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ORIGINAL ARTICLE

Lymphoma in Taiwan: Review of 1347 neoplasms from a single institution according to the 2016 Revision of the World Health Organization Classification

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Background/Purpose: Lymphoid neoplasms are heterogeneous and types of lymphoma vary in different geographic regions. In this study, we aimed at classifying the lymphoid neoplasms at our institution in Taiwan and to compare the relative frequency of various types of lymphoma in different countries.
Methods: We retrospectively searched the files of patients diagnosed with lymphoma at our institution from 2000 to 2015 based on the 2016 Revision of the World Health Organization classification.
Results: We identified 1339 patients with lymphoid neoplasms; among them, eight had two distinct types of lymphoid neoplasms. Of the 1347 neoplasms, 6.09% were Hodgkin lymphomas (HLs) and 93.31%, non-HL (NHLs). Among the 1257 NHLs, 82.66% were of B-cell lineage and 17.34% of T-cell lineage. The most common B-cell lymphoma types were diffuse large B-cell lymphoma, follicular lymphoma, and mucosa-associated lymphoid tissue lymphoma. Among T-cell neoplasms, 37% cases were of nodal origin and 63% cases arose in extranodal sites. The most common nodal and extranodal T-cell neoplasms were angioimmunoblastic T-cell lymphoma and extranodal natural killer/T-cell lymphoma, nasal type, respectively.
Conclusion: We analyzed the largest series of lymphomas to date from Taiwan and concluded that HL was rare and T-cell neoplasms comprised around 17% of all NHLs in Taiwan. The

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relative frequency of the major lymphoma types is similar in East Asian countries, with only a minor difference, but the overall pattern in the East is quite different from that in the West, with the latter showing a higher frequency of HL and a lower rate of T-cell neoplasms.

Introduction

Lymphoid neoplasms are clonal lymphoproliferations and are heterogeneous in clinical presentation, histopathology, immunophenotype, and prognosis. Characterization and classification of lymphoid neoplasms are challenging and evolve with advances in technology. Currently, the 2008 World Health Organization classification is the gold standard in diagnosis and classification of lymphoid neoplasms.[1] Lymphoma types vary across geographic regions, reflecting the impact of ethnicity, socioeconomic status, and various environmental factors on lymphomagenesis.[2]

In our prior studies with smaller numbers of cases, we showed that the frequency of T and natural killer (NK)/T-cell lymphoma in Taiwan was higher than that in the Western countries and there was an increase in the frequency of follicular lymphoma (FL) in the early years of the 21st century in Taiwan.[3,4] In this study, we aimed to systematically review the cases of lymphoma at our institution in the first 16 years of the 21st century and to compare our data with those from different geographical regions.

Materials and methods

We retrospectively searched the files of patients diagnosed with lymphoma at our institution from January 2000 to December 2015. Diagnoses were made according to the 2008 World Health Organization classification of lymphoid neoplasms and the 2016 revision.[5] Plasma cell neoplasms were not included. This study was approved by the Internal Review Board of Chi-Mei Medical Center, Tainan, Taiwan and conducted in accordance with the Helsinki Declaration.

Diagnosis was based on detailed histopathological examination with the aid of immunohistochemistry and/or flow cytometric immunophenotyping. Clonality assay for B-cell and T-cell receptor gene rearrangement was performed for confirmation of clonality and exclusion of morphological mimics of lymphoma/leukemia. *In situ* hybridization for Epstein—Barr virus (EBV) encoded mRNA was applied for cases of peripheral T-cell lymphoma to exclude extranodal NK/T-cell lymphoma (ENKTL), nasal type as previously described.[6] Fluorescence *in situ* hybridization for common lymphoma-associated chromosomal translocation (*IGH*, *BCL2*, *BCL6*, *MYC*, and *CCND1*) was performed mainly for the identification of Burkitt lymphoma (BL) and high-grade B-cell lymphoma, NOS (previously called B-cell lymphoma, unclassifiable, with features between diffuse large B-cell lymphoma (DLBCL) and BL), and the differential diagnoses between cyclin D1-positive DLBCL versus mantle cell lymphoma as previously described.[7—9]

For primary splenic lymphomas, diagnoses were made based on morphological and flow cytometric immunophenotyping of the leukemic cells when present and histological evaluation plus immunohistochemistry of the splenectomy specimens. For those cases of primary splenic lymphoma with leukemic change (confirmed by flow cytometric immunophenotyping) but devoid of surgical or biopsy specimens, "splenic B-cell lymphoma/leukemia, unclassifiable" was diagnosed, since splenic marginal zone lymphoma (MZL), splenic diffuse red pulp small B-cell lymphoma, and even hairy cell leukemia variant may fall into this category if no splenic tissue can be obtained for histopathological examination.[10—12] Patients with lymphocytosis but devoid of organomegaly and not fulfilling the phenotypic criteria of chronic lymphocytic leukemia (CLL; dim CD20 expression and positivity for CD5, CD23, and CD43) were diagnosed with "unclassifiable small B-cell leukemia"; its neoplastic nature was confirmed by flow cytometric immunophenotyping and/or bone marrow aspiration biopsy as mature small B-cell leukemia. We separated lymphoplasmacytic lymphoma from other mature low-grade B-cell leukemia including "unclassifiable small B-cell leukemia" by: (1) morphological identification of plasmacytoid lymphocytes and plasma cells in addition to small lymphocytes in the marrow aspirate smears; (2) flow cytometric immunophenotyping of these plasmacytoid lymphocytes and plasma cells, which was distinct from the mature B-cell leukemic cells; and (3) presence of immunoglobulin M monoclonal gammaglobulin.

Transformed lymphoma, either at disease presentation or at relapse, was counted only once at initial diagnosis. For example, Grade 3A FL and DLBCL at the same site was diagnosed as FL. By contrast, coexistence of two distinct lymphomas, either synchronously or metachronously, is defined as two lymphomas. For example, one patient with primary cutaneous peripheral T-cell lymphoma not otherwise specified (PTCL-NOS) and subsequent development of DLBCL during the disease course was diagnosed as two kinds of lymphoma accordingly.

Results

A total of 1347 cases of lymphoid neoplasms were identified among 1339 patients, including eight with two distinct types of lymphoid neoplasms (1 synchronously and 7 metachronously). Among the 1347 cases, 6.09% (82 neoplasms) were Hodgkin lymphoma (HL), 93.31% (1257) were non-HL (NHL), and 0.59% (8) was other diseases [3 composite lymphomas, 2 mediastinal lymphoblastic lymphoma of ambiguous phenotypes (1 mixed T and myeloid and 1 mixed B, T, and myeloid lineages), 1 mediastinal gray zone lymphoma,

1 follicular dendritic cell sarcoma, and 1 Langerhans cell neoplasm].

In this series, HL accounted for around 6% of cases, comparable with the figures given in the East Asian studies of 4–8%, but significantly lower than 15–30% in the West (Table 1).[13–18] Interestingly, there was only one case of nodular lymphocyte-predominant HL among a total of 82 cases of HL, which meant that classical HL (CHL) accounted for 99% of all HL cases. The 81 CHL cases in our series were subclassified as nodular sclerosis (38 cases; 47%), mixed cellularity (22; 27%), lymphocyte-rich (18; 22%), and unclassifiable (3; 4%).

Among the 1257 neoplasms (NHL), 82.66% (1039 neoplasms) were of B-cell lineage and 17.34% (218) of T-cell lineage. Table 2 lists the case number and relative frequency of all types of B-cell neoplasms. The most common types were DLBCL, FL, and extranodal MZL of mucosa-associated lymphoid tissue (MALT lymphoma). If we classified primary mediastinal large B-cell lymphoma as DLBCL, FL with concurrent DLBCL as FL, and MALT lymphoma, splenic MZL, and nodal MZL as a single category of MZL, the most frequent B-cell neoplasms were DLBCL (50.62%), FL (16.27%), and MZL (12.70%). The second-tier most frequent B-cell neoplasms were CLL/small lymphocytic lymphoma (7.31%), unclassifiable small B-cell leukemia/lymphoma (3.27%), mantle cell lymphoma (2.50%), and BL (2.41%).

Table 3 lists the relative frequency of the 218 T-cell neoplasms. The most common types were angioimmunoblastic T-cell lymphoma (AITL; 18.3%), ENKTL, nasal type (16.5%), PTCL-NOS (15.1%), and systemic anaplastic large cell lymphoma (ALCL; 10.5%, including 5.0% anaplastic lymphoma kinase (ALK)-positive and 5.5% ALK-negative). The second-tier most frequent T-cell neoplasms were T-cell large granular lymphocytic leukemia (T-LGL leukemia; 7.3%), adult T-cell leukemia/lymphoma (4.1%), mycosis fungoides (4.1%), and primary cutaneous CD30-positive T-cell lymphoproliferative disorders [4.1%, including 1.4% (3 cases) of primary cutaneous ALCL and 2.8% (6) of lymphomatoid papulosis]. Ten of the 218 T-cell neoplasms were disseminated, involving both nodal and extranodal sites. They were considered tumors of indeterminate origin. Of the remaining 208 cases, 76 (37%) cases were nodal and 132 (63%) cases arose from extranodal sites. Among the nodal T-cell neoplasms, AITL was by far the most common (53%; 40 cases), followed by PTCL-NOS (21%; 16 cases), and systemic ALCL [17%, including 7 (9%) ALK-positive and 6 (8%) ALK-negative cases]. Of the 132 cases of extranodal T-cell neoplasms, the most common tumor types were ENKTL (35 cases; 26.5%), T lymphoblastic leukemia/lymphoma (18 cases; 13.6%), T-LGL leukemia (16 cases; 12.1%), and PTCL-NOS (10 cases; 7.6%).

Table 2 Relative frequency of 1039 B-cell non-Hodgkin neoplasms in Taiwan.

Lymphoma type	No.	%
B lymphoblastic leukemia/lymphoma	4	0.38
Chronic lymphocytic leukemia/small lymphocytic lymphoma	76	7.31
B-cell prolymphocytic leukemia	2	0.19
Unclassifiable small B-cell lymphoma/leukemia	34	3.27
Splenic marginal zone lymphoma	16	1.54
Hairy cell leukemia	1	0.10
Splenic B-cell lymphoma/leukemia, unclassifiable	9	0.87
Spleen-diffuse red pulp small B-cell lymphoma	3	0.29
Hairy cell leukemia variant	1	0.10
Lymphoplasmacytic lymphoma	14	1.35
Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)	97	9.34
Nodal marginal zone lymphoma	19	1.83
Follicular lymphoma	153	14.73
Follicular lymphoma with DLBCL	16	1.54
Mantle cell lymphoma	26	2.50
DLBCL	499	48.03
Primary mediastinal large B-cell lymphoma	27	2.60
Primary effusion lymphoma	6	0.58
Burkitt lymphoma	25	2.41
High-grade B-cell lymphoma, NOS	8	0.77
Plasmablastic lymphoma	2	0.19
Unclassifiable high grade B-cell lymphoma/leukemia	1	0.10

BL = Burkitt lymphoma; DLBCL = diffuse large B-cell lymphoma; high-grade B-cell lymphoma, NOS = the term in the 2016 Revision for "unclassifiable B-cell lymphoma with features intermediate between BL and DLBCL" used in the 2008 WHO classification.

Discussion

In this study, we reviewed the 1347 lymphoid neoplasm cases in the first 16 years of the 21st century in a single institution, which is by far the largest series in Taiwan. We confirmed the findings of our previous studies with smaller

Table 1 Hodgkin lymphoma and non-Hodgkin lymphoma in various countries/geographic regions.

Countries/region (case no.)	HL % (case no.)	NHL % (case no.)	B-cell lymphoma among NHL	T-cell lymphoma among NHL	Reference
USA (103,936)	9.96% (10,042)	90.34% (93,894)	93.37% (86,666/93,894)	6.63% (6228/93,894)	[21]
UK (5796)	14.41% (835)	85.59% (4961)	93.79% (4653/4961)	6.21% (308/4961)	[16]
Japan (1552)	5.22% (81)	93.62% (1453)	80.25% (1166/1453)	19.75% (287/1453)	[15]
Korea (5318)	4.12% (219)	95.88% (5099)	81.60% (4161/5099)	17.16% (875/5099)	[14]
China (4638)	8.60% (399)	91.40% (4239)	71.05% (3012/4239)	28.95% (1227/4239)	[13]
Taiwan (1347)	6.09% (82)	93.32% (1257)	82.66% (1039/1257)	17.34% (218/1257)	Current study

HL = Hodgkin lymphoma; NHL = Hodgkin lymphoma; UK = United Kingdom; USA = United States of America.

Table 3 Relative frequency of 218 T-cell non-Hodgkin neoplasms in Taiwan.

Lymphoma type	No.	%
T lymphoblastic leukemia/lymphoma	21	9.6
Angioimmunoblastic T-cell lymphoma	40	18.3
Extranodal NK/T-cell lymphoma, nasal type	36	16.5
Peripheral T-cell lymphoma, unspecified	33	15.1
Anaplastic large cell lymphoma, ALK-positive	11	5.0
Anaplastic large cell lymphoma, ALK-negative	12	5.5
T-cell large granular lymphocytic leukemia	16	7.3
Monomorphic epitheliotropic intestinal T-cell lymphoma	6	2.8
Adult T-cell leukemia/lymphoma	9	4.1
Aggressive natural killer cell leukemia	6	2.8
Mycosis fungoides	9	4.1
Lymphomatoid papulosis	6	2.8
Primary cutaneous anaplastic large cell lymphoma	3	1.4
Hepatosplenic T-cell lymphoma	3	1.4
Primary cutaneous CD4-positive small/medium T-cell lymphoproliferative disorder	2	0.9
Subcutaneous panniculitis-like T-cell lymphoma	2	0.9
Systemic EBV+ T-cell lymphoma of childhood	2	0.9
T-cell prolymphocytic leukemia	1	0.5

ALK = anaplastic lymphoma kinase; EBV = Epstein–Barr virus; NK = natural killer.

samples that showed a lower frequency (around 6%) of HL and a higher frequency of T-cell neoplasms (around 16% of all lymphoid neoplasms and 17% of all NHLs) as compared with the Western ones.[3,4,16] Furthermore, we identified eight patients with two distinct lymphomas, occurring at a frequency of 0.60% among 1339 patients with lymphoid neoplasms.

HL accounts for 15–30% of all lymphoid neoplasms in the West.[18] The great majority (90–95%) are CHL, with the remaining being nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) which accounts for 3–8% of HLs in Western countries.[19] The incidence of CHL is higher in affluent, industrialized nations than in developing countries.[18] As shown in Table 1, the frequency of HL is much lower in the East Asian countries as compared with the West; and the frequency of NLPHL is extremely low in the East, ranging from 1.2% to 3.7% among all HLs.[13–16] Interestingly, the frequency of NLPHL among all HLs is lower in the East as compared with the West.

Table 4 summarizes the relative frequency of the more common B-cell neoplasms in different geographic regions.[13–16,20–22] DLBCL is the most common type, accounting for four to five out of 10 lymphoma diagnoses. Among the East Asian countries, FL is the second most common B-cell neoplasms in Taiwan and Japan (16% and 24%, respectively). The reason for the increasing trend of FL in Taiwan is currently unknown. In a recent study, we used the epidemiological data during 1993–2012 from the Taiwan National Cancer Registry Database and confirmed a distinct increasing trend of FL with a strong birth-cohort effect in Taiwan, suggesting that lifestyle alternation is an important factor for the pathogenesis of FL (Wu et al, manuscript in preparation). Interestingly, the frequency of FL was exceedingly low in Korea and China (3% and 4%, respectively). In these two countries, MALT lymphoma was the second most common B-cell lymphoma type, most likely due to a higher prevalence of *Helicobacter pylori* infection and gastric MALT lymphoma in these two countries and the national endoscopy screening program for gastric cancer in Korea.[23,24] In Taiwan, the decreasing frequency of MZL was mostly due to the decreased frequency of gastric MALT lymphoma, the most common type of MZL. The main reason was probably due to the early eradication of *H. pylori* by gastroenterologists for patients with *H. pylori*-related chronic active gastritis and gastric ulcer. The eradication might lead to the decreased frequency of gastric MALT lymphoma, the well-known late complication of *H. pylori*-related gastritis.

Table 4 Relative frequencies of the common B-cell lymphoma types among all B-cell non-Hodgkin lymphoma (NHL) in various countries/geographic regions.

Countries/region (case no.)	DLBCL (case no.)	FL (case no.)	MALT lymphoma (case no.)	CLL/SLL (case no.)	MCL (case no.)	BL (case no.)	Reference
USA (n = 498,057)	38.92% (193,855)	20.48% (101,997)	9.94% (49,508)	22.28% (110,944)	4.91% (24,456)	1.92% (9543)	[22]
CSA (n = 809)	45.8% (371)	23.4% (189)	7.9% (64)	4.3% (35)	5.7% (46)	3.3% (27)	[20]
UK (n = 5488)	43.24% (2373)	16.82% (923)	17.91% (983)	Not included	4.50% (247)	1.88% (103)	[16]
Japan (n = 1166)	51.37% (599)	24.10% (281)	7.89% (92)	1.29% (15)[b]	3.00% (35)	0.60% (7)	[15]
Korea (n = 3399)[a]	47.75% (1623)	2.68% (91)	19.45% (661)	2.85% (97)	2.88% (98)	3.27% (111)	[14]
China (n = 3012)	55.78% (1680)	4.48% (135)	11.78% (355)	5.74% (173)	3.75% (113)	1.56% (47)	[13]
Taiwan (n = 1039)	48.03% (499)	16.27% (169)	7.89% (82)	7.31% (76)	2.50% (26)	2.41% (25)	Current study

BL = Burkitt lymphoma; CLL = chronic lymphocytic leukemia; CSA = Central and South America; DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; MALT = mucosa-associated lymphoid tissue; MCL = mantle cell lymphoma; SLL = small lymphocytic lymphoma; UK = United Kingdom; USA = United States of America.

[a] In this Korean study, plasma cell neoplasms (762 among a total of 4161 cases) were included. In the current table, plasma cell neoplasms were excluded for the purpose of comparison.

[b] In this Japanese study, only small lymphocytic lymphoma SLL but not CLL was included.

Table 5 Relative frequencies of the common mature T-cell lymphoma types among all T-cell non-Hodgkin lymphomas (NHLs) in various countries/geographic regions.

Countries/region (case no.)	AITL (case no.)	PTCL-NOS (case no.)	ENKTL (case no.)	ALCL, ALK+ and ALK− (case no.)	ATLL (case no.)	Reference
USA (n = 6228)	2.83% (176)	16.55% (1031)	NA	13.87% (864)	NA	[21]
CSA (n = 104)	Not specified	60.6% (63)	26.0% (27)	Not specified	9.6% (10)	[20]
UK (n = 308)	17.9% (55)	29.5% (91)	Not specified	14.9% (46)	Not specified	[16]
Japan (n = 287)	14.6% (42)	29.6% (85)	7.0% (20)	5.2% (15)	14.3% (41)	[15]
Korea (n = 667)	6.4% (43)	31.6% (211)	30.9% (206)	15.6% (104)	0.1% (1)	[14]
China (n = 1082)	6.28% (68)	16.82% (182)	47.04% (509)	10.26% (111)	0.09% (1)	[13]
Taiwan (n = 197)[a]	20.3% (40)	19.8% (39)	18.3% (36)	11.7% (23)	4.6% (9)	Current study

AITL = angioimmunoblastic T-cell lymphoma; ALCL = anaplastic large cell lymphoma; ALK = anaplastic lymphoma kinase; ATLL = adult T-cell leukemia/lymphoma; CSA = Central and South America; ENKTL = extranodal natural killer/T-cell lymphoma; NA = not available; PTCL-NOS = peripheral T-cell lymphoma, not otherwise specified; UK = United Kingdom; USA = United States of America.

[a] Twenty-one cases of T lymphoblastic leukemia/lymphomas in the current study were excluded for comparison of mature T-cell neoplasms.

The relative frequency of the more common T-cell neoplasms in various geographic regions is listed in Table 5. ENKTL is strikingly common in China, accounting for half of the T-lineage tumors, and is also numerous in Korea (about one third of the cases). The reason is unknown, although lifestyle and environmental factors such as farming, pesticide exposure, and living near incinerators might be risk factors.[25] In addition, the strong EBV association and racial predisposition suggest a genetic defect in the host immune response to EBV infection.[26,27] AITL is less common than PTCL-NOS in most East Asian countries. However, the relative frequency of AITL has increased in recent years in Taiwan when compared with the data from our previous studies.[3,28] In France AITL is currently the most common T-cell lymphoma as reflected in two new data sets.[29] One of the reasons for the increasing frequency of AITL might be a better understanding and recognition by pathologists of this entity, which was originally considered as an atypical immune response.[30] Since the better definition of this entity in the past two decades,[31–33] the frequency of this lymphoma type seems to be increasing. The prior low frequency of AITL in some studies might be "falsely" low as they might have been misdiagnosed as reactive/atypical lymphoid hyperplasia, particularly in the earlier lesions or partial nodal involvement with presence of residual germinal centers.[3,28,31–33]

The weakness of this study is that the data spanned 16 years and were from a single center in Taiwan, which may not be representative of the whole population in Taiwan. The other limitation was that one study author (SSC) was in charge of the diagnostic flow cytometric immunophenotyping and might have picked up more mature lymphoid leukemia cases (such as T-LGL leukemia) as compared with other pathology laboratories, which relied only on biopsy specimens for lymphoma diagnosis. Accordingly there might be a higher proportion of mature lymphoid leukemia in this study. However, the strength of the study is that we have longitudinal data, since one study author (SSC) has been continuously registering/filing all lymphoma cases for more than 20 years, which enables us to clearly subtype neoplasms in cases with two different types of lymphoid neoplasms.

In conclusion, we analyzed the largest series of lymphoma so far from Taiwan. We showed that HL was rare, accounting for around 6% of all lymphoid neoplasms, and T-cell neoplasms comprised around 17% of all NHLs. The frequency is similar to that in East Asian countries, with only a minor difference, but the overall pattern in the East is quite different from that in the West, where a higher frequency of HL and a lower rate of T-cell neoplasms were observed.

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