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ORIGINAL ARTICLE

Cutaneous lymphomas in Taiwan: A review of 118 cases from a medical center in southern Taiwan

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ABSTRACT

Background: Cutaneous lymphomas (CLs) have not been well characterized in Taiwan.
Methods: We retrospectively reviewed the clinical and pathologic findings of cases of CLs of our department diagnosed from January 2001 to December 2010. The final diagnosis was made according to the 2008 World Health Organization (WHO) classification and its 2016 update.
Results: Our series consisted of 91 primary CLs, 27 secondary CLs. The primary CLs consisted of 84 cases of mature T-cell and NK-cell lymphomas (CTCLs) and 7 cases of B-cell lymphomas, including mycosis fungoides (MF) (57.1%), lymphomatoid papulosis (LyP) (14.3%), anaplastic large cell lymphoma (7.7%), extranodal NK/T cell lymphoma, nasal type (4.4%), extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (3.3%), and diffuse large B-cell lymphoma (4.4%). Most MF (82.6%) cases were early MF (stage I–IIA) and were treated successfully, mainly with ultraviolet B (UVB) 311. The overall 5-year survival rate was 90.7% for early stage MF, 37.5% for stage late MF and 74.9% for all MF cases.
Conclusion: Compared to other larger Western and Asian series of primary CLs, our series showed higher proportions of CTCLs and MF. Over 80% of MF was early MF, a finding consistent with the trend in early diagnosis of MF in recent decades. A nation-wide study is warranted to further characterize CLs in Taiwan.

Introduction

Primary cutaneous lymphomas (CLs) show heterogeneous clinical and pathologic features and account for 19% of extranodal non-Hodgkin's lymphomas.[1–3] Primary CLs arise in the skin and usually remain confined to the skin for a long period of time. Secondary CLs are cutaneous involvement from primary nodal or extranodal lymphomas with different disease progression and prognosis.[3,4] The classification of primary CLs has changed over the last few decades.[3,5,6]

Primary CLs include two main categories based on the cell of origin: mature T-cell and NK cell neoplasms (CTCLs) and mature B-cell neoplasms (CBCLs). Primary CTCLs represent about 80% of the primary CLs and consist of lymphomas with either indolent clinical behavior (5-y survival 75–100%) or aggressive clinical behavior (5-y survival ~24%).[3] The indolent CTCLs include mycosis fungoides (MF), primary cutaneous CD30+ lymphoproliferative disorders (pcCD30 + LPDs), subcutaneous panniculitis-like TCL (SPTCL), and PcCD4+ small/medium lymphoproliferative disorder (LPD). MF and CD30 + LPDs are most common, accounting for about 50% and 20%, respectively, of primary CLs. The aggressive TCLs consist of Sézary syndrome (SS), extranodal NK/TCL, nasal type (ENKL), adult T-cell leukemia/lymphoma (ATLL), pcγ/δ T-cell lymphoma (pcγ/δ TCL), PcCD8+ aggressive epidermotropic cytotoxic T-cell lymphoma (CD8 + AECTCL) (provisional), and pcPeripheral T-cell lymphoma, not otherwise specified (pcPTL-NOS).

Primary CBCLs consist of three main types, namely, extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue

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(MALT lymphoma), primary cutaneous follicle center lymphoma (pcFCL), and primary cutaneous diffuse large B-cell lymphoma (pcDLBCL).

The frequencies of CLs often show a wide regional variation, which can mostly be attributed to genetic and environmental etiologic factors. The variation is even greater among single institution-based studies. Compared with Western series, the Asian studies usually show lower rates of CBCLs but higher rates of CTCLs, particularly ENKL and hydroa vacciniforme-like lymphoma in Korea and ATLL in Japan.[7]

Reports focused on the CLs in Taiwan are very limited, only a few small case series reported to date.[8,9] To further characterize CLs in Taiwan, we reviewed cases of CLs diagnosed in our department over a 10-year period and compared our series to other major Western series and Asian series.

Patients and methods

Cases with the first pathology diagnosis of lymphoma, mycosis fungoides and pseudolymphoma during January 2001 and December 2010 were retrieved from the database system of the Department of Dermatology. In our routine practice, the diagnostically challenging cases were evaluated by both dermatopathologist (JYYL) and hematopathologist (KCC) to reach a final diagnosis. For the present study, we reviewed clinical, laboratory data and pathology slides, including patient's age, gender, age of onset, and clinical features, course and outcome of individual cases. Primary CLs were defined as lymphoma presenting in the skin without evidence of extracutaneous involvement except regional lymph node at the time of diagnosis.[3] Conversely, the diagnosis was secondary cutaneous lymphoma if there is evidence of extracutaneous involvement except regional lymph node at the time of diagnosis. The study protocol was approved by the ethics committee of National Cheng Kung University (No: B-ER-104-066).

We performed immunohistochemical staining for various markers as needed to reach a final diagnosis, including antibodies against CD3, CD8, CD30, Bcl-6, TdT, ALK, Ki-67, κ/λ light chain and MUM-1 (these antibodies from Dako); CD4, CD7 and CD56 (Ventana); CD5 (Cell Marque); CD10 (Novocastra); Bcl-2 (BioGenex); PD-1 (Zeta Corporation); TCR-γ (BOND-MAX) and granzyme B, βF-1 (8A3) (Thermo Fisher Scientific). In-situ hybridization studies were performed using a polymerase chain reaction (PCR)-derived digoxigenin-labeled DNA probe on cases suspicious of SPTCL and ENKL to detect Epstein–Barr virus encoded RNA (EBER). The presence of type I human T-cell lymphotropic virus (HTLV-1) was checked using a particle agglutination assay (PA Serodia-HTLV-1, Fujirebio Inc., Tokyo, Japan) for antibodies to viral antigen in T cell lymphoma.[8] We also performed additional PCR studies for T-cell receptor (TCR) genes or immunoglobulin heavy chain (IgH) gene rearrangement in cases as indicated to reach the diagnosis.[10]

The final diagnosis of lymphomas was made according to the 2008 WHO classification of Hematopoietic and lymphoid Tumors[5] and its 2016 update, and after correlating the clinical and pathologic findings. For diagnostically challenging cases of early lesions of MF, we adopted the 4 points criteria for diagnosis of early MF based on integration of clinical, histopathologic, immunopathologic, and molecular biological characteristics as proposed by the International Society for Cutaneous Lymphoma (ISCL).[11]

Briefly, the ISCL criteria consist of (1) Clinical (maximum 2 points): persistent and/or progressive patches/thin plaques plus two of the additional features (non-sun exposed location, size/shape variation, poikiloderma); (2) Histopathologic (maximum 2 points): superficial lymphoid infiltrate plus two of the additional features (epidermotropism without spongiosis, lymphoid atypia with enlarged hyperchromatic nuclei and irregular or cerebriform nuclear contours); (3) Molecular biological: one point for clonal TCR gene rearrangement; (4) Immunopathologic: one point for reduced or loss of expression of CD2, CD3, CD5 (<50%) or CD7 (<10%) of T cells or epidermal/dermal discordance of these markers.

The variants of MF, including folliculotropic MF, pagetoid reticulosis and granulomatous slack skin, and other clinical manifestations of MF, such as erythrodermic, large cell transformation or hypopigmented MF, were also specified. The staging of lymphomas was based on the new tumor-node-metastasis-blood (TNMB) classification proposed by the International Society for Cutaneous Lymphomas (ISCL) and the cutaneous lymphoma task force of the European Organization of Research and Treatment of Cancer (EORTC).[12]

The responses to treatment were defined as follows: complete response (CR) means complete resolution of skin lesions, partial response (PR) >50% reduction of baseline skin lesions; stable disease, <50% clearance of baseline skin lesions to < 25% growth of tumor; progression, >25% growth of tumor or development of new tumors. Recurrence was defined as patients who achieved CR but then progressed. All statistical analysis was done using Prism version 5.02 (GraphPad software). Survival curves were plotted using Kaplan–Meier analysis. Alpha was set at 0.05 in two-sided comparisons.

Results

Our initial search found 154 cases with diagnoses of lymphoma, mycosis fungoides or pseudolymphoma during the 10-year study period. Among them, 36 cases were excluded after re-evaluation of the clinical and pathologic data, including additional immunohistochemical and PCR clonality studies when deemed appropriate. The 36 cases included 12 cases of questionable MF, 19 cases of pseudolymphoma, 4 cases of cutaneous plasmacytoma and a case of blastic plasmacytoid dendritic cell neoplasm. Most MF cases met 4 points of the ISCL diagnostic criteria based on the clinical and histopathologic features alone. TCR gene rearrangement study was performed in 12 cases of possibly early MF. The scores for these cases were one point (one case), 3 points (4 cases), and 4 points (7 cases). The results were TCR-gamma monoclonal in 4 cases, polyclonal in 7 and equivocal in one. In the 4 cases with positive PCR study, the result helped to clinch the diagnosis in 3 cases; another positive case had 4 points already without PCR study. TCR was polyclonal in 2 of the cases with score of 3 or less; these two cases were excluded.

A total of 120 CLs were diagnosed in 118 patients; 91 patients (77.1%) had primary CLs and 27 (22.9%) had secondary CLs. Two patients had two types of primary CL; one had MF first and later developed LyP (type B), and the other had LyP (type A) preceding unilesional MF. The demographic data of these cases are summarized in Table 1, where only the first diagnosed lymphoma is tabulated.

The 91 primary CLs consisted of 84 NK/TCLs and 7 BCLs, specifically, 52 cases of MF, 13 LyP, 7 ALCLs, 4 ENKL, 2 Sézary syndrome, 3 MALT lymphoma and 4 pcDLBCLs. The 27 secondary CLs included 12 cases of CTCLs and 15 cases of CBCLs. Table 2 listed the frequencies of the primary CLs in our series and other series.

In primary CLs, CTCLs showed a male predominance (M:F = 1.8:1) and younger age (median 50, range 4–86 years), while CBCLs showed a female predominance (M:F = 1:2.5) and older age (median 78, range 53–93 years). After diagnosis of CLs, 111 patients had a median follow-up of 3 years (range one month-16 years).

Mycosis fungoides and Sézary syndrome

There were 52 cases of MF (57.1% of the primary CLs) with a male predominance and median age of 50 years. Fifty patients had

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