De novo CD5$^+$ diffuse large B-cell lymphoma: a clinicopathologic study of 109 patients

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De novo CD5$^+$ diffuse large B-cell lymphoma (CD5$^+$ DLBCL) is known to have phenotypically and genotypically different characteristics than CD5$^-$ DLBCL and mantle cell lymphoma (MCL). To further characterize CD5$^+$ DLBCL, 109 patients with CD5$^+$ DLBCL were reviewed, and the results were compared with those of 384 CD5$^-$ DLBCL and 128 cyclin D1$^+$ MCL patients. Patients with CD5$^+$ DLBCL showed a higher age distribution (median, 66 years; $P = .0083$) and a female predominance (male-female ratio, 49:60, $P = .011$) compared with those with CD5$^-$ DLBCL. CD5$^+$ DLBCL was more closely associated with many aggressive clinical features or parameters than CD5$^-$ DLBCL: 69% older than 60 years ($P = .039$), 34% with performance status greater than 1 ($P = .0016$), 69% with serum lactate dehydrogenase level higher than normal ($P < .0001$), 62% with stage III/IV disease at diagnosis ($P = .0023$), 35% with more than one extranodal site ($P = .023$), and 40% with B symptoms ($P = .0031$). The overall International Prognostic Index score was thus significantly higher for the patients with CD5$^+$ DLBCL than for those with CD5$^-$ DLBCL ($P = .00005$). The most frequent site of extranodal involvement was bone marrow (28%), a higher frequency than that for CD5$^-$ DLBCL ($P < .0001$) but lower than that for cyclin D1$^+$ MCL ($P = .0015$). Histopathologically, CD5$^+$ DLBCL showed centroblastic morphology except for 3 patients with immunoblastic disease, and interfollicular growth pattern (7%) and intravascular or intrasinusoidal infiltration (19%) were observed. Immunophenotypically, CD5$^+$ DLBCL was characterized by a CD5$^+$CD10$^-$CD19$^+$CD20$^+$CD21$^-$CD23$^-$ cyclin D1$^-$ phenotype and a predominance of surface IgMκ. Of particular interest is that CD5$^+$ DLBCL was characterized by a survival curve significantly inferior to that for patients with CD5$^-$ DLBCL ($P = .0026$). These findings suggest that CD5$^+$ DLBCL may constitute a unique subgroup of DLBCL. (Blood. 2002;99:815-821)

Introduction

Diffuse large B-cell lymphoma (DLBCL) is the largest category of aggressive lymphomas; it is regarded as a heterogeneous group of lymphomas in terms of surface markers, histology, and clinical features.[1] Some patients with DLBCL can be cured by combination chemotherapy, but more than half of them die of their disease.[2] Therefore, identification of a high-risk group or a specific subtype of DLBCL is particularly important and long overdue.

The CD5 molecule is a 67-kd glycoprotein that is expressed by most T cells and a subset of B cells.[3] CD5$^+$ B cells are the predominant B-cell population in human fetal spleen and cord blood, but they represent only 10% to 20% of adult peripheral B cells.[3-5] They are distinct from CD5$^-$ conventional B cells with respect to anatomic localization, gene usage, and function.[3,5-10] CD5$^+$ B cells also synthesize low-affinity polyreactive immunoglobulins, and increased numbers of these cells have been reported in many nonneoplastic diseases, including certain types of autoimmune disorders.[3,10,11]

In mature B-cell neoplasms, CD5 is expressed in most patients with chronic lymphocytic leukemia (CLL) and mantle cell lymphoma (MCL), but less frequently in patients with DLBCL[12] and in only few patients with marginal zone B-cell lymphoma[13,14] and Burkitt lymphoma.[15] Of special interest is that CD5$^+$ DLBCL not preceded by any other lymphoproliferative disease have been reported,[16,17] though they are often identified as arising secondarily in a CLL (Richter syndrome). Matolcsy et al[16] have highlighted the phenomenon of CD5 expression in DLBCLs evolving de novo, not as a result of

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transformation, thus suggesting that such DLBCL is genotypically distinct from Richter syndrome–associated DLBCL.

We have also provided evidence that de novo CD5$^+$ DLBCL is phenotypically and genotypically distinct from MCL.[17-22] CD5$^+$ cases account for approximately 10% of DLBCL, which is usually negative for CD10, CD21, and CD23.[17-22] Immunohistochemical examinations have demonstrated that cyclin D1 is not overexpressed in CD5$^+$ cases[18] and that immunoglobulin heavy chain genes are somatically mutated.[19,20,22] These findings support our hypothesis that de novo CD5$^+$ DLBCL constitutes a distinct subtype, but previous reports from a single institution include only a small number of patients.[21,23,24] Therefore, the clinicopathologic features of de novo CD5$^+$ DLBCL remain to be thoroughly identified. This prompted us to investigate these features in a large patient population. To further characterize the de novo CD5$^+$ DLBCL, we performed a collaborative study on 109 patients.

Patients, materials, and methods

Patient selection

We selected 109 patients with de novo CD5$^+$ DLBCL from 12 collaborating institutions. All patients were diagnosed between 1984 and 2000 as having DLBCL according to the REAL classification.[1] They had no history of other lymphoproliferative disorders. All specimens for histologic and immunophenotypic studies were obtained at the initial presentation of the patients. CD5 antigen expression was examined by means of fluorescence-activated cell sorter analysis or immunohistochemistry. All patients were immunohistochemically confirmed to be cyclin D1$^-$.

For the control group, 384 patients with CD5$^-$ DLBCL were selected. They were diagnosed consecutively between 1984 and 2000 at 3 major institutions (Mie University School of Medicine, Aichi Cancer Center, and Fujita Health University School of Medicine). Moreover, the clinical data of 128 of our patients with cyclin D1$^+$ MCL[25] were simultaneously reviewed for comparison with de novo CD5$^+$ DLBCL.

Histopathology

Tissue was fixed in 10% formalin and embedded in paraffin. Sections (5-μm thick) were stained with hematoxylin and eosin, periodic acid-Schiff, Giemsa, and Gomori silver impregnation. Histologic sections were reviewed by 2 independent pathologists.

Immunophenotypic study

Immunohistochemical and flow cytometric analyses were performed as described previously.[18,26] Monoclonal antibodies used were Leu4 (CD3), Leu1 (CD5), and CALLA (CD10) (Becton Dickinson, Mountain View, CA); J5 (CD10) and B1 (CD20) (Coulter, Hialeah, FL); H107 (CD23) (Nichirei, Tokyo, Japan); MHM6 (CD23), UCHL1 (CD45RO), HM57 (CD79a), anti-IgG, anti-IgA, anti-IgM, anti-IgD, anti-κ, and anti-λ (DAKO, Carpinteria, CA); 4C7 (CD5) and NCL-CD10 (CD10) (Novocastra, Newcastle, United Kingdom), and cyclin D1 (IBL, Gunma, Japan). More than 20% positivity of the tumor cells was judged as indicating positivity for the purposes of this study. In fact, most neoplastic cells were confirmed to be positive for CD5 in most patients. In 99 patients with de novo CD5$^+$ DLBCL, CD5 expression was examined by means of flow cytometric analysis or immunohistochemistry in frozen sections and by immunohistochemically in paraffin sections in the remaining 10 patients.

Statistical analysis

Correlations between the 2 groups were examined by chi-square analysis, the Fisher exact test, the Student *t* test, and the Mann-Whitney *U* test. Patient survival data were analyzed by the Kaplan-Meier method and were compared by means of the log-rank test. Univariate and multivariate analyses were performed with the Cox proportional hazard regression model. Data were analyzed with the SAS system (SAS Institute, Cary, NC).

Table 1. Clinical features

	De novo CD5$^+$ DLBCL (n = 109)	CD5$^-$ DLBCL (n = 384)	Cyclin D1$^+$ MCL (n = 128)		
	No. (%)	No. (%)	No. (%)	*P**	*P*†
Age at diagnosis, y					
Median	66	63	65	.0083	.21
Range	22-91	17-92	36-81	—	—
Older than 60	75 (69)	222 (58)	81 (64)	.039	.42
Sex (male/female)	49/60	225/159	89/39	.011	.0001
Performance status higher than 1	37 (34)	76 (20)	23 (20)	.0016	.020
Serum LDH level higher than normal	75 (69)	174 (45)	37 (32)	< .0001	< .0001
Stage				.00004	.011
I	16 (15)	81 (21)	6 (5)	—	—
II	25 (23)	127 (33)	13 (10)	—	—
III	18 (16)	96 (25)	32 (26)	—	—
IV	50 (46)	80 (21)	74 (59)	—	—
III/IV	68 (62)	176 (46)	106 (85)	.0023	.0001
Extranodal involvement	84 (77)	266 (69)	87 (71)	.11	.20
More than 1 site	38 (35)	92 (24)	43 (36)	.023	.94
IPI				.00005	.10
Low	29 (27)	176 (45)	27 (23)	—	—
Low intermediate	23 (21)	75 (20)	40 (34)	—	—
High intermediate	17 (16)	64 (17)	31 (27)	—	—
High	40 (36)	68 (18)	19 (16)	—	—
B symptoms present	44 (40)	100 (27)	31 (39)	.0031	.72

*De novo CD5$^+$ DLBCL versus CD5$^-$ DLBCL.
†De novo CD5$^+$ DLBCL versus MCL.

Table 2. Sites of extranodal involvement in de novo CD5+ DLBCL

Extranodal only			Nodal only			Nodal and extranodal					
No.	Age/Sex	Extranodal involvement	No.	Age/Sex	Extranodal involvement	No.	Age/Sex	Extranodal involvement	No.	Age/Sex	Extranodal involvement
1	61/M	S	1	59/F	None	1	54/M	L	31	53/F	Nasal cavity
2	52/M	BM	2	69/F	None	2	78/F	L	32	75/M	Nasal cavity
3	70/F	BM	3	74/F	None	3	50/M	S	33	46/M	Thyroid gland
4	65/M	BM	4	51/M	None	4	77/F	S	34	57/F	W
5	61/M	S, BM/PB	5	71/F	None	5	38/F	BM	35	39/M	W
6	78/M	L, BM/PB	6	82/F	None	6	61/F	BM	36	63/M	W
7	63/M	L, S, BM	7	70/M	None	7	67/M	BM	37	56/F	W
8	71/F	L, S, BM	8	81/M	None	8	86/M	S, BM/PB	38	64/M	W
9	82/F	L, S, BM	9	*66/F	None	9	80/M	S, BM	39	36/F	W
10	73/F	L, S, BM	10	56/M	None	10	61/F	S, BM	40	63/M	W
11	57/F	L, S, BM	11	85/F	None	11	58/M	S, BM	41	81/F	W
12	73/F	L, S, BM, lung	12	67/F	None	12	77/M	L, S	42	71/F	W
13	84/F	L, S, BM, lung	13	60/M	None	13	59/M	L, S, BM	43	65/F	Small intestine
14	50/F	L, S, BM, lung	14	61/M	None	14	72/F	L, S, BM	44	63/M	W, small intestine
15	70/M	S, BM/PB, lung, brain	15	79/M	None	15	68/F	S, subcutaneous tissue	45	91/M	Pleural effusion
16	61/M	L, BM, CNS	16	70/F	None	16	67/F	BM, W	46	73/F	Pleural effusion
17	74/F	BM, bone	17	82/M	None	17	91/F	BM/PB, stomach	47	56/M	Ascites
18	69/M	Bone, muscle, peritoneum	18	72/F	None	18	78/M	L, S, BM, stomach	48	59/M	Cerebrospinal fluid
19	45/F	Subcutaneous tissue	19	71/M	None	19*	73/F	L, S, BM, pleural effusion	49	60/M	Testis
20	56/M	Skin	20	22/M	None	20	44/M	L, S, lung, pleural effusion	50	62/M	Testis
21	66/F	Skin/subcutaneous tissue	21	62/F	None	21*	64/F	L, lung, breast, kidney, adrenal gland	51	70/F	Bone
22	58/F	Skin/subcutaneous tissue	22	76/F	None	22	72/M	S, BM, testis	52	66/F	Bone, uterus
23	89/M	Skin/subcutaneous tissue	23	65/M	None	23	36/F	L, S, ovary	53*	62/F	Brain, thorax
24	62/F	Stomach	24	69/F	None	24	77/F	S, BM/PB, muscle	—	—/—	—
25	57/F	Stomach	25	65/F	None	25	74/M	Stomach	—	—/—	—
26	54/F	Breast	—	—/—	—	26	51/F	Stomach, breast	—	—/—	—
27	63/F	Breast	—	—/—	—	27	51/F	Breast	—	—/—	—
28	74/M	W	—	—/—	—	28	43/F	Breast	—	—/—	—
29	77/M	W	—	—/—	—	29	40/F	Breast	—	—/—	—
30	81/F	Orbit	—	—/—	—	30	28/F	Breast, W	—	—/—	—
31	79/M	Pleural effusion	—	—/—	—	—	—/—	—	—	—/—	—

S indicates spleen; BM, bone marrow; PB, peripheral blood; L, liver; CNS, central nervous system; W, Waldeyer ring.
*This patient had a history of autoimmune disease.

Results

Patient characteristics for de novo CD5+ DLBCL, CD5− DLBCL, and cyclin D1+ MCL

Table 1 summarizes clinical features of the patients at presentation. In comparison with CD5− DLBCL, patients with de novo CD5+ DLBCL showed a higher age distribution (median, 66 vs 63 years; $P = .0083$, Student *t* test) and a female predominance (female-male ratio, 60:49 vs 159:225; $P = .011$). Especially noteworthy is that the patients with de novo CD5+ DLBCL showed a closer association with the aggressive clinical features or parameters: 75 patients older than 60 (69%, $P = .039$), 37 with performance status (PS) greater than 1 (34%, $P = .0016$), 75 with serum lactate dehydrogenase (LDH) level higher than normal (69%, $P < .0001$), 68 with stage III/IV disease at diagnosis (62%, $P = .0023$), 38 with more than one extranodal site (35%, $P = .023$), and 44 with B symptoms (40%, $P = .0031$). As a result, the International Prognostic Index (IPI) score[27] for the patients with de novo CD5+ DLBCL was significantly higher than that for patients with CD5− DLBCL ($P = .000\,05$), with 40 (36%) of the CD5+ group categorized in the IPI high-risk group.

A comparison with cyclin D1+ MCL (Table 1) showed that the patients with de novo CD5+ DLBCL were characterized by a female predominance ($P = .0001$), worse PS ($P = .020$), higher serum LDH level ($P < .0001$), and lower disease stage ($P = .011$). The IPI score for the patients with de novo CD5+ DLBCL had the tendency to be higher than that for cyclin D1+ MCL ($P = .10$).

Table 2 summarizes anatomic sites of extranodal involvement in de novo CD5+ DLBCL. In 31 (28%) patients of the current

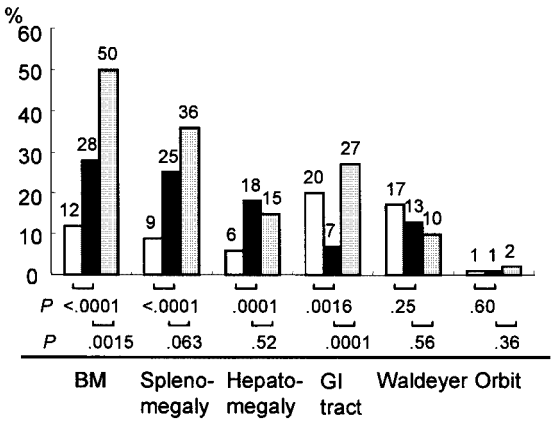

Figure 1. Extranodal involvement of de novo CD5+ DLBCL, CD5− DLBCL, and cyclin D1+ MCL. In de novo CD5+ DLBCL (■), the incidence of bone marrow involvement was higher than that of CD5− DLBCL (□) and lower than that of cyclin D1+ MCL (▤). Hepatomegaly and splenomegaly occurred more frequently in de novo CD5+ DLBCL than in CD5− DLBCL. Gastrointestinal involvement occurred less frequently than in either CD5− DLBCL or cyclin D1+ MCL. BM, bone marrow; GI, gastrointestinal.

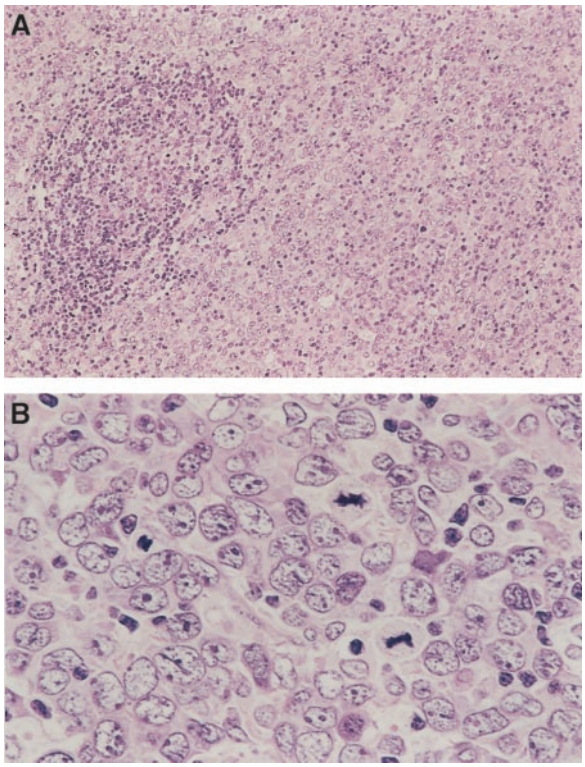

Figure 2. Histopathologic features of de novo CD5$^+$ DLBCL. (A) Lymphoma cells spare a follicle retaining a lymphocyte cuff. (B) Lymphoma cells are large and show a centroblastic feature.

series, the disease was limited to extranodal sites, 25 (23%) had only lymphadenopathies without extranodal involvement, and the remaining 53 had lymphadenopathies with extranodal involvement.

The most frequent site of extranodal involvement in de novo CD5$^+$ DLBCL was bone marrow (n = 31, 28% of patients; Table 2; Figure 1). Atypical lymphocyte contents (range, 3%-53%) were noted at presentation in the peripheral blood smears of 6 patients, whose white blood cell counts ranged from 3700 to 15 100/μL. Twenty-seven (25%) of the patients had splenomegaly and 20 (18%) had hepatomegaly at presentation (Table 2; Figure 1). Sites of extranodal involvement in the patients without lymphadenopathies were relatively limited. Twenty-six of 31 patients had extranodal involvement in at least one in the following sites: bone marrow, liver, spleen, lung, skin, stomach, and breast. Nodal and extranodal disease presented a greater variety of extranodal involvement when compared to extranodal-only disease.

A comparison with CD5$^-$ DLBCL and cyclin D1$^+$ MCL demonstrated that the incidence of bone marrow involvement in de novo CD5$^+$ DLBCL was higher than that of CD5$^-$ DLBCL ($P < .0001$) and lower than that of cyclin D1$^+$ MCL ($P = .0015$). Hepatomegaly and splenomegaly occurred more frequently in patients with de novo CD5$^+$ DLBCL than in patients with CD5$^-$ DLBCL ($P = .0001$ and $P < .0001$, respectively). Gastrointestinal involvement occurred less frequently in de novo CD5$^+$ DLBCL than in CD5$^-$ DLBCL ($P = .0016$) or cyclin D1$^+$ MCL ($P = .0001$). There were no significant differences in the incidence of involvement in Waldeyer ring or the orbit among these 3 groups.

Four (4%) of our patients had a history of autoimmune disease; 2 with rheumatoid arthritis, and one each had a history of rheumatoid arthritis with Sjögren syndrome and of primary biliary cirrhosis. Three patients had nodal and extranodal involvement (Table 2).

Table 3. Summary of morphologic features of de novo CD5$^+$ DLBCL

	No. patients (%)
Morphologic variant	
Centroblastic	106 (97)
Immunoblastic	3 (3)
Residual follicular pattern	
No residual follicles	101 (93)
Sparing of follicles with a mantle cuff	8 (7)
Naked germinal centers	0 (0)
Intravascular or intrasinusoidal infiltration	21 (19)
Focal necrosis	5 (5)
Infiltration of macrophages	2 (2)

Table 4. Immunophenotypic features

	De novo CD5$^+$ DLBCL* (%)	CD5$^-$ DLBCL† (%)	*P*
CD5	109/109‡ (100)	0/384 (0)	
CD10	5/109 (5)	46/360 (13)	.016
CD19	90/92 (98)	334/363 (92)	.031
CD20	104/105 (99)	370/376 (98)	.53
CD21	8/35 (23)	144/316 (46)	.010
CD23	3/77 (4)	13/78 (17)	.0082
IgG	8/50 (16)	67/158 (42)	.0007
IgA	2/49 (4)	16/159 (10)	.16
IgM	71/84 (85)	200/358 (56)	< .0001
IgD	8/66 (12)	65/320 (20)	.12
κ chain	51/81 (63)	168/349 (48)	.016
λ chain	25/81 (31)	100/350 (29)	.68

*n = 109.
†n = 384.
‡Positive/examined patients.

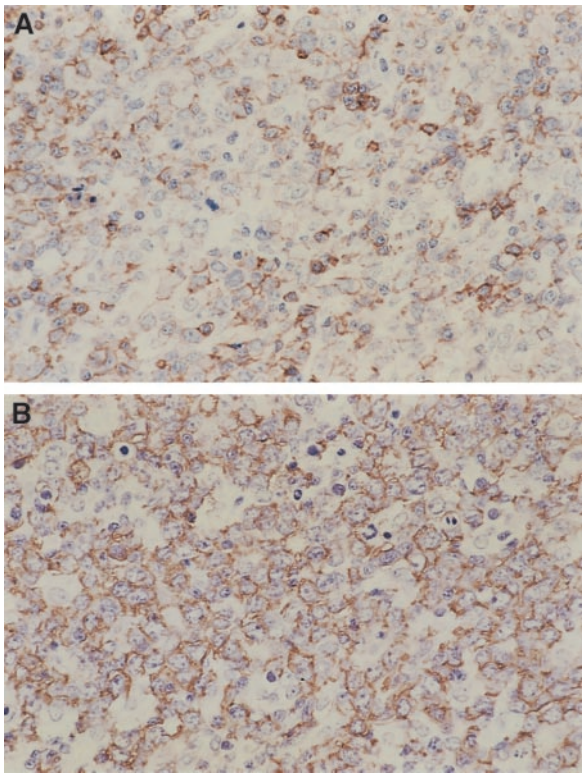

Figure 3. Immunohistochemical features of de novo CD5$^+$ DLBCL. Lymphoma cells are positive for CD5 (A) and CD20 (B).

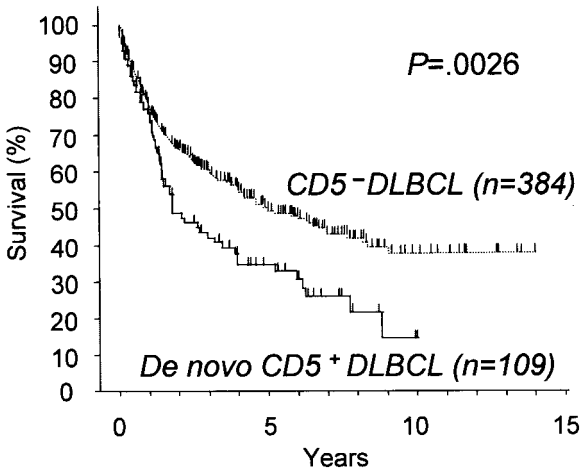

Figure 4. Overall survival for patients with de novo CD5+ DLBCL and with CD5− DLBCL. De novo CD5+ DLBCL showed significantly worse survival than CD5− DLBCL.

Histologic features

De novo CD5+ DLBCL showed a diffuse and monomorphic proliferation of large lymphoid cells (Figure 2). These tumor cells were usually morphologically centroblastic and seldom immunoblastic (3 of 109, 3%; Table 3). In many patients, the tumor cells had a moderate rim of pale basophilic or amphophilic cytoplasm. Nuclei were round or sometimes irregular, indented or multilobated, and they contained vesicular chromatin and small distinct nucleoli. In 8 (7%) of the patients, these tumor cells were distributed throughout the interfollicular area while sparing the follicles, which retained their mantle cuffs (Figure 2). Although they were the subject of special attention, the typical mantle zone pattern or naked germinal centers characteristic of MCL were not observed. Moreover, intravascular or intrasinusoidal infiltration was identified in 21 (19%) patients with de novo CD5+ DLBCL. Focal necrosis and infiltration of macrophages were occasionally seen.

Phenotypic features

Immunophenotypic features are summarized in Table 4. According to the definition adopted for this study, all patients tested positive for CD5 and B-cell markers (CD19 or CD20) (Figure 3) and negative for cyclin D1. Only 5 (5%) of the patients tested positive for CD10, and even fewer (3 [4%]) tested positive for CD23. This immunophenotype also accentuated the follicular dendritic cells on the paraffin sections and showed that few follicular dendritic cells were interspersed among the tumor cells. The immunoglobulin isotype was most commonly IgM (71 patients, 85%). Fifty-one of the patients examined were also positive for κ light chain and 25 for λ light chain. A comparison with CD5− DLBCL demonstrated that de novo CD5+ DLBCL was characterized by a CD5+CD10− CD19+CD20+CD21−CD23− phenotype and a predominance of surface IgMκ (Table 4).

Therapeutic response and prognosis

Treatment consisted of chemotherapeutic regimens containing anthracycline for 91 patients and without anthracycline for 4 patients. Eight patients with stage I disease did not undergo chemotherapy but were treated with radiotherapy or surgical resection alone. Finally, the 6 patients who had not received any therapy because of their poor PS died of the disease. In total, 63% (69 of 109) of the patients with de novo CD5+ DLBCL achieved complete remission with the initial therapy. De novo CD5+ DLBCL thus showed a survival curve significantly inferior to that for the CD5− ($P = .0026$, Figure 4), with a 5-year survival rate of 34% for the former.

Univariate Cox analysis identified the following prognostic factors for the 493 patients with CD5+ and CD5− DLBCL: CD5 expression, age, PS, serum LDH level, clinical stage, extranodal involvement of more than one site, IPI category, and presence of B symptoms (Table 5). Multivariate analysis, including IPI categories, showed age older than 60 years, PS greater than one, high LDH level, and advanced stage (III or IV), but not extranodal involvement of more than one site or CD5 positivity, to be significant and prognostic factors (Table 6). When multivariate analysis was performed for CD5 positivity and IPI categories, CD5 positivity was found to be an almost significant and independent prognostic factor (Table 6).

We also compared the survival of patients with de novo CD5+ DLBCL with that of patients with cyclin D1+ MCL (Figure 5). Although both groups had poor outcomes, several details of the survival curves were different. The curve for cyclin D1+ MCL gradually but steadily declined without any plateau, suggesting that MCL is a generally incurable disease. In contrast, de novo CD5+ DLBCL initially followed a more aggressive clinical course than MCL, but the survival curve crosses that of MCL 5 years after diagnosis and shows superior survival thereafter.

Discussion

An analysis of 109 patients with de novo CD5+ DLBCL highlighted previously unrecognized features of this disease—high age at onset, female predominance, frequent association with poor prognostic components of IPI, and aggressive clinical course. These features were significantly different from those of CD5− DLBCL and MCL. Although it cannot be definitively concluded, on the basis of our results alone, whether CD5+ DLBCL constitutes a distinct subtype of B-cell lymphoma or represents merely a prognostic factor, de novo CD5+ DLBCL seems to constitute a unique subgroup of DLBCL.

The prognosis of de novo CD5+ DLBCL was significantly poorer than that of CD5− tumors. CD5 expression as a biologic marker appeared to be closely associated with the IPI index because 36% (40 of 109) of patients with de novo CD5+ DLBCL were categorized in the high-risk IPI group. Comparison with

Table 5. Prognostic factors affecting overall survival, univariate analysis

Variables	Unfavorable factor	Univariate	
		Relative risk (95% CI)	*P*
CD5 status	Positive	1.60 (1.20-2.13)	.0012
Age	> 60 y	2.00 (1.52-2.63)	.0000007
Performance status	2-4	3.54 (2.72-4.61)	< .0000001
LDH	> Normal	3.14 (2.41-4.10)	< .0000001
Stage	III/IV	2.90 (2.23-3.77)	< .0000001
Extranodal disease	> 1 site	2.58 (1.99-3.35)	< .0000001
IPI	HI/H	3.95 (3.06-5.10)	< .0000001
B symptoms	Present	2.98 (2.30-3.85)	< .0000001

CI indicates confidence interval.

Table 6. Prognostic factors affecting overall survival, multivariate analysis including IPI categories

Variables	Multivariate		Multivariate (final model)	
	Relative risk (95% CI)	*P*	Relative risk (95% CI)	*P*
Comparison with risk factors				
CD5 status	1.11 (0.83-1.49)	.49	—	—
Age	1.85 (1.40-2.45)	.000016	1.89 (1.43-2.50)	.0000082
Performance status	1.82 (1.34-2.46)	.00012	1.90 (1.40-2.57)	.000034
LDH	1.86 (1.38-2.53)	.000057	1.90 (1.41-2.57)	.000029
Stage	1.73 (1.24-2.39)	.0011	1.92 (1.42-2.58)	.000019
Extranodal disease	1.27 (0.94-1.72)	.12	—	—
Comparison with IPI category				
CD5 status	—	—	1.31 (0.98-1.77)	.068
IPI	—	—	3.84 (2.96-4.97)	< .0000001

CI indicates confidence interval.

the data reported by the Non-Hodgkin's Lymphoma Classification Project shows that this frequency is also higher than that for the other lymphomas in the high-risk IPI category—for example, 27% for peripheral T-cell lymphoma and 19% for DLBCL.[2] These findings indicate that de novo CD5$^+$ DLBCL is a highly aggressive subtype. However, a multivariate analysis of CD5 status and the IPI or components did not identify CD5 expression as an independent prognostic factor. Given that CD5 expression is closely correlated with each of the factors making up the IPI, CD5 expression in DLBCL may represent a biologic feature of aggressiveness also detectable by means of these clinical parameters. Interestingly, the other CD5$^+$ B-cell malignancies, CLL and MCL, represent a high incidence of bone marrow involvement and advanced disease, though the clinical behavior of the CLL patients is generally indolent. This finding suggests that CD5$^+$ B cells have a tendency to spread widely within the tissues. Some authors have recently reported that the CD5 molecule on B cells interacts as a ligand with heavy-chain variable framework regions of surface immunoglobulins, which implies a possible role in the maintenance, selection, or expansion of normal, autoimmune, or transformed B cells.[28,29] The molecular bases for these phenomena mediated by CD5 on B cells deserved to be clarified in the future.

De novo CD5$^+$ DLBCL showed a female predominance, which has also been noted in 3 subtypes of malignant lymphoma, ie, follicular lymphoma, marginal zone B-cell lymphoma, and primary mediastinal large B-cell lymphoma; the other types of non-Hodgkin lymphoma usually tend to show male predominance.[2] Indeed, in our series of DLBCL, the male-to-female ratio was significantly different for the CD5$^+$ and CD5$^-$ groups, suggesting that female predominance can be regarded as one of the biologic features of de novo CD5$^+$ DLBCL. This is consistent with the female predominance among autoimmune disorders, in which CD5$^+$ B cells are shown to play, at least in part, an important pathogenetic role.[3,7,8] In our study, however, only 4 patients showed evidence of immune function disorders, including rheumatoid factors, the significance of which deserves further clarification.

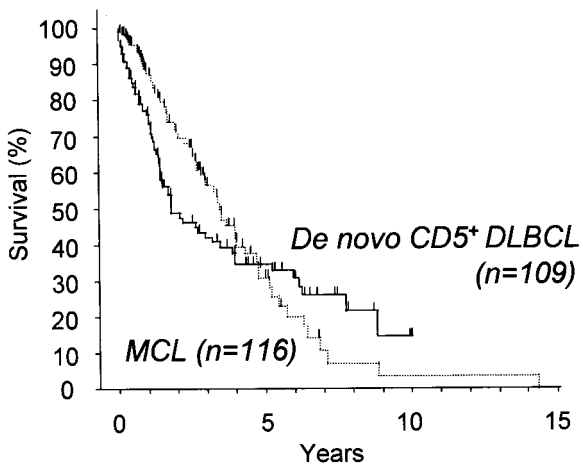

Figure 5. Overall survival for patients with de novo CD5$^+$ DLBCL and with cyclin D1$^+$ MCL. De novo CD5$^+$ DLBCL showed an initially more aggressive clinical course than MCL, but the survival curve crossed that of MCL 5 years after diagnosis and showed superior survival thereafter.

Morphologically, 8 patients with de novo CD5$^+$ DLBCL showed an interfollicular growth pattern not seen in CD5$^-$. Low-grade components were not identified in the lesions, nor were other morphologic findings suggestive of MCL, such as mantle zone patterns and naked germinal centers. Biopsy specimens of another 20 patients with de novo CD5$^+$ DLBCL showed the localization of tumor cells within vessels or sinuses, which may be regarded as intravascular lymphoma (IVL).[30] In addition, frequent involvement in bone marrow, liver, spleen, and lung is shared by both de novo CD5$^+$ DLBCL and IVL. Recently, several patients with CD5$^+$ IVL have been described.[31,32] These clinical and morphologic similarities may indicate that the 2 types might overlap or lie in a continuing spectrum. Further investigation is needed to clarify this issue.

In conclusion, the current study sheds further light on the clinicopathologic features of de novo CD5$^+$ DLBCL, which may constitute a unique subtype of DLBCL with an aggressive clinical course. Innovative therapeutic strategies must be established by a prospective study.

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References

1. Harris NL, Jaffe ES, Stein H, et al. A revised European-American classification of lymphoid neoplasms: a proposal from the International Lymphoma Study Group. Blood. 1994;84:1361-1392.
2. The Non-Hodgkin's Lymphoma Classification Project. A clinical evaluation of the International Lymphoma Study Group classification of non-Hodgkin's lymphoma. Blood. 1997;89:3909-3918.
3. Kipps TJ. The CD5 B cell. Adv Immunol. 1989;47:117-185.
4. Antin JH, Emerson SG, Martin P, Gadol N, Ault KA. Leu-1+ (CD5+) B cells: a major lymphoid subpopulation in human fetal spleen: phenotypic and functional studies. J Immunol. 1986;136:505-510.
5. Fischer M, Klein U, Kuppers R. Molecular single-cell analysis reveals that CD5+ peripheral blood B cells in healthy humans are characterized by rearranged V kappa genes lacking somatic mutation. J Clin Invest. 1997;100:1667-1676.
6. Hardy RR, Hayakawa K. Development and physiology of Ly-1 B and its human homolog, Leu-1 B. Immunol Rev. 1986;93:53-79.
7. Kantor AB. The development and repertoire of B-1 cells (CD5 B cells). Immunol Today. 1991;12:389-391.
8. Kasaian MT, Ikematsu H, Casali P. CD5+ B lymphocytes. Proc Soc Exp Biol Med. 1991;197:226-241.
9. Youinou P, Jamin C, Lydyard PM. CD5 expression in human B-cell populations. Immunol Today. 1999;20:312-316.
10. Lydyard PM, Jewell AP, Jamin C, Youinou PY. CD5 B cells and B-cell malignancies. Curr Opin Hematol. 1999;6:30-36.
11. Arber DA, Weiss LM. CD5: a review. Appl Immunohistochem. 1995;3:1-22.
12. Burns BF, Warnke RA, Doggett RS, Rouse RV. Expression of a T-cell antigen (Leu1) by B-cell lymphomas. Am J Pathol. 1983;113:165-171.
13. Ferry JA, Yang WI, Zukerberg LR, Wotherspoon AC, Arnold A, Harris NL. CD5+ extranodal marginal zone B-cell (MALT) lymphoma: a low grade neoplasm with a propensity for bone marrow involvement and relapse. Am J Clin Pathol. 1996;105:31-37.
14. Ballesteros E, Osborne BM, Matsushima AY. CD5+ low-grade marginal zone B-cell lymphomas with localized presentation. Am J Surg Pathol. 1998;22:201-207.
15. Lin CW, O'Brien SO, Faber J, et al. De novo CD5+ Burkitt lymphoma/leukemia. Am J Clin Pathol. 1999;112:828-835.
16. Matolcsy A, Chadburn A, Knowles DM. *De novo* CD5+ and Richter's syndrome-associated diffuse large B cell lymphomas are genotypically distinct. Am J Pathol. 1995;147:207-216.
17. Ohno T, Oka K, Yamaguchi M, et al. Frequent expression of shared idiotypes in mantle cell lymphoma and extranodal small lymphocytic/non-mantle cell diffuse small cleaved lymphoma. Leukemia. 1995;9:1935-1939.
18. Yatabe Y, Nakamura S, Seto M, et al. Clinicopathologic study of *PRAD1*/CyclinD1 overexpressing lymphoma with special reference to mantle cell lymphoma: a distinct molecular pathologic entity. Am J Surg Pathol. 1996;20:1110-1122.
19. Kume M, Suzuki R, Yatabe Y, et al. Somatic hypermutations in the V_H segment of immunoglobulin genes of CD5+ diffuse large B-cell lymphoma. Jpn J Cancer Res. 1997;88:1087-1093.
20. Taniguchi M, Oka K, Hiasa A, et al. De novo CD5+ diffuse large B-cell lymphomas express VH genes with somatic mutation. Blood. 1998;91:1145-1151.
21. Harada S, Suzuki R, Uehira K, et al. Molecular and immunological dissection of diffuse large B cell lymphoma: CD5+, and CD5− with CD10+ groups may constitute clinically relevant subtypes. Leukemia. 1999;13:1441-1447.
22. Nakamura N, Hashimoto Y, Kuze T, et al. Analysis of the immunoglobulin heavy chain gene variable region of CD5+ diffuse large B-cell lymphoma. Lab Invest. 1999,79:925-933.
23. Yamaguchi M, Ohno T, Oka K, et al. *De novo* CD5+ diffuse large B-cell lymphoma: clinical characteristics and therapeutic outcome. Br J Haematol. 1999;5:1133-1139.
24. Kroft SH, Howard MS, Picker LJ, Ansari MQ, Aquino DB, McKenna RW. De novo CD5+ diffuse large B-cell lymphomas: a heterogeneous group containing an unusual form of splenic lymphoma. Am J Clin Pathol. 2000;114:523-533.
25. Yatabe Y, Suzuki R, Tobinai K, et al. Significance of cyclin D1 overexpression for the diagnosis of mantle cell lymphoma: a clinicopathologic comparison of cyclin D1+ MCL and cyclin D1-negative MCL-like B-cell lymphoma. Blood. 2000;95:2253-2261.
26. Suzuki R, Yamamoto K, Seto M, et al. CD7+ and CD56+ myeloid/natural killer cell precursor acute leukemia: a distinct hematolymphoid disease entity. Blood. 1997;90:2417-2428.
27. The International Non-Hodgkin's Lymphoma Prognostic Factors Project. A predictive model for aggressive non-Hodgkin's lymphoma. N Engl J Med. 1993;329:987-994.
28. Pospisil R, Fitts MG, Mage RG. CD5 is a potential selecting ligand for B cell surface immunoglobulin framework region sequences. J Exp Med. 1996;184:1279-1284.
29. Pospisil R, Silverman GJ, Marti GE, et al. CD5 is a potential selecting ligand for B-cell surface immunoglobulin: a possible role in maintenance and selective expansion of normal and malignant B cells. Leuk Lymphoma. 2000;36:353-365.
30. Warnke RA, Weiss LM, Chan JKC, Cleary ML, Dorfman RF. Intravascular lymphomatosis. In: Warnke RA, Weiss LM, Chan JKC, Cleary ML, Dorfman RF, eds. Atlas of Tumor Pathology, Fasc 14, Tumors of the Lymph Nodes and Spleen. Washington DC: Armed Forces Institute of Pathology; 1995:184-187.
31. Khalidi HS, Brynes RK, Browne P, Koo CH, Battifora H, Medeiros LJ. Intravascular large B-cell lymphoma: the CD5 antigen is expressed by a subset of cases. Mod Pathol. 1998;11:983-988.
32. Kanda M, Suzumiya J, Ohshima K, Tamura K, Kikuchi M. Intravascular large cell lymphoma: clinicopathological, immuno-histochemical and molecular genetic studies. Leuk Lymphoma. 1999;34:569-580.

Appendix

Patient data and specimens were received from collaborators at the following institutions: 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, Matsudo Municipal Hospital, Higashi Matsudo Hospital, Niigata University, Toyama Prefectural Central Hospital, Kanazawa Medical University, Inazawa Municipal Hospital, Aichi Prefectural Hospital, Toyota Memorial Hospital, Fujita Health University School of Medicine, Okazaki Municipal Hospital, Kasugai Municipal Hospital, Japanese Red Cross Nagoya First Hospital, Nagoya Memorial 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 City General Hospital, Kyoto University, Kyoto Prefectural University School of Medicine, 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, and Kyusyu University.