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CLINICAL REPORT

Cutaneous Lymphoma in Korea: A Nationwide Retrospective Study

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**For details, see Appendix S1[1]*

The epidemiological and clinicopathological features of cutaneous lymphoma may vary by geographical area. However, only a few large-scale epidemiological studies of cutaneous lymphoma have been performed, mainly in the USA and Europe. This aim of this study was to determine the recent characteristics of cutaneous lymphoma in Korea according to the WHO/EORTC classification. A total of 422 patients with newly diagnosed cutaneous lymphoma from January 2009 to December 2013 comprising 293 cases of mature T-cell and natural killer (NK)-cell lymphoma and 39 cases of mature B-cell lymphoma were retrospectively reviewed. The incidence of mature B-cell lymphoma was lower in Korea than in Europe and the USA. Diffuse large B-cell lymphoma was more prevalent in Korea than in Western countries. The incidence of extranodal NK/T-cell lymphoma, nasal-type was higher in Korea than in Western countries and Japan. *Key words: cutaneous lymphoma; large B-cell; epidemiology; Korea; World Health Organization-European Organization for Research and Treatment of Cancer classification.*

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Primary cutaneous lymphoma (CL) refers to extranodal lymphoma that presents in the skin without evidence of extracutaneous involvement at the time of diagnosis (1). It presents a distinctive clinical behaviour compared with systemic lymphoma, which subsequently involves the skin, and requires different management (2). In 2005, the WHO and European Organization for Research and Treatment of Cancer (EORTC) classification for CL was established (1). It defined some controversial types of CL, contributing to the standardized diagnostic criteria for CL (3). The current WHO classification (4th edn) in 2008 was the result of a periodic update. It integrated all entities for CL listed in the WHO/EORTC classification into a general classification of nodal and extranodal lymphoid tumours with only minor changes in terminology (2).

The epidemiological and clinicopathological features of CL may vary by geographical area. To date, only a few large-scale epidemiological studies of CL have been performed, mainly in the USA and Europe (1, 4, 5). To our knowledge, 3 epidemiological studies have been reported by dermatologists in Korea, but, of these, one nationwide study was outdated and the other 2 were not nationwide studies (3, 6, 7). Therefore, the Korean Dermatopathologic Research Group sought to demonstrate the recent epidemiological and clinicopathological characteristics of CL in the Korean population through a nationwide retrospective chart review according to the WHO/EORTC classification.

MATERIALS AND METHODS

Patients newly diagnosed with CL from January 2009 to December 2013 at 32 tertiary institutes distributed throughout the entire nation were enrolled in this study. All diagnoses were confirmed by both dermatologists and pathologists. A standardized case report form (CRF), organized by a single institute, was used and completed by the dermatologists in each institute. Age, sex, past history, duration, location or features of the lesion, extracutaneous involvement, histological findings, immunohistochemical findings, treatment modality, and disease course were included in the CRF. Exclusion criteria were: an incomplete CRF, reflecting an incompletely evaluated case, and an ambiguous diagnosis that did not coincide with the WHO/EORTC classification. Patients' data that overlapped between more than 2 institutes were also excluded.

RESULTS

Demographics and frequency of cutaneous lymphoma

A total of 422 cases of CL were diagnosed between 2009 and 2013 (Table I). Overall, the patients' age range was 4–93 years (median 49 years), and the study population comprised 259 males and 163 females (males:females 1.6:1). There were 333 cases of primary CL and 89 cases of secondary CL. Mature T-cell and natural killer (NK)-cell lymphoma was the most common type of CL, followed by mature B-cell lymphoma, precursor haematological neoplasm, and Hodgkin's lymphoma. Mature B-cell lymphoma was diagnosed

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Table I. *Total epidemiological data of 422 patients of cutaneous lymphoma (CL) including the frequency of primary cutaneous lymphoma (PCL) according to the WHO/European Organization for Research and Treatment of Cancer (EORTC) classification*

	Total		Age at diagnosis, years		
	CL, *n* (%)	PCL, *n* (%)	Median	Range	Sex (M:F)
Mature T-cell and natural-killer-cell lymphomas	343 (81.3)	293 (88)	47	4–92	1.5:1
Mycosis fungoides	163 (40.0)	163 (49)	47	4–92	1.6:1
Folliculotropic mycosis fungoides	3 (0.7)	3 (0.9)	60	37–70	2:1
Pagetoid reticulosis	0 (0.0)	0 (0.0)			
Granulomatous slack skin	1 (0.2)	1 (0.3)	40	40	0:1
Sézary syndrome	2 (0.5)	0 (0.0)	37.5	37–38	2:0
Adult T-cell leukaemia/lymphoma	0 (0.0)	0 (0.0)			
Cutaneous $CD30^+$ lymphoproliferative disorders	73 (17.3)	69 (20.7)	41	5–83	1.8:1
Lymphomatoid papulosis	32 (7.6)	32 (9.6)	32.5	5–78	1.7:1
Cutaneous anaplastic large cell lymphoma	41 (9.7)	37 (11.1)	47	9–83	1.9:1
Subcutaneous panniculitis-like T-cell lymphoma	15 (3.6)	15 (4.5)	29.5	23–75	0.3:1
Epstein-Barr virus-associated natural-killer/T-cell lymphoma	38 (9.0)	20 (6.0)	54	17–79	1.7:1
Extranodal natural-killer/T-cell lymphoma, nasal-type	36 (8.5)	18 (5.4)	57	18–79	1.9:1
Hydroa vacciniforme-like T-cell lymphoma	2 (0.5)	2 (0.6)	28.5	17–42	1.6:1
Cutaneous peripheral T-cell lymphoma, unspecified	44 (10.5)	26 (7.8)	50	26–89	1.1:1
Cutaneous $CD8^+$ aggressive epidermotropic cytotoxic T-cell lymphoma (provisional)	2 (0.5)	2 (0.6)	57	31–83	1:1
Cutaneous γ/δ^+ T-cell lymphoma (provisional)	7 (1.7)	6 (1.8)	53	36–82	0.75:1
Cutaneous $CD4^+$ small/medium-sized pleomorphic T-cell lymphoma (provisional)	9 (2.1)	9 (2.7)	52	24–75	1.3:1
Angioimmunoblastic T-cell lymphoma	8 (1.9)	0 (0.0)	61.5	47–79	7:1
Mature B-cell lymphomas	73 (17.3)	39 (11.7)	56	24–93	1.8:1
Cutaneous marginal zone B-cell lymphoma	16 (3.8)	15 (4.5)	41	24–70	1.8:1
Cutaneous follicle centre B-cell lymphoma	4 (1.0)	3 (0.9)	44.5	41–55	0.3:1
Cutaneous diffuse large B-cell lymphoma	50 (11.8)	21 (6.3)	62	37–90	2.5:1
Primary cutaneous diffuse large B-cell lymphoma, leg-type	19 (4.5)	19 (5.7)	57.5	37–87	3.5:1
Primary cutaneous diffuse large B-cell lymphoma, other	2 (0.5)	2 (0.6)	82.5	80–85	2:0
Intravascular large B-cell lymphoma	2 (0.5)	0 (0.0)	63	62–64	2:0
Burkitt lymphoma	1 (0.2)	0 (0.0)	53	53	1:0
Precursor haematological neoplasm	4 (0.9)	1 (0.3)	59.5	16–69	4:0
$CD4^+/CD56^+$ haematodermic neoplasm (formerly blastic natural-killer cell lymphoma)	4 (0.9)	1 (0.3)	59	16–69	4:0
Hodgkin's lymphoma	2 (0.5)	0 (0.0)	51.5	51–52	2:0
Total	422 (100)	333 (100)	49	4–93	1.6:1

in older patients compared with patients diagnosed with mature T-cell lymphoma (median 56 vs. 47 years).

Among the mature T-cell and NK-cell lymphomas, mycosis fungoides (MF) was most prevalent, followed by cutaneous $CD30^+$ lymphoproliferative disorders ($CD30^+$ LPDs), cutaneous peripheral T-cell lymphoma, unspecified (PTCL), extranodal NK/T-cell lymphoma, nasal-type (ENKL), and subcutaneous panniculitis-like T-cell lymphoma (SPTL). Lymphomatoid papulosis (LyP) and SPTL tended to be diagnosed in younger patients compared with other subtypes. Moreover, patients with SPTL exhibited a bimodal pattern of age at diagnosis and more than 3-fold female predominance.

The most common subtype of mature B-cell lymphomas was cutaneous diffuse large B-cell lymphoma (DLBCL), followed by cutaneous marginal zone B-cell lymphoma (MZBCL), and cutaneous follicle centre B-cell lymphoma (FCBCL). The majority of subtypes except FCBCL exhibited male predominance, with more than 3-fold male predominance observed for DLBCL, leg-type.

Extracutaneous involvement of secondary cutaneous lymphoma

Among the 89 cases of secondary CL, lymph nodes were the most frequently involved extracutaneous organs, accounting for 50.6% of secondary cases (Table II). Bone marrow and the ear, nose, and throat (ENT sites) were also highly prevalent extracutaneous organs. In particular, secondary ENKL had a tendency to involve ENT sites (88.9%) compared with other subtypes. DLBCL usually involved the lymph nodes (34.5%), bone marrow (31.0%) and ENT sites (27.6%). Secondary PTCL frequently involved the lymph nodes (77.8%) and bone marrow (55.6%).

Mycosis fungoides

A total of 116 patients (71.2%) clinically presented with patches, with 41 patients (25.2%) presenting with plaques. Most cases with MF were located on the trunk or lower extremities (Table III). Stage I, II, III and IV disease was diagnosed in 76.1%, 6.7%, 11.6% and 5.5% of patients, respectively. In total, 3 of 163 cases of MF were classified as folliculotropic MF, and one case was classified as granulomatous slack skin. Phototherapy (narrow-band ultraviolet B therapy and psoralen ultraviolet A therapy) and excimer laser were the most popular treatment modalities for MF. The prognosis was relatively good, with an overall response rate of 66.9%. However, 2 patients (1.2%) died of complications of chemotherapy (sepsis).

Table II. *Extracutaneous involvement of secondary cutaneous lymphoma at the initial work-up*

	Frequency (pathological confirmation)	
Extracutaneous organ	*n*	%
Lymph node	45 (31)	50.6 (34.8)
Bone marrow	34 (34)	38.2 (38.2)
Ear, nose, throat	29 (22)	32.6 (24.7)
Spleen	12	13.5
Lung	8 (1)	9 (1.1)
Bone	8 (1)	9 (1.1)
Liver	7	7.9
Gastrointestinal organ	4 (2)	4.5 (2.2)
Central nervous system	3 (2)	3.4 (2.2)
Adrenal gland	3	3.4
Peripheral nerve	2 (1)	2.2 (1.1)
Testis	1 (1)	1.1 (1.1)
Muscle	1	1.1
Total patients	89	100

CD30⁺ lymphoproliferative disorders

Most cases diagnosed with primary ALCL manifested as nodules or plaques. Anaplastic lymphoma kinase (ALK)-1 immunostaining, which was performed for 10 patients, was negative in all cases. However, among patients with secondary ALCL, ALK-1 staining was positive in 2 of 4 patients. Primary ALCL was usually treated by chemotherapy and radiotherapy. When the lesion was solitary, surgical excision was performed. The overall response rate was 48.6%, despite a high rate of follow-up loss.

Patients with LyP were relatively young compared with those diagnosed with other subtypes, with an age range of 5–78 years (median 32.5 years). A bimodal age distribution was not observed. Phototherapy/excimer laser were the most commonly used treatment. The overall response rate was 40.6%, which was similar to that for primary ALCL.

Extranodal NK/T-cell lymphoma, nasal-type

Patients with primary ENKL were younger than those with secondary ENKL, with median ages of 54 years and 60 years, respectively. More than 3-fold male predominance was observed among patients with secondary ENKL (males:females 3.6:1). In the secondary ENKL group, the extracutaneous origin of the neoplasm was mainly the nasal cavity (88.9%), rarely the tonsils (5.6%) and the testis (5.6%). ENKL displayed a relatively aggressive course; therefore, most patients were treated with chemotherapy. In the primary ENKL group, 22.4% of patients died, throughout the follow-up period. Secondary ENKL exhibited highly aggressive features with higher mortality rates, including 8 cases (44.4%) of bone marrow involvement and 11 deaths (61.1%).

DISCUSSION

In the present study, we aimed to perform the largest study in Korea to demonstrate the recent epidemiological and clinicopathological characteristics of CL. It was a nationwide multicentre study, which included 32 tertiary institutes. In addition, only Korean patients were enrolled, which minimized racial variation. It is distinctive that patients with both primary and secondary CL were included in this study, compared with several previous reports that included only patients with primary CL.

Table III. *Clinical data of mycosis fungoides (MF), primary cutaneous anaplastic large cell lymphoma (pcALCL), lymphomatoid papulosis (LyP), extranodal NK/T-cell lymphoma, nasal-type(ENKL), and primary cutaneous diffuse large B-cell lymphoma (pcDLBCL)*

	MF *n* = 163 *n* (%)	pcALCL *n* = 37 *n* (%)	LyP *n* = 32 *n* (%)	Primary ENKL *n* = 18 *n* (%)	Secondary ENKL *n* = 18 *n* (%)	pcDLBCL *n* = 21 *n* (%)
Location						
Head/neck	39 (24.0)	7 (18.9)	11 (34.0)	5 (27.8)	4 (22.2)	5 (23.8)
Trunk	105 (64.4)	10 (27.0)	21 (65.6)	6 (33.3)	11 (61.1)	4 (19.0)
Upper extremities	71 (43.6)	15 (40.5)	25 (78.1)	6 (33.3)	4 (22.2)	4 (19.0)
Lower extremities	103 (63.2)	16 (43.2)	26 (81.3)	11 (61.1)	7 (38.9)	10 (47.6)
Treatment						
Chemotherapy	15 (9.2)	11 (29.7)	–	11 (61.1)	18 (100)	17 (81.0)
Phototherapy/excimer laser[a]	130 (79.8)	3 (8.1)	12 (37.4)	2 (11.1)	–	–
Radiotherapy	12 (7.4)	7 (18.9)	–	1 (5.6)	4 (22.2)	6 (28.6)
Methotrexate	10 (6.0)	5 (13.5)	10 (31.0)	–	–	1 (4.8)
Vitamin A derivatives[b]	16 (9.8)	–	–	–	–	–
Systemic steroid	6 (3.7)	–	–	–	2 (11.1)	–
Topical steroid	33 (20.2)	–	8 (25)	–	–	–
Surgical excision	1 (0.6)	5 (13.5)	2 (6.2)	–	–	1 (4.8)
Peripheral blood stem cell transplantation	–	–	–	–	3 (16.7)	1 (4.8)
Observation	4 (2.5)	4 (10.8)	4 (12.5)	2 (11.1)	–	2 (9.5)
Clinical course						
Complete response	50 (30.7)	13 (35.1)	9 (28.1)	4 (22.2)	0 (0.0)	6 (28.6)
Partial response	59 (36.2)	5 (13.5)	4 (12.5)	2 (11.2)	2 (11.1)	3 (14.3)
Follow-up loss	44 (27.0)	15 (40.5)	14 (43.8)	6 (33.6)	5 (27.8)	7 (33.3)
Recurrence	8 (4.9)	2 (5.4)	5 (15.6)	2 (11.2)	0 (0.0)	3 (14.3)
Death	2 (1.2)	2 (5.4)	0 (0.0)	4 (22.4)	11 (61.1)	2 (9.5)

[a]Phototherapy include narrow-band ultraviolet B therapy and psoralen ultraviolet A therapy; [b]Vitamin A derivatives include acitretin and isotretinoin.

Among the patients with primary CL, mature T-cell and NK-cell lymphoma, mature B-cell lymphoma, and precursor haematological neoplasms accounted for 88%, 11.7% and 0.3%, respectively. Compared with the data of 1,733 patients with primary CL from the Japanese Skin Cancer Society Lymphoma Study Group (8), which reported that 85.7% of patients had mature T-cell and NK-cell lymphoma and 12.9% of patients had mature B-cell lymphoma, there were remarkable similarities with our study (Fig S1A[1], Table SI[1]). However, compared with the data of 1,905 patients with primary CL registered with the Dutch and Austrian Cutaneous Lymphoma Group (DACLG) (1), mature B-cell lymphoma was less common in our study (11.7% vs. 23%). In addition, Surveillance, Epidemiology and End Results (4) data from the USA population illustrated that mature B-cell lymphoma accounted for 28.5% of all lesions.

The frequencies of subtypes of the mature T-cell and NK-cell lymphoma in our study were similar to data reported in Japan (8) and Europe (1) (Fig S1B[1], Table SI[1]). However, the incidence of primary SPTL was higher in our study than in Western countries (1%, 0.6% and 4.5% in Europe (1), the USA (4) and our study, respectively). According to the data from Japan, a relatively low frequency of each subtype was observed, which might have resulted from the higher frequency of adult T-cell leukaemia/lymphoma (ATLL). ATLL is caused by malignant $CD4^+$ T-lymphocytes infected with the human T-cell lymphotropic virus type (HTLV)-1 (9). Therefore, high-prevalence regions of HTLV-1, such as Southwest Japan, Central and South America, were included in the endemic area of ATLL (8, 10).

Chemotherapy was the most commonly used treatment for primary ALCL in our study. The 11 patients (29.7%) treated with chemotherapy had generalized or rapidly progressing skin lesions. Treating with chemotherapy instead of radiotherapy or surgical excision might result in overtreatment. The individual preference of oncologists for chemotherapy might have influenced treatment choice.

Concerning ENKL, it is known to develop more frequently in East Asia and Central America than in Europe and the USA (11, 12), and our data were consistent with previous reports (primary ENKL; 1%, 0.3% and 5.4% in Europe (1), the USA (4), and our study, respectively). However, the incidence of ENKL in Japan was much lower than our results (primary ENKL; 2.3% vs. 5.4%) (8). According to other single-institution studies from Japan, ENKL comprised between 3.8% and 8.1% of cases of CL (13, 14). It is speculated that this discordance might have resulted from selection bias caused by the single-institution nature of the studies. The reason why the frequency of ENKL was higher in Asian population has not been fully explained. ENKL is strongly associated with Epstein-Barr virus (EBV) in all geographical areas studied (15). The association is much stronger in the Asian populations, varying from 75% to 100% (16). Some studies in the Caucasian population also detected a strong, but not invariable, association between EBV and ENKL (16, 17). Therefore, the difference in the frequency of ENKL according to the geographical area might be partially explained by the difference in EBV epidemiology (18). Moreover, it is suggested that racial variations, such as human leukocyte antigen determinants, may also play a role in the development of ENKL (7).

In particular, 2 cases were diagnosed as hydroa vacciniforme-like T-cell lymphoma, which has not been described in previous epidemiological studies. It is an exceedingly rare type of EBV-associated lymphoma and is more common in children and young adults in Asia and South America (10). Both patients were positive for EBV according to *in situ* hybridization.

Among mature B-cell lymphomas, DLBCL was the most common subtype. Unlike our data and Japanese data (8), FCBCL was the most common subtype in Europe (1) and Brazil (10) among mature B-cell lymphomas (Fig S1C[1], Table SI[1]).

Two previous Korean reports were also compared with our data. Park et al. (3) enrolled 164 patients with CL in one tertiary institute and Lee et al. (6) enrolled 93 patients with primary CL in 7 tertiary institutes. According to both reports, MF was less common compared with our data (21.9%, 33.3% and 49% in Park et al., Lee et al., and our study, respectively). Furthermore, ENKL accounted for a higher proportion in the study by Park et al. than in our study (primary ENKL; 16.7% vs. 5.4%). This finding could be explained by selection bias, which may have arisen from the inclusion of only relatively large institutions in Korea in both previous reports. It is reasonable that ENKL, which has a relatively poor prognosis, could be more frequently followed up in relatively large institutions.

Compared with a previous nationwide epidemiological study in Korea, conducted from 1998 to 2000 (7), the frequency of mature B-cell lymphoma was greatly increased in our study (Table SI[1]). Although only 80 cases of CL were evaluated in the previous report, the significant increase in the incidence of mature B-cell lymphoma is worthy of attention. In terms of the frequency of mature T-cell and NK-cell lymphoma, the frequencies of ENKL and SPTL decreased remarkably. These transformed epidemiological patterns of CL result in similar findings as observed in Western countries. Contrary to ENKL, the incidence of PTCL was increased compared with previous findings. This might be explained by the fact that primary cutaneous aggressive epidermotropic $CD8^+$ cytotoxic T-cell lymphoma, primary cutaneous γδ T-cell lymphoma, and primary cutaneous small/medium $CD4^+$ T-cell lymphoma were included in PTCL as a provisional entity in the new WHO-EORTC classification, compared with the WHO classification in 2001 (1). The frequency of the subtypes of mature B-cell

lymphoma in the previous study in Korea could be inaccurate because the number of patients was small, including only 2 cases of FCBCL and one case of MZBCL. Recently, a group of pathologists in Korea also reported a nationwide study on the incidence of CL (19). However, in their report, CL was diagnosed only by histological findings, without considering clinical findings, such as the features of the lesion, extracutaneous involvement, treatment modalities, and disease course.

In our data, the median age at diagnosis was 49 years, which was similar to that in previous Korean studies (median 46.2 (7), 47.1 (3) and 52 years (6)). However, the age at diagnosis for each subtype was relatively young compared with that in Japan (median 65 years) (8). Moreover, mature B-cell lymphoma was diagnosed in older patients compared with patients diagnosed with mature T-cell lymphoma (median 56 vs. 47 years). In particular, LyP and SPTL were diagnosed in younger patients compared with other subtypes (median 32.5 and 29.5 years for LyP and SPTL, respectively). Only SPTL displayed a bimodal age distribution in our study, whereas both SPTL and LyP exhibited a bimodal distribution in Japan (8). Male predominance was observed in almost all subtypes, excluding SPTL and FCBCL. Female predominance in SPTL was also observed in previous reports of Korea, Japan and USA (4, 6, 8). Female predominance in FCBCL was only seen in the previous report of Korea (6). In particular, male predominance was more prominent in secondary CL (males:females 2.7:1).

In conclusion, we investigated the nationwide epidemiological features of CL in Korea and confirmed the geographical and racial differences. The incidence of primary cutaneous mature B-cell lymphoma was lower in Korea than in European countries and the USA; however, its incidence has increased over the past 10 years. Primary DLBCL was a more prevalent subtype of mature B-cell lymphoma in Korea than in Western countries. Moreover, the incidence of primary ENKL was higher in Korea than in European countries, the USA, and even Japan, although its incidence has decreased over the past 10 years.

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The authors declare no conflicts of interest.

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