1) Title: Cutaneous lymphoma in Japan: a nationwide study of 1,733 patients.

2) The short running title: Cutaneous lymphoma in Japan.

3) Toshihisa Hamada and Keiji Iwatsuki

4) Departments of Dermatology, Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences, Okayama, Japan.

5) Corresponding author: Toshihisa Hamada, Department of Dermatology, Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences, 2-5-1 Shikata-cho, Kita-ku, Okayama 700-8558, Japan
Tel: +81-86-235-7282, Fax: +81-86-235-7283 (e-mail: t-hamada@cc.okayama-u.ac.jp)

Abstract

Types of cutaneous lymphoma (CL) and their incidences may vary among geographic areas or ethnic groups. The present study aimed to investigate the incidences of various CLs in Japan, using epidemiological data from a nationwide registration system for CLs. Between 2007 and 2011, 1,733 new patients with CL were registered from over 600 dermatological institutes in Japan. The 1,733 patients registered included 1,485 (85.7%) patients with mature T- and NK-cell neoplasms, 224 (12.9%) with B-cell neoplasms and 24 (1.4%) with blastic plasmacytoid dendritic cell neoplasm. Mycosis fungoides (MF) is the most common CL subtype in the present study (750 patients, 43.3%). The proportion of MF patients with early-stage disease was 73%, similar to that of previous studies from other cohorts. The incidence rates of adult T-cell leukemia/lymphoma and extranodal NK/T cell lymphoma, nasal type were 16.7% and 2.0%, respectively, which may account for the higher incidence of mature T- and NK-cell neoplasms in Japan, as compared with that in the United States and Europe. A male predominance was observed in most types of CLs, except for several CL subtypes such as subcutaneous panniculitis-like T-cell lymphoma.

Key words: adult T-cell leukemia/lymphoma, cutaneous lymphoma, extranodal NK/T cell lymphoma, nasal type, Mycosis fungoides, subcutaneous panniculitis-like T-cell lymphoma.

Introduction

Cutaneous lymphomas (CLs) are the second-most common type of extranodal non-Hodgkin's lymphoma, after gastrointestinal lymphomas.[1] CLs are defined as lymphomas with skin infiltration of neoplastic lymphocytic cells, without nodal or internal involvement at diagnosis. The WHO classification for tumors of hematologic and lymphoid tissue, including CLs, was published in 2008, through several consensus meetings, and is based on a combination of clinicopathological, phenotypic, genetic and molecular characteristics.[2] Mycosis fungoides (MF) is the most common type of CL. In 2007, a revised version of the mycosis fungoides/ Sézary syndrome (MF/SS) staging system was published; thereafter, a TNM classification system was proposed for CLs other than MF/SS. [3, 4] Using the new criteria, clinical outcomes including survival data have recently been reported from the United Kingdom and Japan.[5, 6] However, these studies analyzed clinical data from only a single medical center over 25- or 30-year periods.

CL is a rare disease entity, and is difficult to study on a large scale. Thus, most epidemiological surveys on CLs have been limited to case series reports, mainly of single medical centers.[7-12] Epidemiologic data of CLs has not been fully evaluated to date. Entry of data into a comprehensive registry of CLs is required in many parts of the world. To date, a few large-scale epidemiologic studies on CLs have been performed mainly in the United States and Europe.[13-15] The findings from the present study, including the incidence rates of CLs, may be somewhat different from those studies. Indeed, the incidence pattern of CLs has been reported to be different by country or ethnic group, like that of gross lymphoproliferative disorders. For example, adult T-cell leukemia/lymphoma (ATLL) is endemic in southwest Japan, especially on Kyushu Island.[16, 17] However, it is very rare in the United States and Europe.[13-15]

In 2007, we established a nationwide registry system for Japanese CLs, in cooperation with the Japanese Skin Cancer Society (JSCS) Lymphoma Study Group. The present registry covers the whole country, and is aimed at elucidating the distinct pattern of Japanese CLs, mainly using the WHO classification and the revised version of MF/SS clinical staging.[2, 3] In addition, the present registry can minimize the kind of selection bias resulting from single-center analysis because data from hundreds of institutions throughout Japan are included. Such analyses will be conducted over the whole area of Japan each year. Thus, this registry will facilitate further clinical study and basic research in the near future.

Methods

We analyzed the incidence pattern of CLs from 2007 to 2011. The present registry covers the entire nation and includes more than 600 dermatological institutes throughout Japan, all of which have been approved as residency programs for board-certified dermatologists by the Japanese Dermatological Association (JDA) (Table 1). On average, a total of 628 institutes per year participated in the present study. In addition, the total number of the registered institutes of each prefecture is shown in Table 1. The diagnosis of CL was confirmed according to the WHO classification mentioned above.[2] Subjects were newly diagnosed patients with CLs in each institute. Clinical data including age at diagnosis, sex, TNM classification, clinical stage, anatomic site of the primary lesion, nodal or extracutaneous involvement, and initial therapy were retrieved from the medical database of each medical institute. In the present study, unconventional sites such as groin were excluded from the statistical analyses, because of its small number. Those data were submitted electronically without personal information to our data center once a year. This study was approved by the ethics board committee (the review board of JDA).

The comprehensive classification of CL and hematopoietic neoplasms with marked affinity for the skin was presented by the European Organization for Research and Treatment of Cancer (EORTC) in 2005.[13] This framework of CL classification was essentially duplicated by the WHO classification, with several nominal or hierarchical differences.[2] The present registry has dealt with CLs, shown in Table 2. Clinical stage and TNM classification of patients with MF/SS were identified using the International Society for Cutaneous Lymphomas (ISCL)/EORTC proposal in 2007 (which was modified in 2011).[3, 18]

Results

In total, 1,733 patients with CLs have been registered between 2007 and 2011 (Table 2). The patients ranged from 1 to 100 years (median, 65) in age, and included 978 males and 751 females (M: F ratio 1.30). Mature T-cell and NK-cell neoplasm was the most common type of CLs, accounting for 1,485 (85.7%) patients. Next in prevalence, 224 (12.9%) of 1,733 patients had mature B-cell neoplasm. The remaining 24 (1.4%) patients had blastic plasmacytoid dendritic cell neoplasm (BPDN).

MF was the most common subtype of mature T-cell and NK-cell neoplasms, comprising 50.5% of cases, followed by ATLL (290 patients; 19.5%), primary cutaneous CD30+ T-cell lymphoproliferative disorders (208 patients; 14.0%), and peripheral T-cell lymphoma, not otherwise specified (NOS) (100 patients; 6.7%). Other subtypes of mature T-cell and NK-cell neoplasms included 34 (2.3%) subcutaneous panniculitis-like T-cell lymphoma (SPTCL), 34 (2.3%) extranodal NK/T-cell lymphoma, nasal type (ENKL), and 33 (2.2%)

SS cases. The incidences of rare disease entities including primary cutaneous CD4+ small/medium T-cell lymphoma, primary cutaneous γδ T-cell lymphoma and primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma were 25 (1.7%), 5 (0.3%) and 6 (0.4%), respectively.

The most common mature B-cell neoplasm subtype was primary cutaneous diffuse large-cell lymphoma, leg type (95 patients; 42.4%), followed by extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT) (72 patients; 32.1%), primary cutaneous follicle center lymphoma (pcFCL) (37 patients; 16.5%), and IVLBCL (20 patients; 8.9%).

A male predominance was observed in all CLs (M: F ratio 1.30), with over 2-fold male predominance for BPDN (M: F ratio 5.00), SS (M: F ratio 3.71), IVLBCL (M: F ratio 2.33), and pcFCL (M: F ratio 2.08). In contrast, a female predominance was observed in SPTCL (M: F ratio 0.55), followed by in ENKL (M: F ratio 0.62), primary cutaneous CD4+ small/medium T-cell lymphoma (M: F ratio 0.79) and lymphomatoid papulosis (LyP) (M: F ratio 0.83).

The median age at diagnosis was low in patients with LyP (53.5 years) and SPTCL (55 years), as compared with that of all CLs (65 years). In contrast, the median age at diagnosis was high in patients with BPDN (77.5 years) and pcDLBCL, leg type (77 years). In general, the patient's age was high in mature B-cell neoplasm, as compared with those in mature T-cell and NK-cell neoplasm (median ages of 70 and 64 years, respectively). In reference to age distribution, bimodal distributions of age at diagnosis were found in LyP (the fourth and the sixth decades) and SPTCL (the fifth and the seventh decades).

Clinical stage of mycosis fungoides/ Sézary syndrome (Table 4)

In terms of clinical staging, the 744 MF/SS patients included 229 (29.6%) with stage IA, 303 (39.1%) with stage IB, 33 (4.3%) with stage IIA, 86 (11.1%) with stage IIB, 57 (7.4%) with stage IIIA, 7 (0.9%) with stage IIIB, 17 (2.2%) with stage IVA1, 28 (3.6%) with stage IVA2 and 14 (1.8%) with stage IVB. In all, 565 patients (73%) had early-stage disease (stage I + IIA). The remaining 209 (27%) patients had the advanced-stage disease (stage IIB + III + IV). A male predominance was observed in stage IIIA (M: F ratio 4.18), stage IIIB (M: F ratio 2.50) and stage IVA1 (M: F ratio 2.40). In contrast, a female predominance was observed in stage IVA2 (M: F ratio 0.75). The median ages at diagnosis were 61 to 62 years in stage IA to IIB and stage IIIB, and 64 to 70 years in stage IIIA and IV.

Anatomic site of the primary skin lesion (Figure 1A-G)

The skin lesion sites of primary cutaneous anaplastic large cell lymphoma were distributed just about evenly. The most commonly affected sites were the lower extremities in SPTCL (62%) and the head/neck or the trunk in primary cutaneous CD4+ small/medium T-cell lymphoma (52%). In pcFCL and MALT, the head and neck were commonly affected (84% and 56%, respectively). In contrast, the lower extremities were the most commonly affected sites in DLBCL, leg type (45%). BPDN preferentially arose on the trunk (83%).

Discussion

In the present study, we aimed to reveal the distinct characteristics of the Japanese pattern of CL. After the initiation of the annual registry in 2007, 1,733 newly diagnosed patients with CLs have been registered from over 600 dermatological institutes through Japan. The present registry is not a 'population-based' study in a precise sense. However, the data presented herein are believed to be representative of the Japanese CLs. A possible limitation of the study includes uncertainty about the accuracy of the diagnostic procedure in each institute with lack of central pathology review. However, we believe this may not be a matter of great importance, because all enrolled institutes have residency programs for dermatologists to become board-certified by JDA. By the present registry system, trends of overall incidence and disease distribution of CLs in Japan will be evaluated continually.

We showed that the majority (85.7%) of CL cases was mature T-cell and NK-cell neoplasm, more or less similar to findings in previous studies from Japan and elsewhere.[7-15] However, in detail, the incidence rate of mature T-cell and NK-cell neoplasm in the present study was 8.7 to 14.4% higher than in those of the United States and Europe. In contrast, the incidence of mature B-cell neoplasm (12.9%) was much lower: 10.1 to 15.6% lower than in the west (Table 3). It is noteworthy that the incidence rate of MALT in the present study was lower than in those of the United States and Europe. Occasionally, the distinction between B-cell pseudolymphoma and MALT can be very difficult in some patients.[19] Thus, one of possible causes may include the diagnostic difficulty of MALT. The overall incidence pattern of CLs in the present study was similar to that in previous studies from single centers of Japan and Korea (Table 3).[8, 12] As compared with the incidence of CLs in other countries or regions, MF/SS occurred at a similar frequency (45.2%) in Japan, while the incidence rates of ATLL and ENKL were observed to be 16.7% and 2.3%, respectively. The incidence rate of ENKL was higher than those of the United States and Europe, and lower than those of Korea and Taiwan.[11, 12, 20]

ATLL is a distinct hematological neoplasm caused by the human T-cell lymphotropic virus type I

(HTLV-1) - infected malignant CD4 positive T cells.[21-23] The endemic areas of ATLL include high-prevalence regions of HTLV-1, such as southwest Japan, various Caribbean countries, South America, and Central Africa.[24-27] ATLL shows various clinical and prognostic features, and is classified into four categories according to the Shimoyama classification: acute, lymphoma, chronic, and smoldering subtypes.[28] Cutaneous lesions are frequently observed in patients with ATLL, accounting for more than 50%.[21,29] Moreover, many types of ATLL-associated eruption have been reported to date.[30-32] The present study showed high prevalence of ATLL in Japan compared with other countries or regions including Korea (Table 3).

ENKL is characterized by pleomorphic cell infiltration with NK-cell phenotype, which ordinarily demonstrates positivity to Epstein-Barr virus -encoded early small RNA by *in-situ* hybridization.[2] Typically, pathological features include vascular damage and tissue necrosis by angiocentric infiltration of tumor cells. Frequently, ENKL affects the upper aerodigestive tract, followed by skin, soft tissue, the gastrointestinal tract and testes.[2] It is more prevalent in East Asia, Central America and South America than in Europe and the United States.[13, 33-35] Also, the incidence of ENKL in CLs was reported to be significantly higher in Korea (15% and 20.7%) than in Europe and the United States.[12, 20] In three single-institution studies from Japan, the incidence rate of ENKL has ranged from 3.8% to 8.8%.[8, 36, 37] In the present study, the incidence was somewhat lower (2.3%) than these previous studies. The difference may reflect the kind of selection bias specific to single-institution studies. Our results suggest that the high incidence rates of mature T-cell and NK-cell neoplasm are associated with the prevalence of ATLL in Japan, unlike that of ENKL in Korea.

MF is the most common CL subtype in the present study as well as in almost all counties or ethnicities. In the past, staging of MF/SS was performed according to the previously proposed staging system.[38, 39] Prior to the establishment of the new staging system, several clinical studies had been conducted on relatively large cohorts of CTCL for such a rare disease entity.[40-42] In 2007, the revised staging system for MF/SS was released by the ISCL/EORTC (which was in turn modified in 2011).[3, 18] This system adopted a newly proposed classification of tumor-node-metastasis-blood (TNMB) rating. Since then, two clinical studies of MF/SS have been conducted in the United Kingdom and Japan.[5, 6] In the present study, the proportion of patients with early-stage (IA to IIA) was 73%, similar to that of the previous studies (70.7% and 78%) (Table 5). Stage IB accounted for 39.1% of the total MF/SS in the present study, making it the most prevalent clinical stage. This finding is similar to the results of previous studies (38.8% and 38%) (Table 5) .[5, 6] In addition, a predominance of males among MF/SS patients was shown in the present study, as in

previous reports.[5, 6, 8, 9, 12-15, 20, 40-42] Notably, a male predominance was observed in erythrodermic MF or SS, with over 2-fold male predominance for stage IIIA (M: F ratio 4.18), stage IIIB (M: F ratio 2.50), and stage IVA1 (M: F ratio 2.40).

We evaluated the distinct anatomical distributions of the skin lesions in patients with several types of CLs. In patients with pcFCL and MALT, the head and neck were the most commonly affected sites, as in previous reports from the United States and Asia.[15, 43] By contrast, in Europe, the trunk was the most commonly affected site of pcFCL and MALT.[44-46] These results suggest that a difference in preferentially affected anatomic site in patients with pcFCL and MALT may exist, at least between Europe and the United States/Asia. By definition, the lower extremities are the most common site in patients with pcDLBCL, leg type. Primary cutaneous small/medium CD4+ T-cell lymphoma is a rare CL entity with an indolent clinical course, which has been shown to preferentially affect the head and neck.[13, 47, 48] In the present study, the trunk in addition to the head and neck was the most common site of primary cutaneous small/medium CD4+ T-cell lymphoma. SPTCL is a distinct CL entity, characterized by primarily subcutaneous (mainly fat tissue) infiltration of malignant T lymphocytes with cytotoxic molecules. It predominantly affects the legs.[13, 49] Also, we found that the lower extremities were the most commonly affected site in SPTCL (62%). In addition, a female predominance was demonstrated in Japan, as in a previous report.[49]

The present study was conducted to investigate the nationwide incidence patterns of Japanese CL patients, according to the WHO classification. It provides important data about trends in the overall incidence pattern of Japanese CLs. In particular, the high prevalences of ATLL and ENKL in Japan are shown, with considerable accuracy. A male predominance was observed in most types of CLs, except for SPTCL, ENKL, primary cutaneous CD4+ small/medium T-cell lymphoma and LyP. The present study showed that the proportion of patients in each clinical stage of MF/SS was similar to that in previous studies. In the future, accumulated data from the present registry will allow us to investigate the etiology of varying CL subtypes, and to conduct targeted clinical research based on the characteristics of CLs in Japan.

Acknowledgments

The authors thank the dermatological department staff at each medical institute that is contributing data to the present registry. This work was supported in part by Japanese Skin Cancer Society (JSCS).

REFERENCES

1. Groves FD, Linet MS, Travis LB, Devesa SS. Cancer surveillance series: non-Hodgkin's lymphoma incidence by histologic subtype in the United States from 1978 through 1995. *J Natl Cancer Inst* 2000; **92**(15):1240-1251.
2. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Ed. Swerdlow, SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J, Vardiman JW. IARC Press, Lyon, 2008.
3. Olsen E, Vonderheid E, Pimpinelli N, et al. Revisions to the staging and classification of mycosis fungoides and Sezary syndrome: a proposal of the International Society for Cutaneous Lymphomas (ISCL) and the cutaneous lymphoma task force of the European Organization of Research and Treatment of Cancer (EORTC). *Blood* 2007; **110**(6): 1713-1722.
4. Kim YH, Willemze R, Pimpinelli N, et al. TNM classification system for primary cutaneous lymphomas other than mycosis fungoides and Sezary syndrome: a proposal of the International Society for Cutaneous Lymphomas (ISCL) and the Cutaneous Lymphoma Task Force of the European Organization of Research and Treatment of Cancer (EORTC). *Blood* 2007; **110**(2): 479-484.
5. Agar NS, Wedgeworth E, Crichton S, et al. Survival outcomes and prognostic factors in mycosis fungoides/Sezary syndrome: validation of the revised International Society for Cutaneous Lymphomas/European Organisation for Research and Treatment of Cancer staging proposal. *J Clin Oncol* 2010; **28**(31): 4730-4739.
6. Suzuki S, Ito K, Ito M, Kawai K. Prognosis of 100 Japanese patients with mycosis fungoides and Sézary syndrome. *J Dermatol Sci* 2010; **57**(1): 37-43.
7. Bouaziz JD, Bastuji-Garin S, Poszepczynska-Guigné E, Wechsler J, Bagot M. Relative frequency and survival of patients with primary cutaneous lymphomas: data from a single-centre study of 203 patients. *Br J Dermatol* 2006; 154(6): 1206-1207.
8. Fujita A, Hamada T, Iwatsuki K. Retrospective analysis of 133 patients with cutaneous lymphomas from a single Japanese medical center between 1995 and 2008. J Dermatol 2011; **38**(6): 524-530.
9. Jenni D, Karpova MB, Seifert B, et al. Primary cutaneous lymphoma: two-decade comparison in a population of 263 cases from a Swiss tertiary referral centre. Br J Dermatol 2011; **164**(5): 1071-1077.
10. Khamaysi Z, Ben-Arieh Y, Izhak OB, Epelbaum R, Dann EJ, Bergman R. The applicability of the new WHO-EORTC classification of primary cutaneous lymphomas to a single referral center. *Am J Dermatopathol* 2008; **30**(1): 37-44.
11. Liao JB, Chuang SS, Chen HC, Tseng HH, Wang JS, Hsieh PP. Clinicopathologic analysis of cutaneous lymphoma in taiwan: a high frequency of extranodal natural killer/T-cell lymphoma, nasal type, with an extremely poor prognosis. *Arch Pathol Lab Med* 2010; **134**(7): 996-1002.
12. Park JH, Shin HT, Lee DY, et al. World Health Organization-European Organization for Research and Treatment of Cancer classification of cutaneous lymphoma in Korea: A retrospective study at a single tertiary institution. *J Am Acad Dermatol*

2012; **67**(6): 1200-1209.

13. Willemze R, Jaffe ES, Cerroni L, et al. WHO-EORTC classification for cutaneous lymphomas. *Blood* 2005; **105**(10): 3768-3785.
14. Assaf C, Gellrich S, Steinhoff M, et al. Cutaneous lymphomas in Germany: an analysis of the Central Cutaneous Lymphoma Registry of the German Society of Dermatology. *J Dtsch Dermatol Ges* 2007; **5**(8): 662-668.
15. Bradford PT, Devesa SS, Anderson WF, Toro JR. Cutaneous lymphoma incidence patterns in the United States: a population-based study of 3884 cases. *Blood* 2009; **113**(21): 5064-5073.
16. Lymphoma Study Group of Japanese Pathologists. The World Health Organization classification of malignant lymphomas in Japan: Incidence of recently recognized entities. *Pathol Int* 2000; **50**(9): 696-702.
17. Ohshima K, Suzumiya J, Kikuchi M. The World Health Organization classification of malignant lymphoma: incidence and clinical prognosis in HTLV-1-endemic area of Fukuoka. *Pathol Int* 2002; **52**(1): 1-12.
18. Olsen EA, Whittaker S, Kim YH, et al. Clinical end points and response criteria in mycosis fungoides and Sézary syndrome: a consensus statement of the International Society for Cutaneous Lymphomas, the United States Cutaneous Lymphoma Consortium, and the Cutaneous Lymphoma Task Force of the European Organisation for Research and Treatment of Cancer. *J Clin Oncol* 2011; **29**(18): 2598-2607.
19. Prince HM, Yap LM, Blum R, McCormack C. Primary cutaneous B-cell lymphomas. *Clin Exp Dermatol* 2003; **28**(1): 8-12.
20. Lee MW; Korean Dermatopathology Research Group. Characteristics of cutaneous lymphomas in Korea. *Clin Exp Dermatol* 2003; **28**(6): 639-646.
21. Uchiyama T, Yodoi J, Sagawa K, et al: Adult T-cell leukemia: Clinical and hematologic features of 16 cases. *Blood* 1977; **50**(3): 481-492.
22. Poiesz BJ, Ruscetti FW, Gazdar AF, et al: Detection and isolation of type C retrovirus particles from fresh and cultured lymphocytes of a patient with cutaneous T-cell lymphoma. *Proc Natl Acad Sci U S A* 1980; **77**(12): 7415-7419.
23. Yoshida M, Miyoshi I, Hinuma Y: Isolation and characterization of retrovirus from cell lines of human adult T-cell leukemia and its implication in the disease. *Proc Natl Acad Sci U S A* 1982; **79**(6): 2031-2035.
24. Iwanaga M, Chiyoda S, Kusaba E, Kamihira S. Trends in the seroprevalence of HTLV-1 in Japanese blood donors in Nagasaki Prefecture, 2000-2006. *Int J Hematol* 2009; **90**(2): 186-190.
25. Blattner WA, Kalyanaraman VS, Robert-Guroff M, et al. The human type-C retrovirus, HTLV, in Blacks from the Caribbean region, and relationship to adult T-cell leukemia/lymphoma. *Int J Cancer* 1982; **30**(3): 257-264.
26. Nogueira CM, Cavalcanti M, Schechter M, Ferreira OC Jr. Human T lymphotropic virus type I and II infections in healthy blood donors from Rio de Janeiro, Brazil. *Vox Sang* 1996; **70**(1): 47-48.

27. Delaporte E, Dupont A, Peeters M, et al. Epidemiology of HTLV-I in Gabon (Western Equatorial Africa). *Int J Cancer* 1988; **42**(5): 687-689.

28. Shimoyama M. Diagnosis criteria and classification of clinical subtypes of adult T-cell leukemialymphoma: a report from the Lymphoma Study Group. *Br J Hematol* 1991; **79**(3): 428-437.

29. Bunn PA Jr, Schechter GP, Jaffe E, et al. Clinical course of retrovirus-associated adult T-cell lymphoma in the United States. *N Engl J Med* 1983; **309**(5): 257-264.

30. Setoyama M, Katahira Y, Kanzaki T. Clinicopathologic analysis of 124 cases of adult T-cell leukemia/lymphoma with cutaneous manifestations: the smouldering type with skin manifestations has a poorer prognosis than previously thought. *J Dermatol* 1999; **26**(12): 785-790.

31. Chan HL, Su IJ, Kuo T, et al. Cutaneous manifestations of adult T-cell leukemia/lymphoma. Report of three different forms. *J Am Acad Dermatol* 1985; **13**(2 Pt 1): 213-219.

32. Sawada Y, Hino R, Hama K, et al. Type of skin eruption is an independent prognostic indicator for adult T-cell leukemia/lymphoma. *Blood* 2011; **117**(15): 3961-3967.

33. Au WY, Ma SY, Chim CS, et al. Clinicopathologic features and treatment outcome of mature T-cell and natural killer-cell lymphomas diagnosed according to the World Health Organization classification scheme: a single center experience of 10 years. *Ann Oncol* 2005; **16**(2): 206-214.

34. Quintanilla-Martinez L, Franklin JL, Guerrero I, et al. Histological and immunophenotypic profile of nasal NK/T cell lymphomas from Peru: high prevalence of p53 overexpression. *Hum Pathol* 1999; **30**(7): 849-855.

35. Yoon SO, Suh C, Lee DH, et al. Distribution of lymphoid neoplasms in the Republic of Korea: analysis of 5318 cases according to the World Health Organization classification. *Am J Hematol* 2010; **85**(10): 760-764.

36. Yasukawa K, Kato N, Kodama K, Hamasaka A, Hata H. The spectrum of cutaneous lymphomas in Japan: a study of 62 cases based on the World Health Organization Classification. *J Cutan Pathol* 2006; **33**(7): 487-491.

37. Nagasawa T, Miwa H, Nakatsuka S, Itami S, Yoshikawa K, Aozasa K. Characteristics of cutaneous lymphomas in Osaka, Japan (1988-1999) based on the European Organization for Research and Treatment of Cancer classification. *Am J Dermatopathol* 2000; **22**(6): 510-514.

38. Bunn PA Jr, Huberman MS, Whang-Peng J, et al. Prospective staging evaluation of patients with cutaneous T-cell lymphomas. Demonstration of a high frequency of extracutaneous dissemination. *Ann Intern Med* 1980; **93**(2): 223-230.

39. Sausville EA, Eddy JL, Makuch RW, et al. Histopathologic staging at initial diagnosis of mycosis fungoides and the Sézary syndrome. Definition of three distinctive prognostic groups. *Ann Intern Med* 1988; **109**(5): 372-382.

40. Zackheim HS, Amin S, Kashani-Sabet M, et al: Prognosis in cutaneous T-cell lymphoma by skin stage: Long-term survival

in 489 patients. *J Am Acad Dermatol* 1999; **40**(3): 418-425.

41. van Doorn R, Van Haselen CW, van Voorst Vader PC, et al: Mycosis fungoides: Disease evolution and prognosis of 309 Dutch patients. *Arch Dermatol* 2000; **136**(4): 504-510.
42. Kim YH, Liu HL, Mraz-Gernhard S, et al: Long-term outcome of 525 patients with mycosis fungoides and Sézary syndrome: Clinical prognostic factors and risk for disease progression. *Arch Dermatol* 2003; **139**(7): 857-866.
43. Li C, Inagaki H, Kuo TT, Hu S, Okabe M, Eimoto T. Primary cutaneous marginal zone B-cell lymphoma: a molecular and clinicopathologic study of 24 asian cases. *Am J Surg Pathol* 2003; **27**(8): 1061-1069.
44. Hoefnagel JJ, Vermeer MH, Jansen PM, et al. Primary cutaneous marginal zone B-cell lymphoma: clinical and therapeutic features in 50 cases. *Arch Dermatol* 2005; **141**(9): 1139-1145.
45. Senff NJ, Hoefnagel JJ, Jansen PM, et al. Reclassification of 300 primary cutaneous B-Cell lymphomas according to the new WHO-EORTC classification for cutaneous lymphomas: comparison with previous classifications and identification of prognostic markers. *J Clin Oncol* 2007; **25**(12): 1581-1587.
46. Zinzani PL, Quaglino P, Pimpinelli N, et al. Prognostic factors in primary cutaneous B-cell lymphoma: the Italian Study Group for Cutaneous Lymphomas. *J Clin Oncol* 2006; **24**(9): 1376-1382.
47. Garcia-Herrera A, Colomo L, Camós M, et al. Primary cutaneous small/medium CD4+ T-cell lymphomas: a heterogeneous group of tumors with different clinicopathologic features and outcome. *J Clin Oncol* 2008; **26**(20): 3364-3371.
48. Beltraminelli H, Leinweber B, Kerl H, Cerroni L. Primary cutaneous CD4+ small/medium-sized pleomorphic T-cell lymphoma: a cutaneous nodular proliferation of pleomorphic T lymphocytes of undetermined significance? A study of 136 cases. *Am J Dermatopathol* 2009; **31**(4): 317-322
49. Willemze R, Jansen PM, Cerroni L, et al. Subcutaneous panniculitis-like T-cell lymphoma: definition, classification, and prognostic factors: an EORTC Cutaneous Lymphoma Group Study of 83 cases. *Blood* 2008; **111**(2): 838-845.

LEGENDS FOR FIGURE

Figure 1. Anatomic distribution. (A-G) The anatomic sites of the primary skin lesion are shown in the graphic representation: (A) Primary cutaneous anaplastic large cell lymphoma (pcALCL), (B) Subcutaneous panniculitis-like T-cell lymphoma (SPTCL), (C) Primary cutaneous CD4+ small/medium T-cell lymphoma, (D) Primary cutaneous follicle center lymphoma (pcFCL), (E) Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT), (F) Primary cutaneous diffuse large-cell lymphoma, leg type (pcDLBCL, leg type), and (G) Blastic plasmacytoid dendritic cell neoplasm (BPDN).