A Case of Secondary Cutaneous Diffuse Large B-Cell Lymphoma

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We report here on a case of secondary cutaneous diffuse large B-cell lymphoma (DLBCL) that occurred in a 67-year-old man who had a 2-month history of nodular growing masses on the left cheek, plus palpable lymph nodes on the left cervical area. The histopathological findings showed a diffuse infiltration of large atypical lymphocytes with nuclear atypia throughout the entire dermis. These showed positive CD20, bcl-2 and the post-germinal center marker, MUM-1. According to the WHO (World Health Organization) classification, this lymphoma is considered to be diffuse large B-cell lymphoma of the post-germinal center (GC) B-cell type with a secondary cutaneous manifestation. We treated the patient with systemic chemotherapy (CHOP) and anti-CD20 monoclonal antibodies. During the course of treatment, new skin lesions developed on his neck, so we changed the regimen to cytosine-arabinoside and cisplatin. But he died of pneumonia after the third cycle. (Ann Dermatol (Seoul) 18(2) 91–96, 2006)

Key Words: Bcl-2, Post-GC B-cell, Secondary cutaneous diffuse large B-cell lymphoma

INTRODUCTION

Secondary cutaneous diffuse large B-cell lymphoma (DLBCL) is a B-cell lymphoma which has anaplastic cytological features and the expression of CD20 in the skin, and displays evidence of extracutaneous disease at the time of diagnosis or within the first 6 months after diagnosis. Clinically, secondary cutaneous DLBCL usually shows disseminated or multiple nodules, a poorer overall clinical course and prognosis, more frequent nodal relapse and cutaneous lesional relapses in comparison with primary cutaneous DLBCL. DLBCL represents a heterogeneous group of tumors based on their morphological, phenotypic, molecular and clinical features that reflect their marked biological heterogeneity and highly variable clinical course. To date, 2 cases of secondary cutaneous DLBCL have been reported in the Korean dermatologic literature. All the skin lesions were reported to be on the lower extremities and the patients were kept under observation after chemotherapy. There have been no reported cases with skin lesions on the face or a sufficient prognostic marker study.

Our case showed multiple skin lesions on the left cheek and left cervical lymphadenopathies and worse positivity for the prognostic marker, bcl-2 and MUM-1 (post-germinal center marker). Patients with activated B-cell-like DLBCLs have worse outcomes than those patients with germinal center (GC)-like DLBCLs, and bcl-2-expression is associated with a decreased disease-free condition or overall survival in DLBCL. Herein, we report on a case of secondary cutaneous diffuse large B-cell lymphoma which was the post-germinal center (GC) B-cell type and correlate the immunochemical and tumor biologic studies with our case, paying particular attention to their clinical prognostic significance.
CASE REPORT

A 67-year-old Korean man presented with a 2 month history of multiple skin lesions on his left cheek. After the first occurrence, the lesions continued to increase in number and size, but no other systemic symptoms such as fever, night sweats or weight loss were observed. An examination revealed relatively well-demarcated, skin-colored to erythematous nodules on his left cheek (Fig. 1A) and left cervical lymphadenopathies were also found. He was otherwise healthy and there was an absence of any family history for this condition. His hemoglobin was 13.6 gm/dl, the leukocyte count, 6,900/mm³ and the platelet count, 207,000/mm³. The serum chemistry profile, including uric acid, calcium and seric β₂-microglobulin, and the immunoelectrophoresis test were all within normal values. A well-demarcated, bulging, mass-like lesion was noted in the paravertebral area of the retrocardiac space on the chest radiology. The neck CT scan revealed several localized, lobulated thickenings on the left cheek and multiple enlarged lymph nodes along the left II, III and IV levels (Fig. 1B). On the chest CT, multiple, enlarged lymph nodes were seen in the left side internal jugular chain and the posterior cervical triangle. However, the abdomen and pelvis CT scans were normal. No atypical lymphocytes were found in the peripheral blood, the bone marrow aspiration or biopsy.

A biopsy specimen from one of the skin lesions showed large atypical round cells infiltrating from the dermis to the subcutaneous fat, without epidermal invasion (Fig. 2A). This infiltration was composed of large lymphoid cells containing nuclear atypia. The relatively monomorphic individual cells had mainly immunohistochemical features that they showed a large vesicular nucleus, one to two prominent nucleoli in the center of the nuclei and moderately amphophilic to basophilic cytoplasm (Fig. 2B). Sometimes, there were centroblasts having multiple prominent nucleoli along the nuclear membrane, and there were centrocyte-like, small cleaved atypical lymphoid cells found along with mitotic figures. In a nodal biopsy specimen taken from the cervical lymph node, atypical cells had the same cytomorphology as in the skin specimen. On the immunohistochemical studies, the tumor cells expressed the B-cell lineage-associated antigen markers CD20 (Fig. 2C) and CD45, high index of the proliferation and apoptosis markers, Ki67, and the post germinal center stage-specific marker of B-cell differentiation, MUM-1 (Fig. 3A). These cells were weakly positive for GC antigen Bel-6 and they were negative for

Fig. 1. Relatively well-demarcated multiple skin-colored to erythematous nodules on the patient’s left cheek area (A). Multiple, variable-sized, enlarged lymph nodes were seen along the left II, III, IV level on the neck CT (B).
Fig. 2. A skin biopsy specimen showing the heavy infiltration of atypical cells in the mid to lower dermis without epidermal invasion (A) (H&E, ×40). Large round monomorphic cells are seen that consist of immunoblasts and centroblasts along with mitotic figures (B) (H&E, ×400). Infiltrative cells in skin specimens reacting with CD20 (C, ×400).

Fig. 3. Infiltrative cells in the skin specimen reacting with MUM-1 (A, ×400). Diffuse positive reactions of the infiltrative cells to anti-bcl-2 antibody (B, ×100).

lineage-associated antigen CD45RO, CD30, CD56, CD68 and CD3, cell cycle control antigen p53 and GC B-cell antigen CD10. We studied the Bcl-2 expression in the biopsies of his skin lesions and lymph nodes using monoclonal mouse anti-human Bcl-2 antibody, and a diffuse positive reaction of the infiltrative cells to Bcl-2 antigen was found (Fig. 3B). According to the WHO (World Health Organization) classification, this lymphoma was considered as a diffuse large B-cell lymphoma of the post-germinal center (GC) B-cell type with a secondary cutaneous manifestation.
The patient received systemic chemotherapy of cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP), and anti-CD20 monoclonal antibody (rituximab). During the course of treatment, CD20 antigen was not lost and the size of the palpable lymph nodes on his neck increased. Therefore we changed the regimen to cytosinarabinoside and cisplatin, but he died of pneumonia after the third cycle.

**DISCUSSION**

Primary cutaneous B-cell lymphoma (PCBCL) represents a heterogeneous group of lymphoproliferative conditions comprising 20-25% of all cutaneous lymphomas. They are defined as lymphomas of B-cell origin that are localized to the skin, with no evidence of extracutaneous disease within the first 6 months of diagnosis. Most PCBCL are typically indolent, rarely disseminate beyond the skin and respond favorably to radiotherapy. In contrast, secondary cutaneous B-cell lymphoma (SCBCL) usually shows disseminated or multiple nodules, a poorer overall clinical course and prognosis, more frequent nodal relapse and cutaneous lesional relapses in comparison with PCBCL.

There are many classification schemes for cutaneous lymphomas. WHO classification, based on immunophenotypic criteria, recognizes primary as well secondary cutaneous lymphomas. In contrast, EORTC (European Organization for Research and Treatment of Cancer) classification was designed exclusively for the group of primary cutaneous lymphoma, based on clinical criteria. In EORTC classification, primary cutaneous follicle center cell lymphoma (PFCCL) includes all the follicular lymphomas and most DLBCLs (terminology of WHO classification) and primary cutaneous large B-cell lymphoma of the leg (PCLBCL-leg) includes DLBCLs which are located below the hip. According to the WHO classification, this lymphoma was considered as secondary cutaneous DLBCL. In DLBCL, there is a heavy diffuse infiltrate of large centroblasts and immunoblasts throughout the dermis and epidermotropism may be seen on rare occasions. The tumor cells are CD20 (+) and CD79a (+). DLBCL accounts for about 30-40% of all lymphomas seen in western countries and it represents a heterogeneous group of tumors based on their morphological, phenotypic, molecular and clinical features. Clinically, patients differ in their mode of presentation and respond variably to therapy. A combination of clinical parameters can be used to predict the patient's response to therapy and their chance of survival. Recently, numerous antigens linked to different biological aspects of these tumors have been studied. This article summarizes these studies, with particular attention being paid to their clinical prognostic significance (Table 1) and we correlated the immunochemical and tumor biological studies with our case.

**Table 1. Clinical Significance of Phenotypic Markers in Diffuse Large B-cell Lymphoma**

<table>
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<tr>
<th>Marker</th>
<th>Clinical Significance</th>
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<tr>
<td>CD20</td>
<td>Positive in most cases, may be lost following anti-CD20 monoclonal Ab therapy</td>
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<tr>
<td>CD5</td>
<td>Positive in about 10% of de novo DLBCL, associated with extranodal presentation and likely indicator of poor outcome</td>
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<tr>
<td>Ki67</td>
<td>Proliferation fraction typically high, higher proliferation associated with decreased survival</td>
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<tr>
<td>P53</td>
<td>p53 mutation and is associated with poor treatment response</td>
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<tr>
<td>Rb</td>
<td>High RB expression (&gt;80% positive cells) associated with better survival</td>
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<tr>
<td>Bcl-2</td>
<td>High bcl-2 expression is a strong adverse prognosticator</td>
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<tr>
<td>Bcl-6</td>
<td>Positive expression in 60-80% of DLBCL cases; associated with improved survival in a few studies</td>
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<tr>
<td>CD10</td>
<td>Positive expression in 30-40% of DLBCL cases; probably associated with a better prognosis</td>
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<tr>
<td>Bcl-6/CD10</td>
<td>Bcl-6/CD10+ referred to as a 'GC immunophenotype'; associated with improved survival</td>
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<tr>
<td>MUM-1</td>
<td>Positive expression in 50-75% of DLBCL cases, significantly worse outcome</td>
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MUM-1 expression in DLBCLs may reflect derivation from B cells at a late GC or post-GC stage of differentiation, and the expression of MUM-1 has been associated with a significantly worse outcome in a subsequent tissue microarray study. The combined expression of Bcl-6 and CD10 indicates a possible origin of these tumors from the GC-derived cells or the transformed follicular lymphomas, and it is predictive of a better outcome. Bcl-2 is strongly expressed by neoplastic B cells in PCLBCL-leg and secondary cutaneous follicular lymphoma, but it is seldom expressed in PCFCL.14. There is an association between Bcl-2 expression and a decreased disease-free survival or overall survival in DLBCL.14.

The monoclonal anti-Ki67 antibody (MIB-1) is used as a proliferation marker and it is an adverse prognostic factor.15 Mutations in the p53 gene is found to be associated with clinical drug resistance and a poor outcome.16

Chemotherapy, and specifically CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone) is the most widely used regimen, and this should be reserved for multicentric primary cutaneous DLBCL or systemic DLBCL.17. Chimeric antibodies directed against CD20 (rituximab) are being increasing used, in combination with the standard therapies, for the treatment of DLBCL.18. Therapy for B-cell lymphoma with anti-CD20 antibodies can result in the loss of CD20 antigen expression.19. In the systemic lymphomas, the prognosis is dramatically impaired by skin involvement. In a series by Sterry et al.,20 the mean survival time was 6 months instead of 37 months when only the lymph nodes were involved. In our case, the immunohistochemistry displayed poor prognostic factors such as positivity for Bcl-2, MUM-1 and high proliferative index of Ki67 and negativity for CD10. We explained to the patient and his family that the patient had a poor prognosis in spite of his healthy appearance, and we performed intensive chemotherapy with a high dose of CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone) and the anti-CD20 monoclonal antibody (rituximab). In the course of treatment, CD20 antigen was not lost and new skin lesions developed on his neck. Therefore we changed the regimen to cytosin-arabinoside and cisplatin, but he died of pneumonia after the third cycle.

To date, 2 cases of secondary cutaneous DLBCL have been reported in the Korean dermatologic literature. All the skin lesions were reported to be on the lower extremities and the patients were kept under observation after chemotherapy. There have been no reported cases with skin lesions on the face or a sufficient prognostic marker study. Our case shows worse positivity for the prognostic marker, bel-2 and MUM-1 (post-germinal center marker). We report here on a case of bel-2-positive, post-GC B-cell type, systemic DLBCL that occurred in a 67-year-old man.

REFERENCES


