A Case of ALK-Negative Systemic Anaplastic Large Cell Lymphoma

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Anaplastic large cell lymphoma (ALCL) is a T-cell lymphoma with anaplastic cytological features and expression of CD30. Anaplastic lymphoma kinase (ALK) positivity is an important prognostic factor in ALCL because ALK-positive ALCL is more frequent in age groups younger than third decade and shows favorable outcome.

We report a case of ALK-negative systemic ALCL occurred in a 69-year-old women who had a 2 months' history of two polypoid growing masses on the frontal scalp and a palpable lymph node on the right inguinal area. Histopathological findings showed a diffuse infiltration with pleomorphic atypical lymphocytes into the subcutaneous layer sparing epidermis. These atypical cells were positive for CD8, CD30, CD45RO, LCA and CD56, but were negative for ALK and Epstein Barr virus (EBV).

After 6 cycles of high-dose chemotherapy (CHOP) and localized gamma-ray radiotherapy were performed, the scalp tumors and multiple enlarged lymph nodes decreased in size. But a 1.5 × 1.3 cm sized dome-shaped tumor with partial erosion appeared in right perineum seven months after the final radiotherapy. (Ann Dermatol 16(3) 125~131, 2004)

Key Words: ALK-negative anaplastic large cell lymphoma (ALCL), CHOP

INTRODUCTION

Anaplastic large cell lymphoma (ALCL) is a T-cell lymphoma with anaplastic cytological features and expression of CD30[1]. ALCL can be divided into two major groups[1]. The first is systemic ALCL, the most common form, involves multiple nodal and extranodal sites at the time of diagnosis, which can be divided into two subgroups: anaplastic lymphoma kinase (ALK)-positive and ALK-negative systemic ALCL. The second is a spectrum of CD30-positive T-cell lymphoproliferative disorders including lymphomatoid papulosis (LyP), primary cutaneous ALCL and borderline lesions between primary cutaneous ALCL and LyP, which are similar to systemic ALCL histopathologically[2]. ALK expression is of clinical and prognostic importance and strongly related to younger age, lower international prognostic index (IPI) risk groups, and has a better prognosis than ALK-negativity[3,4]. In general, ALK-negative systemic ALCL has a poor prognosis, although the clinical behavior of individual patients remains unpredictable[5].

To date, some cases were reported as a primary cutaneous variants in Korean dermatologic literatures under such names as CD30-positive large cell lymphoma, Ki-1 lymphoma, and primary cutaneous pleomorphic large cell lymphoma. Herein we report a case of a patient with anaplastic large cell lymphoma occurring in multifocal locations including skin and nodal lesions.

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CASE REPORT

A 69-year-old woman admitted with two months' history of polypoid growing masses on the frontal scalp with a lymph node swelling on the right inguinal area (Fig. 1A). Physical examination revealed two polypoid ulcerated masses with central necrosis on the frontal scalp measuring 5.0 × 3.5 cm and 1.5 × 1.0 cm in size that were growing rapidly during the two months and an enlarged lymph node was palpated on the right inguinal area. Complete blood count revealed normal ranged values except WBC count; RBC $3.94 \times 10^6/mm^3$, WBC $20.7 \times 10^3/mm^3$, platelet $2.94 \times 10^4/mm^3$. Erythrocyte sedimentation rate was elevated at 73 mm/hr. A peripheral blood smear revealed marked neutrophilic leukocytosis. Brain magnetic resonance imaging showed a tumor on the scalp which was localized only to the skin without evidence of brain metastasis. A computed tomography (CT) scan of the abdomen showed a hemangioma on the subcapsular area of the liver S7 area. A CT scan of pelvis revealed enlarged numerous inguinal and intra-abdominal lymph nodes (Fig. 2A). Other radiologic studies including chest X-ray revealed non-specific findings.

A skin biopsy was performed at the scalp mass for the purpose of metastatic skin cancer and other cutaneous malignancies to be ruled out. The histopathologic findings showed diffuse infiltration of pleomorphic atypical lymphocytes in the dermis,

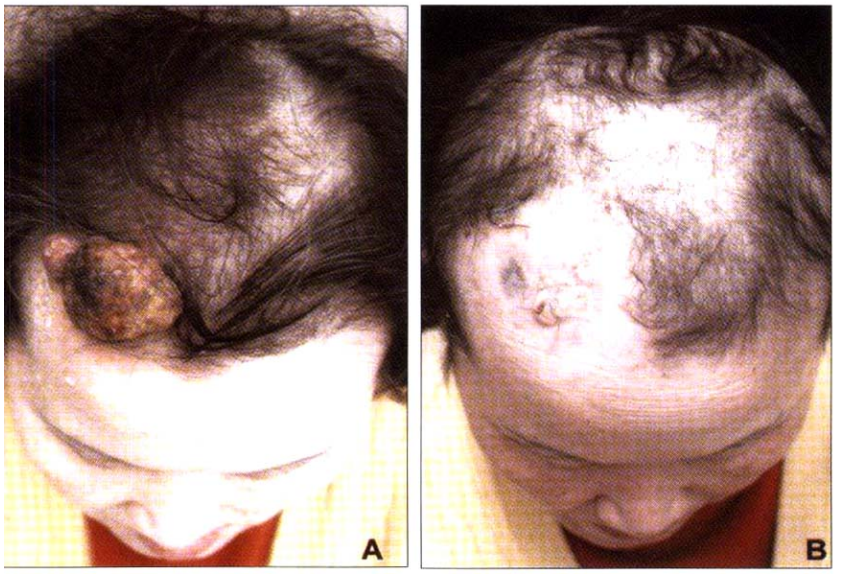

Fig. 1. Two polypoid ulcerated masses with central necrosis on frontal scalp (A). After chemotherapy and radiotherapy, regressed scalp tumor showing slightly elevated yellowish plaque (B).

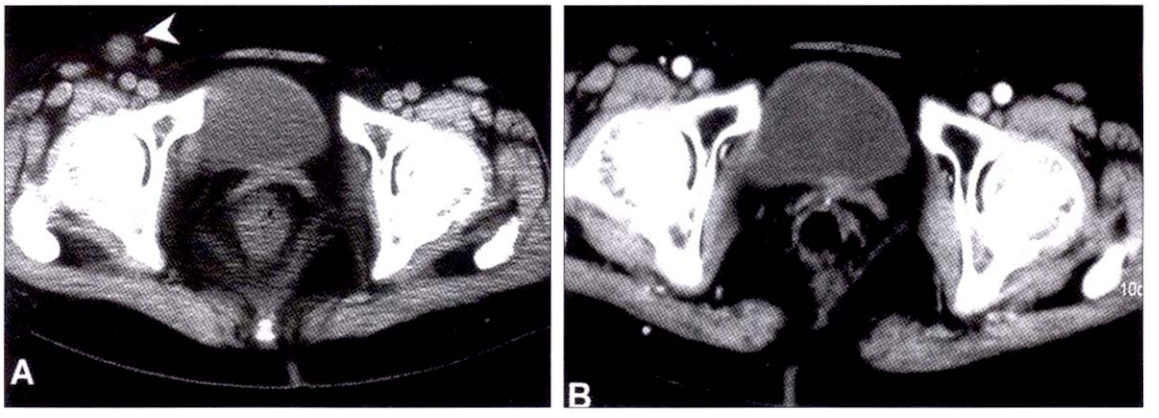

Fig. 2. CT scan of pelvis revealed enlarged right inguinal lymph node (arrowhead) (A). After final treatment, the right inguinal lymph nodes decreased in size (B).

extending into the subcutaneous layer. These lymphocytes consisted of relatively uniform large cells with pleomorphic nuclei and prominent nucleoli, mostly. Some atypical lymphocytes showed Reed-Sternberg cell-like features (Fig. 3)

The majority of the large atypical cells were stained positively for CD8, CD30, CD45RO, LCA, and CD56, but negatively for CD4, CD20, NSE, anaplastic lymphoma kinase (ALK) and pancytokeratin (Fig. 4). Epstein-Barr virus-encoded RNA (EBER) was not detected by in situ hybridization. The neoplastic cells were strongly positive immunoreaction for CD30 with both membranous and cytoplasmic labelling pattern but negative for ALK. In the bone marrow aspiration and biopsy, any atypical cells were not shown. She was diagnosed as ALK-negative, CD30-positive systemic ALCL that was at stage III_E in Ann Arbor staging of lymphoma (Table 1).

High-dose chemotherapy was started with CHOP (cytoxan, adriamycin, vincristine, and prednisolone). After 3 cycles of chemotherapy, the scalp tumor

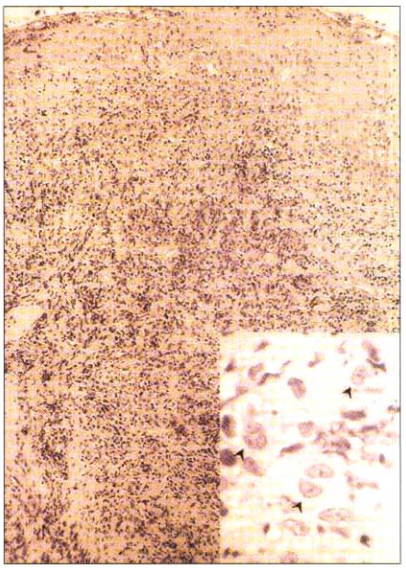

Fig. 3. Photomicrograph showing diffuse infiltration of pleomorphic atypical lymphocytes in dermis, extending into the subcutaneous layer (H&E stain, × 40). Some atypical lymphocytes showed Reed-Sternberg cell-like feature (inlet, H&E stain, × 400).

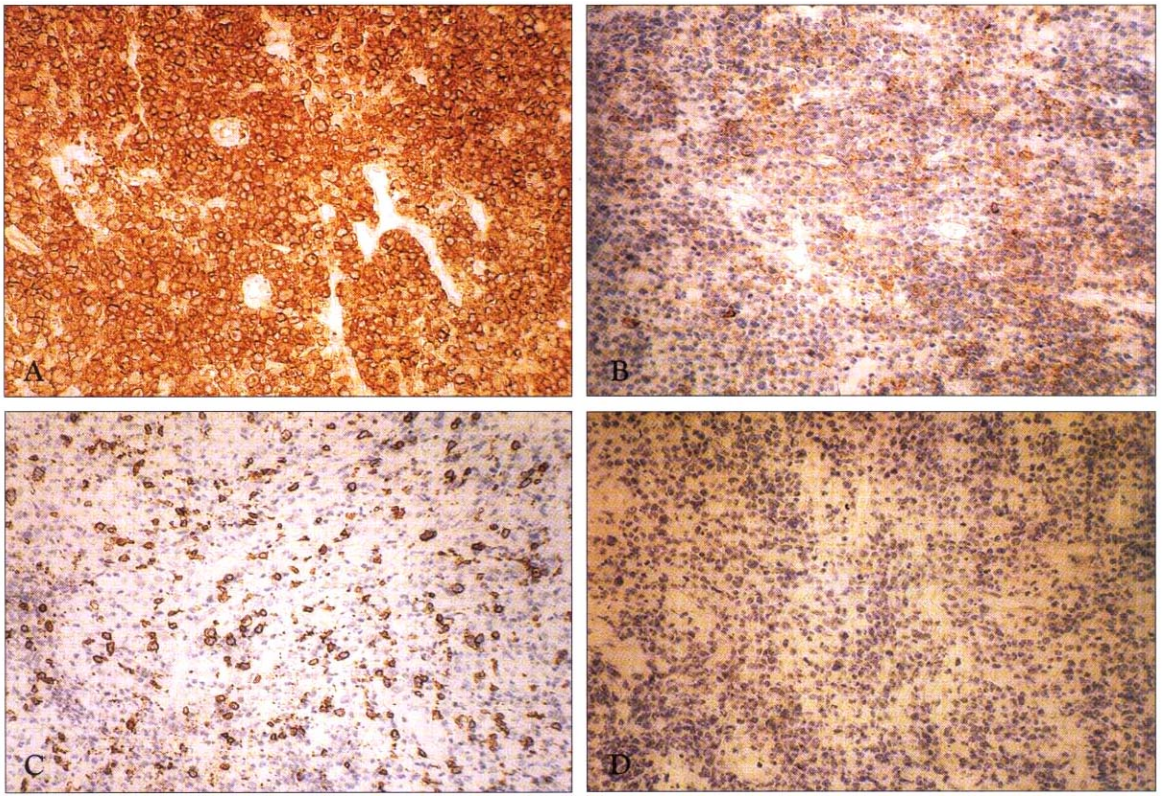

Fig. 4. Immunophenotyping of the ALCL cells showed positive to CD30 (A: × 200), CD56 (B: × 200) and CD8 (C: × 200). But these cells were negatively stained to ALK (D: × 200).

Table 1. An Arbor Staging System

Stage I	
I	Involvement of a single lymph node region
I_E	Involvement of a single extralymphatic organ or site
Stage II	
II	Involvement of two or more lymph node regions on the same side of the diaphragm
II_E	Localized involvement of an extralymphatic organ or site and of 1 or more lymph node regions on the same side of the diaphragm
Stage III	
III	Involvement of lymph node regions on both sides of the diaphragm
III_E	Localized involvement of an extralymphatic organ or site
III_S	Involvement of spleen
III_{SE}	Both involvement (III_S, III_E)
Stage IV	
IV	Diffuse or disseminated involvement of 1 or more extralymphatic organs or tissues with or without associated lymph node enlargement

started regressing with gradual disappearance of intra-abdominal, pelvic lymph nodes and the right inguinal lymph node (Fig. 1B, 2B). The scalp lesions and both inguinal lymph node lesions were managed by additional gamma-ray irradiation. Seven months after the final radiotherapy, a 1.5 × 1.3 cm sized dome-shaped tumor with partial erosion appeared in the right perineum. The histopathologic finding from perineal lesion showed diffuse pleomorphic lymphocytes infiltration in the dermis, whose nuclear chromatin was coarsely dispersed with small nucleoli, with sparse neutrophilic infiltration with epidermal erosion. Immunohistochemical studies showed positivity for CD30, CD56, CD45RO, CD8, LCA, and EMA, but negative for CD3, CD4, Ber-2 and ALK. The follow-up CT scan of the pelvis showed a more enlarged right inguinal lymph node than before. The clinical, histopathologic, and radiologic findings revealed recurred CD30 systemic anaplastic large cell lymphoma.

DISCUSSION

ALCL belongs to CD30-positive disorders such as LyP, Burkitt's lymphoma, body cavity lymphoma, mediastinal B cell lymphoma subtype of diffuse large B cell lymphoma, large cell transformation of mycosis fungoides, and embryonal carcinoma[2,6]. CD30 is a member of the TNF/NGF family that is expressed by highly activated T and B lymphocytes concentrated around the perifollicular area within reactive lymph nodes but its function is not yet clarified.

Most patients with systemic ALCL presents with advanced stage III or IV disease at the time of diagnosis. Systemic ALCL involves lymph nodes, commonly in inguinal area, and extranodal sites including skin, bone, soft tissue, lung, liver and pleura. B symptoms such as fever, night sweats, and unexplained weight loss are common in this disease[6]. Survival is better for systemic ALCL than other types of large cell lymphoma, and significantly better for ALK-positive systemic ALCL, compared with ALK-negative ALCL, regardless of age. Several features must distinguish systemic ALCL from Hodgkin's disease (HD)[7]. In systemic ALCL, lymphadenopathy is noncontiguous in 50% of cases, but HD most often involves the skin by direct extension from contiguous involved lymph nodes. And the atypical cells of ALCL can have aberrant T-cell phenotypes and clonal rearrangement of TCRα and β genes. But HD are found in Ig gene rearrnagement and germline TCR genes[8].

Primary cutaneous ALCL usually presents with one to several skin nodules without evidence of

extracutaneous localization for at least 6 months[9,10]. Primary cutaneous ALCL is generally accepted to be at the malignant end of a spectrum of CD30-positive cutaneous lymphoproliferative disorders that includes clinically LyP. This disease usually presents as solitary, asymptomatic and rarely multicentric tumor, which can be ulcerated. The disease is nearly always limited to the skin at the time of diagnosis but may disseminate extracutaneously mainly to regional lymph node and rarely involved other organs. Spontaneous regression or waxing and waning of skin lesions can occur in primary cutaneous ALCL more than systemic ALCL.

To diagnose and differentiate ALCL from other lymphomas, especially HD, further studies including immunohistochemical staining and chromosomal study would be needed together with some markers, CD56, ALK, and clusterin. The tumor cell phenotype is usually that of CD4-positive activated helper T cell. But ALCL cells usually express an aberrant T-cell phenotype lacking one or more pan-T cell antigens, especially CD3. CD8 positivity occurs in only a few cases and never together with CD4. CD30 cannot always be the marker for good prognosis because it is expressed in various lymphoproliferative disorders. And cutaneous lesions of HD may also pose considerable difficulty in the differential diagnosis of CD30-positive lymphoproliferative disorders[11]. HD, particularly the nodular sclerosis type, may contain Reed-Sternberg cell variants, and resemble ALCL. However, because ALCL is a T-cell neoplasm and HD is in the vast majority of cases a B-cell neoplasm, theses two disorders does not represent a true biological borderlines. Tumor cells in ALCL are usually negative for CD15 and positive for epithelial membrane antigen (EMA) and leukocyte common antigen (LCA) in contrast to HD[12]. Tumor cells usually contain cytotoxic proteins TIA-1, granzyme B, and/or perforin focally[13,14]. Clusterin is a highly conserved glycoprotein implicated in intercellular and cell matrix interactions, regulation of the complement system, lipid transport, stress reponses, and apoptosis. Although its functions in ALCL is unknown, the unique expression of clustrin within ALCL provides an additional marker for the diagnosis of ALCL[15].

ALK protein was found to have anti-apoptotic properties *in vitro*. The pathogenesis of systemic ALCL is linked to the unregulated growth of affected lymphoid cells through the phosphorylation of a protein tyrosine kinase, ALK[16]. When ALK is detected in skin tumor cells, systemic ALCL is strongly suspected because ALK is expressed in higher frequency in systemic ALCL compared to primary cutaneous ALCL. ALK positive ALCL should be carefully staged to determine whether lymph nodes are involved. ALK expression in systemic ALCL is most commonly seen as a result of the t(2:5)(p23;q35), which fuses the ALK gene on 2p23 to the nucleophosmin (NPM) gene on 5q35, and other chromosomal abnormalities are involved in some cases[17]. ALK positivity is the most important prognostic indicator in ALCL because it has been associated with a more favorable prognosis than those of ALK-negative ALCL[4,18]. But there are overwhelming cases of ALK-negative primary cutaneous ALCL with still better prognosis than systemic ALCL[18].

Principally, primary cutaneous ALCL can usually be managed by surgical excision or local radiation therapy with resulting an excellent prognosis. Chemotherapy, CHOP regimen is most widely used, should be reserved in multicentric primary cutaneous ALCL or systemic ALCL[19]. The antiapoptotic effect of ALK has limited influence on the sensitivity of tumor cells to chemotherapy *in vivo*, as evidenced by the good prognosis of ALK-positive ALCL.

Systemic ALCL shows a five year survival of only 30% and more than half the patients have died within one year. ALK-negative ALCL shows a more heterogenous immunophenotype and variable clinical behavior, and prognostic parameters are needed to determine treatment strategies in individual patients[5]. Many literatures report high numbers of activated cytotoxic T-lymphocytes in ALK-negative systemic ALCL which is associated with poor prognosis[20]. And the IPI, comprising five clinical parameters including age, stage, number of extranodal sites, LDH level, and performans status, was shown to be an independent prognostic marker in ALK-negative ALCL[4,13,21]. This parameter is also a useful marker with immunohistochemical markers such as CD8 and CD56. CD56 staining can be seen in a subset of ALCL and is associated with a worse prognosis. ALK expression showed a predilection for younger patients and was significantly related to lower IPI risk groups, and a favorable clinical outcome in systemic ALCLs[21,22].

In summary, we report a case of ALK-negative systemic ALCL at stage III_E in Ann Arbor staging

system occurred in a 69-year-old woman. Immunohistochemistry showed poor prognostic factors such as positivity for CD8 and CD56, and negativity for ALK. In spite of high-dose chemotherapy with radiotherapy, 7 months after final treatment her scalp lesions didn't show complete remission under biopsy, and new lesion appeared in the right perineum. Therefore, we suggest the need to evaluate the prognostic markers for a clinical outcome in the ALCL patients.

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