Extranodal disease, >1 site	3.333 (1.403-7.660)	0.007	2.712 (0.964-7.521)	0.058		
BM involvement, Positive	1.090 (0.362-2.702)	0.863	-			
IPI, High-int/High	3.179 (1.406-7.186)	0.005			2.167 (1.110-6.134)	0.027
PIT, Group 3 or 4	1.311 (0.592-2.9)	0.504				
CCR4, Positive	2.039 (1.660-3.937)	0.033	1.472 (0.492-4.044)	0.469		
CADM1, Positive	3.224 (1.423-6.642)	0.007	4.405 (1.075-16.39)	0.040	3.167 (1.188-8.440)	0.021

Abbreviations: CI, confidence interval; PS, performance status; LDH, lactate dehydrogenase; BM, bone marrow; IPI, international prognostic index; PIT, prognosis index of peripheral T-cell lymphoma, unspecified; CADM1, cell adhesion molecule 1; CCR4, C-C chemokine receptor type 4

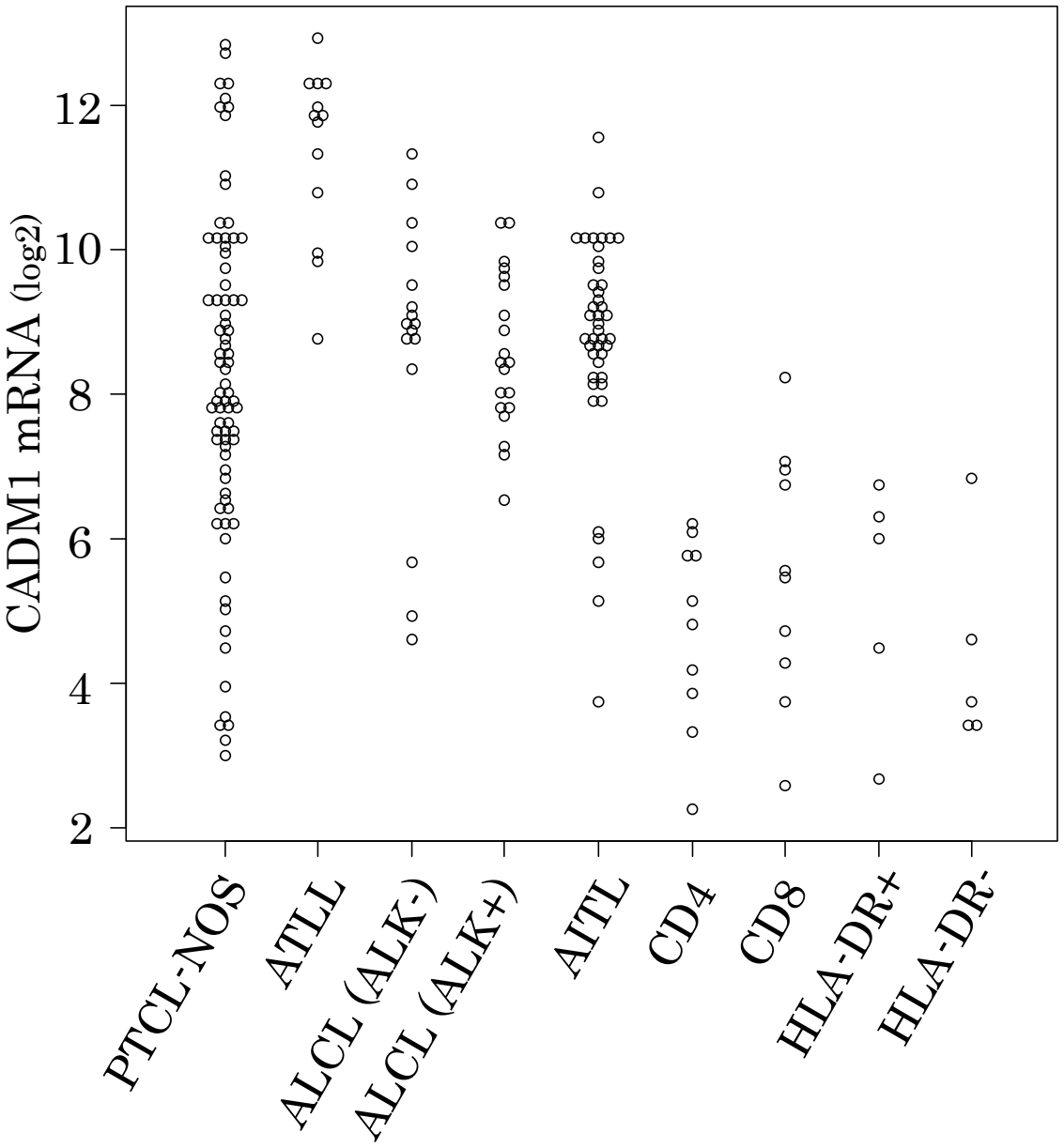
Fig. S1. CADM1 expression among PTCLs.



CADM1 was expressed in 14 of 88 (15.9%) PTCL-NOS cases, 54 of 68 (79.4%) ATLL cases, 4 of 13 (30.8%) ALK-negative ALCL cases, and 2 of 52 (3.8%) AITL cases.

PTCL-NOS, peripheral T-cell lymphoma, not otherwise specified; ATLL, adult T-cell leukaemia/lymphoma, ALCL, anaplastic large cell lymphoma; AITL, angioimmunoblastic T-cell lymphoma

Fig. S2. *CADM1* gene expression levels were determined using published data (GSE6338 and GSE19069).



CADM1 expression was observed not only in ATLL, but also in some PTCLs.

PTCL-NOS, peripheral T-cell lymphoma, not otherwise specified; ATLL, adult T-cell leukaemia/lymphoma, ALCL, anaplastic large cell lymphoma; AITL, angioimmunoblastic T-cell lymphoma