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Retrospective Analysis of Non-Anaplastic Peripheral T-Cell Lymphoma in Pediatric Patients in Japan

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Background. Reports of non-anaplastic peripheral T-cell lymphoma (PTCL) in pediatric patients are relatively rare. ***Procedure.*** We performed a retrospective analysis in patients with PTCL over an 18-year period (1991–2008). ***Results.*** We could analyze clinical data in 21 patients with non-anaplastic PTCL; 10 were female and 10 male. Median age of onset was 11 years (range: 1–21 years). There were nine patients with PTCL, not otherwise specified (PTCL-NOS); ten with extranodal NK/T-cell lymphoma, nasal type; one with angioimmunoblastic T-cell lymphoma; and one with subcutaneous panniculitis-like T-cell lymphoma. Initial lesions involved cervical lymph nodes in five patients, and the skin in five patients. In five patients, hemophagocytic syndrome (HPS) was the initial clinical feature. There were 12 patients with advanced stage disease (stages III and IV). Chemotherapy and radiation was administered in 18 and 2 patients, respectively. Among the two patients who did not receive chemotherapy and radiation, one patient died while being treated for HPS but another improved spontaneously. Although 5 patients relapsed, 18 of 21 patients remained alive without disease at last follow-up. Five-year overall survival rate was 85.2%. ***Conclusions.*** Generally, the outcome results of conventional chemotherapy for high-risk PTCL are poor in adult patients. However, the excellent results in our study suggest that PTCL of childhood is quite different from that of adulthood. Although this study is first report about PTCL of Asian children, the number of patients was small in this study. Larger studies are needed to confirm these findings. Pediatr Blood Cancer 2010;54:212–215. © 2009 Wiley-Liss, Inc.

Key words: child; peripheral T-cell lymphoma

INTRODUCTION

Peripheral T-cell lymphomas (PTCLs) are a heterogeneous group of rare diseases, usually demonstrating clinical aggressiveness [1]. Because of difficulty and variability in diagnosis, improvements in diagnostic technology, and changing classification systems over time, the interpretation of studies is complicated. In addition, the response to current treatments and long-term outcome are generally poor [2–6]. Reports of non-anaplastic PTCL in pediatric patients are relatively rare [7–11]. Moreover, although geographic variation has been well documented, this may reflect exposure to specific pathogenic viruses, such as Epstein Barr (EB) virus and human T-cell leukemia virus-1 in Asian countries. There are no reports about child PTCL from Asia. We therefore performed a retrospective analysis of patients with PTCL over an 18-year period (1991–2008).

METHODS

We performed this retrospective analysis as the lymphoma committee of the Japan Leukemia and Lymphoma Study Group (JPLSG). Data were obtained from the Japan Association of Childhood Leukemia Study (JACLS), Tokyo Children's Cancer Study Group (TCCSG), Japanese Children's Cancer and Leukemia Study Group (JCCLSG), and Kyushu-Yamaguchi Children's Cancer and Leukemia Study Group (KYCCSG). In the 18-year study period, 55 patients were registered as having PTCL or NK/T lymphoma including blastic NK lymphoma and myeloid/NK lymphoma. Clinical data for 21 patients with non-anaplastic PTCL after excluding 34 patients with blastic NK lymphoma and myeloid/NK lymphoma were analyzed.

Pathologic diagnoses were confirmed by central review in 9 of 21 patients. Central review was performed using WHO classification. For the other 12 children, histopathology was performed at the treating center only and confirmed from a copy of the pathology report. In almost all reports, immunophenotyping such as CD79a, CD20, CD3, CD43, TdT, and MPO was included.

The presence of an association with EB virus was determined by detection of EB virus genome in white blood cells or plasma, or the detection of this virus in histological material by EB virus encoded small RNA (EBER) in situ hybridization [12].

Statistical Analyses

Analysis of overall survival was performed using the Kaplan–Meier method, with differences compared by log-rank test. Differences between groups were analyzed using a Fisher exact test and a Mann–Whitney *U*-test. Statistical analyses were

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performed using Dr. SPSS II for Windows (release 11.0.1J, SPSS Japan, Inc.).

RESULTS

In the 18-year study period, we were able to analyze clinical data from 21 patients with non-anaplastic PTCL (Table I). Because 1,711 child and adolescent patients with non-Hodgkin lymphoma were registered in the 18-year period, the proportion of NHL classified as PTCL was 1.2%. Of the 21 patients, 10 were male and 11 were female. Median age of onset was 11 years (range: 1–21 years). There were nine patients with PTCL not otherwise specified (PTCL-NOS); ten with extranodal NK/T-cell lymphoma, nasal type; one with angioimmunoblastic T-cell lymphoma; and one with subcutaneous panniculitis-like T-cell lymphoma. Initial lesions involved the cervical lymph nodes in five patients, and the skin in five patients. In five patients, hemophagocytic syndrome (HPS) was the initial clinical feature. With regard to stage of disease at diagnosis, eight patients were at stages I and II, six were at stage III, and six were at stage IV; this information was not available for one patient. Chemotherapy and radiation were administered in 18 and 2 patients, respectively. Two patients received no treatment. Treatment for PTCL was not consistent in this study. Eight patients received a T-cell lymphoma/leukemia regimen, and four received a B cell lymphoma/leukemia regimen. Among the two patients who did not receive chemotherapy and radiation, one patient died while undergoing treatment for HPS and another improved spontaneously. In the latter patient (patient 5), the initial clinical features were fever, cervical lymphadenopathy, and pancytopenia. He was diagnosed with HPS from laboratory data and bone marrow aspiration. Lymph node biopsy revealed PTCL and there was positive staining on EBER in situ hybridization. However, after several days, the fever abated and laboratory data improved. He received no chemotherapy at the request of his parents and remained disease-free at last follow-up, 9 months after onset.

Eleven patients received stem cell transplantation. Of these, two received an autologous peripheral blood stem cell transplant (PBSCT), five received a related bone marrow transplant (BMT), two received a related PBSCT, two received an unrelated cord blood stem cell transplant (CBSCT), and one received an unrelated BMT. Although 5 patients relapsed, 17 of the 21 patients were alive without disease at last follow-up, giving an overall 5-year survival rate of 85.2% (Fig. 1). Causes of death for the three patients who succumbed to their disease were HPS, progression of disease and complications of stem cell transplantation. Ten of the 21 patients had PTCL associated with EB virus. Compared with patients with extranodal NK/T lymphoma, nasal type, those with PTCL-NOS were younger (median 7 years vs. 15.5 years, $P < 0.05$) and had a lower relapse rate (11% vs. 40%). However, gender (male/female; 5/4 vs. 4/6), proportion with advanced stage disease (56% vs. 60%), survival rate (87.5% vs. 80.0%) and association with EB virus (44% vs. 60%) were similar and statistically non-significant differences.

DISCUSSION

Peripheral NK/T-cell neoplasms are an uncommon group of diseases that show distinct racial and geographic variation. The prognostic significance of the T-cell phenotype has been clearly defined in recent studies by using modern lymphoma classification systems. Anaplastic large cell lymphoma, not rare in childhood, is another type of PTCL. Results of conventional chemotherapy for high-risk PTCL are poor compared with those for their aggressive B-cell counterparts in adult patients.

However, although case reports of pediatric PTCL are sometimes seen [7,10,11], large case series are very rare. The only two such case series published are a report from the United Kingdom [8] and the Children's Oncology Group (COG) Study [9]. In the UK series, 25 cases were identified, 44% of children died and 5-year survival rate was 59%. On the other hand, in the 20 patients in the COG series, 5-year survival rate was 90% in patients with localized disease and 50% in those with advanced disease. In the present study, 21 patients with PTCL were identified; these included 9 with PTCL-NOS; 10 with extranodal NK/T-cell lymphoma, nasal type; 1 with angioimmunoblastic T-cell lymphoma; and 1 with subcutaneous panniculitis-like T-cell lymphoma. Surprisingly, although 57% of patients had advanced stage disease and five patients relapsed after chemotherapy, the 5-year survival rate was 85.2%. However, treatment for PTCL was not consistent in this study. Eight patients received a regimen for T-cell lymphoma/leukemia, and four patients received a B cell lymphoma/leukemia regimen. Moreover, in one patient, symptoms improved spontaneously, and this has not previously been reported. Although five patients had relapse, four patients remained disease free at last follow-up and only two patients had undergone stem cell transplantation. Our study suggests that in the present population, PTCL in childhood does not have a poor outcome compared to adult with PTCL. This reason is not clear. However, the role of stem cell transplantation might be important. Stem cell transplantation had been undergone in eight patients with first complete response or partial response, one patient with progressive disease and two patients after relapse. After stem cell transplantation, only two patients died and nine patients are surviving without relapse.

Many cases of extranodal NK/T-cell lymphoma, nasal type were seen in this study compared with previous reports. Moreover, patients with this type of lymphoma were older at initial presentation than those with PTCL-NOS. Extranodal NK/T-cell lymphoma, nasal type is mostly confined to East Asia, and it predominantly occurs in the nasal or paranasal areas and less frequently in the skin. Most of the tumors show NK-cell phenotypes, although T-cell phenotypes are occasionally seen. The EB virus genome can usually be detected in lymphoma cells. Disease was associated with EB virus in 65% of patients with extranodal NK/T-cell lymphoma, nasal type compared with 50% of patients with PTCL-NOS. Suwiwat et al. [13] detected cell-free EBV DNA in 32/38 (84%) of adult PTCL patients, but failed to find EBV in controls. Rates of EB virus were higher in that report than in our study, possibly because Suwiwat et al. examined adults rather than children. However, we found EB virus in three of four patients who had HPS as the initial clinical feature. EB virus associated with HPS is sometimes seen in childhood, and some of these patients might also have PTCL. T-cell lymphoma-associated hemophagocytic syndrome (T-LAHS) has been frequently reported in Asian countries and is considered to have an extremely poor prognosis. Tong et al. [14] retrospectively analyzed the records of 113 patients with aggressive T-cell lymphoma, of which 28 had LAHS. The therapeutic results of chemotherapy alone or in combination with other modalities were discouraging for T-LAHS and the survival time for most patients was no more than 1 year. In the present study, unlike in other reports, three of four patients with HPS remained disease-free at last follow-up.

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TABLE I. Clinical Characteristics and Outcomes for 21 Patients With Peripheral T-Cell Lymphoma

	Age	Gender	Diagnosis	Initial lesion	Stage	Treatment	Response	Relapse	Transplantation	Association of EB virus	Survival time (months)
1	6	M	PTCL-NOS	Liver, spleen	4	JACLS NHL98ER	PR	N	Y	N	68+
2	4	F	PTCL-NOS	HPS	4	ALL (T)	CR	N	N	Y	60+
3	16	M	PTCL-NOS	Cervical	3	BFM NHL-T	PR	N	Y	N	36+
4	5	F	PTCL-NOS	Skin	1	JACLS NHL98T	CR	N	N	N	12+
5	7	M	PTCL-NOS	Cervical, HPS	1	None		N	N	Y	9+
6	9	M	PTCL-NOS	Cervical, spleen	3	TCCSG NHLT01	CR	N	N	ND	57+
7	11	F	PCTL-NOS	Cervical	1	T-LBL	CR	Y	Y	N	12
8	1	F	PTCL-NOS	HPS		VP16 + DEX	CR	N	Y	Y	30+
9	12	M	PTCL-NOS	Submandibular	3	CHOP	PR	N	Y	Y	30+
10	14	F	Subcutaneous panniculitis-like	Skin	2	Steroid	CR	N	Y	N	8+
11	14	M	AITL	Cervical	4	JACLS NHL98T	CR	N	N	N	96+
12	17	M	Extranodal NK/T nasal type	Adrenal grand, HPS	3	None		N	N	N	0
13	14	F	Extranodal NK/T nasal type	Skin	4	93mix	CR	N	Y	N	132+
14	21	F	Extranodal NK/T nasal type	Sinusoidal	4	HLH94	CR	Y	N	Y	30+
15	10	F	Extranodal NK/T nasal type	Orbit, breast	3	DeVIC	PD	Y	Y	N	36+
16	18	F	Extranodal NK/T nasal type	Nasal sinus, kidney, ovary	4	ALL (B)	PD	N	Y	Y	5
17	11	M	Extranodal NK/T nasal type	Skin	3	TCCSG NHL B96-04	CR	N	N	N	107+
18	18	M	Extranodal NK/T nasal type	Nasopharynx	2	Radiation	CR	Y	N	Y	105+
19	8	F	Extranodal NK/T nasal type	Skin	1	CCLSG NHL960LB	CR	N	N	Y	94+
20	10	M	Extranodal NK/T nasal type	Nasal sinus	1	DeVIC + radiation	CR	Y	Y	Y	45+
21	18	F	Extranodal NK/T nasal type	Nasal sinus, HPS	2	CHOP	PR	N	Y	Y	147+

PTCL-NOS, peripheral T-cell lymphoma, not otherwise specified; AITL, angioimmunoblastic T-cell lymphoma; HPS, hemophagocytic syndrome; CR, complete response, PR, partial response; PD, progressive disease; Y, yes; N, no; ND, no data. The drugs contained in remission introduction of each treatment is as follows: JACLS NHL98ER, vincristine (VCR), pirarubicin (THP-ADR), cyclophosphamide (CPM), L-asparaginase (L-asp), dexamethasone (DEX), prednisolone (PSL), JACLS NHL98T, VCR, CPM, adriamycin (ADR), L-asp, PSL, TCCSG NHLT01, VCR, CPM, ADR, L-asp, THPADR, PSL, CHOP: CPM, ADR, VCR, PSL, HLH94: etoposide (VP16), DEX, cyclosporine, DeVIC: DEX, ifosfamide, carboplatinum, VP16, TCCSG NHL B96-04: CPM, VP16, methotrexate (MTX), PSL, CCLSG NHL960LB: CPM, VCR, PRD, ADR, MTX.

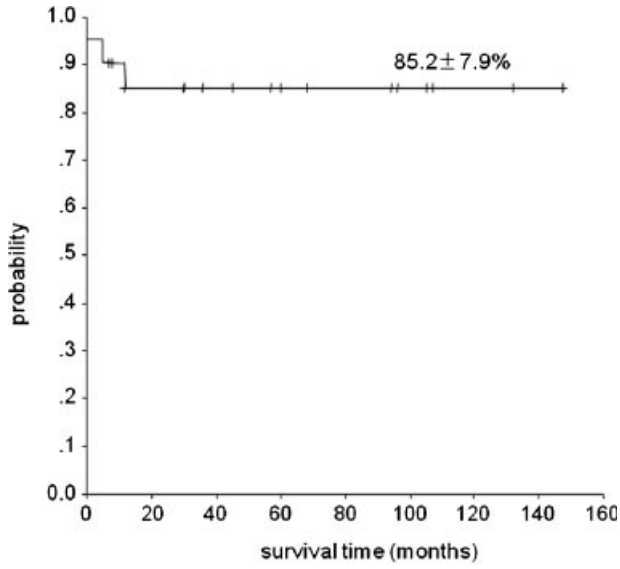

Fig. 1. Survival rate of patients with peripheral T-cell lymphoma. Five-year survival rate was 85.2%.

The findings of the present study differ from those of past reports of PTCL that included adults and children. However, the present study examined only a small number of patients. Larger studies are needed to confirm these findings.

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