who did not achieve a CR/CRu with the initial treatment was alive at the time of the last follow-up. These results suggest that the achievement of a CR or CRu with the initial treatment is important for obtaining a cure in patients with Med-DLBCL. Similar findings were reported in other series [3-5,8,12].

Although the long-term survival rates have ranged widely (from 39% to 82%) in the reports from Western countries [5], it is likely that the progression-free survival and OS rates in our series were worse than those of Western series, as shown in Table 3. In the International Lymphoma Study Group study and in the retrospective analysis by the Nebraska Lymphoma Study Group, the survival rates of patients with Med-DLBCL were not different from those of patients with other DLBCLs, although only 33 and 43 cases of Med-DLBCL, respectively, were analyzed in those studies [13,30-32]. As shown in Table 3, many case series of Med-DLBCL consisted of relatively small numbers of patients and might have had considerable differences in patient characteristics, including age distribution, clinical stage, and treatment modalities. Compared with other studies, the relative frequency of male patients in our series was the highest, the median age was older, and the relative frequency of stage I or II patients was the lowest. The relatively unfavorable outcomes of patients with Med-DLBCL in the present study may be partly explained by these unfavorable features.

In summary, this retrospective study at a single Japanese institution suggests that the clinicopathologic features of Japanese patients with Med-DLBCL are different from those found in Western countries. Because this investigation is a single-institution study of a limited number of patients, however, multicenter confirmatory studies are needed.

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Two Entities of Precursor T-Cell Lymphoblastic Leukemia/Lymphoma Based on Radiologic and Immunophenotypic Findings

Yasushi Onishi,[a] Yoshihiro Matsuno,[b] Ukihide Tateishi,[c] Akiko Miyagi Maeshima,[d] Masahiko Kusumoto,[c] Takashi Terauchi,[c] Shigeru Kusumoto,[a] Naohiro Sekiguchi,[a] Kazuki Tanimoto,[a] Takashi Watanabe,[a] Yukio Kobayashi,[a] Kensei Tobinai[a]

[a]Hematology, [b]Clinical Laboratory, [c]Diagnostic Radiology Divisions, National Cancer Center Hospital; [d]Pathology Division, National Cancer Center Research Institute, Tokyo, Japan

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Abstract

Precursor T-cell lymphoblastic leukemia/lymphoma (T-ALL/LBL) presents a mediastinal mass in one half of cases. Although the immunophenotypic features of T-ALL/LBL have been analyzed in several studies, few studies have been focused on the relationship between the anatomic distribution of lesions and immunophenotypic findings. We analyzed the clinicopathologic findings for 17 patients with T-ALL/LBL diagnosed since 1993 and whose radiologic findings were available. Data on 14 men and 3 women with a median age of 26 years (range, 10-61 years) were analyzed. On the basis of radiologic findings, the cases were divided into thymic type (n = 8) and nonthymic type (n = 9). Patients with the thymic type of T-ALL/LBL had a large mediastinal mass and minimal systemic lymphadenopathy only in the supradiaphragmatic region. Those with the nonthymic type had predominantly systemic lymphadenopathy that included infradiaphragmatic lesions. Expression of CD8 (6/7 versus 0/9) was more frequently found in the thymic type ($P < .001$), whereas expression of CD56 (0/7 versus 5/9) was more frequent in the nonthymic type ($P = .034$). In conclusion, T-ALL/LBL was divided into 2 entities, thymic type and nonthymic type, on the basis of radiologic findings and immunophenotypic features. Analysis of the expression of CD8 and CD56 would be useful for biologically classifying T-ALL/LBL into the 2 types. This study was performed in a single institution, was retrospective, and had a limited number of patients; multicenter confirmatory studies are warranted.
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Key words: Precursor T-cell lymphoblastic lymphoma; Radiologic findings; Mediastinal mass; Immunophenotype; CD56

1. Introduction

Lymphoblastic lymphoma (LBL) is a well-defined clinicopathologic entity indistinguishable from acute lymphoblastic leukemia (ALL) in tissue sections [1]. Precursor T-cell lymphoblastic leukemia/lymphoma (T-ALL/LBL) is a neoplasm of lymphoblasts committed to the T-cell lineage and is the most frequent subtype in male adolescents [1-4]. Approximately 40% to 80% of patients with T-cell LBL (T-LBL) present with a mediastinal mass, and 60% to 75% of patients have systemic lymphadenopathy [1,3-6]. Nathwani et al demonstrated that patients with mediastinal masses were significantly younger than those without it and that a mediastinal mass was found more frequently in male patients [1]. These findings may suggest that T-LBL with a mediastinal mass is biologically different from T-LBL without it.

The immunophenotypic findings for lymphoblasts of T-ALL/LBL are positive for terminal deoxynucleotidyl transferase (TdT). Results for cytoplasmic CD3 (cCD3) and CD7 usually are positive, and CD1a, CD2, CD4, CD5, CD8, CD34, and HLA-DR are variably expressed [7]. The heterogeneity of immunophenotypic profiles in T-ALL/LBL is believed to reflect the origin of neoplastic cells from various stages of T-cell differentiation [8-12]. In addition, several cases of T-LBL expressing natural killer (NK) cell antigens, such as CD16, CD56, and CD57, have been reported [13-20]. CD56 is believed to play an important role in T-cell differentiation from common T/NK cell progenitors in the thymus [21].

Although it was grouped as a single disease in the recent World Health Organization (WHO) classification [7], T-ALL/LBL may include biologically heterogeneous diseases. We analyzed in detail the anatomic distribution of the disease and the immunophenotypic profiles in 17 consecu-

Correspondence and reprint requests: Kensei Tobinai, MD, PhD, Hematology Division, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan; 81-3-3542-2511; fax: 81-3-3542-3815 (e-mail: ktobinai@ncc.go.jp).

tive cases of T-ALL/LBL at a single institution. We found that they were divided into 2 entities: thymic type and non-thymic type.

2. Patients and Methods

2.1. Patient Samples

We conducted a retrospective evaluation of the cases of 17 patients with T-ALL/LBL diagnosed between June 1993 and October 2002 at the National Cancer Center Hospital. All 17 patients had lymphadenopathy and/or a mediastinal mass, and 5 patients presented with 25% or more lymphoblasts in the bone marrow. The histopathologic specimens were reviewed by 2 hematopathologists (Y.M. and A.M.M.) according to previously described criteria [2] and the WHO classification [7]. Morphologic and immunophenotypic studies were performed on lymph nodes from 9 patients, mediastinal masses from 7, and skin tumor from 1, all of which manifested morphologic features compatible with LBL [2]. In all 17 patients, immunohistochemical studies were performed on paraffin-embedded sections. Flow cytometric analysis was carried out on cell suspensions of biopsy specimens from 9 patients, pleural effusion from 3 patients, and peripheral blood and bone marrow from 1 patient. Each specimen contained more than 90% neoplastic cells.

2.2. Tissue Processing, Immunophenotyping, and Southern Blot Analysis

The diagnostic tissue samples were fixed in 10% formalin, embedded in paraffin, and stained with hematoxylin and eosin for routine histopathologic examinations. Surface immunophenotypes of the blasts were examined with a direct immunofluorescence technique using a flow cytometer (FACScan; BD Medical Systems, Franklin Lakes, NJ, USA). Immunohistochemical staining was performed on a frozen section or one of the paraffin-embedded specimens by use of an avidin–biotin–alkaline phosphatase complex method. The antigens analyzed in this study were as follows: CD1a, CD2, CD3, CD4, CD5, CD7, CD8, CD10, CD13, CD14, CD19, CD20, CD33, CD34, CD41, CD45, CD45RO, CD56, CD79a, CD99, TdT, HLA-DR, T-cell receptor (TCR) pan αβ, and TCR pan γδ. Primary antibodies used are listed in Table 1.

For Southern blot analysis, high molecular weight DNA was extracted from frozen stored biopsy specimens and digested with restriction enzymes (*Bam*HI, *Eco*RI, *Bgl*II, or *Hind*III). The DNA was processed according to the method of Southern [22] and was hybridized to digoxigenin-labeled DNA probes. Gene rearrangement analysis was conducted using probes of the Cβ1 fragment for the TCR β-chain gene (*TCRβ*), the Jγ1 fragment for the TCR γ-chain gene (*TCRγ*), the Jδ1 fragment for the TCR δ-chain gene (*TCRδ*), and the JH fragment for the immunoglobulin heavy-chain gene (*IgH*).

2.3. Radiologic Studies and Image Analysis

Whole-body computed tomography (CT) was performed from the level of the head to that of the upper thigh on either a single helical CT scanner or a 4-row multidetector scanner (X-Vigor or Aquilion V-detector, Toshiba Medical Systems, Tokyo, Japan). All patients received 150 mL of nonionic intravenously administered iodinated contrast material at 3.0 mL/sec after a 60-second delay. Two experienced radiologists who were blinded to the diagnosis and any clinical information other than patient age and sex independently reviewed the CT images on hard copies. The two readers analyzed the images for tumor size, number of lesions, contour, margin, location of tumor, and pattern of enhancement (homogeneous or heterogeneous). Three radiologists reviewed all the CT findings, and a consensus interpretation was obtained.

2.4. Statistical Analysis

To investigate a possible correlation between immunophenotypes and radiologic findings, we correlated each of the 13 antigens of CD1a, CD2, CD3, CD4, CD5, CD7, CD8, CD13, CD33, CD34, CD56, TdT, and HLA-DR with radiologic parameters. Fisher exact test or the χ^2 test was used to compare the immunophenotypic variables in each of the radiologic categories, depending on sample size. The probabilities of overall survival (OS) and progression-free survival (PFS) were evaluated by use of the method of Kaplan and Meier. OS was measured from diagnosis until death due to any cause, and data on surviving patients were censored at the last contact date. PFS was defined as the time from diagnosis until the first recognition of progression or death due to any cause. The log-rank test was used to compare PFS and OS in subgroups defined by the radiologic findings.

3. Results

3.1. Clinical Characteristics of Patients

The clinical characteristics of 17 patients with T-ALL/LBL are summarized in Table 2. There were 14 men and 3 women with a median age of 26 years (age range, 10-61 years). At initial presentation, circulating leukemic cells were detected in 4 patients (patients 5, 13, 14, and 16). None of the 17 patients had either thrombocytopenia less than $10 \times 10^4/\mu L$ or anemia. Initial bone marrow involvement of various degrees was detected in 8 patients (patients 3, 5, 6, 9, and 13 through 16). Two patients (patients 1 and 12) did not have bone marrow involvement at initial presentation, but involvement showed at relapse. All patients except 2 (patients 10 and 12) had mediastinal lesions of various sizes. Thirteen patients had peripheral lymphadenopathy, and 6 (patients 1, 2, 4, 5, 7, and 8) presented with dyspnea and/or cough. Superior vena cava syndrome was found in 2 patients (patients 3 and 6), and B symptoms were found in 5 (patients 1, 4, 6, 9, and 14). Meningeal involvement was encountered in 2 patients (patient 5 at initial presentation and patient 7 at relapse).

3.2. Radiologic Findings

CT findings are summarized in Table 3. CT findings revealed that cases could be divided into 2 types: thymic type

Table 1.
Antibodies Used for Flow Cytometry and Immunohistochemistry*

Antigen	Flow Cytometry		Immunohistochemistry	
	Clone	Source	Clone	Source
CD1a	BL6	BC	O10	BC
CD2	MT910	Dako		
CD3	UCHT1	BC	PS1	Novo
CD4	13B8.2	BC	1F6	Novo
CD5	DK23	Dako	4C7	Novo
CD7	8H8.1	BC		
CD8	B9.11	BC	4B11	Novo
CD10	ALB2	BC	56C6	Novo
CD13	SJ1D1	BC		
CD14	RMO52	BC		
CD19	J4.119	BC		
CD20	B-Ly1	Dako	L26	Dako
CD33	D3HL60.251	BC		
CD34	581 (class III)	BC	MY10 (anti HPCA-1)	BD
CD41	P2	BC		
CD45	J.33	BC	2B11 + PD7/26	Dako
CD45RO	None		UCHL1	Dako
CD56	NKH-1(N901)	BC	NCC-Lu-243	Nippon Kayaku
CD79a	HM47	BC	JCB117	Dako
CD99			O13	Signet
TdT	HT-1, 3, 4	Dako	Rabbit anti-TdT	Dako
HLA-DR	IMMU-357	BC	TAL.1B5 (HLA-DRα)	Dako
TCR-αβ	BMA031	BC		
TCR-γδ	IMMU-510	BC		

*BC indicates Beckman Coulter, Fullerton, CA, USA; Dako, Dako Cytomation Denmark A/S, Denmark; Novo, Novocastra Laboratories, Newcastle upon Tyne, UK; Nippon Kayaku, Nippon Kayaku, Tokyo, Japan; Signet, Signet Laboratories, Dedham, MA, USA; BD, BD Biosciences Immunocytometry Systems, San Jose, CA, USA; TdT, terminal deoxynucleotidyl transferase; TCR, T-cell receptor.

(n = 8) and nonthymic type (n = 9). The thymic type presented with a large, well-defined, anterior mediastinal mass that was not a complex of polynodules but was a single mass, indicating enlargement of the thymus, and minimal systemic lymphadenopathy that was limited to supradiaphragmatic regions (Figure 1). The size of the mediastinal mass in the thymic type was 11.8 ± 2.0 cm (mean ± standard deviation). The nonthymic type had predominantly systemic lymphadenopathy, including infradiaphragmatic lesions. In the nonthymic type, mediastinal involvement consisted of small lymphadenopathies at the pretracheal and paratracheal regions and the paraaortic arch or a complex of enlarged lymph nodes that was lobulated and ill-defined (Figure 2). The size of mediastinal mass in the nonthymic type was 3.6 ± 4.0 cm. Differences between the 2 types are summarized in Table 4. The frequency of vascular obliteration was significantly higher in the thymic type than in the nonthymic type (88% versus 0%) ($P < .001$). Infradiaphragmatic lymphadenopathy was recognized only in the nonthymic type ($P = .0021$). Comparisons of the presence of pleural effusion, pericardial effusion, and cutaneous involvement between the 2 types yielded a statistical trend ($P = .35$, $P = .15$, $P = .47$, respectively).

3.3. Morphology

Eighteen biopsy specimens were obtained from 17 patients, including 16 initial specimens and 2 relapse specimens. Biopsy specimens from the anterior mediastinal mass were obtained from 7 patients (patients 1 through 5, 7, and 8) and lymph node biopsy specimens from 10 patients (patient 6 and patients 9 through 17). One tonsil biopsy was obtained from a patient with disease in relapse (patient 1). The histologic sections from all patients showed the morphologic features commonly seen in LBL [2] (Figures 3 and 4). The neoplastic cells from all patients had a fine nuclear chromatin pattern and scanty cytoplasm with ill-defined cell borders. The pattern of involvement was diffuse in all cases. A starry-sky pattern and a single-file arrangement of cells were prominent in some patients.

3.4. Immunophenotypic Findings

Tumor cells were immunophenotyped by both flow cytometry and immunohistochemistry in 13 cases and only by immunohistochemistry in 4 cases. The immunophenotypes of all patients are listed in Table 5. All 15 patients underwent testing, but 1 patient (patient 2) expressed TdT as shown in Figures 3b and 4b. Patient 3 did not undergo testing for TdT but expressed CD99. Patient 15 underwent testing neither for TdT nor for CD99. All but 1 patient (patient 12) expressed cytoplasmic CD3. All 15 patients who underwent testing except for 1 (patient 15) expressed CD5, and all 13 patients who underwent testing expressed CD7.

The differences in immunophenotypic profiles between thymic type and nonthymic type are summarized in Table 4. Patients with thymic-type disease expressed CD8 in 6 of 7 cases examined, but no patient with nonthymic-type disease

Table 2.
Clinical Findings in 17 Cases of Precursor T-Cell Lymphoblastic Leukemia/Lymphoma*

Case No.	Age/ Sex	PS	Presenting Symptoms	B symptoms	WBC, /μL	Hgb, g/dL	PLT, ×10,000/μL	LDH, IU/L	PB Involved	BM Involved	CNS Involved	CS
1	29/M	1	Cough	Sweat	10,400	15.5	30.4	431	0%	0%	No	IEB
2	21/M	1	Dysphagia, cervical LN	None	7500	15.5	21.3	844	0%	0%	No	IIEA
3	28/M	0	SVC syndrome	None	5600	14.6	26.4	477	0%	9%	No	IVA
4	61/M	1	Cough, shortness of breath	Fever	7800	14.2	20.6	452	0%	0%	No	IIEB
5	18/M	1	Cough, dyspnea, cervical LN, chest oppressiveness	None	45,200	15.6	31.1	2384	Involved	32%	Involved	IVA
6	30/M	3	SVC syndrome, chest pain	Fever	4800	14.2	27.7	1781	0%	92%	No	IVB
7	21/F	2	Cough, dyspnea, chest pain	None	10,000	13.0	42.1	1150	0%	0%	No	IVA
8	16/M	1	Cough, dyspnea, dysphagia	None	5500	15.0	30.4	474	0%	0%	No	IA
9	26/M	0	Occipital and axillary LN	Sweat	6200	15.1	10.3	256	0%	41%	No	IVB
10	34/M	0	Bilateral cervical LN	None	13,000	15.5	34.5	487	0%	0%	No	IIIA
11	26/M	1	Cervical LN, anterior chest mass	Fever	6900	14.6	35.4	300	0%	0%	No	IIEB
12	22/M	0	Cervical, axillary, and inguinal LN	None	5300	15.7	25.4	262	0%	0%	No	IIIA
13	41/M	1	Pharyngeal discomfort, cervical and inguinal LN	None	89,200	15.8	13.6	712	88%	98%	No	IVA
14	25/M	1	Cervical LN	Sweat, body weight loss	3900	16.2	17.1	317	32%	62%	No	IVB
15	25/F	1	Cervical, axillary, and inguinal LN, chest pain	None	4900	12.9	35.1	558	0%	9%	No	IVA
16	10/F	0	Cervical, submandibular, and supraclavicular LN	None	3700	14.5	24.6	529	12%	11%	No	IVA
17	35/M	1	Tonsil swelling, cervical LN	None	5500	16.3	17.7	180	0%	0%	No	IIA

*PS indicates performance status; WBC, white blood cell count; Hgb, hemoglobin; PLT, platelet count; LDH, lactate dehydrogenase; PB, peripheral blood; BM, bone marrow; CNS, central nervous system; CS, clinical stage according to Ann Arbor classification; LN, lymph node swelling; SVC, superior vena cava.

expressed CD8 ($P < .001$). On the other hand, CD56 was expressed more frequently in the nonthymic type than the thymic type ($P = .034$). CD1a and CD4 were expressed more frequently in the thymic type ($P = .06$ and $P = .089$, respectively), whereas CD34 was more frequent in the nonthymic type ($P = .06$).

3.5. Genotypic Analysis

Southern blot analysis of biopsy specimens was undertaken in 6 patients (patients 1, 2, 6, 14, 16, and 17). Patient 6 had clonal rearrangement of TCR β- and γ-chain genes. Patient 17 presented clonal rearrangement of the TCR δ-chain gene. Four patients (patients 1, 2, 14, and 17) presented no clonal rearrangement of the TCR gene or the IgH gene.

3.6. Treatments and Clinical Courses

The initial treatment, clinical course, PFS, and OS of the 17 patients are listed in Table 6. Four patients (patients 2, 9, 11, and 15) underwent allogeneic hematopoietic stem cell transplantation (allo-HSCT) without being in remission; the result was progressive disease, and all patients died. Five patients (patients 3, 10, 12, 13, and 14) underwent allo-HSCT in remission. Patients 10, 12, and 14 achieved durable complete response, but patients 3 and 13 had relapses 28 and 6 months, respectively, after allo-HSCT.

There was no significant difference in OS and PFS between the thymic type and the nonthymic type ($P = .41$ and $P = .43$, respectively).

4. Discussion

In this study, we found that cases of T-ALL/LBL can be divided into the thymic type and the nonthymic type on the basis of the anatomic distribution of the disease and immunophenotypic profiles. Immunophenotypic analysis shows thymic-type T-ALL/LBL expresses CD1a, CD4, and CD8 more frequently and that the nonthymic type expresses CD34, HLA-DR, and CD56 more frequently. These findings suggest that the differentiation stage of neoplastic cells of T-ALL/LBL correlates with the anatomic distribution of the disease.

The Pediatric Oncology Group in the United States reported that 64% of 106 children with LBL presented with a mediastinal mass and that 74% of the patients presented with systemic lymphadenopathy, which was distrib-

Table 3.
Computed Tomographic (CT) Findings at Presentation*

Case No.	Involved Site in the Mediastinal Region	Size of Mediastinal Mass, cm	Vascular Obliteration	Pleural Effusion	Pericardial Effusion	Cutaneous Involvement	Supradiaphragmatic Involved Sites Other than Mediastinal Region (no. of sites)	Infradiaphragmatic Involved Sites	Type of CT Finding
1	Thymus	12.2	Yes	Blt	Yes	No	No (0)	No	Thymic
2	Thymus	11.5	Yes	No	No	No	Lt cervical, rt SC, blt IC (4)	No	Thymic
3	Thymus	9	Yes	No	Yes	No	No (0)	NA	Thymic
4	Thymus	11.6	Yes	Blt	Yes	No	Blt IC (2)	No	Thymic
5	Thymus	12.8	Yes	Lt	Yes	No	Lt IC, rt hilar, lt axillary (3)	NA	Thymic
6	Thymus	13.8	Yes	Blt	Yes	No	Lt SC, lt IC, lt axillary (3)	No	Thymic
7	Thymus	9	No	Lt	Yes	No	No (0)	No	Thymic
8	Thymus	14.7	Yes	No	No	No	No (0)	No	Thymic
9	Paratracheal LN	NM	No	No	No	No	Blt cervical, blt hilar, blt axillary (6)	Paraaortic, mesenteric, blt inguinal	Nonthymic
10	None	No	No	No	No	No	Blt cervical (2)	No	Nonthymic
11	Paraaortic and pretracheal LNs	8.7	No	Lt	Yes	Yes	Lt cervical, lt SC, blt IC, lt axillary (4)	NA	Nonthymic
12	None	No	No	No	No	Yes	Blt cervical, blt SC, rt IC, lt axillary (4)	Paraaortic, blt inguinal	Nonthymic
13	Paratracheal LN	6	No	Rt	Yes	No	Blt cervical, rt preauricular, rt SC, lt IC, rt hilar, rt axillary (5)	Paraaortic, blt inguinal	Nonthymic
14	Paratracheal LN	NM	No	No	No	No	Blt cervical, blt SC, blt IC, rt axillary (5)	Paraaortic, mesenteric, blt iliac, rt inguinal	Nonthymic
15	Paraaortic and pretracheal LNs	10	No	Blt	Yes	No	Blt cervical, blt SC, rt IC, rt hilar (4)	NA	Nonthymic
16	Pretracheal LN	3.3	No	No	No	No	Blt cervical, rt preauricular, blt SC, lt IC, blt axillary (5)	Paraaortic, blt inguinal	Nonthymic
17	Paraaortic and paratracheal LNs	4.2	No	No	No	No	Lt tonsil, lt cervical, lt SC (2)	No	Nonthymic

*Blt indicates bilateral; lt, left; rt, right; SC, supraclavicular; IC, infraclavicular; NA, not applicable; LN, lymph node; NM, not measurable.

uted as follows: 46% of the patients had a mediastinal mass and systemic lymphadenopathy; 28%, systemic lymphadenopathy without a mediastinal mass; and 18%, a mediastinal mass without systemic lymphadenopathy [4]. The distribution of disease in adults appeared to be similar [1,3,5,6]. In the present study, 11 (65%) of the patients presented with a mediastinal mass and systemic lymphadenopathy, 2 (12%) with systemic lymphadenopathy without a mediastinal mass, and 4 (24%) with a mediastinal mass without systemic lymphadenopathy. These find-

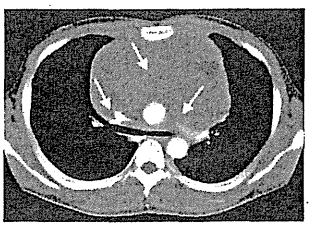

Figure 1. Thymic type T-cell lymphoblastic lymphoma in a 16-year-old man (case 8). Transverse computed tomographic image shows a large anterior mediastinal mass with vascular obliteration (arrows) suggesting enlargement of the thymus.

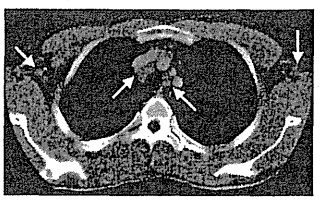

Figure 2. Nonthymic type T-cell lymphoblastic lymphoma in a 25-year-old man (case 14). Transverse computed tomographic image shows multiple lymphadenopathies in both mediastinum and peripheral nodes (arrows).

Table 4.
Comparison of Characteristics between Thymic Type and Nonthymic Type of Precursor T-Cell Lymphoblastic Leukemia/Lymphoma*

Characteristic	Thymic Type (n = 8)	Nonthymic Type (n = 9)	P
Clinical characteristics			
Male	88%	78%	.6
Age, y	28.0 ± 14.3†	27.1 ± 8.9†	.88
Peripheral blood involvement	14%	18%	>.99
Bone marrow involvement	38%	42%	.63
Superior vena cava syndrome	25%	0%	.21
B symptom	38%	33%	>.99
Computed tomographic findings			
Vascular obliteration	88%	0%	≤.001
Pleural effusion	63%	33%	.35
Pericardial effusion	75%	33%	.15
Cutaneous involvement	0%	22%	.47
Supradiaphragmatic lymph node involvement	50%	100%	.029
Number of involved supradiaphragmatic lymph nodes	1.5 ± 1.7†	4.1 ± 1.4†	.0031
Infradiaphragmatic lymph node involvement	0%	71%	.0021
Immunophenotype			
CD1a expression	4/4	2/7	.06
CD4 expression	4/6	1/9	.089
CD8 expression	6/7	0/9	≤.001
CD13 expression	0/4	3/6	.2
CD33 expression	0/4	3/8	.49
CD34 expression	1/7	6/9	.06
CD56 expression	0/7	5/9	.034
HLA-DR expression	1/4	6/8	.22

*Shading indicates $P < .05$.
†Mean ± standard deviation.

ings were compatible with those in previous reports. A large mediastinal mass often leads to dyspnea because of progressive airway obstruction [3,5,23]. In the present series 63% of patients with the thymic type of disease presented symptoms of dyspnea and/or cough, whereas patients with the nonthymic type did not but presented only peripheral lymphadenopathy. Baldit et al [5] and Kjeldsberg et al [24] also reported that most patients without symptoms due to a mediastinal mass presented peripheral lymphadenopathy.

T-LBLs have immunophenotypic profiles comparable with those expressed by developing T-cells during the prethymic and intrathymic stages of normal T-cell differentiation [9,11,12]. Fewer than one third of T-LBL cases express prothymocyte or immature thymocyte phenotypes, that is, express only CD5, CD2, or CD7 and lack surface CD3,

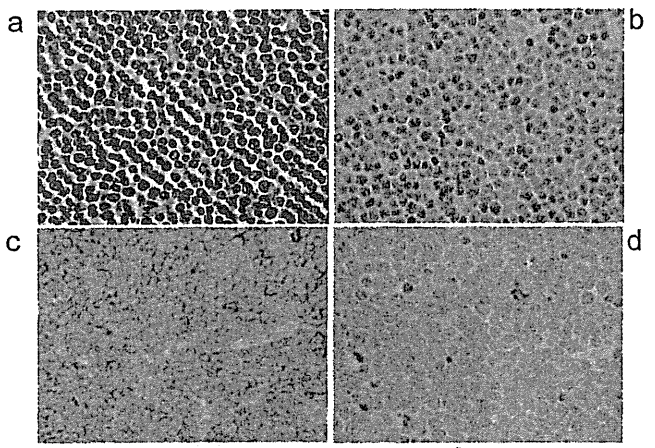

Figure 3. Needle biopsy specimen of an anterior mediastinal mass (case 5, thymic type). a, Hematoxylin and eosin staining. b, c, and d, Immunostaining with antibodies against terminal deoxynucleotidyl transferase (TdT), CD8, and CD56. The tumor cells expressed TdT and CD8 but not CD56 (original magnification, ×600).

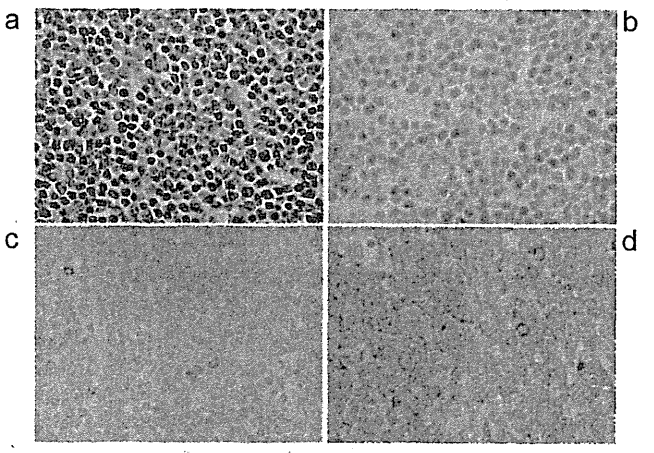

Figure 4. Lymph node from case 14 (nonthymic type). a, Hematoxylin and eosin staining. b, c, and d, immunostaining with antibodies against terminal deoxynucleotidyl transferase (TdT), CD8, and CD56. The tumor cells expressed TdT and CD56 but not CD8 (original magnification, ×600).

Table 5.
*Immunophenotypic Findings of Thymic (n = 8) and Nonthymic (n = 9) Types of Precursor T-Cell Lymphoblastic Leukemia/Lymphoma by Flow Cytometry and Immunohistochemistry**

	Thymic Type, Case No.								Nonthymic Type, Case No.								
Antigen	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16†	17
CD1a	+	+	NA	NA	NA	+	+	NA	–	+	–	–	–	+	NA	–	NA
CD2	+	+	NA	NA	NA	+	+	NA	–	+	+	–	+	+	–	+	+
sCD3	–	+	NA	NA	NA	–	+	NA	–	–	–	–	–	–	–	–	–
cCD3	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+
CD4	–	+	NA	NA	+	+	+	–	–	+	–	–	–	–	–	–	–
CD5	+	+	NA	+	NA	+	+	+	+	+	+	+	+	+	–	+	+
CD7	+	+	NA	NA	NA	+	+	NA	+	+	+	+	+	+	+	+	+
CD8	+	+	NA	–	+	+	+	+	–	–	–	–	–	–	–	–	–
CD10	–	–	NA	–	NA	+	+	+	+	–	–	–	+	–	–	–	–
CD13	–	–	NA	NA	NA	–	–	NA	+	–	NA	+	–	–	NA	+	NA
CD19	–	–	NA	NA	NA	–	NA	NA	–	–	+	+	–	–	–	–	–
CD20	–	–	NA	–	NA	–	–	–	–	–	NA	–	–	–	–	–	–
CD33	–	–	NA	NA	NA	–	–	NA	–	–	+	+	–	–	NA	+	–
CD34	+	–	–	NA	–	–	–	–	+	+	+	+	+	–	–	+	–
CD45	+	+	+	+	NA	+	+	NA	+	+	+	+	+	+	+	+	+
CD56	–	–	NA	–	–	–	–	–	+/–	+	+	+	–	+	+	+/–	+/–
CD79a	–	–	NA	+/–	–	–	–	–	–	NA	NA	+	–	–	NA	–	–
CD99	+	+	+	+	NA	NA	+	NA	–	NA	+	NA	NA	NA	NA	NA	NA
TdT	+	–	NA	+	+	+	+	+	+	+	+	+	+	+	NA	+	+
HLA-DR	+	–	NA	NA	NA	–	–	NA	+	–	+	+	+	+	NA	+	–
TCR-αβ	NA	+	NA	NA	NA	–	+	NA	NA	–	NA	NA	NA	NA	NA	NA	–
TCR-γδ	NA	–	NA	NA	NA	–	–	NA	NA	–	+/–	NA	NA	NA	NA	NA	–

*Antibody staining by flow cytometry analysis was scored as follows: –, 0% to 15%; +, 16% to 100%. Antibody staining by immunohistochemistry was scored as follows: –, no detectable expression; +/–, weakly expressed; +, expressed. NA indicates not applicable; sCD3, surface CD3; cCD3, cytoplasmic CD3; TdT, terminal deoxynucleotidyl transferase; TCR, T-cell receptor.

†Specimen at relapse.

CD1a, CD4, and CD8 [8-11,15]. HLA-DR was also reported to be expressed only on T-LBLs displaying prothymocyte and immature thymocyte immunophenotypes [9,11]. These subgroups are comparable with our cases of the nonthymic type of disease, although expression of CD56 was not examined in the previous reports. Expression of TCR-αβ accompanied by surface CD3 was found in 2 cases (patients 2 and 7) of thymic type. These findings supported the hypothesis that the thymic type is derived from more differentiated T-cells than the nonthymic type.

In our series, all 5 $CD56^+$ cases were classified into the nonthymic type. Several investigators have reported cases of T-LBL expressing NK cell–associated antigens, such as CD16, CD56, and CD57 [13-19]. Ichinohasama et al reported a case of thymic LBL derived from committed precursor NK cells, different from thymic T-cells, with the immunophenotypic profile TdT^+, $cCD3^+$, $CD5^-$, $CD7^+$, $CD34^+$, $HLA\text{-}DR^+$, $CD56^+$, $CD1a^-$, $CD4^-$, and $CD8^-$ [18]. Koita et al reported a case of LBL expressing NK-cell phenotype involving the mediastinum and nasal cavity [19]. The tumor cells of this case had positive results for TdT, cCD3, CD56, CD5, CD7, and HLA-DR but negative results for CD1a, CD2, CD4, CD8, and CD34. The investigators' judgment was based on the model of Sanchez et al, in which human fetal thymocytes contained a T/NK bipotential progenitor population with the ability to differentiate into T-cells and NK cells through separate precursors [21]. The profiles of these 2 cases were compatible with those of the nonthymic type of disease in our series.

Nakamura et al pointed out a relationship between a variant of LBL like that in the case described by Koita et al and blastic NK cell lymphoma, linking the entities of LBL and peripheral T/NK cell lymphoma [20]. They demonstrated that blastic NK cell lymphoma was a distinct entity characterized by involvement of extranodal regions, such as the skin and nasal region, but rarely the mediastinum [25,26]. Myeloid/NK precursor acute leukemia also shares some clinical, morphologic, and immunophenotypic characteristics with $CD56^+$ T-LBL [27-29]. Suzuki et al reported 4 cases with mediastinal mass among 17 cases of myeloid/NK precursor acute leukemia [29]. Myeloid/NK precursor acute leukemia has negative results for CD5 and TdT and was reported to be distinct from $CD56^+$ T-LBL. In our series, all 4 cases (patients 9, 11, 12, and 16) that expressed myeloid antigens, CD13 and/or CD33, were of the nonthymic type, a finding that may support the hypothesis that the nonthymic type overlaps with myeloid/NK precursor acute leukemia.

Karube et al reported 21 cases of non-B and non-T (surface $CD3^-$) lymphoblastic lymphoma classified into 4 subtypes: $CD7^+$ stem cell lymphoma, blastic NK cell lymphoma, myeloid/NK precursor cell leukemia, and $CD4^+CD56^+$ hematodermic malignancy [30]. Nine of the 10 cases classified as $CD7^+$ stem cell lymphoma in that series had negative results for CD8 and CD56, whereas 10 of the 11 cases classified as the remaining 3 subtypes were $CD8^-$ and $CD56^+$. Therefore $CD7^+$ stem cell lymphoma described by Karube et al may overlap with the $CD56^-$ nonthymic type in our series.

Table 6.
Therapeutic Responses and Clinical Courses of 17 Cases of Precursor T-Cell Lymphoblastic Leukemia/Lymphoma*

Case No.	Age/Sex	Initial Therapy to Best Response	Site of Relapse	Treatment after Progression	Response	PFS, d	OS, d
1	29/M	ABVD, RT	BM, LN, pharynx, subcutaneous, PE	Salvage regimens	PR-R-PD	332	669
2	21/M	ALL regimen, auto-HSCT, RT	Mediastinum	ALL regimen, allo-HSCT	CRu-R-PR2-R2-PD	254	647
3	28/M	CHOP, ALL regimen, allo-HSCT	LN	RT	PR-CR-R	1179	1565+
4	61/M	ALL regimen, RT	No		CR	1057+	1057+
5	18/M	ALL regimen, HD-MTX, RT	No		CR	1127+	1127+
6	30/M	ALL regimen, RT	No		CR	763+	763+
7	21/F	ALL regimen, RT	CNS	Whole-brain RT, IT, salvage regimen	PR-R-CR2	189	631+
8	16/M	ALL regimen	No		CR	456+	456+
9	26/M	ALL regimen, auto-HSCT, RT	BM	Salvage regimens, auto- and allo-HSCT	CRu-R-PD	339	707
10	34/M	ALL regimen, allo-HSCT	No		CR	3738+	3738+
11	26/M	CHOP, MCVP	Chest wall	Salvage regimens, allo-HSCT	PR-R-PD	315	461
12	22/M	ALL regimen	BM, cervical LN	AML regimen, allo-HSCT	CR-R-CR2	920	1377+
13	41/M	ALL regimen, allo-HSCT	BM	Salvage regimens	CR-R-PD	401	540
14	25/M	ALL regimen	BM	allo-HSCT	CR-R-CR2	987	1338+
15	25/F	VEPA	Mediastinum, axillary and cervical LN	Salvage regimens, RT, allo-HSCT	PR-R-PD	244	334
16	10/F	AML regimen	BM, cervical LN	Salvage regimen	CR-R-CR2	620	1194+
17	35/M	ALL regimen	No		CR	399+	399+

*PFS indicates progression-free survival; OS, overall survival; ABVD, adriamycin + bleomycin + vinblastine + dacarbazine; RT, radiotherapy; BM, bone marrow; LN, lymph node; PE, pleural effusion; PR, partial response; R, relapse; PD, progressive disease; ALL regimen, cyclophosphamide + adriamycin or daunorubicin + vincristine + prednisolone + L-asparaginase; auto-HSCT, autologous hematopoietic stem cell transplantation; allo-HSCT, allogeneic HSCT; CRu, complete response unconfirmed; CHOP, cyclophosphamide + adriamycin + vincristine + prednisolone; HD-MTX, high-dose methotrexate; CNS, central nervous system; IT, intrathecal chemotherapy; MCVP, mitoxantrone + carboplatin + etoposide; AML, acute myeloblastic leukemia; VEPA, vincristine + cyclophosphamide + prednisolone + adriamycin.

T-LBLs with CD56 expression, blastic NK cell lymphoma, and myeloid/NK precursor acute leukemia may constitute a continuous disease spectrum with overlapping and borderline cases.

In summary, T-ALL/LBL was divided into 2 entities, thymic type and nonthymic type, on the basis of radiologic findings and immunophenotypic features. However, the significance of these findings might be limited owing to the small number of patients. To confirm our unique observation at a single institution and evaluate the prognostic significance of recognition of the 2 entities, further multicenter studies with a larger patient group are needed.

Acknowledgment

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Primary Mediastinal Lymphoma

Characteristic Features of the Various Histological Subtypes on CT

Ukihide Tateishi, MD, PhD, Nestor L. Müller, MD, PhD,† Takeshi Johkoh, MD, PhD,‡ Yasushi Onishi, MD,§ Yasuaki Arai, MD, PhD,* Mitsuo Satake, MD,* Yoshihiro Matsuno, MD, PhD,‖ and Kensei Tobinai, MD, PhD§*

Objective: To assess the characteristic features of the primary mediastinal lymphoma (PML) on CT and to test the relationship between CT findings and the likelihood of the 3 most common subtypes (Hodgkin lymphoma [HL], mediastinal diffuse large B-cell lymphoma [Med-DLBCL], and precursor T-cell lymphoblastic lymphoma [T-LBL]).

Methods: Sixty-six consecutive patients with pathologically proven PML including 29 patients with HL, 21 with Med-DLBCL, and 16 with T-LBL underwent CT prior to therapy. CT scans were independently reviewed by 2 radiologists who were blinded to the pathologic diagnosis for the following considerations: pattern of involvement (i.e., morphologic features, mass size, and contrast enhancement pattern), and ancillary findings at other sites including neck, abdomen, and pelvis. Interobserver agreement was measured by Kappa statistics, and independent predictors were calculated using multiple logistic regression analysis for determining the likelihood of the subtypes based on CT.

Results: Characteristic features of HL included irregular contour of the anterior mediastinal mass (20 of 29, 69%) and high prevalence of associated mediastinal lymphadenopathy (28 of 29, 97%). Characteristic features of Med-DLBCL included regular contour (14 of 21, 67%) and absence of cervical and abdominal lymphadenopathy (0 of 21). Characteristic features of T-LBL included regular contour (12 of 16, 75%) and high prevalence of cervical (9 of 16, 56%) and abdominal (6 of 16, 38%) lymphadenopathy and splenomegaly (11 of 16, 69%). CT findings independently associated with increased likelihood of HL were surface lobulation ($P < 0.01$), the absence of vascular involvement ($P < 0.01$), or pleural effusion ($P < 0.05$). The presence of vascular involvement was associated with increased likelihood of Med-DLBCL ($P < 0.001$). Furthermore, CT findings including the presence of cervical lymph nodes or inguinal lymph nodes ($P < 0.001$), the presence of pericardial effusion ($P < 0.05$), and the absence of surface lobulation ($P < 0.05$) were significantly associated with the likelihood of T-LBL.

Conclusion: The various histologic subtypes of PML have characteristic manifestations in the neck, chest, and abdomen, which allow their distinction on CT.

Key Words: malignant lymphoma, mediastinal tumor, computed tomography

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Malignant lymphoma that involves mainly or exclusively the mediastinum at initial presentation (primary mediastinal lymphoma: PML) is a relatively common condition seen in patients of all ages.[1–4] Most cases are due to 1 of 3 histologic subtypes: Hodgkin lymphoma (HL), mediastinal diffuse large B-cell lymphoma (Med-DLBCL), and precursor T-cell lymphoblastic lymphoma (T-LBL). Distinction of the specific histologic subtype is important as it influences treatment and prognosis.[5–12] Because the specific diagnosis should be confirmed by immunohistochemical analysis and hence requires large tissue samples, it is not always easy to make a confident diagnosis on biopsy specimens.[7–10]

There is a sizable body of literature examining the distribution of nodes or masses in lymphoma.[13–27] However, there is limited information on the characteristic manifestations of the various subtypes of PML and the potential value of CT in the differential diagnosis. CT has been increasingly used for the evaluation of patients with suspected or proven lymphoma. It allows for accurate staging of the disease and follow-up of the therapeutic response.[15–23] The purpose of the present study was to assess the characteristic features of the various histologic subtypes of PML and the diagnostic accuracy of CT evaluation for a specific histologic subtype.

MATERIALS AND METHODS

Patients

Sixty-six cases of PML were registered in the radiologic files of our institute. Clinical details and follow-up information including the presence or absence of recurrence were reviewed retrospectively by a hematologic oncologist who was one of the authors. Our institutional review board does not require its approval or patient informed consent for this type of review. The study included 45 men (mean age 38.4 years, range 16 to 84 years) and 21 women (mean age 34.1 years, range 13 to 63 years). All patients underwent uniform staging that included a physical examination, blood cell counts, routine blood

From the *Division of Diagnostic Radiology, National Cancer Center Hospital, Tokyo, Japan; †Division of Hematologic Oncology, National Cancer Center Hospital, Tokyo, Japan; ‖Division of Pathology, National Cancer Center Hospital, Tokyo, Japan; †Department of Radiology, University of British Colombia and Vancouver Hospital and Health Sciences Centre, Canada; and ‡Department of Medical Physics, Osaka University Graduate School of Medicine, Osaka, Japan.

Reprints: Ukihide Tateishi, MD, PhD, Division of Diagnostic Radiology, National Cancer Center Hospital, Tsukiji, Chuo-Ku, 104-0045, Tokyo, Japan (E-mail: utateish@ncc.go.jp).

chemistries, and bone marrow aspiration. Clinical features, International Prognostic Index (IPI) scores,[28] and clinical stages were recorded.

Histopathologic confirmation of definite diagnosis in all patients was obtained by core needle or excisional biopsy. Biopsy sites included the anterior mediastinal mass in 33 patients, cervical lymph node in 25, and both in 8. Fifty-four patients (82%) were confirmed by the initial biopsy alone and the other 12 patients (18%) underwent subsequent biopsy because of insufficient initial sample.

Immunohistochemical studies to determine histologic subtype were performed in all biopsy specimens. According to a recent classification system[29] devised by the World Health Organization (WHO), 29 patients had classic HL, 21 had Med-DLBCL, and 16 had T-LBL. The presence or absence of nodal involvement in each suspected lesion was determined at biopsy in 36 sites and the remaining with a combination of imaging findings and clinical follow-up. Extranodal involvement in the abdomen confirmed by endoscopic, needle, or excisional biopsy included stomach (n = 1), kidney (n = 1), and spleen (n = 1).

The histopathologic findings were reviewed by an experienced pathologist who was one of the authors. Chart, review of histologic specimens, and patient file reviews were

TABLE 1. CT Findings in Patients With PML and the Other Common Nonlymphomatous Diseases

Disease	PML	Thymoma	Thymic cancer	GCT	SCLC
No. of patients	66	19	26	13	12
Male/female	45/21	8/11	18/8	13/0	9/3
Age (mean ± SD) (y)	37.0 ± 14.9	55.6 ± 12.2	58.4 ± 11.6	26.5 ± 5.4	64.5 ± 8.3
Age range (y)	13–84	29–74	24–74	18–38	51–78
Tumor margins*					
Well-defined margins	39 (59)	18 (95)	22 (85)	1 (8)	0
Ill-defined margins	27 (41)	1 (5)	4 (15)	12 (92)	12 (100)
Size of main mass (mean ± SD) [cm]	8.9 ± 3.0	5.2 ± 1.8	7.2 ± 2.4	11.6 ± 2.2	5.6 ± 1.6
Presence of surface lobulation	31 (47)	7 (37)	19 (73)	0	12 (100)
Presence of vascular encasement	21 (32)	1 (5)	20 (77)	7 (54)	2 (17)
Presence of chest wall invasion	10 (15)	0	13 (50)	3 (23)	0
Presence of cutaneous involvement	3 (5)	0	0	0	0
Presence of lung invasion†	11 (17)	0	0	0	NA
Presence of nodal involvement					
Cervical lymph node (superficial)†	10 (15)	0	0	0	0
Cervical lymph node (deep)§	18 (27)	0	0	0	0
Submandibular lymph node	1 (2)	0	0	0	0
Submental lymph node	2 (3)	0	0	0	0
Parotid lymph node	2 (3)	0	0	0	0
Supraclavicular lymph node	11 (17)	0	0	0	10 (83)
Mediastinal lymph node§	50 (76)	0	12 (46)	1 (8)	12 (100)
Hilar lymph node†	12 (15)	0	2 (8)	2 (15)	12 (100)
Axillary lymph node§	12 (15)	0	0	0	0
Celiac lymph node	4 (6)	0	0	0	0
Paraaortic lymph node§	12 (15)	0	0	0	0
Mesenteric lymph node	2 (3)	0	0	0	0
Iliac lymph node	1 (2)	0	0	0	0
Inguinal lymph node*	5 (8)	0	0	0	0
Presence of pleural effusion	26 (39)	2 (10)	8 (31)	5 (38)	5 (42)
Presence of pericardial effusion*	24 (36)	0	4 (15)	3 (23)	3 (25)
Hepatomegaly	2 (3)	0	0	0	0
Splenomegaly§	13 (20)	0	0	0	0
Presence of metastasis					
Lung metastasis§	0	0	5 (19)	7 (54)	3 (25)
Liver metastasis§	0	0	1 (4)	1 (8)	5 (42)
Splenic metastasis	1 (2)	0	0	1 (8)	0
Adrenal metastasis	0	0	0	0	1 (8)
Presence of pleural dissemination	13 (20)	2 (10)	6 (23)	2 (15)	2 (17)

Data in parentheses are percentages.
*$P < 0.05$, †$P < 0.01$, §$P < 0.0001$.
PML, Primary mediastinal lymphoma; GCT, germ cell tumor; SCLC, small cell lung cancer; NA, not applicable.

conducted independently of the CT analysis. All patients with PML underwent treatment, which included chemotherapy and radiotherapy for HL, chemotherapy and/or radiotherapy for Med-DLBCL, and chemotherapy and radiotherapy for T-LBL. Follow-up documentation was reviewed for any evidence of misdiagnosis at any repeat imaging examinations, biopsies, laboratory tests, or on the basis of ongoing symptoms and signs. At the time of this review, there has been no case of initial misdiagnosis.

To determine whether or not CT findings can accurately differentiate PML from the other common nonlymphomatous diseases, a total of 70 patients including thymoma (n = 19), thymic cancer (n = 26), germ cell tumor (n = 13), and small cell lung cancer (n = 12) were also enrolled in this study (Table 1). Selective criteria of these cases were 1) main anterior mediastinal mass identified on CT at presentation, 2) definite diagnosis confirmed by the pathologic observation of main mass, and 3) CT examination performed prior to therapy. These cases were selected from the radiologic files of our institute, and clinical details and follow-up information were also reviewed retrospectively by a radiologist who was one of the authors.

Imaging Studies

CT was performed on a 4-row multidetector scanner (Aquilion V-detector, Toshiba Medical Systems, Tokyo, Japan). The images were obtained at 240–260 mAs, 120 kV, 7-mm collimation sections overlapped in 3.5-mm intervals from the level of the orbit to the proximal femur, and a pitch of 10.5. All patients received 150 mL of nonionic intravenously administered contrast material at 3.0 mL/s with a power injector (Autoenhance A-250; Nemoto-kyorindo, Tokyo, Japan) after a 60-second delay. All patients also received 200–300 mL of sterile water orally prior to CT examination.

Image Analysis

Two experienced radiologists who had knowledge of the diagnosis of primary mediastinal lymphoma but were blinded to histologic subtypes and any clinical information other than patient age and sex independently reviewed the CT images on hard copies. The 2 readers analyzed the images for tumor size, tumor margins (well defined or ill defined), and presence of surface lobulation. The presence of a single mass or confluent lymphadenopathy in the anterior mediastinum was analyzed as representing the primary tumor mass and the measurement based on the short axis diameter. The contrast enhancement of the primary lesions was compared with that of normal muscle. The tumor was considered homogeneous if it enhanced to the same degree throughout. The patterns of local invasion were recorded: encasement of vascular structures, chest wall invasion, cutaneous involvement, and lung invasion. Vascular encasement was considered present when there was circumferential narrowing or complete obstruction of the superior vena cava or brachiocephalic vein by tumor. The presence or absence of lymphadenopathy, pleural effusion, pericardial effusion, and other organ involvement were also evaluated. Nodes were considered enlarged when their short axis diameter was greater than 10 mm. Hepatomegaly and splenomegaly were considered present when the liver and spleen were greater than 13 cm and 12 cm in longitudinal diameter at the midclavicular line, respectively.[29]

Statistical Analysis

Kruskal-Wallis test was used to compare the clinical variables and all CT findings in the 3 histologic subtypes of PML and the other common nonlymphomatous disorders. Student t test was used to compare mean tumor size of the mediastinal mass. The interobserver variation in the interpretation of all CT findings was analyzed using Kappa statistics. The interobserver agreement was classified as follows: poor, k = 0–0.20; fair, k = 0.21–0.40; moderate, k = 0.41–0.60; good, k = 0.61–0.80; and excellent, k = 0.81–1.00. The relationship between CT findings and the likelihood of the histologic subtypes was tested for independent predictors using multiple logistic regression analysis, which determined the odds ratio after adjusting for the other variables examined. All P values less than 0.05 were considered to indicate a statistically significant difference.

RESULTS

Statistically significant CT findings which have possibility of discriminating PML from the other common nonlymphomatous diseases were tumor margins, the presence of lung invasion, involvement of various lymph nodes including cervical (superficial and deep), mediastinal, hilar, axillary, paraaortic, inguinal lymph nodes, the presence of pericardial effusion, splenomegaly, the presence of lung metastasis, and liver metastasis. Patient demographics are listed in Table 2. Patients with Med-DLBCL were slightly older (mean age ± SD: 46.4 ± 18.0) than those with HL (34.6 ± 10.7) or T-LBL (30.6 ± 12.4) ($P < 0.01$). No other significant difference was seen in patient demographics between the 3 subtypes of PML.

TABLE 2. Demographic and Clinical Data in Patients With PML

Disease	HL	Med-DLBCL	T-LBL
No. of patients	29 (44)	21 (32)	16 (24)
Age (mean ± SD) (y)	34.6 ± 10.7	46.4 ± 18.0	30.6 ± 12.4*
Age range (y)	19–57	23–84	13–64
Gender			
Male	17 (59)	15 (71)	13 (81)
Female	12 (41)	6 (29)	3 (19)
IPI score			
Low	23 (79)	12 (57)	6 (38)
Low–intermediate	5 (17)	2 (10)	8 (50)
Intermediate–high	0	5 (24)	1 (6)
High	1 (3)	2 (10)	1 (6)
Clinical stage			
I	7 (24)	11 (52)	2 (13)
II	15 (52)	3 (14)	2 (13)
III	4 (14)	1 (5)	3 (19)
IV	3 (10)	6 (29)	9 (56)

Data in parentheses are percentages. Significant difference is found in the mean age between Med-DLBCL and T-LBL (*$P < 0.01$).

HL, Hodgkin lymphoma; Med-DLBCL, mediastinal diffuse large B-cell lymphoma; T-LBL, T-cell lymphoblastic lymphoma; IPI, International Prognostic Index.

Enlargement of cervical lymph nodes was seen more commonly in T-LBL (10 of 16 patients, 63%) than in HL (9 of 29 patients, 31%) ($P < 0.05$) and was not present in any of the patients with Med-DLBCL (Fig. 1). Of the cervical nodes, deep cervical nodes were affected more frequently in HL (31% [9 of 29 patients]) or T-LBL (56% [9 of 16 patients]) than those in Med-DLBCL (no patients). Superficial nodes were also involved more often in T-LBL (44% [7 of 16 patients]) than in HL (10% [3 of 29 patients], $P < 0.05$). Involvement of supraclavicular lymph nodes was seen more frequently in T-LBL (50% [8 of 16 patients]) compared with that in HL (10% [3 of 29 patients], $P < 0.01$). Submandibular, submental, and parotid lymph nodes were involved only in T-LBL (19% [3 of 16 patients]).

No significant difference was found in the size and margin of the primary lesion between the three histologic subtypes (Table 3). Surface lobulation (Fig. 2) was more common in HL (69% [20 of 29 patients]) than in both Med-DLBCL (33% [7 of 21 patients]) and T-LBL (25% [4 of 16 patients]) ($P < 0.01$, Table 3). The prevalence of vascular involvement including encasement of superior vena cava and left brachiocephalic vein in Med-DLBCL (62% [13 of 21 patients], $P < 0.0001$) and T-LBL (38% [6 of 16 patients],

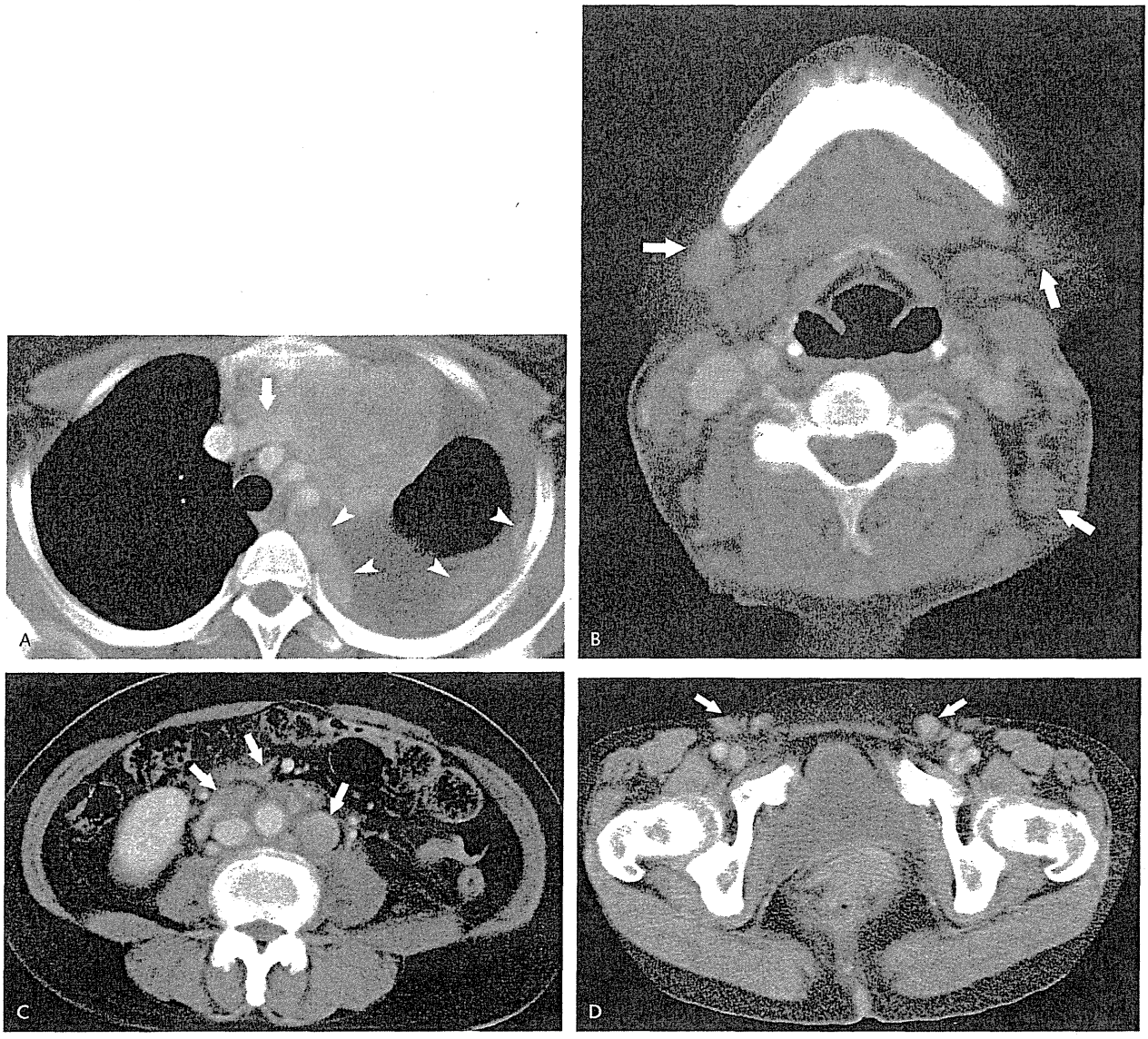

FIGURE 1. Thirty-two-year-old man with T-cell lymphoblastic lymphoma (T-LBL). A, Image obtained at the level of the great vessels shows a large anterior mediastinal mass with encasement and stenosis of the left brachiocephalic vein (arrow). Also noted are left pleural effusion and soft-tissue masses (arrowheads) in the left pleura suggestive of pleural dissemination. B, Image at the level of the upper neck demonstrates several enlarged of cervical nodes (arrows). C, Image at the level of the lower pole of the right kidney shows multiple enlarged paraaortic and mesenteric nodes. D, Image at the level of the inguinal region shows enlarged inguinal lymph nodes (arrows).

TABLE 3. CT Findings in Patients With PML

Disease	HL	Med-DLBCL	T-LBL
No. of patients	29 (44)	21 (32)	16 (24)
Tumor margins			
Well-defined margins	19 (66)	10 (48)	10 (62)
Ill-defined margins	10 (34)	11 (52)	6 (38)
Size of main mass (mean ± SD) (cm)	9.7 ± 2.8	9.7 ± 2.5	10.2 ± 3.3
Presence of surface lobulation*	20 (69)	7 (33)	4 (25)
Presence of vasular encasement†	2 (7)	13 (62)	6 (38)
Presence of chest wall invasion	4 (14)	4 (19)	2 (13)
Presence of cutaneous involvement	0	2 (10)	1 (6)
Presence of lung invasion	8 (28)	2 (10)	1 (6)
Presence of nodal involvement			
Cervical lymph node (superficial)*	3 (10)	0	7 (44)
Cervical lymph node (deep)†	9 (31)	0	9 (56)
Submandibular lymph node	0	0	1 (6)
Submental lymph node‡	0	0	2 (13)
Parotid lymph node‡	0	0	2 (13)
Supraclavicular lymph node§	3 (10)	0	8 (50)
Mediastinal lymph node†	28 (97)	14 (67)	8 (50)
Hilar lymph node‡	10 (34)	1 (5)	1 (6)
Axillary lymph node†	4 (14)	0	8 (50)
Celiac lymph node	3 (10)	0	1 (6)
Paraaortic lymph node*	6 (21)	0	6 (38)
Mesenteric lymph node‡	0	0	2 (13)
Iliac lymph node	0	0	1 (6)
Inguinal lymph node†	0	0	5 (31)
Presence of pleural effusion‡	6 (21)	12 (57)	8 (50)
Presence of pericardial effusion‡	5 (17)	10 (48)	9 (56)
Hepatomegaly‡	0	0	2 (13)
Splenomegaly†	1 (3)	1 (5)	11 (63)

Date in parentheses are percentages.
*$P < 0.01$, †$P < 0.001$, ‡$P < 0.05$, §$P < 0.0001$.
HL, Hodgkin lymphoma; Med-DLBCL, mediastinal diffuse large B-cell lymphoma; T-LBL, T-cell lymphoblastic lymphoma.

$P < 0.05$) was greater than that in HL (7% [2 of 29 patients], Figs. 1 and 2). Complete obstruction of the superior vena cava (SVC syndrome) was present in one of 29 patients with HL (3%), 4 of 21 with Med-DLBCL (19%), and 2 of 16 patients with T-LBL (13%). Forty-one of 66 tumors (62%) showed heterogeneous enhancement on CT, with no significant difference between 3 histologic subtypes.

Enlarged mediastinal nodes distinct from the primary lesion were present more commonly in HL (97% [28 of 29 patients]) than in Med-DLBCL (67% [14 of 21 patients], $P < 0.05$) and T-LBL (50% [8 of 16 patients], $P < 0.0001$, Table 3). Involvement of hilar nodes (Fig. 3) was significantly more common in HL (34% [10 of 29 patients]) compared with Med-DLBCL (5% [1 of 21 patients], $P < 0.05$) and T-LBL (6% [1 of 16 patients], $P < 0.05$). Involvement of bilateral axillary nodes was significantly more common in T-LBL (50% [8 of 16 patients]) than in Med-DLBCL (no patients, $P < 0.0001$) and HL (14% [4 of 29 patients], $P < 0.05$). Pleural effusion (Figs. 1 and 2) was significantly more common in Med-DLBCL (57% [12 of 21 patients], $P < 0.01$) or T-LBL (50% [8 of 16 patients], $P < 0.05$) than in HL (21% [6 of 29 patients]). Of the patients with pleural effusion, tumor cells were confirmed by cytology in 6 of 6 patients with HL (100%), in 5 of 12 with Med-DLBCL (42%), and in 2 of 8 patients (25%) with T-LBL. Pericardial effusion (Fig. 4) was significantly more common in T-LBL (56% [9 of 16 patients], $P < 0.01$) and Med-DLBCL (48% [10 of 21 patients], $P < 0.05$) than in HL (17% [5 of 29 patients]).

Statistically significant CT findings in the abdomen included splenomegaly, and involvement of paraaortic, mesenteric, and inguinal lymph nodes (Table 3). Splenomegaly was present more commonly in T-LBL (63% [11 of 16 patients]) than in HL (3% [1 of 29 patients], $P < 0.0001$) and Med-DLBCL (5% [1 of 21 patients], $P < 0.0001$). Involvement of abdominal paraaortic nodes (Fig. 1) was more common in T-LBL (38% [6 of 16 patients], $P < 0.01$) or HL (21% [6 of 29 patients], $P < 0.05$) than in Med-DLBCL (no patients). Involvement of inguinal (31% [5 of 16 patients]) or mesenteric lymph nodes (13% [2 of 16 patients]) was found only in T-LBL (Fig. 1). Extranodal lesions in the abdomen were proved pathologically in 3 patients. Two patients with Med-DLBCL had mass lesions in the stomach and kidney, and the

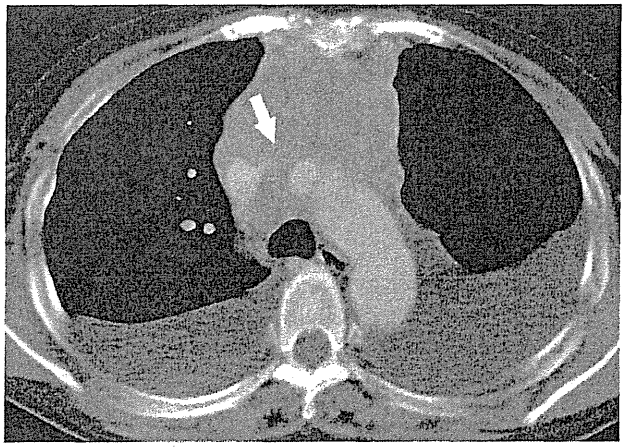

FIGURE 2. Thirty-two-year-old man with mediastinal diffuse large B-cell lymphoma (Med-DLBCL). CT image at the level of the aortic arch demonstrates a large, homogeneous enhancing anterior mediastinal mass without surface lobulation that compresses the left brachiocephalic vein (arrow). Also noted are bilateral pleural effusions.

other patient with HL had focal splenic mass. None of patients with T-LBL had evidence of extranodal involvement on the abdominal CT images.

There was excellent interobserver agreement for CT findings, including morphology and extent of main mass, enhancement pattern, lymph node enlargement, the presence of pleural effusion, pericardial effusion, hepatomegaly, and splenomegaly (Kappa = 0.82–1.00). Multiple logistic regression analysis demonstrated that the CT finding independently associated with increased likelihood of HL was surface lobulation ($P < 0.01$; Table 4), the absence of vascular involvement ($P < 0.01$), or pleural effusion ($P < 0.05$). The presence of vascular involvement was independently associated with increased likelihood of Med-DLBCL ($P < 0.001$, Table 4). In addition, CT findings including the presence of cervical lymph nodes or inguinal lymph nodes ($P < 0.001$; Table 4), the presence of pericardial effusion ($P < 0.05$), and the absence of surface lobulation ($P < 0.05$) were significantly associated with the likelihood of T-LBL.

DISCUSSION

Several studies have described the CT manifestations of PML. The typical presentation consists of an anterior mediastinal mass often associated with enlarged nodes in the middle and posterior mediastinum, and hila.[13–24] The mediastinal mass may involve vascular structures, pericardium, heart, pleura, lung, and chest wall on CT.[13–27] PML often affects extrathoracic sites at the time of diagnosis, particularly abdomen, head, and neck.[28,29]

The current study demonstrates that the different subtypes of PML often have characteristic manifestations that allow their distinction on CT. HL is characterized by the presence of a discrete anterior superior mediastinal mass with surface lobulation. Surface lobulation was present in 69% of patients with HL compared with 33% of patients with

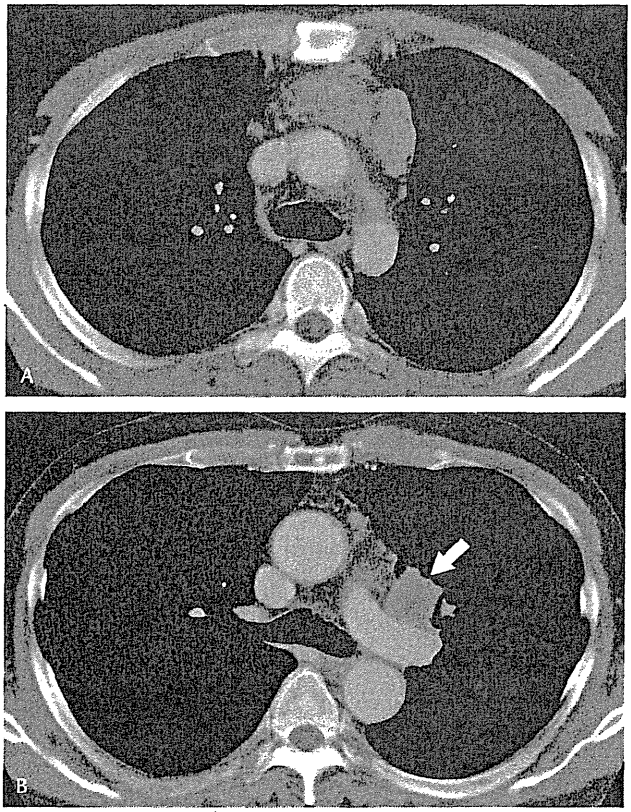

FIGURE 3. Twenty-nine-year-old man with Hodgkin's lymphoma (HL). A, Image at the level of the aortopulmonary window shows anterior mediastinal mass with surface lobulation and heterogeneous enhancement. B, Section obtained at the level of the carina demonstrates enlarged left hilar nodes (arrow).

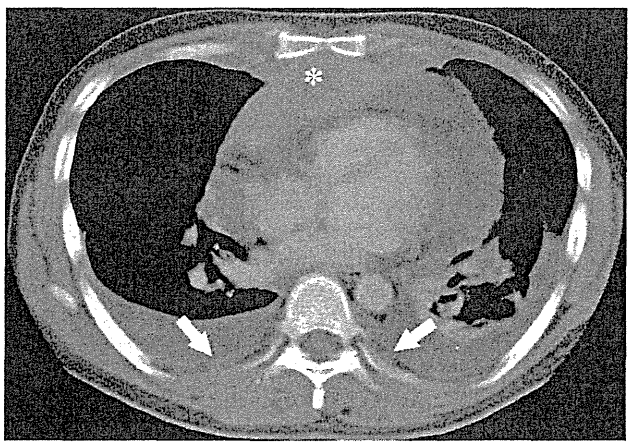

FIGURE 4. Thirty-two-year-old man with T-LBL. Image obtained at the level of the right ventricle shows a large anterior mediastinal mass (asterisk) with marked pericardial effusion. Also noted are pleural effusion bilaterally and soft-tissue nodular dissemination (arrows) in the pleura.

TABLE 4. Relationship Between CT Findings and the Likelihood of the PML Hisologic Subtypes

	CT findings	OR	95% CI	*P*
HL	Presence of surface lobulation	11.9	2.5–56.0	<0.01
	Absence of vascular involvement	11.8	1.9–71.9	<0.01
	Absence of pleural effusion	6.6	1.3–33.2	<0.05
Med-DLBCL	Presence of vascular involvement	7.5	2.3–24.1	<0.001
T-LBL	Presence of cervical or inguinal lymph node	33.9	4.7–244.6	<0.001
	Presence of pericardial effusion	11.4	1.7–77.6	<0.05
	Absence of surface lobulation	7.0	1.2–43.1	<0.05

HL, Hodgkin lymphoma; Med-DLBCL, mediastinal diffuse large B-cell lymphoma; T-LBL, T-cell lymphoblastic lymphoma; OR, odds ratio; CI, confidence interval.

Med-DLBCL and 25% with T-LBL. The surface lobulation of the main mass is due to involvement of multiple nodes and coalescence, a finding previously noted in HL at CT.[13,14] Enlarged nodes elsewhere in the mediastinum were seen in 97% of patients with HL in the current study and less commonly in the other subtypes.

Masses typically exhibit homogeneous soft-tissue attenuation, while large tumors may demonstrate heterogeneity with complex low attenuation representing necrosis, hemorrhage, and cystic degeneration.[20] Sixty-two percent of our cases showed heterogeneous enhancement on CT, with no significant difference between 3 histologic subtypes.

Med-DLBCL typically is initially confined to the mediastinum and contiguous nodal areas without showing extrathoracic disease at presentation.[3,5] Med-DLBCL may present with hematogenous spread to parenchymal organs such as kidney, liver, ovary, adrenal gland, gastrointestinal tract, and central nervous system during disease progression or at recurrence.[3] Extranodal involvement was found on the initial CT assessment and was confirmed by biopsy in 2 of our Med-DLBCL cases, whereas extrathoracic nodal involvement was not found in any of our patients with Med-DLBCL. Some observers consider that Med-DLBCL is a pathologic and clinical entity of non-Hodgkin lymphoma derived from mature thymic B-cells recognized by previous immunophenotypic studies.[30,31] However, the histogenesis is controversial, because Med-DLBCL can result in diffuse nodal involvement in advanced stages.[3,5]

Extrathoracic lymphadenopathy including superficial cervical, supraclavicular, submandibular, submental, parotid, mesenteric, and inguinal nodes, was seen in the majority of patients with T-cell lymphoblastic lymphoma in the present study. Another common finding in T-cell lymphoblastic lymphoma in the current study was the presence of splenomegaly, which was seen in 63% of cases. HL often involved axial lymph nodes including cervical, mediastinal, axillary, and paraaortic regions. However, none of the patients with HL in the current study had submandibular, submental, parotid, mesenteric, and inguinal lymphadenopathy. The low prevalence of nonaxial lymphadenopathy in HL had been recognized in previous studies.[29,32]

Diagnosis of subtypes in all patients was established by core or excisional biopsy in all cases. The ability to classify PML in small samples has improved considerably in the last few years because of progress of pathologic criteria and immunocytochemistry.[33,34] HL is characterized by a large inflammatory cell reaction within a fibrotic stroma, and the diagnosis is established by the identification of Hodgkin and Reed-Sternberg (HRS) cells.[2] Med-DLBCL is composed mainly of large clear cells within a characteristic background of compartmentalized fibrosis.[5] T-LBL is composed of a homogeneous population of immature lymphoblastic cells cytologically similar to acute lymphoblastic leukemia.[8–10] Biopsy provides sufficient information for the diagnosis of and subsequent therapeutic decision to treat patients with PML, because the definitive selection of therapeutic regimen is needed.

Our study has several limitations. It is retrospective and includes a relatively small number of patients. In clinical practice, the differential diagnosis would need to include a variety of other conditions that can present with an anterior mediastinal mass. However, we believe that the study demonstrates that the various histologic subtypes of PML have features on CT that allow distinction in the majority of cases. The anatomic distribution of the disease varies among the histologic subtypes of HL. Mediastinal involvement is most frequently seen in the nodular sclerosis HL subtype, while splenic involvement is more common in the mixed cellularity HL subtype.[29]

In conclusion, we found that CT findings often allowed differentiation of the various subtypes of PML. HL commonly presents as a mediastinal mass with surface lobulation and involves cervical, mediastinal, hilar, and paraortic nodes. Med-DLBCL demonstrates mediastinal mass without surface lobulation, often associated with vascular involvement, and pleural or pericardial effusion. T-LBL is characterized by mass without surface lobulation involving vascular structures often associated with pleural or pericardial effusion, by systemic nodal involvement including cervical, axillary, paraaortic, mesenteric, and inguinal, and by hepatomegaly and splenomegaly.

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Original Article

Reproducibility of the diagnosis of small adenocarcinoma of the lung and usefulness of an educational program for the diagnostic criteria

Masayuki Noguchi,[1] Yuko Minami,[1] Tatsuo Iijima[1] and Yoshihiro Matsuno[2]

[1]*Department of Pathology, Institute of Basic Medical Sciences, Graduate School of Comprehensive Human Sciences, University of Tsukuba, Ibaraki and* [2]*Pathology Division, National Cancer Center Hospital, Tokyo, Japan*

Using 32 small adenocarcinomas of the lung including bronchioloalveolar carcinoma (BAC), the reproducibility of diagnosis by the modified diagnostic criteria for small adenocarcinoma (Cancer 75; 2844, 1995) and the effectiveness of an educational program for 27 volunteer general pathologists were examined. The average coincidence rate of the diagnosis before and after the program was 42.4% and 56.6%, respectively. The coincidence rate after the program was significantly higher than that before the program ($P < 0.05$). In contrast, the average coincidence rate of six lung cancer specialists was 71.4%, and this was significantly higher than that for general pathologists after the program ($P < 0.05$). When the cases were divided into two groups (*in situ* adenocarcinoma (BAC and BAC with alveolar collapse) and early invasive adenocarcinoma), the average coincidence rate for the general pathologists after the program increased to 85.3%, which was significantly higher than that before the program (80.3%; $P < 0.05$). The rate for the specialists was 89%, which was higher than that for the general pathologists after the program but not significantly so. This trial was thought to provide a theoretical background for the histological diagnosis of peripheral type adenocarcinoma of the lung and to justify the existing diagnostic criteria.

Key words: diagnostic criteria, lung adenocarcinoma, reproducibility

Bronchioloalveolar carcinoma (BAC) is a revised entity defined by the World Health Organization (WHO) classification of histological typing of lung and pleural tumors.[1,2] It is an adenocarcinoma with a pure bronchioloalveolar growth pattern and no evidence of stromal, vascular or pleural invasion. Histologically, it is subdivided into three subtypes: non-mucinous, mucinous and mixed mucinous and non-mucinous. There may be some increase in the thickness of the alveolar septa and a central or subpleural area of alveolar collapse with increased elasticity of the fibers, but a diagnosis of BAC requires exclusion of an invasive component, such as vascular invasion or pleural invasion.

Clinicopathologically, the concept of BAC is very important because BAC is an *in situ* adenocarcinoma and it has a very favorable prognosis. Noguchi *et al.* reported a unique criterion for small peripheral type adenocarcinoma.[3] They stressed that small early adenocarcinomas can be divided into two groups: those with replacement growth of alveolar structure and those with non-replacement growth. The former group can be classified further into three subtypes: localized bronchioloalveolar carcinoma (LBAC; type A); LBAC with alveolar collapse (type B); and LBAC with a focus of fibroblastic proliferation (type C). The latter group can also be classified further into three subtypes: poorly differentiated adenocarcinoma (type D); tubular adenocarcinoma (type E); and true papillary adenocarcinoma (type F).[4] Type A adenocarcinoma (LBAC) and type B adenocarcinoma (LBAC with alveolar collapse) align with BAC in the WHO classification; they show no lymph node metastasis and have a favorable prognosis (100% 5 year survival rate). However, 28% of type C cases having replacement growth as type A and B tumors are associated with lymph node metastasis and the 5 year survival rate of patients is approximately 75%. In contrast, type A and B tumors show significantly lower overall frequencies of allelic loss and activated expression of matrix metalloproteinase 2 (MMP-2) than type C tumors.[5,6] These findings indicate that types A and B tumors are *in situ* peripheral-type adenocarcinoma, whereas type C tumors appear to represent an advanced stage of types A and B tumors.

With recent advances in the methodology of radiological diagnosis, computed tomography (CT) has become very effective for diagnosis of BAC and non-BAC. Preoperative CT

Correspondence: Masayuki Noguchi, MD, Department of Pathology, Institute of Basic Medical Sciences, Graduate School of Comprehensive Human Sciences, University of Tsukuba, Japan.
Email: nmasayuk@md.tsukuba.ac.jp

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