

Primary Cutaneous Diffuse Large B-cell Lymphoma with Multifocal Subcutaneous Lesions

Min-Ja Jung, M.D., Young-Hoon Kim, M.D., Jeong-Joon Eim, M.D.,
Baek-Yeol Ryoo, M.D.*, Seung-Sook Lee, M.D.**, Ki-Ho, Kim, M.D.

Department of Dermatology, Dong-A University College of Medicine, Pusan, Korea
Departments of Internal Medicine (Hemato-oncology)* and Pathology**
Korea Cancer Center Hospital, Seoul, Korea

We report herein a case of primary cutaneous diffuse large B-cell lymphoma with multiple skin lesions in a Korean woman. A 56-year-old woman presented with rapidly growing multiple subcutaneous nodules in her right flank and right upper arm. Microscopic examination of skin biopsy specimen showed diffuse infiltrates of large atypical lymphocytes with vesicular nuclei, prominent nucleoli and moderate degree of mitotic figures in deep dermis and subcutis. Immunophenotypic studies revealed the lymphoid infiltrates reacted with CD45, CD20 and bcl-2 protein, but none of the sections expressed CD3, bcl-6 protein and CD30. In physical examination and staging work-up, we could not find any other extracutaneous or systemic involvement. She was treated with 2 cycles of high-dose multiagent chemotherapy with the Vanderbilt and the BEAM regimen combined with the autologous peripheral blood stem cell transplantation. Until now, 10 months after termination of treatment, she has shown improvement of all skin lesions and no development of extracutaneous disease.

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Key Words : Primary cutaneous diffuse large B cell lymphoma, Multifocal skin lesions

Primary cutaneous B cell lymphomas (PCBCLs) constitute 20-25 % of all cutaneous lymphomas in Western literatures and those with multiple skin involvement are less frequent¹. Though various classification systems for PCBCLs are still debatable between Western and Oriental series in many aspects, PCBCLs are divided into primary cutaneous follicular center cell lymphoma (PCFCCL), primary cutaneous immunocytoma (PCI) and primary cutaneous large B-cell lymphoma (PCLBCL) of the leg, according to the European Organization for Research and Treatment of Cancer (EORTC) classification². Among them, PCLBCL of the

leg is a very unique entity in that it predominantly affects elderly patients and its extent at presentation is fairly evenly distributed between stages and also it presents on and confined to legs². Most of the patients could have additional nodules and/or tumors at adjacent sites such as flank, back and pubic areas or at distant sites like arms and forehead besides the legs, and the prognosis of this lymphoma is known as less favorable compared with morphologically similar large follicular center cell lymphoma (FCCL) on the head and trunk^{2,3}. However, many investigators recently prefer to use the unifying term 'large B-cell lymphoma of the leg' at a clinical point of view and the subset of patients with PCLBCL of the leg did not have a worse outcome than in other locations and one could argue that the poor prognosis of this subset is age related¹.

However, there have been few reports of Korean patients with PCBCLs. A series of PCBCL cases from Japan recently reported Japanese

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Reprint request to : Ki-Ho Kim, M.D. Department of Dermatology, College of Medicine, Dong-A University #1, 3Ga, Dongdaeshin-Dong, Seo-Ku, Pusan, 602-103, Korea

Tel. (051) 240-5435, Fax. (051) 241-6726

E-mail. khkim@seunghak.donga.ac.kr



Fig. 1. Multiple subcutaneous nodules in the right flank (A) and right upper arm (B).

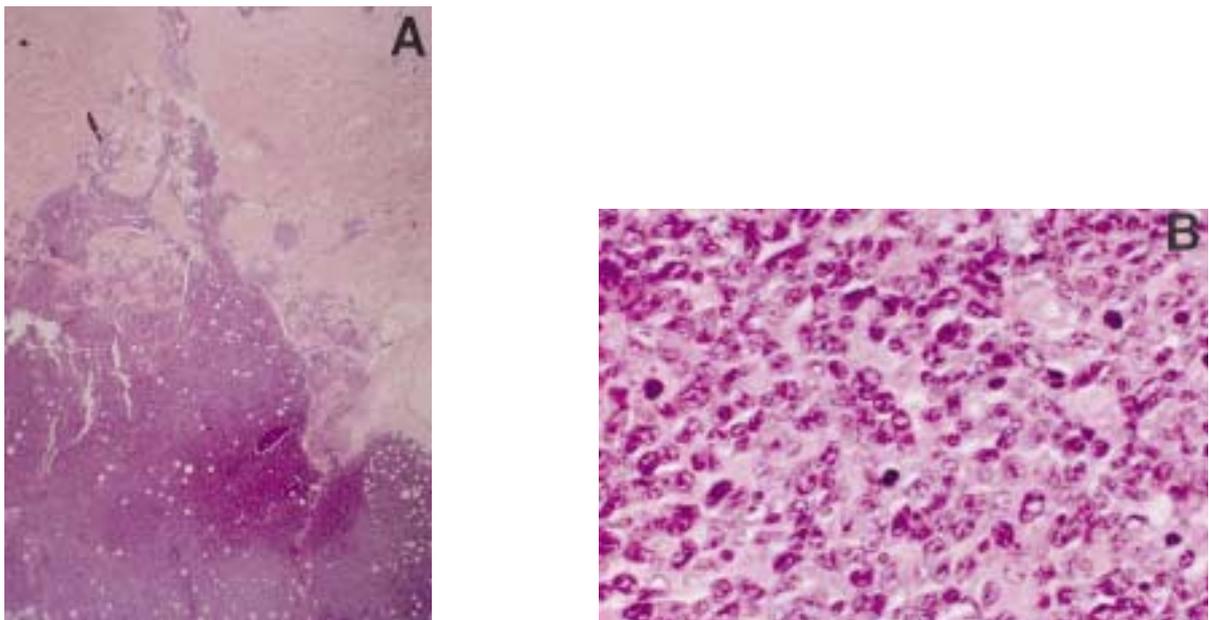


Fig. 2. These slides show diffuse cellular infiltration in the deep dermis and subcutis (A: H&E stain, $\times 1$). The infiltrative cells are large atypical lymphoid cells with vesicular nuclei, prominent nucleoli and mitotic figures (B: H&E stain, $\times 400$).

patients seemed to be different from those in EORTC series in aspects of frequency, histomorphological growth pattern, and prognosis^{4,5}.

Despite the EORTC classification defines a primary cutaneous lymphoma rather strictly as a non-Hodgkin lymphoma presenting in the skin

without any evidence of extracutaneous disease at the time of diagnosis and within the first 6 months after diagnosis, PCBCLs including our case can present as multifocal skin lesions and even as extracutaneous diseases¹.

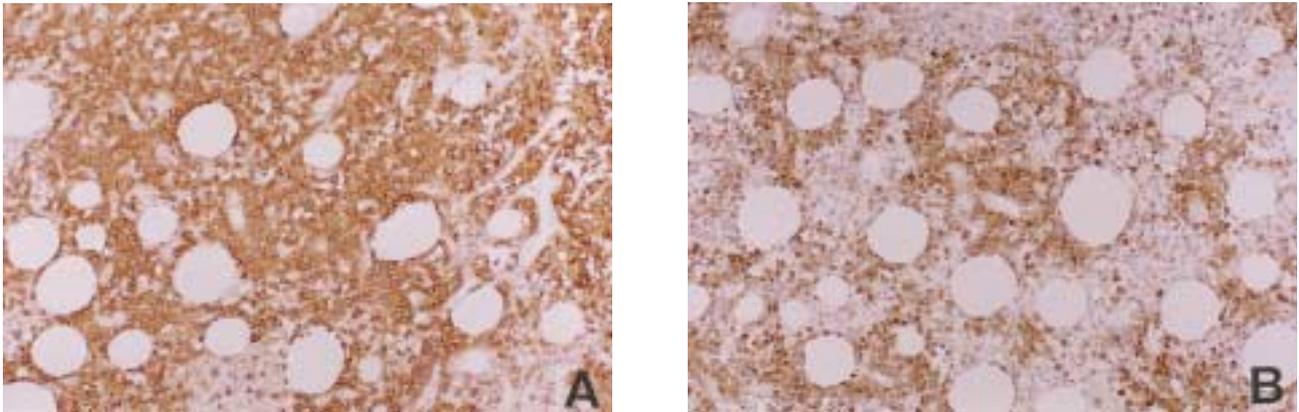


Fig. 3. Immunohistochemical stains of paraffin section show positive reaction to CD20 (A) and bcl-2 oncoprotein (B) ($\times 200$).

CASE REPORT

A 56-year-old Korean woman visited our department in March, 1999 with multiple subcutaneous nodules in her right flank and right upper arm. Those lesions were rapidly growing since she had recognized them only 7 days before. She noted 4 subcutaneous nodules of firm consistency without any symptoms or signs like pain, tenderness, generalized fever, night sweating or weight loss (Fig. 1). A complete physical examination, laboratory findings including blood chemistry, peripheral blood smear, serum protein electrophoresis, and bone marrow biopsy and aspiration, and radiologic evaluation including chest and abdominal computed tomography (CT) and bone scan revealed no abnormal findings. The skin biopsy specimen from the right upper arm showed the diffuse infiltration of bottom-heavy pattern in deep dermis and subcutis without epidermal and subepidermal changes. It was composed of large atypical lymphoid cells with vesicular nuclei, prominent nucleoli and moderate degree of mitotic figures, seemingly, mixtures of immunoblasts and centroblasts (Fig. 2). Immunophenotypic studies revealed the lymphoid infiltrates reacted with CD45 (LCA; leukocyte common antigen), CD20 (L26; a pan B cell marker) and bcl-2 protein, but none of the sections expressed CD3 (a pan T cell marker), bcl-6 protein and CD30 (Ki-1) (Table 1)(Fig. 3).

We concluded that the patient had a primary cutaneous diffuse large B-cell lymphoma (DLB-

CL) with multifocal skin lesions and then treated her with 2 cycles of high-dose multiagent chemotherapy with the Vanderbilt regimen (VP-16, cyclophosphamide, vincristine, bleomycin, methotrexate, prednisolone) and the BEAM regimen (BCNU, VP-16, Ara-C, melphalan) combined with the autologous peripheral blood stem cell transplantation at Department of Hemato-oncology, Korea Cancer Center Hospital. Until now, 10 months after termination of treatment, she has shown the disappearance of all skin lesions and no further development of extracutaneous disease.

DISCUSSION

Cutaneous B-cell lymphomas (CBCLs) contribute 10% to 25% of all cutaneous lymphomas in Western literatures and may be PCBCLs or non-Hodgkin lymphomas with secondary cutaneous involvement. CBCLs occur as a monomorphous picture of solitary or multiple deep-red colored nodules or tumors without surface change, arising from normal-looking skin within less than 1 year, and the lesions are sometimes disseminated all over the body or located in aggregates in the preferential localizations, trunk or head and neck¹.

Primary CBCLs are recently recognized as a distinctive disease entity from extracutaneous or nodal B-cell lymphomas with the advent of improved immunophenotyping and immunogenotyping^{2,3}. Even though most cases of

Table 1. Immunophenotypic studies on our patient.

Markers	Specificity	Results
CD 45	leukocyte common antigen	positive
CD 20	pan B lymphocytes	positive
CD 3	pan T lymphocytes	negative
Bcl-2	proto-oncogene	positive
Bcl-6	proto-oncogene	negative
CD 30	lymphocyte activation antigen	negative

CBCLs have an indolent course and tend to remain localized, CBCL lesions occurring anywhere may metastasize to the extracutaneous sites including lymph node, bone, and bone marrow in 3% to 18% of all cases⁶. Conversely, 25% of non-Hodgkin's lymphoma cases occur in extranodal sites including the skin, the next most common site of extranodal involvement to the gastrointestinal tract³ and a systemic B cell lymphoma can involve the skin in 6 to 20% of cases⁷. Usually, secondary CBCLs substantially show the same but a little different clinical features, e.g. disseminated or multiple nodules, a poorer overall prognosis, more frequent relapses in nodal and cutaneous lesions, compared with primary CBCLs⁶.

Due to such difficulties in discerning primary CBCLs from secondary CBCLs, we have to adopt the classification system proposed by the EORTC. According to this classification system, primary cutaneous lymphoma is defined as a non-Hodgkin lymphoma presenting in the skin, with no evidence of extracutaneous disease at the time of diagnosis and within the first 6 months after diagnosis, as assessed by appropriate staging procedures⁶.

Diffuse large B cell lymphoma (DLBCL) comprise a histogenetically heterogenous group. According to a model proposed by Dalla-Favera et al and Kärner et al, at least two distinct genetic pathways, *bcl-2* and *bcl-6*, may lead to DLBCL development; the *bcl-2* rearrangement consorts with the DLBCL transformed from a clinically undetectable follicular phase and the *bcl-6* pathway would be responsible for 'de novo' DLBCL^{8,9}.

Bcl-2 is a proto-oncogene located in the 18q21 band. By karyotyping, *t(14;18)* has been identified in 85%-90% of follicular lymphoma

and also in 12%-30% of the DLBCL. This translocation leads to constitutive activation and increased expression of *bcl-2*, which has been shown to inhibit apoptosis and may block chemotherapy-induced cell death⁹. But expression of *bcl-2* is also found in lymphomas without a translocation¹⁰. Several studies reported that *bcl-2* expression was found in 40%-45% of DLBCL, more often in extensive and primary nodal lymphomas than in extranodal cases^{10,11}. And *bcl-2* protein expression seemed to be related to a reduced disease-free survival and a worse prognosis^{9,11}. However, there seems to be almost no correlation between *bcl-2* rearrangement and *bcl-2* expression especially in DLBCL⁹. Recent studies suggest that amplification of the *bcl-2* gene at chromosome 18q21 is an important mechanism for *bcl-2* protein overexpression in diffuse large B cell lymphomas¹². And so it would be better to consider *bcl-2* rearrangement as a more meaningful prognostic factor rather than *bcl-2* protein expression itself.

Bcl-6 is a novel proto-oncogene located in the 3q27 region and acts as a transcriptional repressor. Several studies found that the *bcl-6* rearrangements occur in 30%-35% of DLBCL and *bcl-6* rearrangements are the most frequent genetic lesion in nodal DLBCL^{13,14}. But any possible correlation between the *bcl-6* rearrangement and clinical prognosis remained to be clarified in future^{9,14}.

A series about the patients with multifocal PCLBCL of the leg reported to have a more unfavorable prognosis than those with localized PCLBCL of the leg or multifocal and localized PCFCL or PCI. And so, they suggest that primary cutaneous DLBCL with multifocal skin lesions should always be treated with the more aggressive treatment including multiagent chemotherapy¹⁵.

To our knowledge, 6 cases of cutaneous B cell lymphoma¹⁶, 2 cases of primary CBCL^{17,18} and 3 cases of primary cutaneous DLBCL¹⁹⁻²¹ have been reported in Korean dermatologic literatures. Primary cutaneous DLBCL with multifocal subcutaneous nodules was not yet reported in Korea, but we expect a rather more primary cutaneous DLBCL cases should be underreported regardless of its multifocality.

According to Japanese series recently reported^{4,5},

DLBCL was the most frequent subtype of PCBCL in Japanese patients and the prognosis of Japanese patients with DLBCL was worse than that of reported European cases. Also, the unfavorable clinical course was at least partly related to high expression of bcl-2, and the site-related difference in clinical prognosis in Japanese patients was not as great as that observed in European patients.

The presenting case showed that microscopically, large atypical cells infiltrated in the subcutaneous fat layer and adjacent deep dermis. And, the lymphoid infiltrates reacted with pan B cell marker and bcl-2 protein. Clinically, there presented with multiple subcutaneous nodules at noncontiguous anatomic sites without evidence of extracutaneous disease at the time of diagnosis and within the first 6 months after diagnosis, as assessed by appropriate staging procedures. And so, we think that this case is a primary cutaneous diffuse large B-cell lymphoma presented as multifocal subcutaneous nodules.

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