affecting both ORR and PFS, while other factors as listed in IPI were not unfavorable. However, when we compared the median PFS of the low/low-intermediate subgroup with that of the high-intermediate/high subgroup, there was a significant difference, suggesting that IPI is an important predictor of efficacy of rituximab monotherapy. Tsai et al. reported that rituximab has significant activity in intermediate-grade B-cell lymphoma that has relapsed after AHSCT [30]. Similar results were obtained in the present study.

The trough levels and AUCs of rituximab were significantly higher in the responders than in the non-responders. Berinstein et al. reported, based on their analyses of the pivotal study in the USA, that there was a correlation between response and serum rituximab level [31]. In our previous study of indolent B-cell lymphoma, patients with higher serum rituximab levels had longer PFS [9]. These results suggest that PK-guided treatment may be worthy of future investigations to further improve the efficacy of rituximab.

In conclusion, rituximab monotherapy is effective in relapsed or refractory patients with aggressive B-cell lymphoma with acceptable toxicity. Several pretreatment variables, including refractoriness to prior chemotherapy, elevated LDH and higher IPI score, and serum rituximab level are useful for predicting the efficacy of rituximab. Further investigations on rituximab-incorporating combination chemotherapy are warranted for improving the outcome in untreated and relapsed or refractory patients with B-cell lymphoma.

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HEMATOLOGY

Primary Mediastinal Large B-Cell Lymphoma: A Single-Institution Clinical Study in Japan

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Abstract

Several clinicopathologic studies of primary mediastinal large B-cell lymphoma (Med-DLBCL) have been reported from Western countries; however, only a few series of at most 10 cases are available in Japan. To further clarify the Med-DLBCL occurring in Japan, we analyzed the clinical features of 28 patients with Med-DLBCL diagnoses who were treated at the National Cancer Center Hospital between 1982 and 2002. The median age was 37 years (range, 18-80 years). The ages of 16 male patients ranged widely from 18 to 80 years, whereas the 12 female patients appeared to show a single age peak at 20 to 40 years. Only 13 patients (46%) achieved a complete response with initial treatments, mostly by CHOP-like regimens (cyclophosphamide, doxorubicin, vincristine [Oncovin], and prednisolone) followed by radiotherapy. The estimated 3-year overall and failure-free survival rates were 32% and 33%, respectively, indicating the relatively unfavorable prognosis of the patients in our series. The following factors were found to be significantly associated with shortened survival prospects: age >60 years, serum lactate dehydrogenase level greater than normal, performance status >1, and presence of bulky mediastinal mass. In conclusion, the clinical features of Japanese patients with Med-DLBCL may be different from those with the disease in Western countries. Because this investigation was a single-institution study with a limited number of patients, however, multicenter confirmatory studies are needed.
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Key words: Primary mediastinal large B-cell lymphoma; Japan; Geographical variation; Treatment; Prognostic factor

1. Introduction

Primary mediastinal large B-cell lymphoma (Med-DLBCL) is a diffuse large B-cell lymphoma (DLBCL) that arises from thymic B-cells, and it has been recognized as a distinct entity in the revised European-American lymphoma classification [1] and in the World Health Organization (WHO) classification [2]. According to the reports from Western countries, patients with Med-DLBCL are typically young, of slight to moderate female preponderance compared with patients with other DLBCL, and with an anterior and superior mediastinal mass that frequently causes superior vena cava syndrome (SVCS), cough, chest pain, and hoarseness [2-5]. Many case series have been reported from Western countries [3-13], although only a few series of at most 10 cases are available from Japan [14-16].

Recent investigations have revealed that the molecular signature of Med-DLBCL differs from that of other types of DLBCL and shares features with Hodgkin's lymphoma [17-19]. Considering the low incidence of Hodgkin's lymphoma in Japan and other East Asian countries [20], the incidence and clinical features of patients with Med-DLBCL in Japan may also be different from those of patients in Western countries. To further clarify the features of patients with Med-DLBCL in Japan, we analyzed the clinical features of 28 patients with Med-DLBCL diagnoses who were treated in the past 20 years at our institution. To our knowledge, this is the largest case series of Med-DLBCL in Asia.

2. Patients and Methods

2.1. Patients

The cases of 28 patients with Med-DLBCL diagnoses and who were treated at the National Cancer Center Hospital

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between September 1982 and September 2002 were analyzed. The diagnostic criteria of Med-DLBCL in the present study were (1) the presence of a mediastinal mass of at least 5 cm in the largest diameter and the absence of other larger masses in the mediastinum and (2) a histopathologic diagnosis of DLBCL, which is a diagnostic criterion of Med-DLBCL proposed by the Nebraska Lymphoma Study Group [13]. Clinical data were obtained from medical charts and included age, sex, clinical stage, serum lactate dehydrogenase (LDH) level, performance status (PS), any bulky disease, any pleural and pericardial effusions, site of involvement, number of extranodal sites, International Prognostic Index (IPI) [21], and treatment. Clinical stage was determined according to the revised American Joint Committee on Cancer staging system for lymphoid neoplasms [22], which is a modified version of the Ann Arbor staging classification [23]. In this study, bulky disease was defined as a mass greater than 10 cm in the largest diameter as detected by computed tomography. PS was determined according to the Eastern Cooperative Oncology Group scale [24].

2.2. Histopathologic Review

Diagnostic tissue materials were obtained by computed tomography–guided percutaneous needle biopsy in 18 patients (64%), open-thoracic biopsy or surgical resection in 7 patients (25%), and superficial lymph node biopsy in 3 patients (11%). To ensure the diagnosis of Med-DLBCL, we performed in all cases a histopathologic review on hematoxylin-eosin–stained sections as well as paraffin-section immunostains. Primary antibodies used for immunohistochemistry analyses included anti-CD3 (PS1; Novocastra Laboratories, Newcastle upon Tyne, UK) and anti-CD20 (L26; DakoCytomation, Glostrup, Denmark). Anti-CD30 antibody (BerH2; DakoCytomation) was also used in selected cases. Tumor phenotype was judged as B-cell when the tumor cells were stained positively for CD20.

2.3. Assessment of Response and Survival

Complete response (CR) was defined as a disappearance of all clinical evidence of lymphoma that lasted for a minimum of 4 weeks. Unconfirmed or uncertain CR (CRu) was defined as a greater than 50% decrease in the sum of the products of the greatest perpendicular diameters (SPD) of all measurable lesions with no clinical evidence of disease lasting for 3 months or longer without treatment, in accord with Cotswolds' response criteria for Hodgkin's lymphoma [25]. In this study, CRu was included in the category of CR. Partial response was defined as a greater than 50% decrease in the SPD of all measurable lesions lasting for at least 4 weeks. No change was defined as either a decrease of less than 50% or an increase of less than 25% in the SPD of any previously identified measurable lesions. Progressive disease was defined as any increase of greater than 25% in the SPD of any measurable lesions or the appearance of a new lesion.

Overall survival (OS) was measured from the beginning of treatment until death from any cause, and surviving patients were censored at the last contact date. Failure-free survival was defined as the time from the beginning of treatment until the first recognition of disease progression, change of chemotherapy regimen, or death from any cause. Disease-free survival for patients who achieved a CR or CRu was defined as the time from the day of achieving a CR or CRu until relapse or death related to therapy.

2.4. Initial Treatments

Twenty-two (79%) of the 28 patients received chemotherapy initially. Surgical resection was performed in 4 patients (14%), and all of them received chemotherapy after diagnosis. Thus, these 26 patients (93%) were categorized as the chemotherapy group in initial treatments. The remaining 2 patients (7%) received radiotherapy of 40 Gy and 46.8 Gy, which was followed by combination chemotherapy. Of the 26 patients who received chemotherapy as initial treatments, 18 (69%) received CHOP-like regimens (cyclophosphamide [CPA], doxorubicin [DOX], vincristine [VCR], and prednisolone [PSL]). Seventeen of the 18 patients received standard-dose CHOP therapy, and the remaining patient received VEPA therapy (VCR, CPA, PSL, and DOX) [26]. Two patients (8%) were treated with a second-generation regimen (LSG4) consisting of VEPA-B (VEPA plus bleomycin [BLM]), M-FEPA, (methotrexate [MTX], vindesine [VDS], CPA, PSL, and DOX), and VEPP-B (VCR, etoposide [ETP], procarbazine [PCZ], PSL, and BLM) [27]. Four patients (15%) received a dose-intensified third-generation regimen (LSG9) consisting of VEPA-B, M-FEPA, and FEPP-AB (VDS, ETP, PCZ, PSL, DOX, and BLM) [28], and 2 patients (8%) were treated with other chemotherapy regimens.

2.5. Statistical Analysis

To compare the mean ages of male and female patients, we performed a 2-sample Student t test with the Welch correction after the confirmation of each variance and the histograms of the 2 groups. All survival curves were evaluated by means of the method of Kaplan and Meier. The log-rank test was used in univariate analyses to identify factors affecting OS. The following factors were analyzed: age, clinical stage, serum LDH level, PS, number of extranodal lesions, bulky disease, pleural effusion, pericardial effusion, initial chemotherapy regimen, additional radiotherapy, and IPI. P values of .05 or less were considered indicative of statistical significance.

3. Results

3.1. Histopathologic Review

Histopathologic review confirmed the filed diagnosis of DLBCL in all cases. However, there were 2 cases in the 1980s in which an incorrect diagnosis was given at the time of biopsy. One was called a thymoma, and the other was called a germ cell tumor.

In all cases, there were aggregations of atypical large lymphoid cells to some extent. Occasionally, they formed sheet-like nests compartmentalized by sclerotic fibrous stroma, mimicking epithelial tumors. The extent of sclerosis or

Table 1.
Characteristics of Patients with Primary Mediastinal Large B-Cell Lymphoma at Initial Diagnosis

Median age (range), y	37 (18-80)
M/F sex, n (%)	16 (57)/12 (43)
Lactate dehydrogenase >1× normal, n (%)	22 (79)
Clinical stage >II, n (%)	13 (46)
Performance status >1, n (%)	11 (39)
Extranodal lesions >1, n (%)	8 (29)
IPI high-intermediate or high, n (%)*	11 (39)
Bulky mediastinal mass (>10 cm), n (%)	17 (61)
Chest symptoms, n (%)	20 (71)
Superior vena cava syndrome, n (%)	5 (18)
B symptoms, n (%)	5 (18)
Pleural effusion, n (%)	9 (32)
Pericardial effusion, n (%)	10 (36)

*IPI indicates International Prognostic Index.

hyalinization of fibrous stroma varied among cases. Extensive coagulation necrosis was seen in 1 of the patients who underwent surgical resection.

The tumor cells stained positively for CD20 and negatively for CD3 in all cases, confirming the determination of B-cell lymphoma. Although the amount of $CD30^+$ neoplastic B-cells varied, these cells could readily be differentiated from nodular sclerosis Hodgkin's lymphoma by their morphologic characteristics, such as the confluent growth of tumor cells, the loss of typical Reed-Sternberg cells or lacular cells, and the loss of granulomatous background accompanied by granulocytes.

3.2. Clinical Features

The clinical characteristics of the 28 patients at diagnosis are summarized in Table 1. The median age was 37 years (range, 18-80 years). There were 16 male patients with a median age of 39 years and 12 female patients with a median age of 31 years (Figure 1). The 16 male patients ranged widely in age from 18 to 80 years, whereas the 12 female patients appeared to show a single age peak at 20 to 40 years. The female patients were younger than the male patients (mean, 31.8 years versus 43.5 years; $P = .04$). Bulky mediastinal mass with the largest diameter greater than 10 cm was found in 17 patients (61%). At diagnosis, 20 patients (71%) presented with chest symptoms caused by a mediastinal mass. SVCS and B symptoms were present in 5 patients (18%) each. Pleural effusion was found in 9 patients (32%), including 6 patients with positive cytologic findings, and pericardial effusion was found in 10 patients (36%), all with negative or unknown cytologic findings. In 21 patients (75%), we recognized direct extension to intrathoracic or extrathoracic extranodal sites adjacent to the mediastinal mass (lung parenchyma in 11 patients, chest wall in 9, pleura in 8, and thyroid in 1). Six patients (21%) showed extrathoracic involvement at diagnosis (para-aortic abdominal lymph nodes in 4 patients, ovary in 2, stomach in 2, spleen in 1, and adrenal gland in 1). No patient had bone marrow involvement or central nervous system involvement at initial diagnosis. Four patients (14%) had stage I disease, 11 (39%) had stage II disease, and the remaining 13 (46%) had stage IV disease. Eleven patients (39%) were categorized in a group of high or high-intermediate risk according to the IPI.

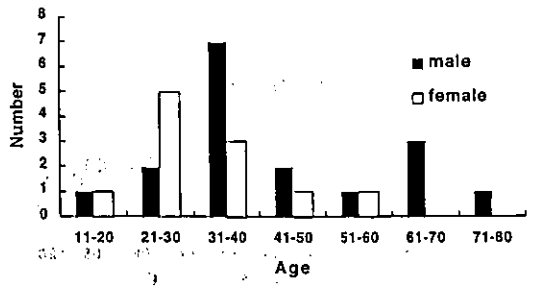

Figure 1. Age distribution of 28 patients with Med-DLBCL. Male patients showed a bimodal age distribution with 1 peak at 30 to 50 years of age and another peak in the 60s, whereas female patients showed a single peak at 20 to 40 years.

A diagnosis different from Med-DLBCL (malignant thymoma, germ cell tumor) was initially made in 5 patients (18%), 3 of whom had clinical their diagnoses determined by computed tomography or magnetic resonance imaging without histopathologic diagnosis because of the rapid progression of disease. Two of these 3 patients received 1 course of a DOX-containing chemotherapy regimen under the clinical diagnosis of malignant thymoma. They received CHOP therapy immediately after the accurate diagnosis of Med-DLBCL was obtained by a needle biopsy within 1 month of the initial diagnosis. Thus, these patients were included in the CHOP-like regimen group in this study to reflect the initial treatment. The remaining patient with an initial clinical diagnosis of germ cell tumor received radiotherapy, and the accurate Med-DLBCL diagnosis by needle biopsy was made 14 months after the initial diagnosis. One patient received surgical resection after an erroneous diagnosis of thymoma was made after a needle biopsy; after the accurate diagnosis was obtained, the patient received CHOP therapy. One patient received an erroneous diagnosis of germ cell tumor in 1982 and received vindesine, cisplatin, and radiation therapy.

3.3. Responses and Survival

All 28 patients were assessable for response to initial treatment, OS, and failure-free survival. The median follow-up duration for all 28 patients was 21 months and that for the 11 surviving patients was 35.7 months. Nine patients achieved a CR, and 4 achieved a CRu; thus, the CR rate was 46% (13/28). Nine patients (32%) achieved a partial response. Three patients (11%) showed progressive disease during initial treatment, and the remaining 3 (11%) showed no change. The overall response rate was 79% (22/28).

Ten patients (36%), including the 9 in continuous first CR, were alive at the time of the last follow-up. One treatment-related death was caused by interstitial pneumonia related to thoracic irradiation during the initial treatment. All 3 patients who relapsed after achieving a CR experienced the relapse within 1 year of the beginning of treatment. The estimated 3-year disease-free survival rate of the 13 patients who

achieved a CR or CRu with initial treatment was 66% (Figure 2). One patient was alive in CR with second-line chemotherapy that included high-dose chemotherapy with autologous hematopoietic stem cell transplantation (AHSCT). All 14 patients who did not achieve a CR or CRu with any therapy died. One patient who underwent high-dose chemotherapy with AHSCT died from treatment-related causes. The remaining 13 patients died of disease progression. The estimated 3-year failure-free survival and OS rates for all 28 patients were 33% and 32%, respectively (Figure 2). Five of the 12 patients who received radiation as 1 of the initial treatments did not achieve a CR.

3.4. Factors Affecting OS

The results of univariate analyses of various factors affecting OS are shown in Table 2. The following factors were found to be significantly associated with shortened survival times: age >60 years, serum LDH level higher than normal, PS >1, and presence of a bulky mediastinal mass. The OS curves according to the responses to initial treatment are shown in Figure 3. There were significant differences among the groups ($P < .001$).

4. Discussion

One of the unique findings in the present study is the lack of a female preponderance, although a slight to moderate preponderance of female patients was observed in most reported series, as shown Table 3. Another unique finding is that the age distributions of male patients and female patients may be different. Most previous studies did not show such a difference, although a sex-related difference in age distribution was also recognized in the series reported from the Massachusetts General Hospital in the United States [29].

In a clinical evaluation by the International Lymphoma Study Group that examined 1403 patients with non-Hodgkin's lymphoma (NHL) from 8 countries [30,31], the relative frequency of Med-DLBCL among NHL cases was 2.4%, and an increased relative incidence (9%) of Med-DLBCL in Locarno/Bellinzona in southern Switzerland, which is adjacent to Italy, has been reported [32]. Many reports on Med-DLBCL from Italy are available [3,6-8]. In contrast, only a few reports are available from Japan [14-16] and Southeast Asia [33]. Of the 3025 cases of NHL according to the WHO classification that were examined in a Japanese multicenter clinicopathologic study, only 8 patients (0.26%) were categorized as having Med-DLBCL

Table 2.
Univariate Analysis of Factors Affecting Overall Survival (OS)*

Characteristic	3-Year OS, %	Median OS, mo	P
Age			.001†
>60 y (n = 4)	0	6	
≤60 y (n = 24)	38	25	
Clinical stage			.115
I, II (n = 15)	47	34	
III, IV (n = 13)	18	23	
Serum LDH level			.028†
>1× normal (n = 22)	18	19	
≤1× normal (n = 6)	80	Not reached	
Performance status			.01†
>1 (n = 11)	0	19	
0 or 1 (n = 17)	53	Not reached	
Extranodal lesions			.958
>1 (n = 8)	30	23	
≤1 (n = 20)	33	23	
Bulky mediastinal mass			.004†
Yes (n = 17)	8	16	
No (n = 11)	71	Not reached	
Pleural effusion			.465
Yes (n = 9)	28	23	
No (n = 19)	36	23	
Pericardial effusion			.944
Yes (n = 10)	30	23	
No (n = 18)	35	23	
Chemotherapy regimen			.291
CHOP-like (n = 18)	36	23	
2nd or 3rd generation (n = 6)	65	Not reached	
Radiotherapy (after initial chemotherapy)			.646
Yes (n = 10)	46	23	
No (n = 8)	57	Not reached	
International Prognostic Index			.071
Low or low-intermediate risk (n = 17)	46	34	
High-intermediate or high risk (n = 11)	11	23	

*LDH indicates lactate dehydrogenase; CHOP, regimen of cyclophosphamide, doxorubicin, vincristine [Oncovin], and prednisolone.
†P values <.05 are statistically significant.

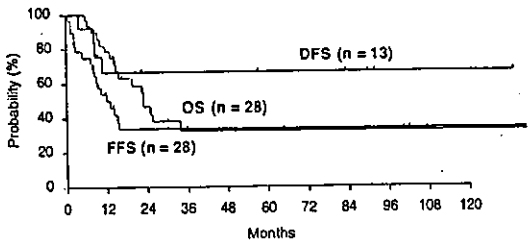

Figure 2. Survival curves. Overall survival (OS) and failure-free survival (FFS) of the 28 patients and disease-free survival (DFS) of the 13 patients who achieved a complete response with initial treatments.

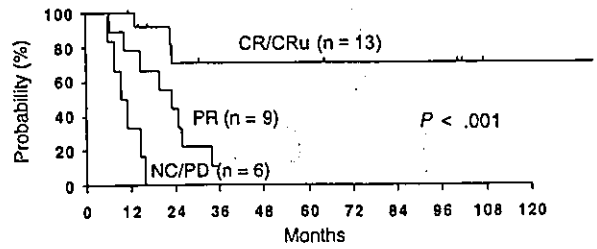

Figure 3. Overall survival according to response to initial treatment. The survival rates of the 3 groups were significantly different ($P < .001$). CR indicates complete response; CRu, unconfirmed or uncertain CR; PR, partial response; NC, no change; PD, progressive disease.

Table 3.
Main Features and Clinical Outcomes of Patients with Primary Mediastinal Large B-Cell Lymphoma in Reported Studies and the Present Study*

First Author	Country	Patients, n	B-Cell Phenotype, %	M/F, n	Median Age (Range), y	Stage I or II, %	Regimen (No. of Patients)	Radiation	ORR, %/ CR, %	OS, %
Falini, 1995 [6]	Italy	18	100	5/13	31 (18-44)	94	MACOP-B (7) F-MACHOP (11)	No	100/57 91/18	NA
Lazzarino, 1997 [3]	Italy	106	100	49/57	30 (14-73)	86	CHOP-like (70), 3rd generation (29)	Yes	65/23	50 (3 y)
Zinzani, 1999 [8]	Italy	50	100	20/30	31 (21-55)	84	MACOP-B (50)	Yes	86/86	82 (8 y)
Bieri, 1999 [9]	Switzerland	27	100	10/17	45 (21-87)	67	CHOP (11), 3rd generation (12)	Yes	70/56	50 (10 y)
Haioun, 1989 [10]	France	20	82	3/17	33 (17-52)	90	DOX-containing	Yes	100/45	33 (7 y)
Cazals-Hatem, 1996 [4]	France	141	100	58/83	37 (19-70)	77	DOX-containing	No	NA/79	66 (3 y)
Zinzani, 2002 [7]	Europe	426	NA	165/261	32 (13-87)	74	1st Generation (105) 3rd Generation (277) HDC/AHSCT (44)	Yes Yes Yes	81/49 87/51 88/53	44 (10 y) 71 (10 y) 77 (10 y)
Jacobson, 1988 [11]	USA	30	NA	10/20	34 (15-71)	76	CHOP (22)	Yes	80/80	65 (5 y)
Kirn, 1993 [12]	USA	57	80	30/27	30 (NA)	NA	CHOP (10), m/M-BACOD (38)	Yes	93/53	50 (5 y)
Abou-Elella, 1999 [13]	USA	43	100	20/23	42 (15-92)	58	DOX/MIT-containing	No	NA/63	39 (5 y)
Toh, 1998 [33]	Singapore	7	NA	3/4	22	NA	DOX-containing	Yes	NA/43	NA
Yonetani, 2001 [14]	Japan	10	100	5/5	25.5 (19-63)	90	CHOP-like (7), MACOP-B (3)	Yes	90/90	70 (2 y)
Present study	Japan	28	100	16/12	37 (18-80)	54	CHOP-like (18)	Yes	79/46	32 (3 y)

*ORR indicates overall response rate; CR, complete response; OS, overall survival; MACOP-B, regimen of methotrexate (MTX), doxorubicin (Adriamycin) (DOX), cyclophosphamide (CPA), vincristine (Oncovin) (VCR), prednisolone (PSL), and bleomycin (BLM); F-MACHOP, regimen of 5-fluorouracil, MTX, DOX, CPA, cytarabine, VCR, and PSL; NA, not applicable; CHOP, regimen of CPA, DOX, VCR, and PSL; HDC/AHSCT, high-dose chemotherapy with autologous hematopoietic stem cell transplantation; m/M-BACOD, regimen of moderate/high–dose MTX and BLM, DOX, CPA, VCR, and dexamethasone; MIT, mitoxantrone.

[34]. These results suggest that the incidence of Med-DLBCL has some geographical variation, although there may also be some differences in the recognition of this disease entity [32].

The conventional treatment strategy for other DLBCLs, such as a CHOP-like regimen followed by involved-field radiotherapy, was successful in fewer than half of the patients in the present study, although the researchers at the Massachusetts General Hospital reported superior results (65% 5-year OS) with primarily CHOP and radiotherapy [11]. On the other hand, several investigators have concluded that the survival prospects of patients treated with the third-generation regimens may be superior to those of patients treated with CHOP therapy [5,7], although different outcomes among patients who were treated with different third-generation regimens have been reported [6]. Zinzani et al reported the results of a phase II study of a MACOP-B regimen (MTX, DOX, CPA, VCR, PSL, and BLM) [35] and mediastinal radiotherapy that was conducted at 2 institutions in Italy [8]. Forty-three (86%) of 50 previously untreated patients achieved a CR, the OS was 82% at 8 years, and the relapse-free survival of the 43 patients who achieved a CR was 93% at 8 years. In their study, a negative test result of gallium Ga 67 uptake in the residual mass was a favorable factor. Recently, Zinzani and the members of the International Extranodal Lymphoma Study Group conducted a retrospective European multinational study of 426 previously untreated patients with Med-DLBCL and reported that the long-term survival of patients treated with MACOP-B–type third-generation regimens was superior to that of patients treated with CHOP therapy [7]. These retrospective data need to be confirmed in prospective studies. Radiotherapy for the mediastinal mass is commonly used after the completion of chemotherapy [5,16], although its benefit has not been established in randomized studies, and excellent results have been obtained without radiotherapy in the Groupe d'Etude des Lymphomes de l'Adulte studies [4], as shown in Table 3. The usefulness of high-dose chemotherapy as consolidation and salvage therapy has also been suggested [5,7,36,37].

In the present study, there were significant differences in survival according to the responses to initial treatment, as shown in Figure 3. Approximately two thirds of the patients who achieved a CR or CRu appeared to achieve a cure, as shown in Figure 2, whereas only 1 of the remaining 15 patients

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

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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-

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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	1388.2	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-

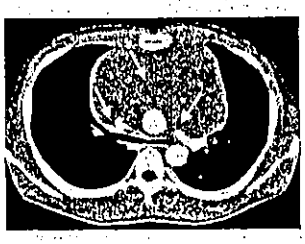

Figure 1. Thymic type T-cell lymphoblastic lymphoma in a 16-year-old man (case 8). Transverse computed tomographic image shows a large anterior mediastinal mass with vascular obliteration (arrows) suggesting enlargement of the thymus.

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,

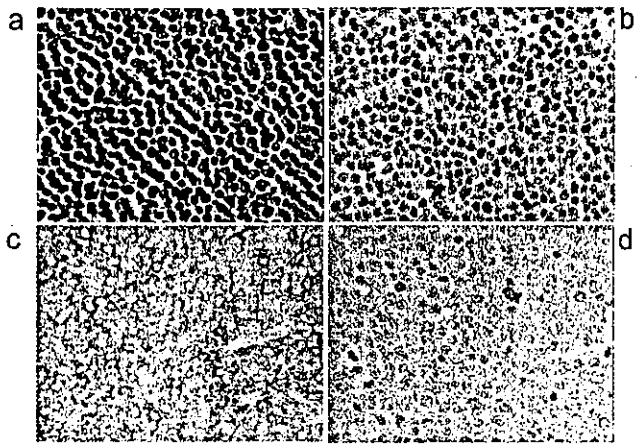

Figure 3. Needle biopsy specimen of an anterior mediastinal mass (case 5, thymic type). a, Hematoxylin and eosin staining. b, c, and d, Immunostaining with antibodies against terminal deoxynucleotidyl transferase (TdT), CD8, and CD56. The tumor cells expressed TdT and CD8 but not CD56 (original magnification,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

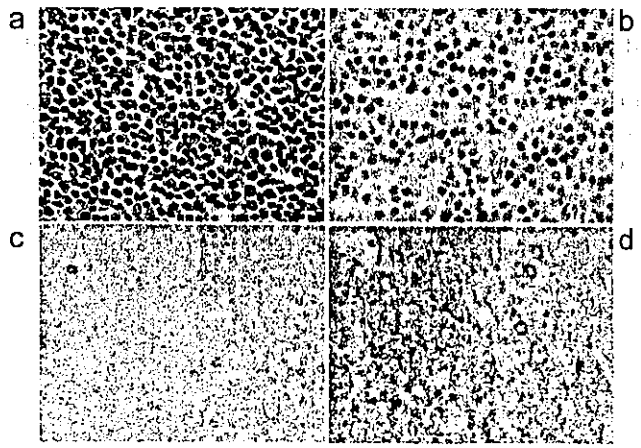

Figure 4. Lymph node from case 14 (nonthymic type). a, Hematoxylin and eosin staining. b, c, and d, immunostaining with antibodies against terminal deoxynucleotidyl transferase (TdT), CD8, and CD56. The tumor cells expressed TdT and CD56 but not CD8 (original magnification, ×600).

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	A8VD, 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

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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

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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.