

Non-Hodgkin's Lymphomas in Osaka, Japan

K. AOZASA,* M. TSUJIMOTO,* M. SAKURAI,* M. HONDA,† K. YAMASHITA,‡ M. HANADA§ and A. SUGIMOTO||

*Department of Pathology, Osaka University Medical School, †Osaka Kaisei Hospital, ‡Kinki Chuo Hospital, §Toyonaka Municipal Hospital and ||Sumitomo Hospital, Osaka, Japan

Abstract—Six hundred and eighty-four cases with non-Hodgkin's lymphomas (NHL) in Osaka, Japan were reviewed, using current histopathological classification to obtain a general feature of Japanese lymphomas. There were no remarkable differences in the distribution of age, sex and the location of primary tumors between Japanese NHL and the disease in Western races. Histologically, however, several differences were present; in particular, the lower frequencies of nodular lymphomas of nodal origin and lymphocytic type of nodal and extranodal origin in the present cases. About 10% of the cases show a peculiar histology characteristic for adult T cell lymphomas. From this study, it appears that the ratio of low-grade malignant NHL in Japan is much lower than in the Western countries.

INTRODUCTION

RECENTLY it has been shown that adult T cell leukemia/lymphoma (ATL), a rarity in Western countries, is not an uncommon disease in Japan [1, 2]. Patients with ATL are clustered in southwestern Japan (ATL endemic area), and a viral etiology of ATL has been suggested [3]. The nationwide survey by the Lymphoma Study Group of Japan showed that three-quarters of patients with non-Hodgkin's lymphomas (NHL) were ATL in the ATL endemic area [1]. By comparison, in the ATL non-endemic area the frequency of ATL was between 25 and 36%. The histology of ATL is characterized by pleomorphism of tumor cells, and tends to be misdiagnosed as Hodgkin's disease. Indeed, an earlier study dealing with malignant lymphomas from parts of Japan now known to be ATL endemic and non-endemic areas reported a much higher frequency of Hodgkin's disease in the ATL area [4].

In the present study seven hundred and sixty-five cases of malignant lymphomas diagnosed in Osaka, Japan were reviewed. The frequency of ATL among NHL in the Osaka region was previously reported by us to be 23% [5], and is similar to that of ATL in areas in Japan where ATL is not endemic. The present cases comprise 684 cases (89.4%) of NHL and 81 cases (10.6%) of Hodgkin's disease. This study reports the age, sex,

location of tumors and histology in 684 cases of NHL. Rappaport [6], Kiel [7] and the Lymphoma Study Group (Japan) [8] classifications are applied to subdivide the cases. The results are compared to those in the literature, mainly from the Western countries, to provide the general characteristics of NHL in Japan, excluding the ATL endemic areas.

MATERIALS AND METHODS

Biopsy specimens of 15 hospitals situated in Osaka and Hyogo prefectures, Japan (ATL non-endemic area) were reviewed, a total of 984 cases being diagnosed as malignant lymphomas and related disorders during the period 1964-1983. Paraffin blocks were obtained in all cases and sectioned at 4 mm for hematoxylin and eosin stain or, if necessary, additional stains (periodic acid-Schiff reaction, silver impregnation). The slides were reviewed by one of us (KA). Two hundred and twenty-one cases were diagnosed as non-lymphoid malignancy, reactive diseases or undefined diseases; these were eliminated. The remaining 765 cases were diagnosed as malignant lymphomas, of which 684 cases (89.4%) were NHL and 81 cases (10.6%) Hodgkin's disease. The Hodgkin's disease will be analyzed separately; the NHL are the subject of the present study. They were classified histologically according to the Rappaport, Kiel and the Lymphoma Study Group (Japan) classifications. Brief clinical

information including age, sex, location and numbers of tumors were available.

RESULTS

Mean age at diagnosis, sex ratio and location of tumors are listed in Table 1. The 684 cases comprised 379 cases (57.7%) of nodal and 278 cases (42.3%) of extranodal NHL. Specific site locations were unknown in 27 cases. Among the cases with extranodal NHL, the gastrointestinal tract and the Waldeyer's ring were the commonest sites of the primary tumors and comprised 58.6% of all extranodal NHL. Both nodal and extranodal NHL were more frequent in males, except for thyroid NHL. The preponderance of males was remarkable in the cases of gastrointestinal NHL (males:female ratio = 2.57). Age distribution in nodal and extranodal NHL is shown in Figs 1 and

2. Those of gastrointestinal tract and Waldeyer's ring are shown in Fig. 3. Nodal NHL had a peak incidence at the sixth decade of life, whereas a peak of age was not observed in extranodal NHL. Gastrointestinal NHL had a peak incidence in the fifth decade, in contrast with the gradual increase of incidence until the seventh decade in NHL of Waldeyer's ring.

Histologic classifications

The distribution of the NHL material according to the Rappaport and the Kiel classifications is given in Tables 2 and 3. The percentage of nodular lymphomas among nodal and extranodal NHL were 13.6 and 6.9% respectively. Diffuse histiocytic was the commonest type of NHL in both the nodal (42.9%) and the extranodal (63.3%) NHL. Mixed type was far more frequent in nodal than in extranodal NHL.

The Kiel classification showed that the percentage distribution between low- and high-grade malignancy was 43 and 57% in nodal NHL and 57 and 43% in extranodal NHL respectively. Germinal center cell tumors were the major type

Table 1. Location, age and sex of lymphomas

Sites	No. of cases	M:F	Mean age (yr)
Nodal	379	1.66:1	54.5
Extranodal	278	1.75:1	54.7
Gastrointestinal tract	82	2.57:1	55.4
Waldeyer's ring	81	1.3:1	53.5
Skin	25	3.17:1	54.1
Nose and paranasal sinus	19	1.1:1	54.6
Thyroid	15	1:2	62.3
Oral cavity	14	2.5:1	51.9
Genital tract	8	3:1	59.9
Brain	5	1.5:1	47.6
Bone	5	4:1	64.0
Mediastinum	5	5:0	31.8
Respiratory tract	2	1:1	63.5
Breast	1	0:1	76.0
Spleen	1	1:0	64.0
Ill-defined	15	1.5:1	56.5
Unknown	27	1.25:1	47.8

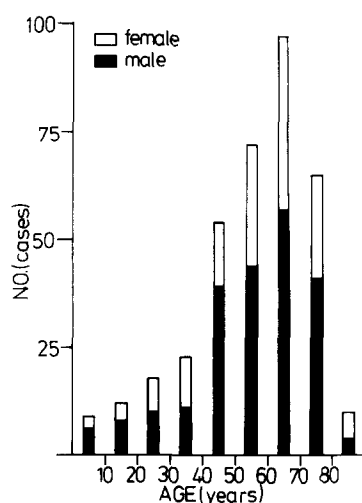


Fig. 1. Age and sex distribution in nodal lymphoma.

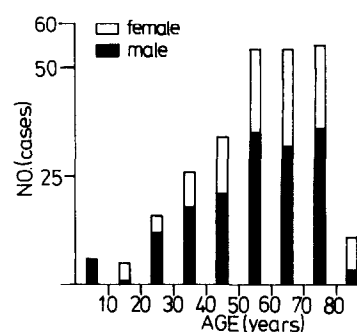


Fig. 2. Age and sex distribution in extranodal lymphoma.

Table 2. Result of Rappaport classification

	Nodal		Extranodal	
	%	M:F	%	M:F
Nodular lymphoma				
LPD	2.7	2.33:1	1.8	1.50:1
M	8.8	1.75:1	1.8	4.0:1
H	2.1	1:1	3.3	3.50:1
Diffuse lymphoma				
LWD	4.3	1.29:1	4.7	2.25:1
LPD	16.6	1.70:1	14.2	2.0:1
M	19.6	1.52:1	9.1	1.27:1
H	42.9	1.62:1	63.3	1.76:1
Burkitt	1.3	4.0:1	0.7	1.0:1
Undefined	1.6	6.0:1	1.1	0:3
Total	100	1.66:1	100	1.75:1

LPD: lymphocytic poorly differentiated; M: mixed; H: histiocytic.

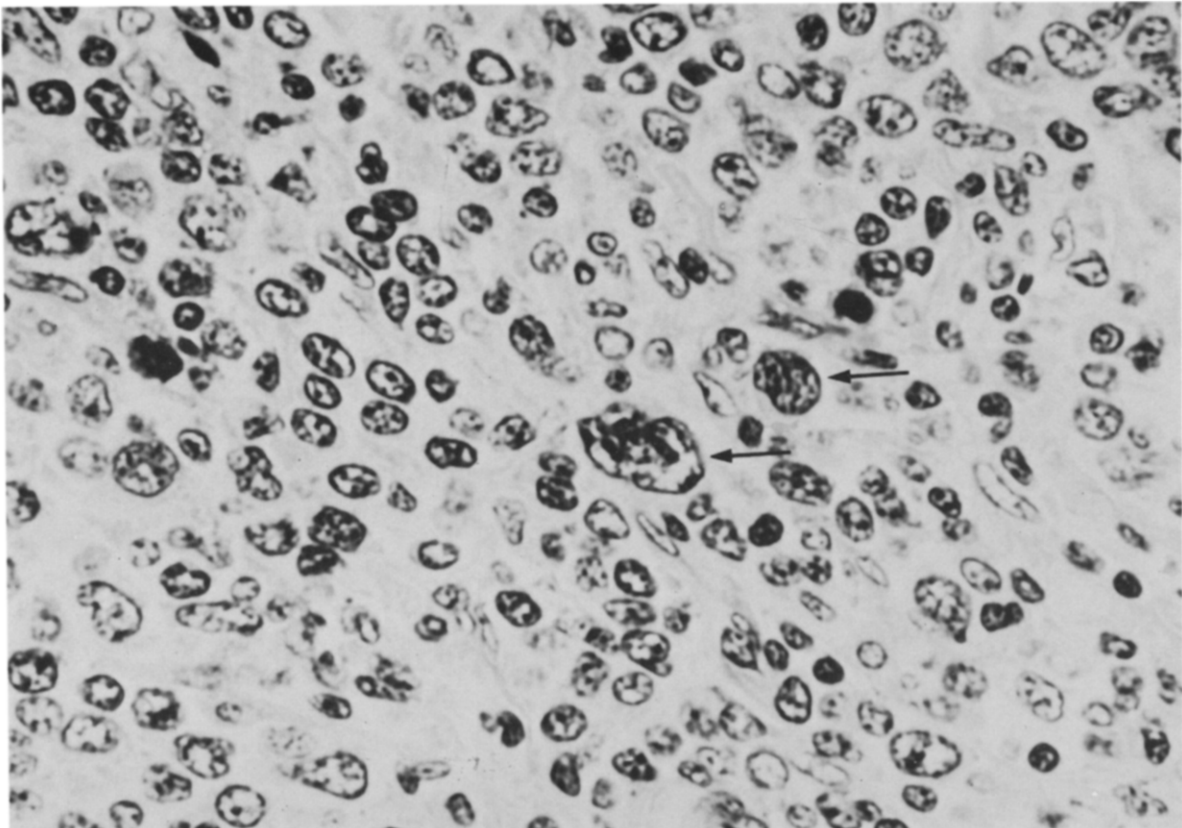


Fig. 4. Diffuse pleomorphic type. Large cells with a convoluted nucleus (arrows) are noted (H & E; $\times 738$).

Table 3. Result of Kiel classification

	Nodal		Extranodal	
	%	M:F	%	M:F
Low-grade malignancy				
LY	2.1	1.67:1	2.6	6.0:1
LP	4.0	1.50:1	5.9	1:1.67
CC	7.3	1.73:1	9.3	1.36:1
CB/CC: foll.	13.4	1.63:1	6.6	2.60:1
CB/CC: diff.	16.0	1.0:1	32.5	1.75:1
High-grade malignancy				
CB	8.3	3.42:1	15.5	1.10:1
LB	10.2	2.80:1	5.5	4.0:1
IB	15.3	1.38:1	12.9	1.83:1
Undefined	23.3	1.72:1	9.2	4.0:1
Total	100	1.66:1	100	1.75:1

LY: lymphocytic; LP: lymphoplasmacytic/lymphoplasma-cytoid; CC: centrocytic; CB/CC: centroblastic/centrocytic; foll.: follicular; diff.: diffuse; LB: lymphoblastic; IB: immunoblastic.

in both the nodal (45%) and the extranodal (64.2%) NHL. The germinal center cell tumors were much more prevalent in Waldeyer's ring and the gastrointestinal tract, the ratios being 76.6 and 73.3% respectively.

Sixty-one cases (16%) of nodal NHL, categorized as diffuse histiocytic or diffuse mixed type by the Rappaport classification, did not fit into the classification scheme of the Kiel classification. In these, medium-to-large-sized tumor cells with a convoluted nucleus showed diffuse proliferation intermingling with lymphocytes, plasma cells and histiocytes. Multilobated giant cells were occasionally found in these tumors giving a pleomorphic appearance (Fig. 4). The classification by the Lymphoma Study Group (Japan) placed these tumors in a special category, i.e. diffuse pleomorphic type. This disease was common during the fourth to seventh decades, with a peak at the sixth decade. The male to female ratio was 2.35:1. Seven cases (2.5%) of extranodal NHL were also of the diffuse pleomorphic type.

DISCUSSION

Hodgkin's disease was a minor constituent (10.6%) of malignant lymphomas in the present series of lymphomas; this confirmed a previous report from Japan [4]. The frequencies of extranodal lymphomas among all NHL were 37.6% in the present cases, and ranged from 24 to 48% in the previous studies [9]. The gastrointestinal tract and Waldeyer's ring were the commonest sites for extranodal NHL, and the combined frequency of them among all extranodal NHL in the present and previously

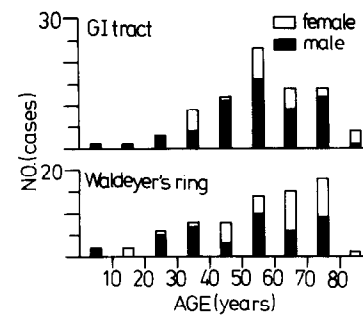


Fig. 3. Age and sex distribution in gastrointestinal and Waldeyer's ring lymphomas.

reported cases [9] were 58.6 and 50.2% respectively.

Studies in North America have indicated that NHL have a maximum incidence between the fifth and seventh decades, and are slightly more common in males than in females [10]. In the present series, both the extranodal and nodal NHL were likewise common in the fifth to seventh decades, and with a male preponderance. Most nodal NHL occurred in the sixth decade, but such a peak was not observed in the extranodal NHL, in which the incidence of disease continued to increase and reached its plateau during the fifth decade. However a peak was found in the fifth decade in both the present series and those with gastrointestinal NHL studied by Weingrad *et al.* in New York [11]. A gradual increase of incidence until the seventh decade was found in both the present and previously reported cases [12] of NHL of Waldeyer's ring. Sex ratios in the present series was generally in agreement with those in the literature [9, 10], i.e. except for thyroid NHL, there were more males than females in the nodal and extranodal NHL.

The percent of nodular NHL in the present cases with nodal NHL was 13.6%, which was much lower than the 44% reported by Jones *et al.* [10]. However, there was no significant difference between the frequencies of nodular NHL of extranodal origin between the present cases (6.9%) and the 0-34% recorded as nodular in the literature [13]. By the Rappaport classification, frequencies of each histologic subtypes of diffuse NHL in the present series and those reported by Jones *et al.* [10] were nearly the same. Diffuse histiocytic was the most common type of NHL. Much larger amounts of 'reticulum cell sarcoma' in Japan compared to America and England have been reported previously [4]; however, this was not confirmed in the present study.

When the Kiel classification was used, the main differences between the nodal and extranodal NHL were the higher frequencies of lymphoblastic and undefined types in the nodal tumors and germinal center cell tumors in the extranodal tumors. The undefined type, especially of nodal

origin, will be discussed later. Compared to Lennert's data [7], the very low frequencies of lymphocytic type (2.1% of nodal and 2.6% of extranodal NHL) in our cases are striking. Lennert reported a frequency of 20.7%. This was one of the main reasons for the much lower percentage of low-grade malignancy in the present cases, 43% in nodal and 57% in extranodal NHL, than that observed by Lennert (72%).

In 70% of nodal NHL and 28% of extranodal NHL that could not be classified by the Kiel classification, the tumor was characterized by pleomorphic tumor cells and infiltration of various numbers of inflammatory cells. Tumors showing these histologic features were identical with diffuse pleomorphic type of NHL, a term designated by the Lymphoma Study Group (Japan) for the correct subtyping of the appearance commonly observed in ATL [8]. Of the present cases about 10% of all NHL were of the diffuse pleomorphic type. In our previous report

describing immunologic and histologic study on 39 cases with NHL [5] six cases (15%) were of the diffuse pleomorphic type, with an immunologic marker for T cells in 5 cases and null cells in one case. It is well-known that the cases with diffuse pleomorphic type behave as high-grade malignancy.

In conclusion, malignant lymphomas in Japan compared to those in Western countries were characterized as follows: lower frequencies of (1) Hodgkin's disease, (2) nodular lymphomas of nodal origin, (3) lymphocytic type of nodal and extranodal origins and (4) the pleomorphic type of NHL was not uncommon.

From this study, it appears that the ratio of low-grade malignant NHL in Japan is much lower than in Western countries.

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