Blastic NK-Cell Leukemia / Lymphoma
— A Case Report —

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Blastic natural killer (NK) cell lymphoma / leukemia is a rare NK cell malignancy of unknown etiology. It occurs in multiple sites and with a propensity for skin involvement. We report such a case in a 35-year-old male suffering from erythematous and purpuric papules and plaques on his face and trunk for 6 months. A biopsy specimen of the skin showed diffuse infiltration of blast-like lymphoid cells in the dermis and subcutis. Immunohistochemical study showed the tumor cells were only positive for CD56 and CD45 and negative for other T-cell, B-cell, and myeloid cell markers. T-cell receptor (TCR) gene rearrangement was germline. In situ hybridization for Epstein-Barr virus (EBV) encoded small ribonucleic acid was negative. Aspiration specimen of the bone marrow revealed diffuse infiltration of CD56+ lymphoid cells in interstitial spaces. The diagnosis of a blastic NK-cell lymphoma / leukemia was made. Because of its rarity, the case is reported. (Dermatol Sinica 21 : 408-412, 2003)

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INTRODUCTION
Blastic NK-cell lymphoma is characterized by its blastoid or monomorphic morphology with positive expression of CD56 and lacking EBV association. The patients usually exhibit extranodal tumors, most common in the form of skin lesions. Furthermore, it can simultaneously involve lymph node, soft tissue, peripheral blood or bone marrow. A majority of the patients show widespread diseases at the initial presentation. We herein describe a case of blastic NK-cell lymphoma/leukemia with typical clinical, histological, and immunohistochemical findings.

CASE REPORT
A 35-year-old male had a 6-month history of erythematous skin lesions over the face and trunk without pruritic or painful sensation. The skin lesions showed poor response to topical therapy prescribed at local medical clinics. Neither body weight loss, fever, cold sweating nor other discomforts were noted. Physical examination revealed numerous ill-defined erythematous and purpuric indurated papules and plaques over the face and trunk (Fig. 1 & 2). There was no palpable lymph node. Biopsy specimen of a skin lesion showed diffuse infiltration of monotonous, medium-sized mononuclear cells in the dermis and subcutis (Fig. 3). The tumor cells had medium to large nuclei, with fine chromatin patterns, and scanty cytoplasm (Fig. 4). The paraffin-embedded specimen was treated with citrate buffer. Monoclonal antibody of CD56 (Novocastra) (Fig. 5) and CD45 (DAKO) were positive but showed negative for CD2 (Novocastra), cCD3 (DAKO), CD4 (VENTANA), CD8 (DAKO), CD20 (DAKO), CD30 (DAKO), CD34 (DAKO), CD68 (DAKO), CD79A (DAKO), TIA-1 and myeloperoxidase (DAKO). T cell receptor (γ) gene rearrangement was not detected. No positive identification of EBV by in situ hybridization for EBER-1 was found.

The peripheral blood counts revealed normal WBC count 8500 / cmm (normal range
3900-10600), atypical lymphocyte 9% (normal range 0%) and mild anemia, Hb10.7 g/dl (normal range 13.5-17.5). The biochemistry study showed elevation of LDH 775 u/l (normal range 47-140), and alkaline phosphatase 304 u/l (normal range 28-94). The chest X-ray showed no active lung lesion or hilar lymphadenopathy. However, a bone marrow specimen aspirated from the left iliac crest showed diffuse infiltration of malignant cells, mostly with uniform medium-sized nuclei, clumped chromatin, scanty cytoplasm and indistinct nucleoli in the interstitial space. The malignant cells also showed positive for CD56. Therefore, we made a diagnosis of blastic NK-cell lymphoma / leukemia involving the skin and the bone marrow.

After the diagnosis, the patient was then treated with 4 courses of CHOP (cyclophosphamide 750mg/m², doxorubicin 50mg/m², vincristine 2mg, and dexamethasone 8mg po q6h). However, there was no sign of remission and the skin lesions persisted.

**DISCUSSION**

Blastic NK-cell lymphoma, a relatively rare NK-cell malignancy was first described by Suchi and Mori in 1994.1 It is unclear whether it has racial predilection such as in extranodal NK/T-cell lymphoma, nasal type. It can occur at any age, but most commonly in the middle and older-aged males. This disease tends to involve multiple sites, with a tendency for the skin showing erythematous and purpuric indurated plaques or nodules. Moreover, lymph node, soft tissue, peripheral blood or bone marrow can be simultaneously involved. A majority of patients show widespread disease at the initial presentation.

Histologically, this disease is characterized by a diffuse monotonous proliferation of medium-sized cells with fine chromatin, resembling the malignant cells of lymphoblastic or myeloblastic leukemia. In Giemsa-stained touch preparations, azurophilic granules may or may not be found.

A special immunophenotypical feature of blastic NK cell lymphoma is the positivity of CD56 antigen, which recognizes the neural cell adhesion molecule.2 It is a useful marker for NK and NK-like T cells. The neoplastic cells are negative for surface CD3 and positive for CD56, while CD4 and CD43 are generally expressed. CD68 is usually negative, or weakly expressed.3,4 Furthermore, T-cell receptor genes are germline, and specific chromosomal aberrations have not been found. Frequent expression of terminal deoxynucleotidyl transferase is also reported compared with the other types of NK-cell malignancy.5,6

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**Fig. 4**
The tumor cells have medium-sized nuclei with a fine chromatin pattern and scanty cytoplasm (H & E, x400).

**Fig. 5**
The lymphoid cells are positive for CD56 (immunoperoxidase, x400).
Differential diagnosis includes other CD56 positive lymphoma with cutaneous involvement. In general, lymphomas expressing CD56 are very uncommon, and encompass several clinicopathological entities including nasal-type NK/T-cell lymphoma, aggressive NK/T-cell lymphoma, myeloid/NK cell precursor leukemia and blastic NK-cell lymphoma/leukemia.\textsuperscript{3-5, 7-9} The characteristics of these lymphomas are summarized in Table I. The clinical presentation and histopathological finding of the present case are compatible with blastic NK-cell lymphoma/leukemia. However, with consideration of the morphological similarity between lymphoblastic and myeloblastic neoplasms and the fact that CD56 may be expressed in both neoplasms, the diagnosis should only be made in the absence of commitment to the T-cell or myeloid lineages. In our case, the CD3, CD20, myeloperoxidase and CD33 were all negative, and the TCR gene rearrangement was not detected. The diagnosis of blastic NK-cell lymphoma was therefore made.

In this case, no positive identification of EBV by in situ hybridization for Epstein-Barr virus encoding small ribonucleic acid was found. The nasal, nasal-type and aggressive NK-cell lymphoma, are almost invariably associated with EBV infection but blastic NK cell lymphoma has no such association.\textsuperscript{3, 5} The relationship between these lymphomas and EBV remains unclear.

The clinical course of blastic NK-cell lymphoma is aggressive with a poor response to regimens used for non-Hodgkin lymphomas. Most patients die within 2 years of diagnosis despite aggressive multiregimen-chemotherapy treatment.\textsuperscript{4} Partial response to "acute myeloid leukemia" regimens has been reported in few cases. Patients with localized skin lesions have a better prognosis. These aggressive clinical

| Table I. Differential diagnosis of blastic NK-cell lymphoma/leukemia |
|---------------------------|---------------------------|---------------------------|---------------------------|
| Nasal-type NK cell lymphoma | Aggressive NK cell lymphoma | Blastic NK cell lymphoma/leukemia | Myeloid/NK cell precursor acute leukemia |
| Morphology | Polymorphic | Large granular lymphocyte | Lymphoblastoid | Immature blastoid |
| Extramedullary disease | Invariable | Frequent | Invariable | Frequent |
| Specifically affected sites | Skin, GI tract | Liver, spleen | Skin, soft tissue | Lymph node |
| Phenotype | CD56+, cCD3+, sCD3-, CD5-, CD16+, HLADR+, TdT- | CD56+, sCD3-, CD2+, CD5+, CD16+, CD7+, HLADR+, TdT- | CD56+, sCD3-, CD4+/−, CD16+, CD15+/−, CD16−, CD16+, CD16−, CD33-, CD33+ HLADR+/−, CD34+ |
| EBV | + | +/− | − | − |
| Response to chemotherapy for lymphoid malignancy | Sensitive to chemotherapy | No standard therapy | Sensitive to chemotherapy | Sensitive to AML chemotherapy |
| Prognosis | Poor | Very poor | poor | poor |
features may be related to the expression of the multi-drug resistance gene, which is overexpressed on both normal and malignant NK-cells.\textsuperscript{10} Recently, Osamu et al found specific cytotoxic T-cell against autologous tumor cells in 2 patients, which may provide the principles to the design of immunotherapy.\textsuperscript{11}

In conclusion, we present a typical case of blastic NK-cell lymphoma/leukemia. This disease is highly malignant and until now, has no effective treatment. Appropriate therapeutic approaches to this disease should be explored.

REFERENCE