Adult T-cell leukaemia/lymphoma (ATLL) and T-cell leukemia virus type 1 (HTLV1)

Koichi Ohshima  Department of Pathology, School of Medicine, Kurume University, Asahimati 67, Kurume 830-0011 Japan. Mail: ohshima_kouichi@med.kurume-u.ac.jp

**Definition of ATLL**

Adult T-cell leukaemia/lymphoma (ATLL) is a peripheral T-cell neoplasm most often composed of highly pleomorphic lymphoid cells. The disease is usually widely disseminated, and is caused by the human retrovirus known as human T-cell leukemia virus type 1 (HTLV-1) (Figure 1).

**Epidemiology**

The disease has a long latency, and affected individuals usually are exposed to the virus very early in life. The virus may be transmitted in breast milk, and through exposure to blood and blood products. The cumulative incidence of ATLL is estimated to be 2.5% among HTLV-1 carriers in Japan (1). Sporadic cases have been found in the United State and elsewhere. It occurs in adults only and the age at onset ranges from the 20s to the 80s, with an average of 58 years. The male to female ratio is 1.5:1 (2). While infection with HTLV-1 is a direct cause of ATLL, it can indirectly cause many other diseases via the induction of immunodeficiency and/or immune reaction, such as chronic lung disease, opportunistic lung infections, chronic renal failure, nonspecific dermatomycosis, nonspecific arthritis, HTLV-1 associated lymphadenitis, HTLV-1 uveitis, and HTLV-1 associated myelopathy/tropical spastic paraparesis (HAM/TSP) (Table 1) (1).

ATLL is endemic in several regions of the world, in particular Japan, the Caribbean basin and parts of Central Africa. The distribution of the disease is closely linked to the prevalence of HTLV-1 in the population.

**Clinical features**

Several clinical variants have been identified: acute, lymphomatous, chronic and smoldering ATLL (4). The most common acute variant is characterised by a leukaemic phase, often with a markedly elevated white blood cell count, skin rash and generalised lymphadenopathy. The leukaemic cells are medium-sized to large lymphoid cells with irregular nuclei and basophilic cytoplasm. Characteristic ATLL cells have been described as “flower cells”, with many nuclear convolutions and lobules. Hypercalcaemia, with or without lytic bone lesions, is a common feature.

Patients with acute ATLL have a systemic disease accompanied by hepatosplenomegaly, constitutional symptoms, and elevated LDH. Leukocytosis and eosinophilia are common complications. Many patients have an associated T-cell immunodeficiency, with frequent opportunistic infections such as Pneumocystis carinii pneumonia and Strongyloidiasis. The lymphomatous variant is characterised by prominent lymphadenopathy but without peripheral blood involvement. Most patients present with advanced stage disease similar to the acute form, although hypercalcaemia is seen less often.

The chronic variant is associated with skin lesions, most commonly exfoliative. While an absolute lymphocytosis may be present, atypical lymphocytes are not numerous in the blood. ATLL cells in the chronic variant are generally small with slight nuclear abnormalities,
such as notching, indentation, and convolution. Hypercalcaemia is absent.

In the smoldering variant, the white blood cell count is normal with >5% circulating, neoplastic cells. ATLL cells are generally small with a normal appearance. Patients frequently have skin or pulmonary lesions, but there is no hypercalcaemia. Progression from the chronic or smoldering to the acute variant occurs in 25% of the cases, but usually after a long duration (4). (Figure 2, Figure 3, Figure 4)

**Sites of involvement**

Most ATLL patients present with widespread lymph node involvement as well as involvement of peripheral blood. The number of circulating neoplastic cells does not correlate with the degree of bone marrow involvement, suggesting that circulating cells are recruited from other organs such as the skin. In fact, the skin is the most common extralymphatic site of involvement (>50%).

The distribution of the disease is usually systemic, involving the spleen and extranodal sites including skin, lung, liver, gastrointestinal tract and central nerve system (5).

**Morphology**

【Lymph nodes】Histopathological examination of the HTLV-I associated lymph nodes usually, but not always, shows a pleomorphic (medium and large cell) type. Some cases show a pleomorphic small cell, anaplastic large cell or AILT-like type (6). In addition, some patients with pre-overt ATLL show a Hodgkin's disease-like morphology and lymph nodes in non-neoplastic carriers with features of lymphadenitis.

Pleomorphic (medium and large cell) type. This is a typical feature of ATLL. The medium and large tumour cells vary in size and clearly show some form of nuclear irregularity. Giant cells with cerebriform, Reed-Sternberg type or bizarre nuclei, are frequently seen in these tissues. Pleomorphic small cell type. These tumour cells are as large as or slightly larger than normal blood lymphocytes and show mild nuclear irregularities with only a few cells displaying mitotic features. Anaplastic large cell type. These tumour cells are much larger than the cells of large cell lymphoma and show a uniform pattern of cell proliferation with a cohesive growth pattern similar to that of anaplastic large cell lymphoma (ALCL). Tumour cells with prominent nucleoli and an abundant cytoplasm have been found, as have multinucleated giant cells such as Reed-Sternberg cells detected with CD30 antigen. In addition, a rare morphological variant of ATLL is the angioimmunoblastic T cell lymphoma (AILT)-like type (6).

Some patients with early or smoldering adult T-cell lymphoma/leukaemia may show a Hodgkin-lymphoma-like histology in the lymph nodes. Involved lymph nodes feature an expanded paracortical area with diffuse infiltrates of small to medium-sized lymphocytes with mild nuclear irregularities, indistinct nucleoli and scant cytoplasm, interspersed with Reed-Stemberg (RS)-like cells and giant cells with lobulated or convoluted nuclei. These cells are EBV-positive B-lymphocytes that express CD30 and CD15 (7).

The pleomorphic (medium and large cell) type, which displays features typical of ATLL, and the anaplastic large cell type have been associated with a rapidly deteriorating survival curve. Hodgkin's type was found to be associated with a progressive decrease and pleomorphic small cell type lymphoma with an initial steep increase in mortality, which reached a plateau during the mid- and late period of observation. On the other hand, all cases with lymphadenitis entered were alive (8). (Figure 5)
Marrow infiltrates are usually patchy, with their presence ranging from sparse to moderate. Osteoclastic activity may be prominent, even in the absence of bone marrow infiltration by neoplastic cells. In the cutaneous lesions, the macroscopical findings have been classified as erythema, papules, and nodules, and the histological findings as perivascular infiltration of atypical lymphoid cells, diffuse infiltration of medium-sized to large atypical lymphoid cells, and infiltration of large atypical lymphoid cells. Epidermal infiltration with Pautrier-like microabscesses is frequently observed. Involvement of the liver is mainly seen in the portal area, which shows infiltration of atypical medium-sized to large lymphoid cells with irregular nuclei, occasional destruction of limiting plates, and in some cases sinus infiltration, but rarely fibrosis. In the gastro-intestinal tract lesions, macroscopic examination shows three patterns (ulcerated mass, erosion, and tumour). The histological patterns have been identified as diffuse medium cell type, diffuse pleomorphic medium-sized, large cell type, or anaplastic large cell type (6). (Figure 6)

**Immunophenotype**

Tumour cells express T-cell-associated antigens (CD2, CD3, CD5), but usually lack CD7. While most cases are CD4+, CD8+, a few are CD4+, CD8+ or double positive for CD4 and CD8. CD25 is expressed in nearly all cases. The large transformed cells may be positive for CD30, but are ALK negative (7) And are negative for TIA-1 and granzyme B. In addition, tumour cells frequently express CCR4 of the chemokine receptor, and FoxP3 of the regulatory T-cell marker (8). Postulated cell origin has been suggested that CD4+CD25+FoxP3+ regulatory T cells in particular may be associated with cell origin (8).

**Genetics**

Most ATLL cases are characterized by monoclonal integrated HTLV-1, and some by its oligoclonal counterpart. Otherwise, no clonal integration is present in carriers (9). T-cell receptor genes are clonally rearranged in ATLL. Almost ATLL cases have clonal chromosome abnormalities of numerical and structural abnormalities, but here are no specific karyotype abnormalities in ATLL.

**Prognosis and predictive factors**

Clinical subtypes, age, performance status, serum calcium and LDH levels are major prognostic factors. The survival time for acute and lymphomatous variants ranges from two weeks to more than one year. Death is caused by infectious complications. Chronic and smoldering forms have a more protracted clinical course and better survival, but can change to an acute phase with an aggressive course (4).

**Etiology**

HTLV-1 is causally linked to ATLL, but HTLV-1 infection alone is not sufficient to result in neoplastic transformation of infected cells. The p40tax viral protein leads to transcriptional activation of many genes in HTLV-1 infected lymphocytes (10). In addition, the HTLV-1 basic leucine zipper factor (HBZ) is thought to be important for T-cell proliferation and oncogenesis (11). However, additional genetic alterations acquired over time may result in the development of a malignancy.
References

Figure 1.
Adult T-cell leukaemia/lymphoma. Southern blot analysis. In the HTLV-I analysis, lane 1 shows placental DNA for the negative control, and lanes 2,3 and 4 ATLL, which displays one proviral HTLV-1 DNA band. The difference in band sizes for different cases is the result of the difference in integration sites.
Table 1.
HTLV-1 associated diseases

<table>
<thead>
<tr>
<th>Neoplastic disorders</th>
<th>Reactance disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral blood (leukemia)</td>
<td>Conditioned</td>
</tr>
<tr>
<td>Smoldering type</td>
<td>HTLV-associated myelopathy (HAM)</td>
</tr>
<tr>
<td>Chronic type</td>
<td>HTLV-associated esophageal cancer</td>
</tr>
<tr>
<td>Acute type</td>
<td>HTLV-associated prolymphocytic leukemia</td>
</tr>
<tr>
<td>Lymphoid (lymphoma)</td>
<td>HTLV-associated lymphadenopathy</td>
</tr>
<tr>
<td>Hodgkin's like type</td>
<td>HTLV-associated lymphoma</td>
</tr>
<tr>
<td>Plasmocytic small type</td>
<td>Not conditioned</td>
</tr>
<tr>
<td>Malignant (medullary and large cells)</td>
<td>ATLL-associated lymphoblastoid leukemia</td>
</tr>
<tr>
<td>Amyloid large cell type</td>
<td>Autoimmune lymphoproliferative syndrome</td>
</tr>
<tr>
<td>Skin</td>
<td>Strongyloides stercoralis</td>
</tr>
<tr>
<td>Erythema</td>
<td>Varicella zoster virus</td>
</tr>
<tr>
<td>Papule</td>
<td>Opportunistic infections</td>
</tr>
<tr>
<td>Nodule</td>
<td>Plasmodium malaria</td>
</tr>
<tr>
<td>Cutaneous tract</td>
<td>Cryptosporidium</td>
</tr>
<tr>
<td>Excision</td>
<td>Aspergillus fumigatus</td>
</tr>
<tr>
<td>Ulcer</td>
<td>Candida albicans</td>
</tr>
<tr>
<td>Lesion</td>
<td>Cryptosporidium watkins</td>
</tr>
<tr>
<td>Polyradiculoneuritis</td>
<td>Carcinoma (not continued)</td>
</tr>
<tr>
<td>Infection with or without illness</td>
<td></td>
</tr>
</tbody>
</table>

Figure 2.
ATLL. HTLV-I proviral DNA integration and clinical subtypes. In some of the patients with carriers, the disease may develop into chronic, smoldering or acute type with clonal selection and clinical progression.

Figure 3.
ATLL. Survival curves. Acute and lymphomatous forms have an aggressive clinical course, whereas longer survival is seen in patients with chronic or smoldering disease.

Figure 4.
ATLL. Peripheral blood films. In the acute variant, the leukaemic cells are medium-sized to large lymphoid cells with irregular nuclei and basophilic cytoplasm. The characteristic ATLL cells have been described as “flower cells”, with many nuclear convolutions and lobules. In the chronic variant, they are generally small with slight nuclear abnormalities.
Figure 5.
ATLL. Histology of HTLV-I associated lymph nodes. The pleomorphic (medium-sized and large cell) type shows a diffuse proliferation of atypical medium-sized to large lymphoid cells with irregular nuclei, intermingled with cerebriform giant cells. The lymph nodes of pleomorphic small cell type show a diffuse proliferation of atypical medium-sized to small lymphoid cells. Anaplastic large cell type shows a diffuse proliferation of atypical large lymphoid cells with prominent nucleoli. The lymphoma cells react with CD30 antibody. The lymph nodes of Hodgkin-like ATLL show Reed-Sternberg-like giant cells, which react with CD30 and CD15 antibody. The giant cells express EBV-LMP proteins and EBER RNA. The background lymphocytes react for CD4.

Figure 6.
ATLL Cutaneous lesions. Macroscopic findings of cutaneous lesions. The macroscopic findings have been classified as erythema, papules, nodules, and tumor. Histopathological findings. The lymphoma cells infiltrate the epidermis, producing Pautrier-like microabscesses.