A Case of Unspecified Mature T-cell Leukemia with Clover-shaped, Multi-lobated Nuclei

Seung-Tae Lee, M.D., Su-Yon Park, M.D., Hee-Jin Kim, M.D. and Sun-Hee Kim, M.D.

Department of Laboratory Medicine, Samsung Medical Center,
Sungkyunkwan University School of Medicine, Seoul, Korea

Mature T-cell leukemias are a group of neoplasms derived from mature or post-thymic T-cells, and a number of distinctive disease entities have been defined in the World Health Organization (WHO) classification. Here we report a 54-year-old female patient with multi-lobated atypical cells expressing the classic T-cell antigens involving multiple lymph nodes, peripheral blood, and bone marrow. The clinical, laboratory, and pathologic features of her disease did not fit into any of the entities in the WHO Classification. There was no evidence of rapidly rising lymphocyte counts, TCL1 expression, eosinophilia, erythroderma, Sezary cells, autoimmune phenomena, cytotoxic granules, nor evidence of HTLV-1 infection, and thus, T-cell prolymphocytic leukemia, Sezary syndrome, T-cell granular lymphocytic leukemia, and adult T-cell leukemia/lymphoma were all ruled out. This case suggests that further characterization and definition of the "unclassifiable" cases of mature T-cell neoplasm is needed to better understand the group of disorders. ***(Korean J Hematol 2007;42:172-175.)***

Key Words: Mature T-cell leukemia, WHO classification, Multi-lobated

INTRODUCTION

Mature T-cell leukemias are a group of relatively uncommon neoplasms derived from mature or post-thymic T-cells. The World Health Organization (WHO) classification of hematologic malignancies defines a number of distinctive disease entities of mature T-cell leukemia including T-cell prolymphocytic leukemia (T-PLL), T-cell granular lymphocytic leukemia (T-LGL), Sezary syndrome (SS), and adult T-cell leukemia/lymphoma (ATLL).[1,2] These neoplasms can be discriminated by their clinical or phenotypic features, but sometimes show overlapping features with each other and with T-cell lymphomas involving peripheral blood (PB).[1,3]

T-PLL is characterized by proliferation of small- to medium-sized prolymphocytes with post-thymic T-cell phenotype.[2] A rapidly rising leukocyte count, a prominent nucleolus (more distinct on electron microscopy), chromosomal rearrangements involving chromosome 14, and expression of the oncoprotein TCL1 are common and dis-

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교신저자 : 김선희, 서울시 강남구 일원동 50
㉾ 135-710, 삼성서울병원 진단검사의학과
Tel: 02-3410-2704, Fax: 02-3410-2719
E-mail: sunnyhk@smc.samsung.co.kr

Correspondence to : Sun-Hee Kim, M.D., Ph.D.
Department of Laboratory Medicine, Samsung Medical Center
50, Ilwon-dong, Gangnam-gu, Seoul 135-710, Korea
Tel: +82-2-3410-2704, Fax: +82-2-3410-2719
E-mail: sunnyhk@smc.samsung.co.kr

tinct features of T-PLL.[2,4] Several morphologic variants including cerebriform (Sezary-like cells), multi-lobated (flower-cells), and small cell variants have been described.[5] T-LGL is an indolent lymphoproliferative disorder composed of lymphocytes with cytoplasmic cytotoxic granules that are usually greater than 2.0×10^9/L in number for more than 6 months. T-LGL is commonly derived from CD8+ T-cells or, less commonly, from CD4+ T-cells and is frequently associated with autoimmune phenomena and multi-lineage cytopenias.[1,2] SS is defined by the presence of generalized erythroderma, lymphadenopathy, and neoplastic T-lymphocytes in the blood.[2] The atypical cells (Sezary cells) have cerebriform nuclei and typically infiltrate the epidermis, which can be specifically differentiated from other disorders.[2,6] ATLL is an aggressive lymphoproliferative disorder etiologically linked to human T-cell leukemia virus type-1 (HTLV-1). The atypical cells are most often composed of highly pleomorphic (multi-lobated) lymphoid cells, showing mature T-cell phenotypes and various systemic manifestations.[2,7] Various efforts have been made to classify these mature T-cell leukemias with systematic approaches, but there are still some cases having overlapping features.[3]

Here we report a case of mature T-cell leukemia composed of atypical lymphoid cells with multi-lobated nuclei expressing the classic T-cell antigens, which shares or lacks some of the characteristics of mature T-cell leukemias and does not fit into any of the disease entities in the WHO Classification.

CASE REPORT

A 54-year-old woman was referred to our hospital because of multiple palpable masses on the right side of the neck. Physical examination revealed multiple lymphadenopathy of the cervical, axillary and inguinal lymph nodes with mild splenomegaly. A computed tomographic scan of the chest revealed enlargement of lymph node chains in the lower neck, thorax, and upper abdomen accompanied by a large amount of pleural effusion on both sides. Her laboratory data were as follows: hemoglobin 11.3g/dL, white blood cells 44.8×10^9/L with 49% atypical lymphoid cells, platelets 381×10^9/L, lactate dehydrogenase 3,519IU/L, and serum calcium 9.0mg/dL. The atypical lymphoid cells were medium-sized and had multi-lobated nuclei, basophilic cytoplasm, and inconspicuous nucleoli (Fig. 1A). Bone marrow (BM) examination showed an infiltration of the atypical cells (20% of total nucleated cells) with less pleomorphic nuclear outlines than those

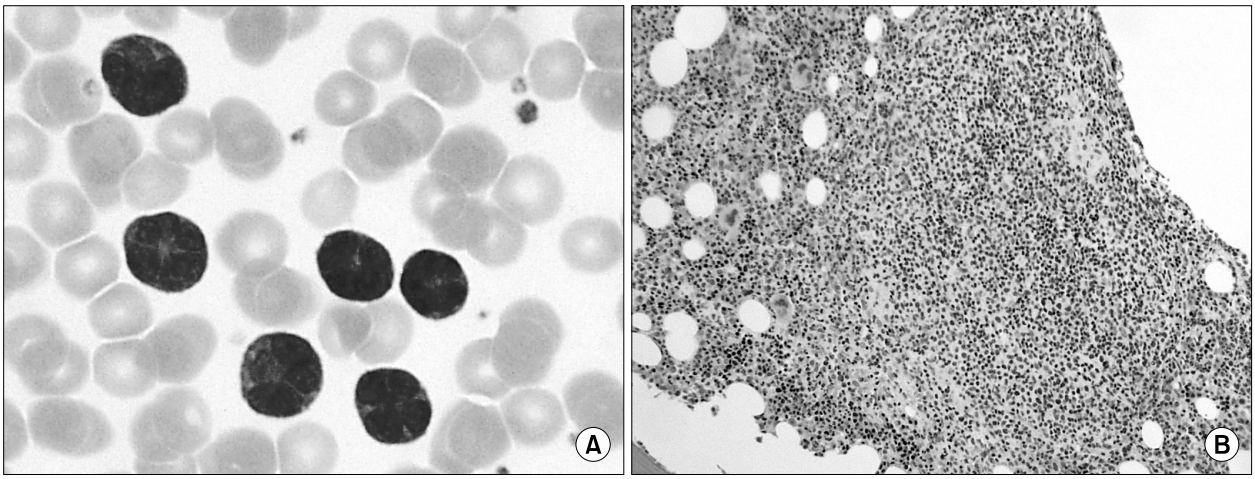

Fig. 1. (A) Medium-sized atypical lymphocytes with clover-shaped multi-lobated nuclei on marrow aspirate (Wright- Giemsa stain, ×1,000). (B) Nodular infiltration of the atypical neoplastic cells on marrow biopsy (Hematoxylin-Eosin stain, ×100).

on PB. Nodular infiltrates of the atypical neoplastic cells were observed on the biopsy section (Fig. 1B). Flow cytometric analyses showed expression of mature T-cell markers including CD2, CD3, CD4, and CD5, with an aberrant loss of CD7. The atypical cells were negative for CD8, CD10, CD14, CD19, CD20, CD23, CD25, FMC7, surface kappa/lambda, and terminal deoxynucleotidyl transferase (TdT). Immunohistochemical studies on the biopsy section specimen showed the neoplastic cells were weakly positive for CD30 and were negative for CD21, CD56 and ALK-1. Karyotype analyses of twenty metaphases from BM cells showed 46~48, XX, t(1;10)(q21;q11.2), dup(2)(q33q37), +3, +9, add(18)(p11.3)[cp17]/46, XX[3]. An antibody study for HTLV-1 was negative, and reverse transcriptase polymerase chain reactions (RT-PCR) for HTLV-1 and HTLV-2 were also negative. There was no evidence of EBV infection on in-situ hybridization on the BM specimen. An ultrastructural study under transmission electron microscopy showed heterochromatin marginated to the periphery of the nucleus, but the nucleolus was not prominent. RT-PCR for the *TCL1* gene was negative. The white blood cell counts remained $40\sim50\times10^9$/L for 7 days before the initiation of chemotherapy. Based on the clinical, laboratory, and pathologic findings, we made a diagnosis of a mature T-cell neoplasm, unspecified. Chemotherapy with VECP regimen (vincristine, etoposide, carboplastin, and prednisolone) was initiated, and CBC was normalized and the atypical cells disappeared in PB. Soon after discharge, the patient experienced skin lesions appearing as whole body rash without itching sensation, and the skin biopsy revealed a periappendiceal and perivascular infiltration of the atypical cells in the dermis but not in the epidermis. Despite the white blood cell counts within reference range, the atypical cells were still observed on the follow-up BM study that was done 3 months after the initial diagnosis, and the patient expired 6 months later from initial diagnosis.

DISCUSSION

Herling et al.[3] systematically examined HTLV-negative mature T-cell leukemias and described following findings as the most useful discriminating features: (1) rapidly rising PB lymphocyte counts, presence of effusions and TCL1 expression for T-PLL; (2) generalized erythroderma, PB eosinophilia, and lymphadenopathy for SS; and (3) the association of autoimmune phenomena and multi-lineage cytopenias for T-LGL.

Our patient did not show rapidly increasing PB lymphocyte counts or TCL1 expression, although the clinical features such as pleural effusions resembled T-PLL. In addition, there was no visible nucleolus, involvement of chromosome 14, nor CD7 expression; these findings are unusual for T-PLL.[2,4] PB eosinophilia was not observed, and SS was also excluded because there were no apparent Sezary cells. Erythroderma or infiltration of epidermis that typically characterizes SS was also absent. There was no evidence of autoimmune phenomena, and cytotoxic granules were not apparent on the neoplastic cells, which ruled out T-LGL. ATLL could be also ruled out because there was no evidence of HTLV-1 infection. Moreover, CD25, which is positive in nearly all cases of ATLL,[2] was not expressed in this case. However, there are a few reports on HTLV-negative ATLL cases despite the diagnostic criteria of ATLL which include anti-HTLV-I antibody as an essential part.[7-9] Therefore, further consideration on whether to HTLV-negative ATLL could be categorized would be followed investigating more similar cases. Differentiation from the leukemic manifestation of peripheral T-cell lymphoma (PTCL) could still remain in ambiguity and controversy because this case showed both lymphadenopathy and PB involvement. However, the extensive involvement of PB and BM by the atypical cells implied that the leukemic component was more prominent than that of lymphoma.

In summary, we described a case of mature

T-cell neoplasm of which the clinical, laboratory, and pathologic characteristics do not belong to any of the disease entities in the WHO classification. Further characterization and definition of these “unclassifiable” cases is needed to better understand mature T-cell neoplasms.

요 약

성숙T-세포백혈병(mature T-cell leukemia)은 성숙한 흉선후 T-세포로부터 기인한 일련의 혈액종양을 일컫는 말이며, World Health Organization (WHO)의 혈액종양 진단분류에서 몇 가지 특징적인 질환으로 나뉘어진다. 본 증례에서 저자는 통상적인 T-세포 항원을 표현하면서 다엽성(muti-lobated) 핵 모양을 보이는 비정형적인 림프구의 전신적(림프절, 말초혈액, 골수 등) 침범을 특징으로 하는 54세 여자 환자를 보고하고자 한다. 환자의 임상적, 진단검사적 및 병리학적 특징은 WHO 분류기준 중 어떠한 특이 진단명에 분류되지 않았다. 급속하게 증가하는 림프구 숫자, TCL1 유전자 발현, 호산구증가증, 홍피증(erythroderma), Sezary 세포, 자가면역 현상, 살해과립(cytotoxic granule), HTLV-1 감염의 증거 등이 이 환자에서는 보이지 않으므로, T-세포전림프구백혈병, Sezary 증후군, T-세포거대과립림프구성백혈병, 성인T-세포백혈병림프종 등을 배제할 수 있었다. 본 증례는 성숙 T-세포 종양에 있어서 이러한 비전형적인 환자들에 대하여 보다 심도 있는 연구와 정의가 필요하다는 것을 시사한다.

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