i.e., indented or multilobated, and were usually characterized by a mixed morphology, which was referred to as the polymorphic variant. Pure proliferation of immunoblasts was seen in only two patients (1%), and was termed the immunoblastic variant. Intravascular/sinusoidal infiltration was observed in 26% of the common variants, 62% of the giant cell-rich variants, 14% of the polymorphic variants, and 0% of the immunoblastic variants. The giant cell-rich variant was associated with intravascular/sinusoidal infiltration more frequently than the common variant (p=0.01).

Clinical features according to morphological variants

The patients' main characteristics and therapeutic results according to morphological categorization are summarized in Table 1. We compared the clinical characteristics between the current group of 120 patients with *de novo* CD5$^+$ DLBCL and 384 patients with CD5$^-$ DLBCL in our previous study.[11] Our previous findings on the clinical features of *de novo* CD5$^+$ DLBCL such as an older age, at onset, female predominance, frequent extranodal involvement, and higher International Prognostic Index (IPI)[31] score were confirmed in the current group of 120 patients (*data not shown*).

Table 1. Clinical features of the patients with *de novo* CD5$^+$ diffuse large B-cell lymphoma.

	Total (n=120) (%)	Common (n=91) (%)	Giant cell-rich (n=13) (%)	Polymorphic (n=14) (%)	Immunoblastic (n=2) (%)
Age at diagnosis, years.					
Median	66	66	63	67/71	62/69
Range	22-91	22-91	36-81	52-89	62,69
Over 60 years old	84 (70)	64 (70)	9 (69)	9 (64)	2 (100)
Sex (male:female)	58:62	40:51	9:4	8:6	1:1
Performance status >1	39 (33)	27 (30)	4 (31)	6 (43)	2 (100)
Serum LDH level >normal	85 (71)	61 (67)	11 (85)	11 (79)	2 (100)
Stage III/IV	73 (61)	54 (59)	9 (69)	8 (57)	2 (100)
Extranodal involvement	75 (63)	55 (60)	8 (62)	11 (79)	1 (50)
More than one site	29 (24)	20 (22)	4 (31)	5 (36)	0 (0)
International Prognostic Index					
Low	30 (25)	25 (27)	1 (8)	4 (29)	0 (0)
Low-intermediate	30 (25)	26 (29)	4 (31)	0 (0)	0 (0)
High-intermediate	19 (16)	11 (12)	4 (31)	4 (29)	0 (0)
High	41 (34)	29 (32)	4 (31)	6 (43)	2 (100)
B-symptoms present	49/117 (44)	35/88 (40)	5 (38)	7 (50)	2 (100)
Complete response rate	77/114 (68)	64/86 (74)	5/12 (42)	7/14 (50)	1/2 (50)
5-year OS rate	(38)	(44)	(15)	(21)	(0)

LDH: lactate dehydrogenase; OS: overall survival.

The clinical features, including the five factors of the IPI,[31] were not significantly different among the four morphological variants of *de novo* CD5$^+$ DLBCL. The bone marrow, liver, and spleen were the most frequently involved anatomical sites irrespective of the morphological variant (*data not shown*).

Atypical lymphocyte concentrations (range, 11 to 78%) were noted at presentation in the peripheral blood smear of four cases, whose white blood cell counts ranged from 6,000 to 41,000/mm^3. None of these patients showed marked splenomegaly and the morphology of leukemic cells differed from that of B-cell prolymphocytic leukemia cells.

Immunophenotypic features

BCL2 protein was expressed in 86 out of 96 tumors, and observed in more than 70% of the tumor cells in almost all positive cases (Figure 2B). This incidence was significantly higher than that in the CD5$^-$ DLBCL cases (105/150, 70%; p=0.0003).

As for the molecular classification system established by Hans *et al.*,[30] 36 of 44 cases (82%) of *de novo* CD5$^+$ DLBCL were classified as the non-germinal center B-cell type. Thirty patients (68%) showed the CD10$^-$BCL6$^-$MUM1$^+$ immunophenotype. CD10 was positive in seven patients (16%), BCL6 was negative in 79% of the cases examined (33/42), and MUM1 was positive in 95% of the cases (42/44). Only one patient showed the CD10$^+$BCL6$^+$MUM1$^-$ immunophenotype.

Among the four morphological variants, the common variant was positive for Ig-κ more frequently than either the giant cell-rich (p=0.05) or polymorphic (p=0.03) variant. As for other expression of other antigens there were no significant differences among the morphological variants of *de novo* CD5$^+$ DLBCL (*data not shown*).

Therapeutic outcome and long-term survival according to histopathological variants

Clinical follow-up data and information about the first-line therapy were available for all patients. The treatment consisted of chemotherapeutic regimens including anthracycline for 104 patients and without anthracycline for three. No patient was treated with rituximab in the first-line therapy. Seven patients with localized disease were treated with radiotherapy or surgical resection alone as first-line therapy. Six patients who did not receive any therapy because of their poor performance status all died of their disease. A complete response was achieved on first-line therapy in 77 (68%) out of the 114 patients who received treatment. Seven patients were lost to follow-up within 5 years after the diagnosis. The median observation time of surviving patients was 81 months. The 2-year overall survival rate of all 120 patients, estimated by the Kaplan-Meier method, was 52%, and the 5-year overall survival rate was 38% (Figure 3A).

We collected data on sites of involvement at relapse/progression. Among all 120 patients with *de novo* CD5$^+$ DLBCL, 16 patients (13%) developed central nervous system (CNS) recurrence (Table 2). All these patients were treated with anthracycline-containing chemotherapy as a front-line treatment. One patient had brain

involvement at diagnosis. She achieved a complete response following front-line therapy, but develop recurrence in the thoracic spinal cord. The other patients did not show any CNS involvement at diagnosis. Twelve patients experienced CNS relapse after achieving a complete response. Of these, eight experienced isolated CNS relapse while the CNS relapse was associated with a systemic relapse in the others. Four patients experienced CNS disease progression during the first-line treatment. The median age of all 16 patients with CNS relapse was 64 years (range, 28 to 85). Of note, all but three patients were over 60 years old. Seven were male and nine were female. The serum lactate dehydrogenase level was elevated in 13 of these patients and performance status was higher than one in seven patients. Five patients showed more than one extranodal site of involvement. Nine patients were categorized as having a high-intermediate or high risk, according to the IPI. The median time from diagnosis to CNS recurrence was 16 months. We compared therapeutic outcome and survival data in the 120 paients with *de novo* CD5+ DLBCL according to the morphological variants. The complete response rate was lowest (42%) in patients with the giant cell-rich variant of *de novo* CD5+ DLBCL, and was significant different from that in patients with the common variant (p=0.02, Table 1). Five-year overall survival rates for patients with common, giant cell-rich, polymorphic, and immunoblastic variants were 44%, 15%, 21%, and 0%, respectively (Table 1, Figure 3B). The survival curve of patients with the common variant was significantly better than that of patients with the other three variants combined (p=0.011, Figure 3C). The presence of intravascular/sinu-

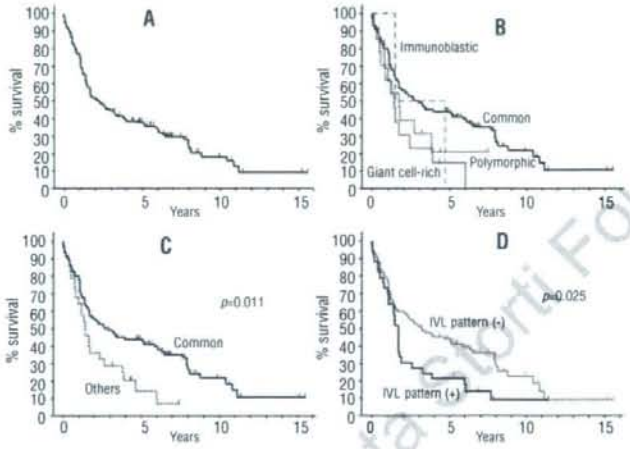

Figure 3. Survival according to the histological features of *de novo* CD5+ diffuse large B-cell lymphoma (DLBCL). (A) Overall survival in all 120 patients with *de novo* CD5+ DLBCL. (B) Overall survival of patients with different histological variants of *de novo* CD5+ DLBCL. (C) Patients with the common variant had a better survival than those with the other three variants of *de novo* CD5+ DLBCL. (D) The presence of intravascular/sinusoidal infiltration had an impact on the overall survival. IVL, intravascular/sinusoidal.

Table 2. Clinicopathological features of patients with *de novo* CD5+ diffuse large B-cell lymphoma who experienced central nervous system recurrence.

N.	Age/sex	Stage	Sites of extranodal involvement	PS >1	LDH >N	IPI score	Histological variant	IVL pattern	CR	Sites of recurrence	Period from diagnosis to CNS recurrence (months)	Survival, (months) outcome
1	62/M	IIIA	Lung, stomach, kidney, gingiva		Y	4	Common			CNS	2	8, DOD
2	77/M	IA		Y	Y	3	Polymorphic			CNS	2	4, DOD
3	76/M	IIA			Y	2	Common			CNS	3	9, DOD
4	61/F	IVB	BM	Y	Y	4	Common	Y	Y	CNS	5	9, DOD
5	67/M	IVB	Liver, BM	Y	Y	5	Common	Y	Y	CNS	6	23, DOD
6	85/M	IIIA		Y	Y	4	Common			CNS	<7	7, DOD
7	62/F	IIIA	Brain, pleura	Y	Y	5	Common	Y	Y	CNS	8	18, DOD
8	62/F	IIIB		Y	Y	4	Immunoblastic		Y	CNS, LN, liver, ascites, BM	8	18, DOD
9	38/F	IVB	BM		Y	2	Common		Y	CNS	24	72, DOD
10	66/F	III	Bone, uterus		Y	4	Common		Y	CNS (intraocular)	37	43, AWD
11	62/M	IVB	Liver, BM	Y	Y	5	Common		Y	Pelvis,CNS	39	40, DOD
12	28/F	IIA	Breast			0	Common		Y	CNS (intraocular)	57	86, AWD
13	50/M	IIIB			Y	2	Giant cell-rich	Y	Y	CNS	60	74, DOD
14	69/F	IA				1	Common		Y	CNS, etc.	71	80, DOD
15	67/F	IA			Y	2	Common	Y	Y	CNS (intraocular)	84	84, AWD
16	74/F	IA				1	Common		Y	CNS, LN	96	99, DOD

PS: performance status; LDH: lactate dehydrogenase; IVL: intravascular/sinusoidal; CR: complete response; Y: yes; BM: bone marrow; LN: lymph node; DOD: died of disease; AWD: alive with disease.

soidal infiltration also had an impact on survival (p=0.025, Figure 3D). The results of univariate and multivariate analyses to assess the impact of clinical and morphologic features on overall survival in *de novo* CD5$^+$ DLBCL patients are shown in Table 3. Univariate analysis identified the five risk factors of IPI, morphological variants, and intravascular/sinusoidal infiltration as prognostic factors important for overall survival. The presence of either *snowman-like* cells or a higher mitotic ratio (> 4/one high-power field on average) was not associated with a reduced overall survival (*data not shown*). Multivariate analysis adjusted for the five risk factors of the IPI confirmed the independent prognostic significance of histological categorization for overall survival (Table 3). Among the prognostic factors, the morphologic variant, age, performance status, and serum lactate dehydrogenase level were significantly associated with survival.

Table 3. Prognostic factors affecting overall survival of patients with *de novo* CD5$^+$ diffuse large B-cell lymphoma.

Variables	Unfavorable factor	Univariate HR	Univariate (CI)	Univariate p	Multivariate HR	Multivariate (CI)	Multivariate p
Comparison with risk factors							
Morphological variants	Not common	1.85	(1.14-3.01)	0.01	1.67	(1.02-2.75)	0.04
IVL pattern	Present	1.66	(1.06-2.60)	0.03		-	-
Age	>60 years	2.37	(1.44-3.92)	0.001	1.91	(1.15-3.19)	0.01
Performance status	2-4	2.81	(1.81-4.37)	<0.001	1.77	(1.11-2.85)	0.02
LDH	>Normal	3.71	(2.14-6.43)	<0.001	2.56	(1.43-4.61)	0.002
Stage	III/IV	2.34	(1.48-3.69)	<0.001		-	-
Extranodal diseases	>1 site	1.72	(1.07-2.77)	0.03		-	-
B symptoms	Present	2.09	(1.36-3.19)	<0.001		-	-
Comparison with IPI category							
Morphological variants	Not common	1.85	(1.14-3.01)	0.01	1.44	(0.87-2.36)	0.15
IPI category	HI/H	3.32	(2.14-5.15)	<0.001	3.14	(2.00-4.92)	<0.001
IVL pattern	Present	1.66	(1.06-2.60)	0.03	1.81	(1.14-2.86)	0.01
IPI category	HI/H	3.32	(2.14-5.15)	<0.001	3.46	(2.21-5.41)	<0.001

HR: hazard ratio; CI:confidence interval; HI/H: high-intermediate or high risk category of IPI; IVL: intravascular/sinusoidal; LDH, lactate dehydrogenase.

Discussion

We clarified detailed cytomorphological features of *de novo* CD5$^+$ DLBCL. A German study also documented morphological features in their series of 13 cases of *de novo* CD5$^+$ DLBCL, identifying eight centroblastic (62%), three immunoblastic (23%), and two unclassified DLBCL with irregular nuclei (15%).[13] Our findings generally appeared to be in keeping with those of the German study; however, the percentage of immunoblastic lymphoma cases (23%) was higher in the German study than in ours (2%). DLBCL developing in the setting of small lymphocytic lymphoma/chronic lymphocytic leukemia (Richter's syndrome) evidently tend to be characterized by an immunoblastic morphology and the expression of CD5.[32] In Japan, the incidence of chronic lymphocytic leukemia is one fifth of that in Western countries.[33,34] Moreover, CD5 expression was mainly examined using fresh material in the majority of studies of *de novo* CD5$^+$ DLBCL in Japan, while it was examined in paraffin-embedded material in the studies in Western countries. In Japan, the incidence of *de novo* CD5$^+$ DLBCL ranges from 4% (4/101)[35] to 10% (24/240),[36] which seems to be almost the same as that reported in Western series.[10,37] Since only two cases have been included in the current study, the clinicopathological features of the immunoblastic variant of *de novo* CD5$^+$ DLBCL remain unknown. International cooperative studies are needed to verify the hypothesis that these facts may explain the conflicting data. Since *de novo* CD5$^+$ DLBCL has various histopathological appearances, CD5 immunostaining should be performed routinely in cases of DLBCL.

In the current study, intravascular/sinusoidal patterns to various extents were observed in 38% of the cases of *de novo* CD5$^+$ DLBCL. As Murase *et al.* demonstrated recently,[21] *de novo* CD5$^+$ DLBCL with an intravascular/sinusoidal pattern showed intermediate features in terms of aggressive clinical behavior and prognosis between *de novo* CD5$^+$ DLBCL without an intravascular/sinusoidal pattern and CD5$^+$ intravascular large B-cell lymphoma, suggesting that a part of the two diseases overlaps. In the present study *snowman-like*, binucleated cells were frequently observed in *de novo* CD5$^+$ DLBCL. Further studies in CD5$^-$ DLBCL and CD5$^+$ intravascular large B-cell lymphoma are needed to evaluate their diagnostic significance in *de novo* CD5$^+$ DLBCL.

The aggressive clinical feature of *de novo* CD5$^+$ DLBCL that we previously reported[11] was confirmed by the current study and a recent study that was conducted using tumor specimens from patients with DLBCL uniformly treated with anthracycline-based chemotherapeutic regimens in a prospective, multi-center clinical trial.[37] In contrast, it has been reported that the expression of CD5 in DLBCL did not affect overall survival.[13] Recent studies revealed that patients with *de novo* CD5$^+$ DLBCL with 8p21-associated chromosomal abnormalities[18] and with 9p21 loss in comparative genomic hybridization analysis[16] have an extremely short survival. The existence of these highly aggressive subgroups of *de novo* CD5$^+$ DLBCL may explain the heterogeneity in the prognosis of this disease. The possible role of the CD5 molecule in the aggressiveness of *de novo* CD5$^+$ DLBCL remains unknown. It has been reported that CD5 supports the survival of B cells by stimulating the production of interleukin-10 and by down-regulating B-cell receptor signaling.[38] This molecular basis may explain in part why *de novo* CD5$^+$ DLBCL shows more aggressive clinical features than CD5$^-$ DLBCL.

According to the criteria established by Hans *et al.*,[30] 82% of the cases examined in the present study were non-germinal center B-cell DLBCL. Our results suggest that *de novo* CD5$^+$ DLBCL is mainly classified into the non-germinal center B-cell type, and may provide a clue to clarify the aggressiveness of such DLBCL. Our present study also revealed that *de novo* CD5$^+$ DLBCL typically shows the BCL2$^+$ BCL6$^-$ immunophenotype.

Recent clinical studies suggest that the prognosis of DLBCL expressing BCL2 protein, BCL6 protein-negative DLBCL, and DLBCL of the non-germinal center B-cell subgroup is improved by rituximab-containing chemotherapy.[39-41] In our previous study published in 2002, no patients had been treated with rituximab.[11] In the present study, some patients had been treated with rituximab as a part of salvage therapy; however, the overall survival was almost the same as that in the previous study and was not clearly improved. The therapeutic impact of adding rituximab to first-line therapy in *de novo* CD5+ DLBCL needs to be evaluated in the setting of a well-designed clinical trial.

The overall incidence of CNS recurrence in aggressive non-Hodgkin's lymphoma excluding lymphoblastic lymphoma/acute lymphoblastic leukemia and Burkitt's lymphoma is approximately 5%,[42-44] and the incidence in DLBCL seems to be less than 5%. The incidence of CNS recurrence in the present study, 13%, was marked. Most of our patients with CNS recurrence had an elevated level of serum lactate dehydrogenase, which has been reported as a potential risk factor for CNS recurrence in aggressive lymphoma.[42] In contrast, most of the patients with CNS recurrence were over 60 years old, which was reported to be a favorable factor in a study of a large number of patients.[42] To establish an optimal therapeutic strategy for CNS prophylaxis in DLBCL, the relationship between CD5 expression and CNS recurrence in DLBCL should be examined in future studies.

In conclusion, our study provides new clinicopathological information on *de novo* CD5+ DLBCL. *De novo* CD5+ DLBCL shows many unique clinicopathological and genetic features. Further studies are needed to clarify molecular mechanisms in highly aggressive subgroups of *de novo* CD5+ DLBCL.

Appendix

List of participating institutes in the CD5+ DLBCL histology project: Akita University School of Medicine, Akita Kumiai General Hospital, National Miyagi Hospital, Saka General Hospital, Tohoku University School of Medicine, Sendai City Hospital, Furukawa City Hospital, Fukushima Medical College, Iwaki General Hospital, Ohta Nishinouchi General Hospital, Takeda General Hospital, Tokyo Women's Medical University Daini Hospital, Saitama Medical School, Matsudo Municipal Hospital, Higashi Matsudo Hospital, Kameda General Hospital, Niigata University, Toyama Prefectural Central Hospital, Kanazawa University, Noto General Hospital, Nagano Municipal Hospital, Nagano Red Cross Hospital, Hamamatsu Medical Center, Inazawa Municipal Hospital, Aichi Prefectural Hospital, Toyota Memorial Hospital, Fujita Health University School of Medicine, Nishio Municipal Hospital, Toyohashi Municipal Hospital, Okazaki Municipal Hospital, Ichinomiya Municipal Hospital, Japanese Red Cross Nagoya First Hospital, Nagoya Memorial Hospital, Nagoya City University Medical School, Nagoya Ekisaikai Hospital, Aichi Cancer Center, Suzuka Chuo General Hospital, Suzuka Kaisei General Hospital, Mie University School of Medicine, Matsusaka Municipal Hospital, Matsusaka Chuo General Hospital, Matsusaka Saiseikai General Hospital, Yamada Red Cross Hospital, Ise Municipal General Hospital, Kyoto University, Kyoto Prefectural University of Medicine, Rinku General Medical Center, Okayama University Medical School, Okayama Saiseikai General Hospital, Chugoku Central Hospital of the Mutual Aid Association of Public School Teachers, Okayama Red Cross General Hospital, Fukuoka University School of Medicine, Kyushu Cancer Center, Kyushu University, and University of the Ryukyus.

Authorship and Disclosures

MY, NN, RS, TM, and SN contributed to the design of the study, provided clinical data and samples, analyzed the data, and wrote the manuscript. YK, MO, RI, TY, JS, TM, IM, KO, MN, JT, and MT provided clinical data and samples and critically reviewed the manuscript. MH, YM, RU, and HS provided clinical data and gave critical advice on the study to improve its intellectual content.

The authors reported no potential conflicts of interest.

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