

Adult T-cell Leukemia Virus (ATLV)-associated Lymphoma

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SUMMARY

An autopsy case of malignant lymphoma presenting T-cell phenotype in life and B-cell phenotype at autopsy is reported. The histology of a biopsy of right cervical lymph nodes in a 56-year-old woman revealed "non-Hodgkin's lymphoma, diffuse, medium-sized cell type". 74.5% of lymphoid cell suspensions formed the spontaneous rosettes with sheep erythrocytes.

Proviral DNA of adult T-cell leukemia virus was found after cell fraction. She was treated as adult T-cell leukemia. On the 69th hospital day, however, she died and autopsy was performed. The histology of lymph nodes of the neck at autopsy showed a diffuse proliferation of small to medium-sized neoplastic cells with the interspersed immunoblasts. Electron microscopically, these proliferating neoplastic cells differentiated into the immunoblasts to plasma cells. Also, they showed positivity for the PAP immunostaining method with anti-IgA and κ sera.

INTRODUCTION

Adult T-cell leukemia (ATL) was described by Takatsuki and his coworker.¹⁾²⁾¹⁴⁾¹⁶⁾ Many studies have been reported in ATL.¹⁾³⁾⁴⁾⁶⁾⁹⁾ The clinical and hematological characteristics are i) onset in adulthood ii) acute or chronic leukemia with rapid progression iii) resistance to treatment with current antileukemic agents iv) appearance of pleomorphic leukemic cells with a markedly deformed nuclei v) frequent accompaniment by

lymphadenopathy, hepatosplenomegaly, and hypercalcemia vi) absence of mediastinal tumor, and vii) these patients had been born in and around Kyushu region in Japan.

Recently human retrovirus adult T-cell leukemia virus (ATLV) has been shown to be closely associated with ATL.²⁾⁷⁾⁸⁾¹⁵⁾ YAMAMOTO *et al.* stated that ATLV infected not only T but also B, non-T and non-B cells.¹³⁾

We described a rare case of ATL presenting neoplastic B-cell phenotype at autopsy.

CASE REPORT

A 56-year-old woman complained of common cold-like symptoms at the beginning of February, 1983. Since she noticed painful lymphadenopathy at neck, she visited Nagasaki Citizens' Hospital on February 23, 1983.

On admission, generalized lymphadenopathy and skin eruption of the trunk were present. Hepatosplenomegaly was not recognized. Laboratory studies showed the followings: red blood cell count 354×10^4 /cmm, white blood cell count 4900/cmm with a differential of 63% segmented neutrophils, 8% bands, 6% eosinophils, 7% monocytes, 21% lymphocytes and no abnormal cells.

On March 2, 1983, a biopsy of right cervical lymph nodes was carried out. The histology revealed "non-Hodgkins lymphoma, diffuse, medium-sized cell type". 74.5% of lymphoid cell suspensions formed the spontaneous rosettes with sheep erythrocytes. They showed positivity for Leu-1 monoclonal antibody. The provirus of ATLV was found in DNA of lymphoid cell suspensions. Therefore she was diagnosed as ATL.

On March 15, a combination chemotherapy with vincristine, endoxan, predonisolone and adriamycin was begun. Her lymphadenopathy gradually reduced, but this chemotherapy paused for a time owing to its side effect.

At the middle decade of May, her chest X-ray showed fine nodular densities scattered throughout lung fields. The blood gases showed impaired diffusion with severe hypoxemia. She was treated with cotrimoxazole and oxygen inhalation. Dyspnea, however, persisted and she became cyanotic. She died on June 3, 1983 and autopsy was performed.

MATERIALS AND METHODS

Cell markers and analysis of proviral DNA of ATLV

Cell suspensions were prepared from fresh right cervical lymph node biopsy by mincing and filtering the tissue through gauze. The cell suspension was centrifuged through a Ficoll-Conray gradient to obtain viable mononuclear cells. The mononuclear cells at the interphase were collected, washed three times with phosphate-buffered saline (PBS), and examined for viability by the exclusion of trypan blue. Free cells were tested for spontaneous rosettes with neuraminidase treated sheep erythrocytes (SRBC) (JIMRO Co., Ltd.). Moreover, SRBC-rosette forming lymphoid cells were examined for reactivity with monoclonal antibodies to T-cells (Leu-1, Leu-2a and Leu-3a). DNA was extracted from cell suspension and analyzed to detect the integrated proviral DNA.

Light microscopy

Materials were obtained from the right cervical lymph node biopsy and lymph nodes of the neck at autopsy. The tissues were fixed in 10% neutral formalin, and hematoxylin-eosin (H. E.), periodic acid-Schiff (PAS), silver impregnation and methyl green pyronin were performed.

For light microscopic detection of cytoplasmic immunoglobulins (Ig), immunoperoxidase method (PAP method) was carried out employing anti-Ig, κ and λ sera (DAKO).

Electron microscopy

The formalin-fixed lymph nodes at autopsy were cut into small piece of blocks, fixed for 2 hours in Karnovsky's solution at 4°C and postfixed in 1% osmium tetroxide. They were dehydrated in graded ethanol series and embedded in Quetol 812.

RESULTS

Cell markers and analysis of proviral DNA of ATLV

SRBC-rosette forming cells were 74.5% of lymphoid cells in suspensions prepared from fresh right cervical lymph node biopsy, and positive for Leu-1 monoclonal antibody and negative for Leu-2a and Leu-3a monoclonal antibodies. Proviral DNA of ATLV was found in cell fraction. But no examination of cell marker and analysis of proviral DNA of ATLV were performed before death.

Light microscopy

The lymph node biopsy revealed a diffuse proliferation of medium-sized monomorphic neoplastic cell with frequent mitoses (Fig. 1). The reticulin fibers were very fine and sparse (Fig. 2). These neoplastic cells were round or oval with indistinct nucleolus and narrow cytoplasm. Sometimes nuclear convolution was found. The cytoplasm was negative for PAS reaction and lightly stained by methyl green pyronin. The histologic

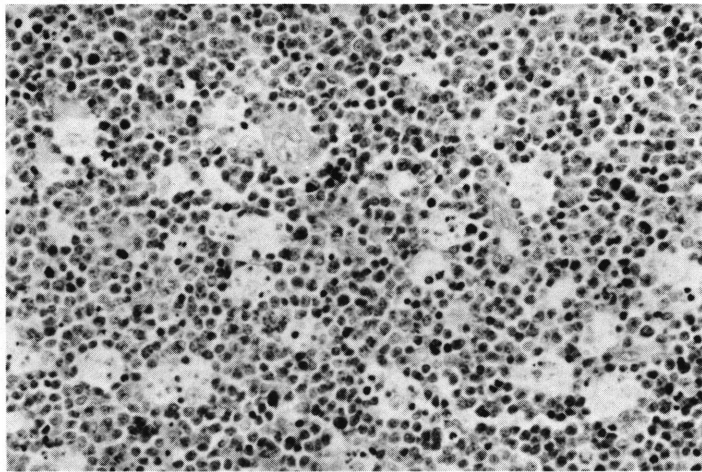


Fig. 1. The histology of right cervical lymph node biopsy shows a diffuse, monotonous proliferation of medium-sized cells. H. E. $\times 200$.

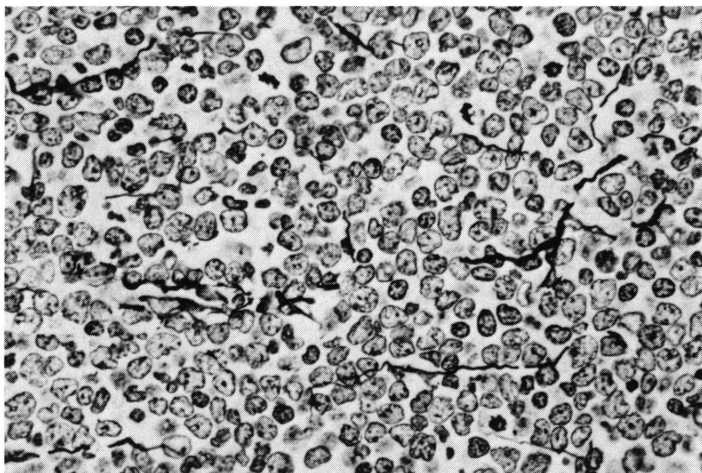


Fig. 2. Reticulin fibers are sparse. Sometimes nuclear convolution is found. Silver stain. $\times 400$.

diagnosis was "non-Hodgkin's lymphoma, diffuse, medium-sized cell type", according to LSGJ classification. All of proliferating cells were negative for anti Ig, and sera.

The histology of lymph nodes of the neck at autopsy showed a diffuse proliferation of small to medium-sized neoplastic cells with the interspersed immunoblasts. The small neoplastic cells showed differentiation into plasma cells and plasmacytoid cells (Fig. 3). The immunoblasts had hyperchromatic, large nucleus with distinct nucleolus and slightly basophilic cytoplasm which showed strong pyroninophilia. The neoplastic cells were partially positive for anti IgA and κ sera employing the PAP immunostaining method (Fig.

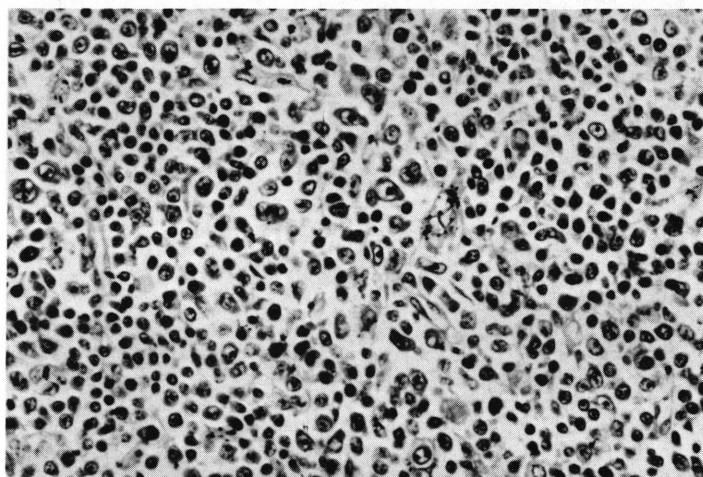


Fig. 3. The histology of lymph node at autopsy shows a diffuse proliferation of small to medium-sized cells. H. E. $\times 200$.

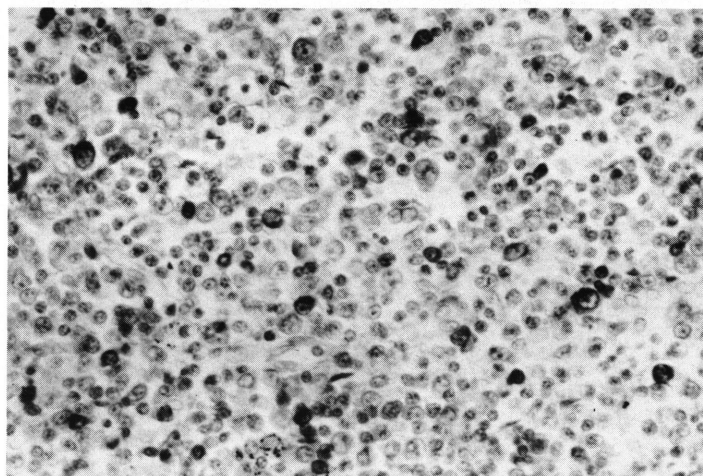


Fig. 4a. Immunohistochemical stain. a. anti IgA and b. anti κ . $\times 100$.

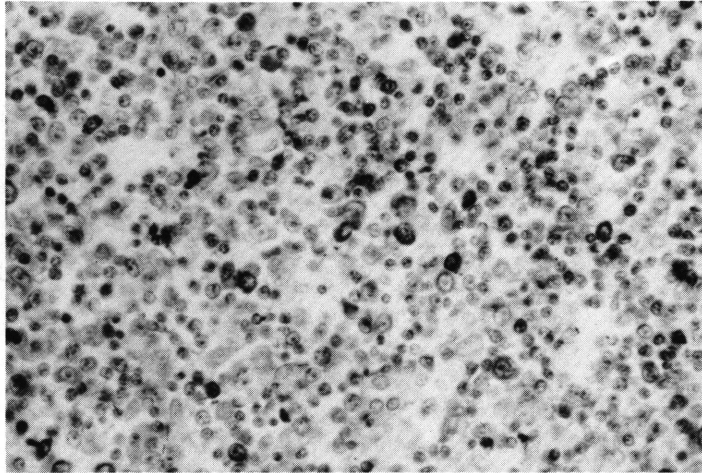


Fig. 4b.

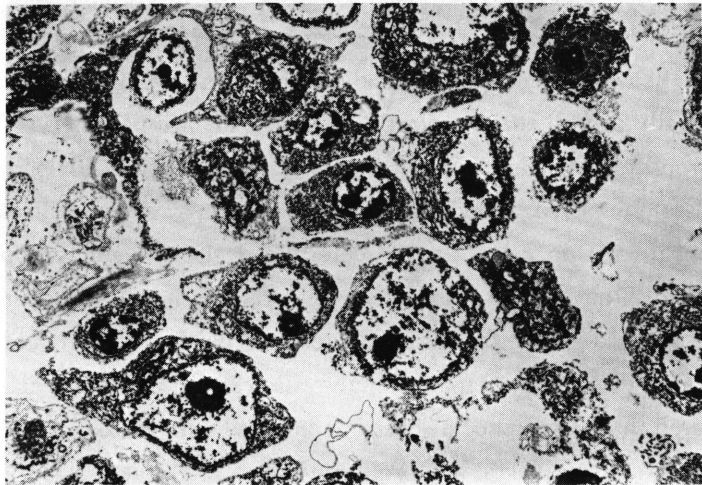


Fig. 5. Electron microscopic findings of the lymph node at autopsy. \times 2500.

4).

Electron microscopy

The neoplastic cells had large nucleus with delicate chromatin and large distinct nucleolus. Some of the small neoplastic cells had eccentric round nucleus with clumped chromatin and abundant cytoplasm. The rough endoplasmic reticulum was well developed throughout the cytoplasm. Electron microscopically, these proliferating neoplastic cells differentiated into the immunoblasts, plasmacytoid cells and plasma cells (Fig. 5).

DISCUSSION

Adult T-cell leukemia have been found in Japan. This disease revealed clinically and hematologically several characteristics.

In 1981, HINUMA *et al.*²⁾ detected ATL-associated antigen on MT-1, which originated from patients with ATL,⁵⁾ by indirect immunofluorescence. Also they observed type C virus particle on MT-1 cells. The provirus genome was detected in the chromosomal DNA of ATL.^{7,8,15)} It has been interpreted that ATL is related with retrovirus. In this case, also, proviral DNA of ATLV was found in cell fraction of right cervical lymph nodes. Therefore, the present case was confirmed in life.

Cell suspensions from patients with ATL form spontaneous rosettes with sheep erythrocytes and are frequently positive for Leu-1, Leu-3a and Leu-4 monoclonal antibodies¹²⁾. In our case, however, SRBC-rosette forming cells were positive for Leu-1 and negative for Leu-3a monoclonal antibody, which was atypical reaction as ATL.

It is generally agreed that neoplastic cells of ATL are peripheral T-cells.³⁾ ATL has never been reported to be associated with a proliferation of B-cell phenotype cells. In this case, the histology of lymph nodes of the neck at autopsy showed diffuse proliferation of immunoblasts to plasma cells. It was determined electron microscopically and immunohistochemically that the neoplastic cells were B-cell phenotype. YAMAMOTO *et al.*¹³⁾ reported that B-cells acted as reservoir in infected individuals. Consequently no examination of cell markers and chromosomal anomaly were carried out in our case before death, but it is considered that B-lymphocytes became infected with ATLV, and ATLV-infected B-lymphocytes became neoplastic and proliferated.

Although proviral DNA of ATLV was found, the present case differs from ATL in point of reactivity with monoclonal antibodies to T-cells (Leu-1, Leu-2a and Leu-3a) and a proliferation of B-cell phenotype at autopsy. Therefore, our case prefers to be called ATLV-associated lymphoma rather than ATL.

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