A Case of Secondary Cutaneous Diffuse Large B-cell Lymphoma

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We herein report a case of secondary cutaneous diffuse large B-cell lymphoma(DLBCL) occurring in a 66-year-old woman. The skin lesions were erythematous infiltrative nodules on the right inguinal area. Histologically, the skin lesion disclosed DLBCL mainly composed of immunoblasts. Concurrently, she showed lymph node involvement. Initially, however, we could not define the conclusive temporal sequences between nodal lesions and skin lesions. Finally, additional further studies revealed this case as secondary cutaneous B-cell lymphoma, and she was managed with systemic chemotherapy. (Ann Dermatol 10:(2) 123~128, 1998).

Key Words : Secondary cutaneous diffuse large b-cell lymphoma

According to the cytodifferentiation pathway and clinical grading, cutaneous B-cell lymphoma(CBCL) encompasses various subtypes[1-3]. Although CBCL rarely represents grave clinical courses with lymph nodal spread, DLBCL which is characterized by admixed infiltrations of immunoblasts and centroblasts, shows frequent locoregional lymph nodal relapses, extranodal spreading and poor clinical courses[4-6]. CBCL is subdivided into primary forms arising from the skin and secondary forms metastasized from the lymph node[1]. A secondary CBCL shows a more aggressive clinical course than the primary form[1,2,5,7,8]. But primary DLBCL does not show a different clinical course compared with the secondary form. Accordingly, history taking, histopathological studies and even thorough staging workups have limited efficacy of defining whether DLBCL is the primary or secondary form, if a patient shows concurrent nodal involvement as in this case. We herein report a case of secondary DLBCL which was distinguishable from the primary form.

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CASE REPORT

A 66-year-old woman had had multiple skin lesions on her right inguinal area for 3 months. Over the 6 months prior to her visit, intermittent fever, weight loss and night sweat were experienced. An examination revealed ill-delimited purplish colored nodules on her right inguinal area(Fig. 1). Both inguinal lymphadenopathies were also found. She could not remember the temporal onset between development of lymph node swelling and skin lesions. Her hemoglobin was 11.3 gm/dl, the leukocyte count, 15,900/mm^3, and platelet count, 100,000/mm^3. No atypical lymphocytes were found in peripheral blood and bone marrow aspirations. An abdominal CT scan revealed paraaortic lymphadenopathy. A skin biopsy specimen taken from her nodular lesion, showed large atypical round cells infiltrating in the mid to lower dermis without epidermal invasion(Fig. 2-A). The relatively monomorphic individual cells had mainly immunoblastic features in that they showed a large vesicular nucleus, one to two prominent nucleoli in the center of the nuclei and moderately amphophillic to basophilic cytoplasms. Sometimes centroblasts having multiple prominent nucleoli along the nuclear membrane and centrocyte-like, small cleaved atypical lymphoid cells were found along with mitotic figures(Fig. 2-B).

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In a nodal biopsy specimen taken from the inguinal lymph node, atypical cells having the same cytomorphology as in the skin specimen disclosed a typical indian-file array(Fig. 5). Until 3 cycled intensive chemotherapy with CVP regimen(cyclophosphamide, vincristine, prednisolone) over 8 months was finished, she was not free of the preseptic condition and did not show improvement of her skin lesions.

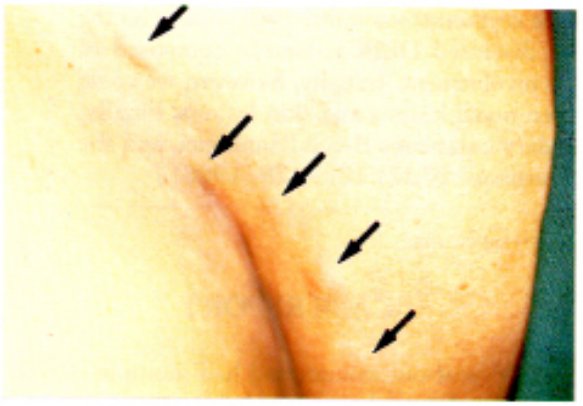

Fig. 1. ill-delimited purplish colored nodules on her right inguinal area.

Immunophenotypic Studies

The standard avidin-biotin complex(ABC) immunoperoxidase method was used to determine the immunophenotypes of infiltrative cells in paraffin-embedded sections taken from her skin specimens and inguinal lymph node biopsy specimens, using a wide panel of monoclonal antibodies(DAKO, Carpinteria, CA, U.S.A.). In skin specimen, the atypical infiltrative cells reacted with CD45(LCA), CD20(L26) and CD22(Fig. 3-A, B). However, they were negative against CD43, CD45RO(UCHL-1), CD30(Ki-1) and CD68(Kp-1). In a biopsy specimen of her inguinal lymph node, positiveness to CD45(LCA) and CD20(L26) was also found.

Immunohistochemical Detection of bcl-2

We studied bcl-2 expression in biopsies of her skin lesions by the labelled streptavidin biotin detection method using monoclonal mouse anti-human bcl-2 antibody(DAKO, Glostrup, Denmark, 1:100 diluted) on paraffin-embedded tissue sections. A diffuse positive reaction of infiltrative cells to bcl-2 antigen was found(Fig. 3-C).

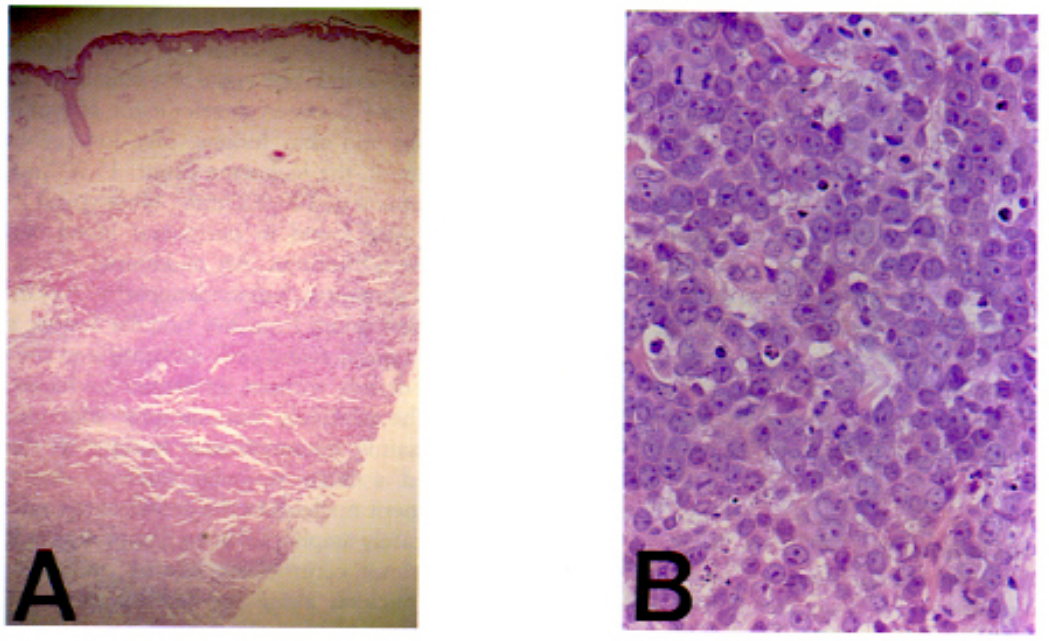

Fig. 2. A skin biopsy specimen showing heavy infiltration in the mid to lower dermis without epidermal invasion(A, H & E, ×100). Large round monomorphic cells consisting of immunoblasts and centroblasts along with mitotic figures(B, H & E, ×400).

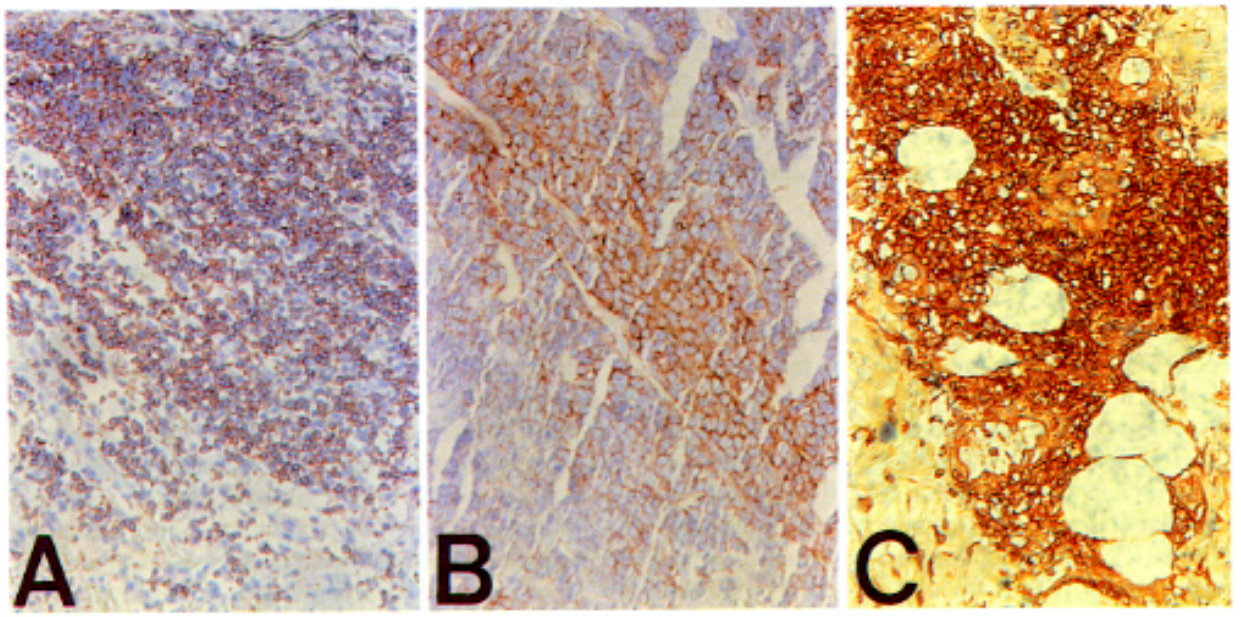

Fig. 3. Infiltrative cells in skin specimens reacting with CD20(A, ×200) and CD22(B, ×200). Diffuse positive reactions of infiltrative cells to anti-bcl-2 antibody(C, ×200).

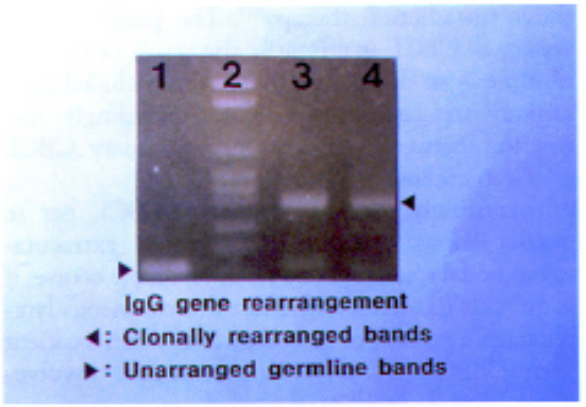

Fig. 4. Two positive bands of lane 3 and 4, representing clonality of IgG gene rearrangement and expression of bcl-2 oncoprotein arising from t(14;18) simultaneously(lane 1: intestinal lymphoma specimen of other patient, lane 2: molecular marker, lane 3: peripheral blood sample of patient, lane 4: skin specimens of patient)

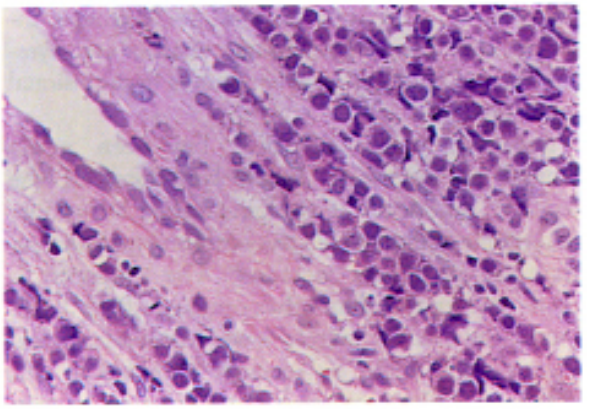

Fig. 5. Nodal biopsy specimen showing atypical cells with typical Indian-file array(H & E, ×400).

Light-chain Restriction Studies

For identification of light-chain monoclonal restriction of surface Ig, sections were stained using an ABC immunoperoxidase method with antisera toκ-andλ-light chains(DAKO). Though we could not find positive finding toλ-light chains, double labelling techniques of both light chains revealed positive responses toλ-light chains.

RT-PCR Amplification Identifying bcl-2 Expression and Clonality of IgG Gene

Peripheral blood and skin samples from this patient were subjected to RT-PCR(reverse transcription-polymerase chain reaction) amplification of DNA, using JH probe of immunoglobulin G(IgG) heavy chain of chromosome 14 as a primer to analyze the molecular level for the chromosomal translocation t(14;18) and clonality of IgG genes simultaneously.

RT-PCR amplification of DNA obtained from fresh lesional tissue sections revealed positive bands of 158 KDa, representing a clonal gene rearrangement of heavy chain genes and the expression of bcl-2 oncoprotein by t(14;18). Also in the peripheral blood sample, the identical positive finding was found(Fig. 4).

DISCUSSION

Considering a cytodifferentiation pathway of tumor cells, CBCL can be subdivided as follows; lymphoblastic B-cell lymphoma in immature B-cell types, follicular center cell lymphoma(FCCL)(e.g. centroblastic B-cell lymphoma(CBL), CBL-centrocytic lymphoma, centrocytic B-cell lymphoma) in memory cell pathways, immunoblastic B-cell lymphoma(IBL), lymphoplasmacytoid lymphoma(immunocytoma), intravascular B-cell lymphoma, and plasma cell lymphoma in Ig-producing cell pathways[3,9]. Also according to clinical grading, CBCL can be subspecified into FCCL and immunocytoma in benign grade groups, DLBCL(e.g. IBL, IBL-CBL) in intermediate grade groups, intravascular B-cell lymphoma, mantle cell lymphoma and marginal zone lymphoma in provisional grade groups[2,6].

Recently, primary DLBCL has been newly named as "cutaneous B-cell lymphoma of the leg(s)"[3,6]. Clinically it is characterized by solitary or multiple nodules to plaques occurring on lower extremities of elderly women[3-6]. The prognosis is more unfavorable than other primary CBCL[3,4]. IBL previously named merely from histopathological view points, might be recently included in this category[3,4,6]. Our case occurring in an elder woman showed nodules localized on the unilateral inguinal area.

Histologically, DLBCL often contains heterogeneous cell components as centroblasts or centrocytes besides immunoblasts[3,4,6]. Supposedly, DLBCL encompasses varied large B-cell lymphomas such as IBL, IBL-CBL and CBL-IBL-centrocytic lymphoma except FCCL consisting of only centroblasts or centrocytes[3,6,10]. IBL, which was originally diagnosable when more than 30% of infiltrative cells were compatible with immunoblasts, is actually notified in less than 8% among total DLBCL[3,6]. So admixed types such as IBL-CBL or CBL-IBL-centrocytic lymphoma are mostly dominant(>60%) in comparison with pure IBL[6]. In our case, more dominant immunoblasts having one or two prominent nucleoli in nuclear centers and centroblasts were admixed in her skin specimen.

CBCL might be specifically considered as secondary lymphoma when a nodal involvement is primarily identified earlier than a cutaneous lymphoma, and as a primary lymphoma when concurrent nodal lymphoma is absent or when nodal relapse is not found despite thorough staging workups for at least 6 months from diagnosis[3,12]. Essentially, primary CBCL takes a comparatively favorable course, responds readily to non-aggressive treatment, and is lacking in the evidence of extracutaneous spread[1,2,5,8,13]. Clinically, secondary CBCL usually shows disseminated or multiple nodules, a poorer overall clinical course and prognosis, more frequent nodal relapses and cutaneous lesional relapses in comparison with primary CBCL[14,15]. In response to treatment, primary CBCL is responsive to orthovolt local irradiation but secondary CBCL needs systemic chemotherapy for nodal remission in that it tends to be resistant to orthovolt-irradiation therapy[6,14]. The prognostic diversity of CBCL is primarily the result of the fact that previous numerous studies had included both primary and secondary CBCL. Accordingly, distinction between primary and secondary CBCL has been crucial.

Interestingly, because primary DLBCL per se usually shows frequent locoregional extracutaneous nodal spreading and an unfavorable course, it is difficult to identify whether the cutaneous lymphoma is a primary or secondary form when a patient with DLBCL shows concurrent nodal involvement[3].

There are recent reports that the expression rate of bcl-2 oncoprotein and t(14;18) in secondary lymphoma are significantly higher than inprimary lymphoma[2,6,11,15-17]. This is due to the tact that cellular bcl-2 oncogene is formed through t(14;18), a balanced reciprocal translocation between chromosome 14(14q32, Ig heavy-chain gene locus) and chromosome 18(bcl-2 oncogene foci)[16,18]. The t(14;18) occurs in 70% of FCCL and in some high grade nodal non-Hodgkin's lymphomas. The expression of bcl-2 oncoprotein in lymphoma has been initially demonstrated in primary FCCL[2,16]. However, the subsequent studies disclosed that bcl-2 expression is more frequently found in sec-

ondary lymphoma than in the primary form[2,6,11,15,16]. Cerroni et al[16] concluded that although bcl-2 protein is expressed in 25.4% of CBCL, the expression rate is significantly more frequent in secondary than in primary CBCL and one-third of cases expressing bcl-2 are characterized by t(14;18)[16]. So bcl-2 oncoprotein expression might indicate that the cutaneous manifestation of lymphoma represents a secondary spreading from a node-based lymphoma.

Clonal rearrangement of one or more Ig genes was also significantly more frequent in secondary than in primary CBCL[8,18]. Sepp et al[8]. emphasized that Southern blot analysis of peripheral blood and bone marrow samples is useful in the differential diagnosis of primary and secondary CBCL. The PCR results of specimens taken from peripheral blood, bone marrow and skin lesions, using a primer as Ig heavy-chain JH probe of chromosome 14, could discriminate secondary B-cell lymphoma from the primary form by identifying gene rearrangements in peipheral blood specimens[5]. Therefore, a presence of gene rearrangement both in skin specimens and peripheral blood specifically represent that the tumor is not primary B-cell lymphoma but secondary lymphoma arising from lymph nodes because the primary form invariably shows positive findings only in skin specimens.

In our case, initial evaluation such as history taking, an abdominal CT scan, bone marrow biopsy and lymph node biopsy could not identify the origin of the tumor. However, through an immunohistochemical staining for bcl-2 oncoprotein and PCR techniques using peripheral blood specimens in addition to skin specimens, we could determine this case as not a locoregional spreading of primary lymphoma but DLBCL which was metastasized from nodal lymphoma.

In summary, we concluded that in a case of CBCL with concurrent nodal involvement, it might be mandatory to perform (a) bcl-2 staining immunohistochemically and (b) PCR studies using peripheral blood sample besides skin specimens to determine whether it is primary or secondary CBCL.

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