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Case Report Open Access

CD30+ Cells in Lung of Indolent Type Adult T-Cell Leukemia/Lymphoma and Elevated Serum Levels of Soluble CD30 Associated with Acute Crisis and Relapse of Disease

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Abstract

Changes in the serum level of the soluble form of CD30 (sCD30) in a patient with adult T-cell leukemia/lymphoma were monitored throughout the indolent phase, acute crisis, and relapse. The level of sCD30 was elevated prior to the development of laboratory data abnormalities. In addition, the elevated sCD30 level was associated with clinical manifestations in the lung, including malignant pleural effusion, which is a diagnostic criterion of acute crisis. The sCD30 level correlated with clinical aggressiveness, and the lung lesion reoccurred on the same side as the original lesion. These data suggest that microenvironment or minimal residual disease formed in the right lung. Pathological examination of lung biopsy at the indolent phase revealed accumulated CD30+ cells among CD3+CD45RO+ T cells. The serum level of sCD30 correlated with clinical aggressiveness, indicating that the small population of CD30+ cells plays an important role in the progression of adult T-cell leukemia/lymphoma.

Keywords: CD30; Adult T-cell leukemia/lymphoma (ATLL); Human T-leukemic virus type 1 (HTLV-1); Indolent type; Acute crisis

Abbreviations:

ATLL: Adult T-Cell Leukemia/Lymphoma; CCR4: C-C Chemokine Receptor Type 4; CR: Complete Remission; HTLV-1: Human T-Leukemic Virus Type 1; LDH: Lactate Dehydrogenase; Scd30: Serum Soluble form of CD30; Sil-2R: Soluble Interleukin-2 Receptor Alpha Chain

Introduction

Adult T-cell leukemia/lymphoma (ATLL) is a highly aggressive leukemia/lymphoma that was first proposed as a new disease entity in 1977 [1,2]. More than 1,000 patients die of ATLL every year in Japan. More than 50% of Japanese ATLL patients are from Kyushu in the southwestern part of Japan. ATLL has a broad clinical spectrum and is classified into different subtypes (acute, chronic, smoldering, and lymphoma-type ATLL) according to clinical and laboratory criteria [3,4]. Previous studies reported 4-years survival rates with the median survival time for chronic and smoldering type were 26.9% (24.3 months) and 62.8% (not yet reached), while those for acute and lymphoma-type were 5.0% (6.2 months) and 5.7% (10.2 months), respectively [5]. This is the reason why chronic and smoldering types of ATLL are considered indolent and are managed without conventional chemotherapy until disease progresses to acute crisis [6]. Approximately 70% of cases of indolent-type ATLL progressed to acute ATLL with a median duration of follow-up of 4.1 years, and 65.1% of these patients died of acute ATLL after crisis [6]. It was demonstrated that soldering/chronic ATLL peripheral blood mononuclear cells (PBMC) spontaneously proliferated ex vivo in a cytokine–dependent manner, while acute type ATLL PBMC proliferated independent of cytokines [7]. Such a transition of HTLV-1-infected cells from cytokine–dependent to cytokine–independent growth requires a constitutive activation of STAT proteins [8]. Therefore, indolent-type ATLL are thought to be as the early stage of ATLL development. Lung lesions and cutaneous lesions are involved in the early stage of ATLL.

CD30 is a member of the tumor necrosis factor receptor superfamily and induces proliferation or apoptosis depending on the cell type [9]. Activation of CD30 via its ligand, CD153, or antibodies triggers the activation of cells and the shedding of CD30. We previously investigated the clinical significance of membrane-bound CD30 expression and the serum soluble form of CD30 (sCD30) levels and determined the relationship between sCD30 levels and other serum markers in ATLL [7].

To explore the correlation between the progression of ATLL and the serum level of soluble cytokine receptors, we studied one patient throughout the indolent phase, acute crisis, and relapse of ATLL.

Case Report

A-58-year-old man was referred to the National Hospital Organization (NHO) Kumamoto Medical Center in August 2006 due to cutaneous lesions, abnormal chest x-ray, and abnormal peripheral blood test results. He had experienced pulmonary tuberculosis 10

years earlier. A positive antibody for human T-leukemia virus type 1 (HTLV-1) was identified. Physical examination of the patient revealed cutaneous lesions that appeared similar to mycosis fungoides. A biopsy of a skin lesion was performed, and the diagnosis was T-cell lymphoma compatible with ATLL. Bronchial endoscopy was performed, because diffuse bronchiolitis was suspected. A diagnosis of HTLV-1-associated bronchoalveolar disorder was considered. However, the findings from a transbronchial lung biopsy were not remarkable. The patient was admitted to the hospital for further examination via video-assisted thoracic surgery. The pathological findings showed lymphoma cell infiltration, compatible with T-cell lymphoma (Figures 1A and 1B). Therefore, this patient was diagnosed with HTLV-1-associated bronchopneumopathy and smoldering-type ATLL. Antibiotics were administered for methicillin-resistant *Staphylococcus aureus*, and itraconazole was administered for *Candida albicans*. The cutaneous lesions disappeared without anti-tumor therapy.

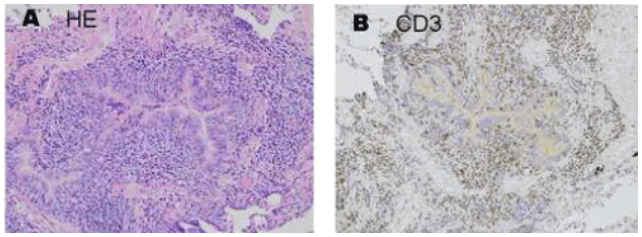

Figure 1: Biopsy Specimen from lung lesion of indolent ATLL showing HTLV-1 associated branchoneumopathy

ATLL is diagnosed according to Shimoyama's criteria, and there are four subtypes of ATLL [5]. Acute crisis was later proposed as an additional condition in the clinical course of ATLL. There are no established criteria for acute crisis, but the critical features from a comparison between acute-type and chronic-type ATLL are summarized in Table 1. In acute-type ATLL, the lactate dehydrogenase (LDH) level is higher than twice the upper limit of normal. Acute-type ATLL is also characterized by hypercalcemia, which can cause death; hypercalcemia can be diagnosed by clinical symptoms and a blood test. Finally, central nervous system tumors, malignant ascites, malignant pleural effusion, and gastrointestinal tract tumors are very specialized to acute-type ATLL.

In May 2007, the patient developed pulmonary complications associated with pleural effusion (Figure 2A). Treatment with antibiotics had no effect. Clinical laboratory data indicated progression of anemia, hypoalbuminemia, and ATLL. Serum levels of LDH, sIL-2R, and sCD30 were elevated as compared with data of indolent phase (142 days before crisis) (Table 2). Only the appearance of pleural effusion indicated the acute crisis in addition to the pulmonary invasion of ATLL cells and lymphadenopathy as a feature of indolent type ATLL (Figures 2A and 2B). We started three cycles of multi-agent chemotherapy (mLSG15) for aggressive ATLL, which was based on the Japan Clinical Oncology Group protocol (Figure 3A) [10]. This therapy led to a complete remission (CR). The soluble CD30 level was elevated prior to acute crisis and normalized during the CR state (Figure 3). The patient elected to receive chemotherapy but not allogeneic hematopoietic stem cell transplantation because of his desire to continue his employment without prolonged interruption. Although the patient's condition remained stable for more than 1 year during supportive therapy, cutaneous lesions subsequently appeared, and the patient relapsed (Figure 3B). He then underwent mogamulizumab treatment, a new monoclonal antibody therapy against C-C chemokine receptor type 4 (CCR4) on the surface of ATLL cells (KW-0761) [11]. However, the level of soluble CD30 increased, and the right lung lesion reoccurred; therefore, the mLSG-15 regimen was started again following four cycles of KW-0761. The development of pancytopenia and immunodeficiency resulted in the discontinuation of chemotherapy. Cytomegalovirus antigenemia testing indicated reactivation of this virus.

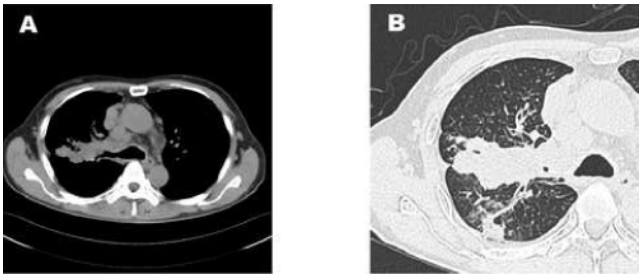

Figure 2: Chest computed tomography (CT) scan showing pulmonary involvement at acute crisis

To investigate the sCD30-producing cells, immune staining was performed with an antibody panel including CD30 (Ki-1), CD3, CD45RO (UCHL-1), and CD20 (B26). Pathophysiological study demonstrated that accumulated CD30+ cells were shown among the T cells but not among B cells (Figure 4).

Discussion

In this case report, we described the clinical course of a patient who progressed from indolent-type to acute-type ATLL with lung invasion following elevation of the serum sIL-2R and sCD30 levels. The serum levels of both soluble proteins remained high and were elevated prior to the acute crisis of ATLL. Furthermore, the level of sCD30 increased according to the formation of pulmonary lesions at relapse as well as during the acute crisis of disease. The sCD30-producing cells corresponded to accumulated CD30+ T cells in the lung.

The lungs are the preferential site for HTLV-1–infected cells, and this peculiar tropism is responsible for the high incidence of pulmonary involvement [12-14]. In our case, massive lymphadenopathy in the mediastinum and pleural effusion was observed, and infections were excluded as a cause, because these findings improved in response to mLSG15 therapy. The same right lung was involved at relapse, suggesting that there was microenvironment or minimum residual disease in the right lung. In the lung, Tax, a trans-activator of the HTLV-1 genome and cellular genes, is preferentially expressed in HTLV-1-infected cells [14,15], and the CD30 and CD30 ligand interaction plays an important role in inflammation [16,17]. Therefore, a sustained high level of sCD30 may be associated with Tax expression and pulmonary involvement of ATLL.

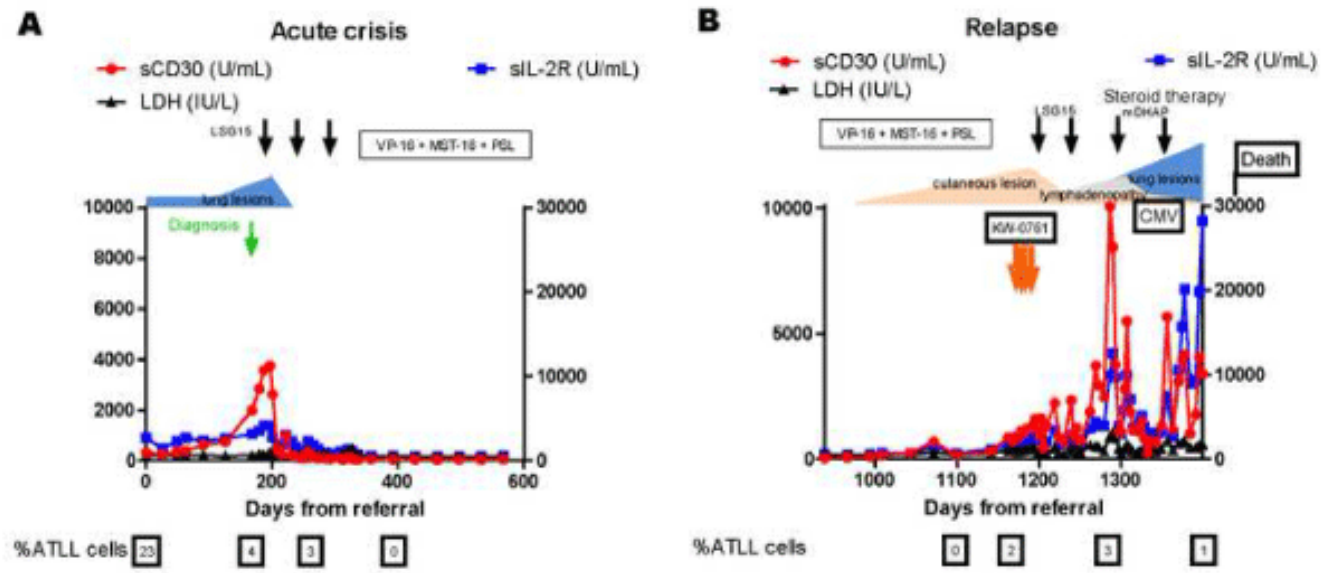

Figure 3: ATLL microenvironment or minimal residual disease in lung and elevation of sCD30

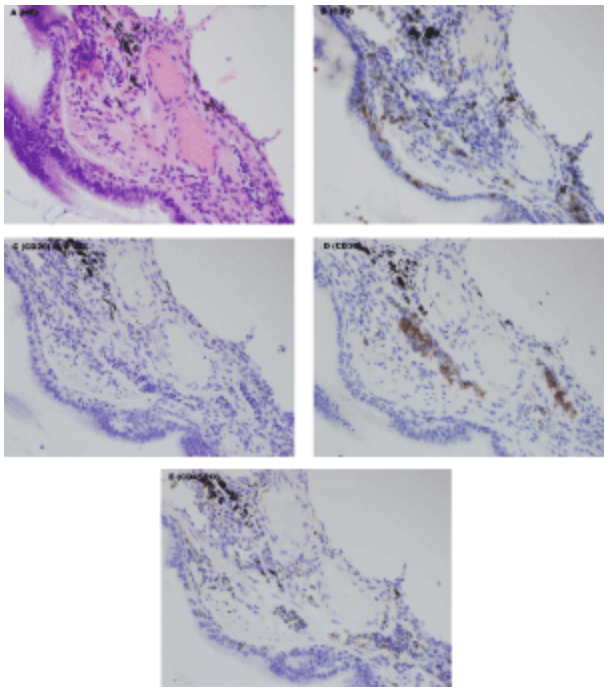

Figure 4: CD30+ T cells in lung lesion of ATLL in the indolent phase

The main limitation of the present study is that only one patient was studied. Although HTLV-1 is endemic in Kyushu, the incidence of ATLL is very low, and a long latency period exists between HTLV-1 infection and the development of ATLL. A multicenter cohort study is needed to confirm our results.

In conclusion, we demonstrated that the level of sCD30 was elevated during the process of acute crisis and of ATLL. Chronic immune activation in the lung and in pulmonary lesions may be a major cause for the sustained proliferation of ATLL cells and the progression of ATLL. Therefore, prospective monitoring using sCD30 may be effective to confirm the progression of disease.

	Chronic-type	Acute crisis
Flower cells	Sometimes	Yes
LDH	≤2N*	>2N*
Corrected Ca† (mEq/L)	<5.5	≥5.5
Tumor lesions		
Central nervous system	No	Yes
Bone	No	Yes
Ascites	No	Yes
Pleural effusion	No	Yes
Gastrointestinal tract	No	Yes

*indicates normal upper limit (229 IU/L at Kumamoto Medical Center)
†[Serum Ca (mEq/L)×2 – serum albumin (g/dL)+4]×1/2
ATLL, adult T-cell leukemia/lymphoma; LDH, lactate dehydrogenase

Table 1: Differences between indolent phase and acute crisis in ATLL

	Indolent phase	At crisis	Before LSG15

Peripheral blood			
Red blood cells	556×10^4/μL	494×10^4/μL	437×10^4/μL
Hemoglobin	17.8 g/dL	15.2 g/dL	12.8 g/dL
Hematocrit	52.60%	47.90%	39.80%
Platelet count	20.6×10^4/μL	32.6×10^4/μL	33.5×10^4/μL
White blood cells	18700/μL	9000/μL	8700/μL
Neutrophils	72.50%	49%	65%
Lymphocytes	14.50%	33%	25%
Monocytes	4%	12%	6%
Eosinophils	0%	1%	2%
Atypical lymphocytes	1%	1%	0%
ATLL cells	8%	4%	2%
Blood chemistry			
Total protein	7.2 g/dL	7.3 g/dL	6.2 g/dL
Albumin	3.8 g/dL	3.5 g/dL	3.0 g/dL
Blood urea nitrogen	9 mg/dL	13 mg/dL	10 mg/dL
Creatinine	0.69 mg/dL	0.70 mg/dL	0.63 mg/dL
Total bilirubin	1.4 mg/dL	0.7 mg/dL	0.5 mg/dL
AST	15 IU/L	13 IU/L	16 IU/L
ALT	11 IU/L	9 IU/L	9 IU/L
LDH	197 IU/L	206 IU/L	340 IU/L
Sodium	136 mEq/L	145 mEq/L	143 mEq/L
Potassium	3.5 mEq/L	4.3 mEq/L	3.7 mEq/L
Chloride	102 mEq/L	105 mEq/L	105 mEq/L
Amylase	66 IU/L	44 IU/L	97 IU/L
Serological tests			
C-reactive protein	6.65 mg/dL	2.78 mg/dL	3.27 mg/dL
IgG	N/A	N/A	1360 mg/dL
IgA	N/A	N/A	383 mg/dL
IgM	N/A	N/A	69 mg/dL
sIL-2R	1469 U/mL‡	3126 U/mL	4136 U/mL
sCD30	228 U/mL	1983 U/mL	3748 U/mL

N/A, not available.

ATLL, adult T-cell leukemia/lymphoma; AST, aspartate transaminase; ALT, alanine transaminase; LDH, lactate dehydrogenase; Ig, immunoglobulin; sIL-2R, soluble interleukin-2 receptor alpha chain; sCD30, serum soluble form of CD30

Table 2: Laboratory findings on referral and on admission

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