INVESTIGATIVE REPORT

Relative Frequency, Clinical Features, and Survival Outcomes of 395 Patients with Cutaneous Lymphoma in Korea: A Subgroup Analysis per 10-year Period

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Long-term changes in the relative frequency of cutaneous lymphoma (CL) have not been investigated in Asian populations. The aim of this study was to investigate the relative frequency, clinical characteristics, and survival outcomes of CL in Korean patients, and to evaluate the changes in relative frequency of CL over a 20-year period. The present retrospective cohort study included 395 patients, of whom 289 had primary CL and 106 secondary CL, seen at a tertiary referral hospital in Seoul, Korea. Primary CL included T-/NK-cell lineage lymphoma (CTCL, 85.1%) and B-cell lineage lymphoma (CBCL, 14.9%). The relative frequency of CBCL increased over time, as shown by a decrease in the CTCL/CBCL ratio from 10.3 in 1994 to 2003 to 4.5 in 2004 to 2013. CTCL was more commonly associated with multiple and extensive skin lesions than CBCL. Extranodal NK/T-cell lymphoma and subcutaneous panniculitis-like T-cell lymphoma were commonly associated with extensive skin lesions. The 5-year overall survival rate for all patients with primary CL was 81%. Key words: lymphoma; skin; relative frequency; survival outcome; primary cutaneous lymphoma.

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Several studies have documented the incidence and relative frequency of cutaneous lymphoma (CL), although most of this earlier work has focused on primary cutaneous lymphoma (PCL) (1–6). Cases of PCL account for 19% of extranodal non-Hodgkin’s lymphomas and represent a diverse group of lymphoid neoplasms that manifest heterogeneous clinical, histological, cytogenetic, and molecular features (7). In 2005, the WHO-EORTC joint PCL classification system was established (8). Studies on the incidence of CL according to age, race, sex, and stage have shown racial disparities in terms of the age and stage of presentation (9, 10). In Asia, there have been few reports from Korea, Japan, and Singapore (11–15), whilst large-scale studies on CL have been performed mainly in the USA and Europe (3, 7, 16, 17). Few reports include patients in the Asia-Pacific region, and all such studies are limited by relatively small sample sizes (13–15, 18, 19).

The aim of this retrospective cohort study was to assess the relative frequency, clinical characteristics, and survival outcomes of CL by reviewing the medical records of 395 patients who presented to the dermatology department of a tertiary referral hospital in Korea and were diagnosed with CL, as defined by the WHO-EORTC classification system. A further aim was to measure changes in CL relative frequency trends by comparing subgroups of patients diagnosed in one of the two 10-year periods between 1994 and 2013. In addition, the clinical features and survival outcomes according to cell lineage of PCL were investigated. Since we have previously reported the clinical features and survival outcomes of secondary cutaneous lymphoma (SCL) (20), the present study focused mainly on PCL.

METHODS

After obtaining approval from the Institutional Review Board of the Asan Medical Center, the centre’s database was searched for all cases of CL that had been confirmed by skin biopsy between January 1994 and December 2013. PCL was defined as non-Hodgkin’s lymphoma that was present in the skin with no evidence of extracutaneous disease at the time of diagnosis. Mycosis fungoides (MF) and Sézary syndrome were classified as PCL, even when extracutaneous dissemination was noted at the time of diagnosis. SCL was defined as skin lesions that developed after the diagnosis of systemic disease that was not characterized by skin lesions at the time of initial diagnosis. CL was classified according to the 2005 WHO-EORTC classification system (8).

Variables studied

Subgroup analysis per 10-year period between 1994 and 2013 was performed. The following clinical data were collected from the patient medical records: age at diagnosis; sex; location, multiplicity, extent, and morphology of the skin lesion(s); follow-up results; and survival. The degree of skin involvement in MF was evaluated according to the proposed tumour-node-metastases (TNM) classification system for MF (21). The extent of skin lesions in PCLs other than MF was evaluated using the International Society for Cutaneous Lymphomas (ISCL)-
EORTC TNM classification (22). The number of skin lesions was grouped as single or multiple (≥2 lesions). Overall survival (OS) was calculated from the date of initial diagnosis to the date of death from any cause or the last follow-up examination.

**Statistical analysis**

Comparison between subgroups was performed using a χ² test for categorical variables and a t-test or Mann-Whitney test for continuous variables. Survival was analysed using the Kaplan–Meier method. Differences between subgroups in terms of survival were tested for significance using the log-rank test. The end-point was patient death or the last follow-up. For surviving patients, the study end-point was 31 December 2014. All analyses were performed with a statistical software package (SPSS, version 18.0; SPSS Inc., Chicago, IL, USA). p-values < 0.05 were considered to indicate statistical significance.

**RESULTS**

**Relative frequency of cutaneous lymphoma**

A retrospective review of the medical database of the Asian Medical Center between January 1994 and December 2013 revealed 395 cases of CL. Of these, 289 cases were PCL and 106 cases were SCL. Among the 289 cases of PCL, 246 (85.1%) were T-/NK-cell lineage PCL (244 (84.4%) of mature T-/NK-cell lymphoma and 2 (0.7%) of blastic plasmacytoid dendritic cell neoplasm (BPDCN)), and 43 (14.9%) were B-cell lineage lymphoma (40 (13.8%) of mature B-cell lymphoma and 3 (1.0%) of B-cell lymphoblastic lymphoma (LBL)). Of the 106 SCL cases, 68 (64.1%) were T/NK-cell lineage lymphoma (59 (55.7%) of mature T/NK-cell lineage lymphoma and 9 (8.5%) of immature haematopoietic malignancy) and 38 (35.8%) were B-cell lineage lymphoma cases (37 (34.9%) of mature B-cell lymphoma and 1 (0.9%) of Hodgkin’s lymphoma).

PCL cases included 85 (29.4%) of MF, 46 (15.9%) of lymphomatoid papulosis (LYP), 34 (11.8%) of anaplastic large cell lymphoma (ALCL), 30 (10.4%) of peripheral T-cell lymphoma (PTCL), unspecified, 28 (9.7%) of extranodal natural killer (NK)/T-cell lymphoma (NKTL), 21 (7.3%) of subcutaneous panniculitis-like T-cell lymphoma (SPTL), 24 (8.3%) of marginal zone B-cell lymphoma (MZBL), 14 (4.8%) of diffuse large B-cell lymphoma (DLBCL), 1 (0.4%) of follicle centre lymphoma (FCL), 3 (1.0%) of LBL, 2 (0.7%) of BDPCN, and 1 (0.4%) of intravascular B-cell lymphoma (Table I). MF with large cell transformation was differentiated from LYP and ALCL. ALCL was defined based on histopathological findings characterized by cohesive sheets with predominance (>75%) of large CD30-positive cells showing anaplastic, pleomorphic, or immunoblastic morphology.

The most frequent SCL subtype was DLBCL (n = 31, 29.2%), followed by PTCL (n = 22, 20.8%), NKTL (n = 20, 18.9%), ALCL (n = 11, 10.4%), LBL (n = 7, 6.6%), and angioimmunoblastic lymphoma (n = 5, 4.7%). These data are summarized in Table I.

**Table I. Relative frequency and demographic data for patients with cutaneous lymphoma in this study and in reports from other countries**

<table>
<thead>
<tr>
<th>T-cell lymphoma</th>
<th>This study</th>
<th>Korea (7)</th>
<th>Swiss (1)</th>
<th>Netherlands (2)</th>
<th>Austrian (8)</th>
<th>Age distribution</th>
<th>Sex distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age distribution</td>
<td>Mean (range)</td>
<td>Sex distribution (male:female)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mature T- and natural killer-cell lymphoma</td>
<td>n = 289</td>
<td>n = 106</td>
<td>n = 96</td>
<td>n = 263</td>
<td>n = 1,905</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mature B-cell lymphoma</td>
<td>n = 40</td>
<td>n = 37</td>
<td>n = 34.9</td>
<td>n = 28</td>
<td>n = 22.5</td>
<td>49.3 (15–81)</td>
<td>1:1</td>
</tr>
<tr>
<td>Adult T-cell lymphoma/leukaemia</td>
<td>n = 0</td>
<td>n = 1</td>
<td>n = 0.9</td>
<td>n = 0</td>
<td>n = 0</td>
<td>No data found</td>
<td>No data found</td>
</tr>
<tr>
<td>Mature B-cell lymphoma</td>
<td>n = 24 (8.3)</td>
<td>n = 1 (0.9)</td>
<td>n = 9.4</td>
<td>n = 14</td>
<td>n = 6.7</td>
<td>42.2 (15–74)</td>
<td>0.71:1</td>
</tr>
<tr>
<td>Cutaneous follicle centre lymphoma</td>
<td>n = 1 (0.4)</td>
<td>n = 0</td>
<td>n = 0</td>
<td>n = 8</td>
<td>n = 10.9</td>
<td>52 (52)</td>
<td>1:0</td>
</tr>
<tr>
<td>Cutaneous diffuse large B-cell lymphoma, leg type</td>
<td>n = 14 (4.8)</td>
<td>n = 0</td>
<td>n = 4</td>
<td>n = 4</td>
<td>n = 4.4</td>
<td>60.3 (37–81)</td>
<td>1:8:1</td>
</tr>
<tr>
<td>Cutaneous diffuse large B-cell lymphoma, others</td>
<td>n = 0</td>
<td>n = 31</td>
<td>n = 29.2</td>
<td>n = 2.1</td>
<td>n = 0</td>
<td>62 (62)</td>
<td>0:1</td>
</tr>
<tr>
<td>Intravascular large B-cell lymphoma</td>
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<td>n = 0</td>
<td>n = 1</td>
<td>n = ND</td>
<td>n = ND</td>
<td>ND</td>
<td>1:0</td>
</tr>
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<td>No data found</td>
</tr>
<tr>
<td>Mantle cell lymphoma</td>
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<td>n = 1</td>
<td>n = 0.9</td>
<td>n = ND</td>
<td>n = ND</td>
<td>No data found</td>
<td>No data found</td>
</tr>
<tr>
<td>Immature haematopoietic malignancies</td>
<td>n = 5 (1.7)</td>
<td>n = 9 (8.5)</td>
<td>n = 1</td>
<td>n = ND</td>
<td>n = ND</td>
<td>13.6 (1–34)</td>
<td>1:5:1</td>
</tr>
<tr>
<td>Lymphoblastic lymphoma</td>
<td>n = 3 (1.0)</td>
<td>n = 7 (6.6)</td>
<td>n = 1</td>
<td>n = ND</td>
<td>n = ND</td>
<td>5.7 (1–11)</td>
<td>3:0</td>
</tr>
<tr>
<td>Blastic plasmacytoid dendritic cell neoplasm</td>
<td>n = 2 (0.7)</td>
<td>n = 2 (1.9)</td>
<td>n = ND</td>
<td>n = ND</td>
<td>n = ND</td>
<td>25.5 (17–34)</td>
<td>0:2</td>
</tr>
</tbody>
</table>

*Primary cutaneous lymphoma patients. Secondary cutaneous lymphoma.
Demographics of the patients with CL

Demographic data for the patients with CL according to cell lineage are listed in Table SI1. Analysis of the age and sex ratio in the lymphoma subtypes revealed that patients with cutaneous B-cell lineage lymphoma (CBCL) were significantly older than those with cutaneous T-/NK-cell lineage lymphoma (CTCL) in both the PCL ($p=0.031$) and SCL ($p=0.027$) groups. Patients with SCL were significantly older than patients with PCL ($p=0.023$), while LYP, SPTCL, and LBL typically affected younger individuals (Table I).

Changes in the relative frequency of PCL

The relative frequency of PCL during the 1994 to 2003 and 2004 to 2013 periods are summarized in Table II. The most common subtype of PCL in both the 1994 to 2003 and 2004 to 2013 periods was MF. The relative frequency of B-cell lineage PCL was significantly higher in the more recent 10-year period than in the previous 10-year period ($p=0.033$), which is indicated by a CTCL/CBCL ratio of 10.3 (93/9) in 1994 to 2003 compared with 4.5 (153/34) in 2004 to 2013. The relative frequency of extranodal NKTL decreased from 13.7% to 7.5%. A decreasing trend in the relative frequency of LYP over time was also found. An increasing tendency was observed in the relative frequency of MZBL, from 4.9% to 10.2%, and in DLBCL, from 2.9% to 5.9%, over the 2 decades.

Changes in the relative frequency of SCL

The relative frequency of SCL in subgroups per 10-year period between 1994 and 2013 is summarized in Table SIII1. There was a statistically significant increase in the relative frequency of B-cell lineage SCL over time ($p<0.001$), which is indicated by a CTCL/CBCL ratio of 4.5 (27/6) in 1994 to 2003 decreased to 1.3 (41/32) in 2004 to 2013. The relative frequency of DLBCL increased significantly, from 12.1% (4/33) to 35.6% (26/73), in the 10-year subgroups between 1994 and 2013. The most common type of SCL changed from PTCL in 1994 to 2003 to DLBCL in 2004 to 2013.

Characteristics of the cutaneous lesions in PCL

The clinical features of patients with CL are summarized in Table SIV1. The most common clinical features in MF and LYP were patch lesions and papules, respectively, but cutaneous nodules were the most common clinical manifestations in all other subtypes of PCL. Cellulitis-like swelling or ulceration was noted in patients with extranodal NKTL and SPTL. The trunk was the most common site for T-/NK-cell lineage PCL (134/246, 54.5%), followed by the leg (124/246, 50.4%), the arm (108/246, 43.9%), and the head and neck area (59/246, 24%). Skin lesions in B-cell lineage PCL patients were most commonly located in the head and neck area (23/43, 53.5%), and anatomical distribution was significantly different compared with those of a T-/NK-cell lineage PCL ($p<0.001$). The most common B-cell lineage PCL, MZBL was characterized with a cutaneous nodule on the eyelid (18/24, 75%).

Survival outcomes in primary cutaneous lymphoma

The clinical features of patients with CL are summarized in Table SIII1. The most common clinical features in MF and LYP were patch lesions and papules, respectively, but cutaneous nodules were the most common clinical manifestations in all other subtypes of PCL. Cellulitis-like swelling or ulceration was noted in patients with extranodal NKTL and SPTL. The trunk was the most common site for T-/NK-cell lineage PCL (134/246, 54.5%), followed by the leg (124/246, 50.4%), the arm (108/246, 43.9%), and the head and neck area (59/246, 24%). Skin lesions in B-cell lineage PCL patients were most commonly located in the head and neck area (23/43, 53.5%), and anatomical distribution was significantly different compared with those of a T-/NK-cell lineage PCL ($p<0.001$). The most common B-cell lineage PCL, MZBL was characterized with a cutaneous nodule on the eyelid (18/24, 75%).

More than 90% of MF and LYP patients, and only approximately half (81/158, 51.2%) of patients with PCL other than MF and LYP, presented with multiple skin lesions. When we analysed the multiplicity of skin lesions excluding MF and LYP, T-/NK-cell lineage PCL (70/115, 60.9%) was more commonly associated with multiple skin lesions than B-cell lineage PCL (11/43, 25.6%, $p<0.001$). The TNM classification in PCL cases is indicated in Table SIV1. Erythroderma (T4 category) was noted in 6 of 85 (7.1%) patients with MF. Evaluation using the ISCL-EORTC TNM classification in PCL other than MF showed that T3 category was found in 49.6% (57/115) of T-/NK-cell lineage PCL cases (excepting MF and LYP) and 9.3% (4/43) of B-cell lineage PCL cases. Among PCL subtypes SPTL (17/21, 80.9%) and NKTL (15/28, 53.6%) were most commonly associated with T3 category (extensive skin lesions). There was a significant difference in the extent of skin lesions between T-/NK-cell lineage PCL and B-cell lineage PCL ($p<0.001$).

Lymph node involvement was detected during disease course in 37 (15.0%) of the 246 T-/NK-cell lineage PCL cases and in 8 (18.6%) of the 43 B-cell lineage PCL cases, but this difference was not statistically significant ($p=0.552$, Table SIV1). The frequency of extracutaneous visceral involvement did not differ between T-/NK-cell lineage PCL (8.1%) and B-cell lineage PCL (7.0%; $p=0.797$, Table SIV1). Extracutaneous lymph

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node and viscera dissemination, in 54% and 43% of patients, respectively, was most common in extranodal NKTL among all subtypes of PCL (Table SIV1).

**Survival outcomes of patients with PCL**

The follow-up period of all patients ranged from 1 to 276 months (median follow-up, 49.5 months). Of the 289 patients with PCL in the study cohort, 44 (15.2%) died of disease between 1 and 168 months after initial diagnosis (T-/NK-cell lineage PCL: 1–168 months, median 25 months; B-cell lineage PCL: 7–68 months, median 39 months). Survival outcomes according to PCL subtype are summarized in Table II and Fig. 1a. The 5-year OS rate for all 289 PCL patients irrespective of diagnosis was 81%. No significant difference in the 5-year OS rate was seen between T-/NK-cell lineage PCL and B-cell lineage PCL groups (p = 0.686, Fig. 1b). Survival outcomes in T-/NK-cell lineage PCL patients when MF and LYP were excluded were also not different from those of B-cell lineage PCL patients (p = 0.193). Extranodal NKTL was associated with the poorest survival outcomes (2-year OS rate: 57%, 5-year OS rate: 24%), with a median OS of 37 months (95% confidence interval (95% CI): 23.45–50.55 months). DLBCL, leg type showed the worst prognosis among B-cell lineage PCL (5-year OS rate: 65%, median OS: 67 months (95% CI: 39.29–91.23 months)). When survival outcomes of MF were compared between the 2 10-year subgroups, no significant change in the OS was observed (p = 0.329).

**DISCUSSION**

CL involves the skin in either a primary or secondary manner. Because of the rarity of PCL, which has an estimated annual incidence of 1:100,000, epidemiological data are lacking (23). In our present study, the mean age of patients with PCL was 43.9 years, which is similar to the mean age reported previously for PCL (40–50 years) (18, 19, 24). Our current findings showed that patients with B-cell lineage PCL were older than patients with T-/NK-cell lineage PCL, which is also in agreement with previous reports (15, 19, 24). LYP, SPTL and LBL more often occurred in younger individuals compared with other subtypes.

Studies on the incidence of CL according to age, race, sex, and stage have shown racial disparities in terms of patient age and stage at presentation (9, 10). Geographical and racial variations may contribute to the differences in patterns of CL subtypes among previous studies. The subtype distribution of malignant lymphoma other than CL also indicated geographical variations, such as a higher proportion of Asian patients with mature T-/NK-cell lineage lymphoma and mucosa-associated lymphoid tissue (MALT) lymphoma and lower proportion with follicular lymphoma compared with Western populations (25). The higher proportions of MALT lymphoma and NKTL are attributed to the high prevalence of *Helicobacter pylori* and Epstein-Barr virus (EBV), respectively, in Asian countries (25).

The incidence of T-/NK-cell lineage PCL appears to be higher in Asians than in Westerners (1, 7, 13, 15,
The proportion of B-cell lineage PCL in Asians was lower than that in Western populations (1, 7, 13, 15, 19, 24). Similarly, compared with data based on Western patients with PCL, the present results showed a higher rate (85.1%) of T-/NK-cell lineage PCL and a lower rate (14.9%) of B-cell lineage PCL in our Asian population. An analysis of the relative frequency of SCL also demonstrated that T-/NK-cell lineage lymphomas were more common (64.1%) than B-cell lineage lymphomas (35.8%) in this cohort.

Extranodal NKTL, SPTL, and adult T-cell leukaemia/lymphoma are considerably more frequent in Asian than in Western populations (8, 12, 13, 15, 18, 19). Primary cutaneous FCL is rare in Asian countries, but is the most common subtype of B-cell lineage PCLs in European cohorts (7, 15, 18, 26, 27). Meanwhile, the most common B-cell subtype in CL cohorts from the USA and Japan is primary cutaneous DLBCL (7, 18, 28). The most common PCL subtype in our cohort was MF, but the frequency of MF (29.4%) was lower than in a previous US study (38.3%) (7) and in European studies (47.5% and 54%) (1, 8). LYP was the second most common PCL subtype in our cohort, with a higher frequency (15.9%) than previously reported in Japanese (4.4%) (28) and European (5%) (1) studies. The relative frequency of extranodal NKTL (9.7%) in our current study was also higher than reported previously in the USA (0.3%) (7) and Europe (0.4%) (8). The relative frequencies of SPTL and MZBL were also higher, while those of primary DLBCL was lower compared with the finding of earlier Western studies (1, 7, 8). MZBL was the most common B-cell lineage PCL, which is in accordance with a previous Korean study (19). However, DLBCL was found to be the most common subtype of SCL in our present study.

To the best of our knowledge, the present report is the first to analyse variations in the pattern of subtypes in Asian CL patients during two 10-year intervals. Jenni et al. (1) have also analysed variations in demographics and patterns of PCL subtypes during two 10-year intervals (1990 to 1999 and 2000 to 2009) in Western patients. These authors reported an increasing relative frequency of marginal cell lymphoma and CD30+ lymphoproliferative disorders between 1990 to 1999 and 2000 to 2009 (1). The increasing relative frequency of these subtypes may be attributed to increased awareness of these diseases.

Park et al. (19) recently reported that the proportion of B-cell lineage PCL was higher than reported in a precedent Korean study (13). Our present data also revealed an increasing frequency of B-cell lineage CL over time for both PCL and SCL. The proportion of B-cell lineage PCL increased significantly from 9% to 18% over the two 10-year periods we evaluated. MZBL doubled in relative frequency in the more recent 10-year period compared with the precedent 10-year period in our analysis. Primary extranodal NKTL decreased significantly from 13.7% to 7.5% over these 2 decades. The reason for the increased frequency of B-cell lineage lymphoma remains unclear, but may be attributed to the increased awareness of B-cell lineage PCL resulting from the new WHO-EORTC classification, which allows for a more reliable distinctive diagnosis. The diagnosis of B-cell lineage PCL, especially MZBL, is challenging because it can appear similar to pseudolymphoma (29). This means that MZBL could be misdiagnosed as pseudolymphoma before the characteristic histopathological features of this entity become apparent. Moreover, the more westernized lifestyle in Asia may contribute to the increasing frequency of this CL.

Survival data in our present study revealed the overall indolent course of PCL. The 5-year OS rate of PCL (81%) in our present study was similar to that of previous studies (15, 27, 30). Among PCL subtypes, extranodal NKTL, which is commonly associated with T3 category skin lesion extent and extracutaneous dissemination during disease course, had the poorest survival outcomes. There was some discordance in survival outcomes between our present study and previous reports. The 5-year OS rate in MF was 94% in our study; whilst it was 80.5% in a European study (30) and 90.9% in a US study (7).

In conclusion, this study of the demographic and clinical features of CL diagnosed at single tertiary referral centre in Korea over the past 20 years reveals a higher relative frequency of T-/NK-cell lineage PCL, such as ENKTL and SPTL, in Korea compared with the rates reported in Western studies. However, comparison between two 10-year intervals reveals an increasing trend in the incidence of B-cell lineage PCL and SCL in Korea.

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The authors declare no conflicts of interest.

REFERENCES


3. Imam MH, Shenoy PJ, Flowers CR, Phillips A, Lechowicz...


