A Case of Non-T, Non-B Primary Cutaneous Lymphoblastic Lymphoma

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We herein present a case of a 2-year-old girl with non-Hodgkin's lymphoma(NHL) of the lymphoblastic type involving cutaneous sites at the time of diagnosis. The histological finding was typical of lymphoblastic lymphoma. However, immunophenotypically, this lymphoma was not of the T-cell or B-cell type, although the vast majority of lymphoblastic lymphomas involving the skin are usually of the pre-B cell or T-cell type. Until now, there have been few reports of non-T, non-B primary cutaneous lymphoblastic lymphoma expressing surface CD10 and CD56 antigens as in this case. (Ann Dermatol 10:(2) 138~142, 1998).

Key Word : non-T, Non-B primary cutaneous lymphoblastic lymphoma

Lymphoblastic lymphoma(LBL) is known to be a clinically unique form of NHL though it had been simply considered to be a T-cell malignancy for a long time[1,2]. Cutaneous involvement in patients with LBL at the time of presentation is an unusual occurrence[3]. LBL is characterized by immunophenotypic diversity despite the relative morphological uniformity[4-6]. Although the vast majority of nodal(or systemic) LBL has an immature T-cell phenotype, conversely it was shown that pre-B cell LBL has a predilection for cutaneous involvement[2,4-6]. However, the recent availability of monoclonal antibodies has conceptualized new variants of non-T, non-B immunophenotypes in cutaneous LBL[1,2,5]. We herein report a rare case of non-T, non-B primary cutaneous LBL expressing CD10 and CD56 antigens.

CASE REPORT

A raised scalp nodule developed in the parietooccipital region of a 2-year-old girl. This nodule had been present for 1 year. A physical examination revealed a solitary erythematous, smooth surfaced infiltrative nodule up to 3.5 cm on her scalp and bilaterally enlarged non-tender, cervical lymph nodes(Fig. 1). This cervical lymphadenopathy developed 6 months after the development of the skin lesion. A complete blood cell count showed a hemoglobin of 12.2 gm/dl, a leukocyte count of 11,700/mm^3, and platelet count of 405,000/mm^3. A peripheral blood smear showed lymphocytosis and neutropenia without atypicality. Radiological studies of the head demonstrated a nodular soft tissue density on the vertex without bony infiltration. A staging workup, including a bone marrow biopsy and serial CT scans of the mediastinum, abdomen and pelvis, revealed negative findings. The patient was treated with cyclophosphamide, doxorubicin, vincristine, prednisone and intrathecal methotrexate. The patient is currently well, 1 month after the induction therapy.

Histopathological Study

On hematoxylin-eosin-stained sections, a biopsy specimen of her scalp lesion demonstrated a monotonous infiltrate of small to medium sized lymphoid cells that diffusely replaced the dermis(Fig. 2-A). A grenz zone was present below a relatively normal appearing epidermis. The neoplastic cells had finely distributed nuclear chromatin, small inconspicuous nucleoi, and minimal cytoplasm(Fig.

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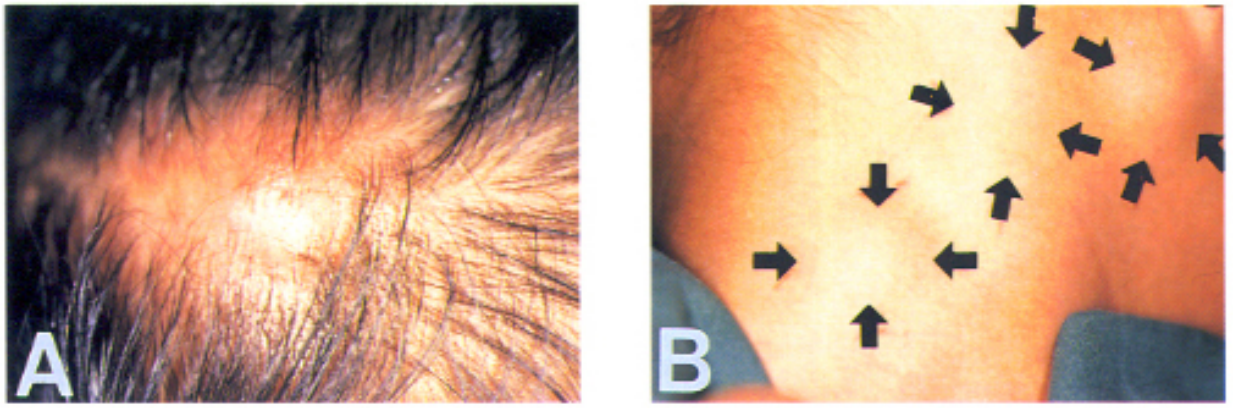

Fig. 1. A solitary erythematous infiltrative nodule on scalp(A). Enlarged non-tender, cervical lymph nodes(B).

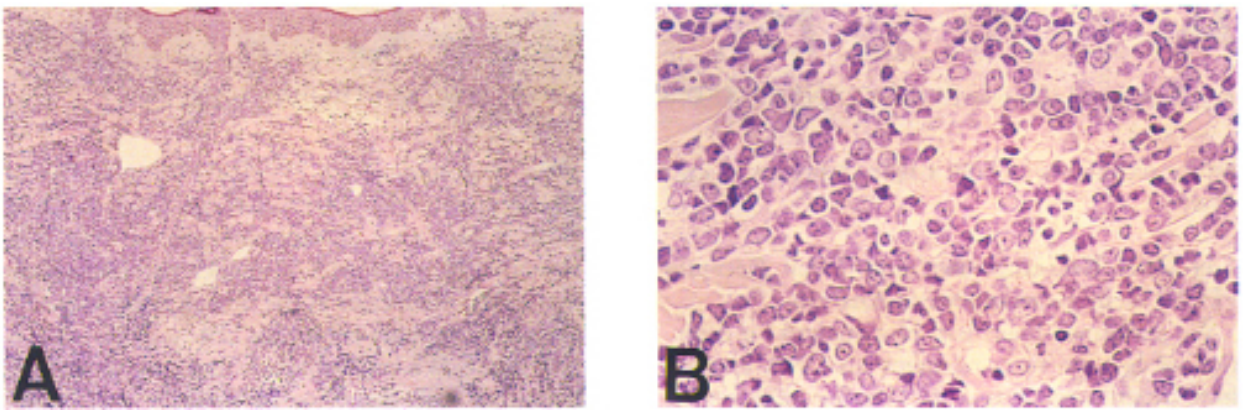

Fig. 2. A biopsy specimen of a skin lesion showing a monotonous infiltrate of small to moderate lymphoid cells that diffusely replaced the dermis(H & E, ×50, A). The atypical lymphoid cells with finely distributed nuclear chromatin, small nucleoi and minimal cytoplasm(H & E, ×400, B).

2-B). Mitotic figures were also found. A biopsy specimen taken from her cervical lymph node had the same cytomorphology as in the skin specimen.

Immunophenotypic Studies

Immunohistochemical staining was performed on the specimens from her skin lesion and cervical lymph nodes in a frozen state. The standard avidin-biotin complex(ABC) immunoperoxidase method was used to determine the immunophenotypes of the infiltrative cells, using a wide panel of monoclonal antibodies. In the skin specimen, the lymphoid infiltrates reacted with CD10(CALLA, Zymed, San Francisco, CA, U.S.A), CD45(LCA, Dako, Carpinteria, CA, U.S.A.) and CD56(NCAM, NKH-1, Zymed)(Fig. 3). However, none of the sections expressed CD2(Leu5a, Becton-Dickinson, Sunnyale, CA, U.S.A), CD3(polyclonal, Dako), CD4(Leu3a, Becton-Dickinson), CD8(OKT8, Ortho Diagnostics, raritan, U.S.A), CD30(Ki-1, Dako), CD43(MT1, Becton-Dickinson), CD45RO(UCHL-1, Dako), CD19(Leu12, Becton-Dickinson), CD20(L26, Dako), CD22(Leu14, Dako), CD45RA(4KB5, Dako) or CD68(Kp-1, Dako). In the biopsy specimen from her cervical lymph node, positivity to CD10, CD45 and CD56 were also found.

Light-chain Restriction Studies

For identification of light-chain monoclonal restriction of surface Ig, specimen sections were stained using an ABC immunoperoxidase method with antisera to κ-and λ-light chains(Dako). We could not find positive findings to λ-light chains. Additionally, there was no positivity to double la-

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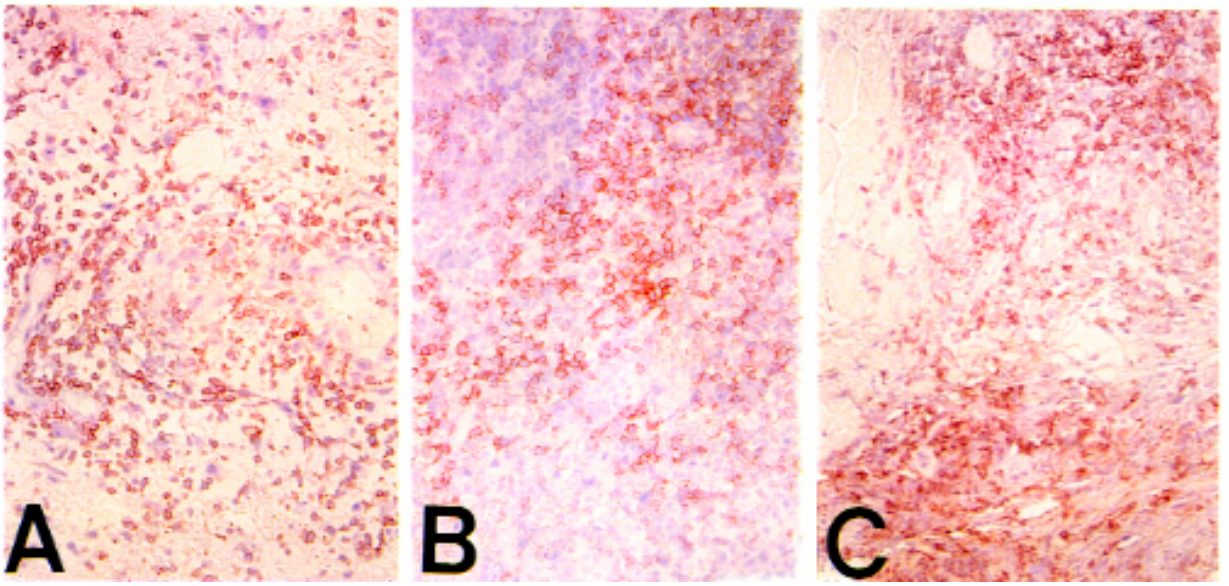

Fig. 3. Atypical cells reacted with CD10(PAP, X200, A), CD56(PAP, ×200, B), CD45(PAP, ×200, C).

belling techniques for both κ-light chains and λ-light chains.

Ig Gene Rearrangement and T-cell Receptor (TCR) Gene Rearrangement Analysis

We performed Sourthern blot analysis for detection of Ig gene rearrangement on DNA extracts from frozen specimens of the skin lesion. After the DNA had been extracted from the specimens by a phenol-chloroform method, it was then digested with Bam HI + Hind III for JH probe, Eco RI for Cκ probe, and Eco RI + Hind III for Cλ probe. It was hybridized with a ^{32}P-labelled probe after size-fractionation by a 0.8% agarose gel electrophoresis. In this case, Sourthern blot analysis using three probes did not reveal clonality of Ig gene rearrangement. For the study of TCR-ß, γ chain gene rearrangement, tumor DNA was digested with restriction endonuclease Bam HI, Eco RI, and Hind Ⅲ, and was hybridized with a probe of constant region of TCR-ß, γ gene. However, we could not find a clonal rearrangement finding because this case showed a germ-line pattern of TCR-ß, γ gene after analyses using the three endonucleases.

DISCUSSION

LBL is the most aggressive, high grade form of NHL[1]. It accounts for 4-5% of all NHL and 33% of all childhood NHL[1,7]. Approximately, 3.5% to 7% of NHL of the skin is of the lymphoblastic type[2]. Cutaneous LBL comprises a smaller percentage(less than 20%) of all cases at the time of presentation[1-3]. Moreover, primary cutaneous LBL as in this case is very rare[1,2]. We could diagnose our case as primary cutaneous LBL involving regional cervical lymph nodes secondarily because nodal involvement occurred 6 months after the development of the skin lesion.

The presentation of LBL typically occurs in childhood or young adulthood[3-6]. Especially, CD56+ non-T, non-B LBL as in this case, seems to be most prevalent in non-white females although LBL is overally twice as common in males than females[5,6]. There is no preferential localization in adult patients, whereas in children, LBL is localized essentially on the scalp, face, and neck[1]. Clinically, cutaneous lesions are red to purple nodules or papules on the head and neck area[3]. Our patient was a 2-year-old girl having a solitary nodular lesion on scalp.

Histopathologically, the infiltrate is non-epidermotrophic and dermal[2,3]. The individual neoplastic cells have slight to moderately convoluted large nuclei with finely dispersed regular chromatin, a high nuclear/cytoplasmic ratio, smaller inconspicuous nucleoli and scant cytoplasm[1-3,6].

Our case showed histologically compatible findings with that of typical LBL.

Although morphologically homogeneous, LBL is an immunophenotypically diverse group of neoplasms[2,4-6]. In the immunophenotype, pre- and intrathymic immature T-cell LBL account for the vast majority(about 80%) of noncutaneous nodal LBL[3-6]. However, some recent reports concluded that pre-B cell LBL has a predilection for cutaneous sites or for arising in the skin, or both[2,7]. Recently, cutaneous LBL tends to be categorized into five groups immunophenotypically; Pre-B cell LBL, biphenotypic LBL(both T-cell and B-cell), non-T non-B or undifferentiated LBL, T-cell LBL and B-cell LBL[2,5]. This immunophenotypic heterogeneity in LBL seems to be correlated to cytogenetic developmental stages of the T-cell[4]. Non-T, non-B LBL as in this case, is known to have the lowest incidence among 5 groups[1,2,5-7]. Bernard et al[7]. described cases of cutaneous non-T, non-B LBL that did not express T-cell and B-cell markers. Vallant et all[1]. reported that this non-T, non-B LBL showed HLA-DR+, CD3-, CD4-, CD8-, CD10-, CD19- and CD20-. Sander et al[2]. proposed that previously named non-T, non-B phenotypes might be pre-B cell phenotype showing CD10+, CD19+, CD22+/- or CD20+, CD74+. Sheibani et al[5]. additionally proposed "CALLA(CD10) expressing LBL" as a second subgroup of LBL instead of biphenotypic LBL. However, that subgroup did not contain CD10+ CD56+ LBL as in this case, but LBL co-expressing both T-cell markers and CD10. Moreover, a third subgroup of NK(natural killer)-associated LBL which he had described, also reacted with T-cell markers. Accordingly, our case does not correspond to any subtype by Sheibani's classifying mode though it is compatible with non-T, non-B LBL among 5 subgroups.

CD56 has been recently used as a diagnostic antigen for identifying CD56 positive nasal or nasal type T/NK-cell lymphoma and aggressive T/NK-cell leukemia[9]. CD56 expressing, non-T, non-B LBL as in this case is very rare though there have been a few recent reports of LBL possessing NK-cell function[5]. The tumorigenic origin of this CD56+ non-T, non-B LBL is untill now undefined. A differentiation of non-T, non-B LBL from T/NK-cell lymphoma is possible[9]; First, T/NK cell lymphomas invariably reveal the biphenotype of T-cell and NK-cell(e.g. CD56+ CD2+ CD45RO+). Second, LBL has a characteristic cytomorphology such as neoplastic cells possessing slight to moderately convoluted large nuclei, finely dispersed regular chromatin, and smaller inconspicuous nucleoli, which are distinguishable from T/NK-cell lymphoma.

CD10(CALLA) is usually expressed in T-cell or non-T, non-B acute lymphoblastic leukemia(ALL)[2,4,5]. However, there are recent reports that some T-cell LBL and non-T, non-B LBL may express CD10[2,4,5,7]. Many workers have come to regard LBL as the lymphomatous variant of ALL, due to the apparent overlap of immunonological, cytological and clinical features[1,4]. However, until now, there have been few reports of non-T, non-B LBL co-expressing both CD10 and CD56 as in this case[7].

CD45 antigens may represent a lymphoid origin of the neoplastic cells[3]. However, the positivity of the tumor cells to CD45 in LBL had not presented consistent results[4,5,7]. In this case, infiltrative cells showed no positivity except for CD10, CD45 and CD56 antigens with a large panel of monoclonal antibodies.

In addition, determining the immunophenotype of cutaneous LBL may prove to have clinical and prognostic significance in that the different clinical pictures seem to be correlated with the immunophenotypic heterogeneity in LBL. LBL with B-cell phenotype and non-T, non-B cell LBL have a more aggressive course than T-cell LBL[2,4-6]. Although a mediastinal invasion is notoriously remarkable in T-cell LBL, LBL with a non-T, non-B phenotype seldom shows mediastinal involvement and extracutaneous spreading[1,4-7,9,12]. However, non-T, non-B LBL shows more frequent cutaneous involvement than T-cell LBL[7,9,12]. Our patient of non-T, non-B LBL did not show any extracutaneous spreading such as mediastinal invasion except cervical lymph nodal spreading.

The prognosis of patients with cutaneous LBL is known to be the same as that of other patients with nodal LBL[2]. The median survival time is 2 years and the rate of relapse-free survival at 5 years is 26% in nodal LBL[1]. Also in primary cutaneous LBL, the median survival time is about 2 years and the mean survival rate is 33%[1]. Accordingly, this presented patient is supposed to have a poor prognosis though she is relatively well now after completion of induction therapy.

For treatment, it has been agreed that managing

primary cutaneous LBL with multiagent systemic chemotherapy as in ALL, is advisable because LBL has a notoriously aggressive course independent of whether the cutaneous involvement occurs primarily or secondarily[2,6,7,10,11]. LBL patients have been treated according to a four phase protocol consisting of induction, CNS prophylaxis, consolidation with 4 cycles of the drugs used in induction, and maintenance therapy[2,6]. In this case, the patient is continuing to receive maintenance therapy after completion of induction.

In summary, our case of cutaneous LBL is unique in two view points; First, it is a rare primary cutaneous type that arose in the skin and invaded cervical lymph nodes secondarily. Second, it revealed rare non-T, non-B phenotypes with positivity to CD56 and CD10.

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