

# Soluble CD30 and peripheral blood or pulmonary involvement of adult T-cell leukemia/lymphoma

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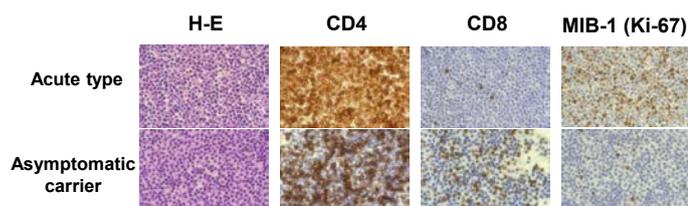
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Adult T-cell leukemia/lymphoma (ATL) is a highly aggressive leukemia/lymphoma which was discovered in Japan [1,2]. The long clinical latency and low incidence of ATL indicate that ATL is an age-related disease and some genetic changes are involved in malignant transformation and monoclonal expansion of the human T-cell leukemia virus type 1 (HTLV-1)-infected cells [3]. HTLV-1-mediated T-cell transformation presumably arises from a multistep oncogenic process in which the virus induces chronic T-cell proliferation with accumulation of genetic defects followed by dysregulation of cell growth [4]. Monoclonal proliferation of HTLV-1-infected cells is observed in upwards of 5% of patients who ultimately develop ATL, constituting the high risk group for ATL development [5]. We previously reported that HTLV-1-infected cells and ATL cells exhibit CD30 and soluble CD30 (sCD30) is elevated in the sera of patients with ATL [6]. CD30, a 120 kDa type I cell surface glycoprotein, is a member of the tumor necrosis factor receptor superfamily [7]. CD30 expression is dependent on mitogen or viral activation and proliferation of B and T cells. CD30+ cells release sCD30 *in vitro* and *in vivo* [8], detected at low levels in the sera of healthy donors [9]. The question remains as to where the ATL cells proliferate and produce sCD30? We have focused on the monoclonal proliferation of T cells and chronic inflammation in the microenvironment *in vivo*.

Peripheral Blood (PB) is known as one of unique involvements in ATL. Mononuclear cells from PB of acute type ATL patient show the proliferation of CD4+ T cells (Figure 1). In contrast, some T cells are shown in PB of HTLV-1 carrier. Levels of sCD30 are elevated in HTLV-1 carriers, becoming highly elevated in ATL. Lately, we found serum levels of sCD30 is correlated with the number of ATL cells in PB (data not shown). Furthermore, sCD30 elevation is followed by acute crisis from chronic type of ATL (paper preparation).

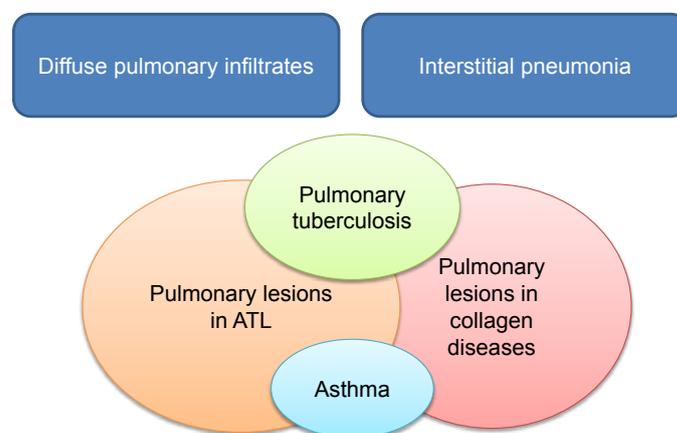
Ohshima et al. demonstrated that not only CD3+ and CD4+ T cells



**Figure 1.** Proliferation of CD4+ T cells in peripheral blood of HTLV-1-infected patient. Paraffin embedded specimens of peripheral blood mononuclear cells (PBMCs) were compared between an acute type of ATL patient and a HTLV-1 carrier. Most of PBMCs from a patient with ATL showed the proliferating CD4+CD8- T cells (MIB-1, Ki-67) but not PBMCs from a HTLV-1 carrier.

but also CD30+ giant cells are infected with HTLV-1 in lymph node (LN) [10]. However, CD30+ cells are not always found in LN (Table 1).

Lung involvements are often found from the onset of ATL, suggesting that lung is suitable for the formation of the tumor microenvironment [4]. The tumor viruses such as HTLV-1 and Epstein Barr virus induce CD30 expression and sCD30 production in virus-infected cells. Furthermore, those viruses are associated with unique lung diseases including HTLV-1 associated bronchiolo-alveolar disorder, HTLV-1 associated bronchopneumopathy, and pyothorax-associated lymphoma. We recently found the elevation of sCD30 is associated with pulmonary involvement during therapy (data not shown). In case of *allogeneic* hematopoietic stem cell transplantation, serums CD30 level is significant predictor of overall survival and specially detector of early death with lung lesions (paper preparation).



**Figure 2.** Lung diseases with tissue remodeling.

Activation of matrix metalloproteinases, ADAM10 and ADAM17, are associated with severe lung diseases which accompany tissue remodeling.

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**Table 1.** Serum levels of soluble cytokine receptors and tumor involvement.

Involved organs	Soluble IL-2R $\alpha$ chain (sIL-2R)	Soluble CD30 (sCD30)
Peripheral blood (PB)	High ~Very high	High ~Very high
Lymph node (LN)	High	Low (~High)
Lung	High	High

Serum levels of sCD30 may be not only biomarker of ATL, but also marker of Matrix Metalloproteinases (MMPs) activation on HTLV-1-infected cells and/or other cells in microenvironment. A disintegrin and metalloproteinase (ADAM)10 and ADAM17 play a role for shedding of CD30 [11]. These MMPs also cleave collagen and elastin which is structural proteins of lung. It is speculated that lung diseases with tissue remodeling share a common factor which is possible target of therapy (Figure 2).

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