

A Case Report of Adult T-Cell Leukaemia/Lymphoma (ATLL)

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Abstract

Adult T-cell leukaemia/lymphoma (ATLL) is a unique disease with distinct manifestations, a characteristic phenotype and a likely retroviral aetiology. It is unusual in Southeast Asia, though more commonly seen in some countries like Japan. We report a case of this disease in a 71-year-old man in Singapore who presented with papular erythematous eruptions for 6 years and subsequently developed generalised lymphadenopathy. He was diagnosed to have ATLL and, despite an initial response, became resistant to combination chemotherapy. We discuss the aetiology, characteristics and management of this interesting disease.

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Case Report

Our patient was a 71-year-old Chinese man who presented with a 6-year history of recurrent papular erythematous eruptions to the dermatologist.

Skin biopsy was done which showed "granulomatous dermatitis with an interstitial type granuloma annulare". The skin biopsy was repeated 1 month later and showed "superficial perivascular dermatitis" and "superficial and deep perivascular dermatitis consistent with lymphomatoid papulosis".

He later developed generalised lymphadenopathy over the right axillary and both inguinal regions, though physical examination was otherwise unremarkable with no liver or splenic enlargement.

Lymphocytosis was noted and the total white cell count was 29,200/mm³ with a differential count of 21% polymorphs, 57% lymphocytes and 19% monocytes.

Bone marrow aspiration showed presence of "a few atypical lymphoid cells with erythroid and megakaryocytic hyperplasia". The trephine biopsy was reported as "reactive marrow with normal cellularity and presence of erythroid, granulopoietic and megakaryocytic cell lines with mature foci are seen and scattered single atypical cells of uncertain lineage". There were no granulomas and immunoperoxidase stains showed no abnormal cellular aggregate.

Flow cytometry revealed elevation of the following cell surface markers:

- B and T-cell marker CD5 89.9% (normal range 25.4% to 41.8%)
- Cytoplasmic-CD3 84.4%
- T helper cell-CD4 85.8% (normal range 11.6% to 19.4%)
- Pan T-cell-CD2 85.8% (normal range 37.1% to 54.9%)

Cytogenetics also revealed deletion of the long arm of chromosome 6 at breakpoint q23 (Fig. 1), while an excision biopsy of the left inguinal lymph node revealed that the patient had a peripheral T-cell lymphoma.

Further investigations revealed an elevated β_2 microglobulin (8835 ug/L), raised lactate dehydrogenase levels (2240 U/L) and hypercalcaemia (2.99 mmol/L). Computed tomographic (CT) scans of the thorax revealed two irregular nodules in the middle lobe while CT scan of the abdomen revealed mild splenomegaly with a normal sized liver and a 3-cm hypodense lesion in the right lobe of the liver. Peripheral blood film showed typical "clover-leaf" cells of adult T-cell leukaemia/lymphoma (ATLL) (Fig. 2).

A repeat flow cytometric analysis was done on the peripheral blood on 20 November 1997 which revealed:

- Terminal deoxynucleotide transferase (Tdt) 0.1% (low)
- B and T-cell CD5 99.5% (normal range 44.3% to 72.8%)
- Pan T CD3 93.6% (normal range 51.3% to 71.1%)
- T-cell CD4 98.9% (normal range 22.6% to 41.3%)

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Fig. 1. Cytogenetics of the patient revealing deletion of the long arm of chromosome 6 at breakpoint q 23[del(6)(q23)].

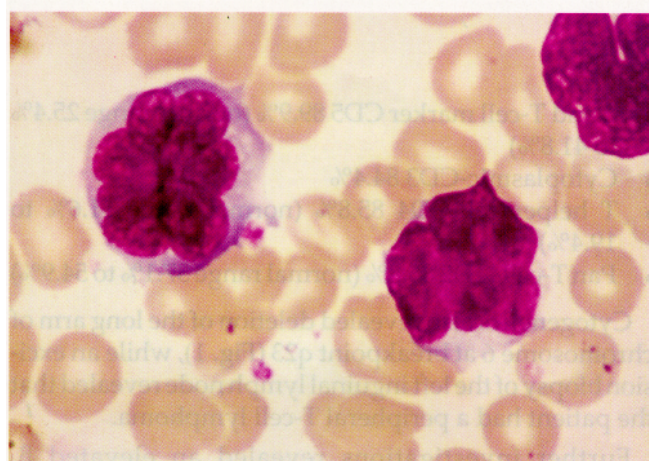


Fig. 2. Blood film of the patient showing flower or clover cells, which are 2 to 4 times the size of a small lymphocyte, have deeply indented nuclei, coarse chromatin, inconspicuous nucleoli and scant cytoplasm. It is flanked by another less classical, atypical lymphocyte.

- T-cell/T ALL CD7 1.1% (normal range 43.8% to 69.1%)
- T-cell CD8 0.7% (normal range 11.3% to 29.3%)
- Pan T-cell CD2 98.3% (normal range 61.4% to 80.6%)
- Interleukin 2 receptor (IL-2R) CD25 82.1% (normal range 0.5% to 7.0%) (elevated)

A diagnosis of ATLL was made and the patient was treated with chemotherapy but his condition continued to deteriorate and he died two months later from resistant disease and infection.

Discussion

The above illustrates a case of ATLL. The patient was initially in indolent chronic phase until he progressed to the typical acute and rapidly fatal terminal course.

ATLL, a disease entity first described by Takatsuki et al,¹ is rare in Southeast Asia and many parts of the world but is endemic in south-western Japan, the Caribbean Islands, Colombia, Africa and in several isolated populations in Papua New Guinea, the Solomon Islands

and Vanuatu. Human T-cell lymphotropic virus

I) the first human retrovirus to be characterised, is associated with ATLL and the general belief is that a primary viral infection leads to polyclonal proliferation and a subsequent second genetic change.

Since the discovery of HTLV-I in patients with ATLL, this endemic infection with HTLV-I has now been detected worldwide and attracted a great deal of attention.² The disease is particularly interesting as it illustrates very vividly how a retrovirus can stimulate a malignant disease. The major transmission routes of this virus are breast-feeding, transplacental³ and sexual intercourse.⁴ However, only 1% of individuals infected with HTLV-I develop clinical disease.

ATLL is a mature T-cell malignancy which is aggressive with lymph node, liver, spleen, skin involvement and pulmonary infiltrates, with lymphocytosis of multilobed T lymphocytes (the “flower” or “clover-leaf” cells seen in Figure 1).

Patients are prone to secondary infections associated with impaired cell mediated immunity e.g. bacterial, pneumocystis, cryptococcal, cytomegaloviral and candidal infections. They may also present with pharyngopathy, hypercalcaemia and osteolytic lesions. Central nervous system, pulmonary and gastrointestinal tract (including liver) involvement is not uncommon.⁵

Central nervous system involvement with the development of progressive weakness and lymphomatous leptomeningitis is particularly interesting as infection with HTLV-I may be associated with chronic progressive disease of the central nervous system termed tropical spastic paraparesis, or HTLV-I associated myelopathy. The various manifestations of HTLV-I infections may be related to differences in the genetic backgrounds of individuals, infection with variant strains of HTLV-I, differences in viral tropism or host immune response to the virus.

Lymph nodes demonstrate diffuse involvement with varying sizes and shapes of cells. Occasional subcortical multilobed cells may also be found. As in our patient, there are atypical lymphoid cells seen in the peripheral blood film and, sometimes, various body fluids including the cerebrospinal fluid. These cells are frequently referred to as flower or clover cells, which are 2 to 4 times the size of a small lymphocyte, have deeply indented nuclei, coarse chromatin, inconspicuous nucleoli and scant cytoplasm (Fig. 2). Large cells with variably cleft nuclei, prominent nucleoli, and abundant amphophilic cytoplasm with perinuclear clearing are also frequently present, most notably in aspirates of lymph nodes and soft tissues. Skin biopsy may reveal dense nodules of malignant cells or may be non-specific as with our patient.

Patients typically have histological evidence of malig-

nant lymphoma with T-cell receptor rearrangement. Pan-T markers, e.g. CD2 and CD5, are usually positive although CD7 is frequently negative. Negative expression of the 'terminal deoxynucleotidyl transferase (Tdt) and CD1a, as well as a mature T helper (CD4+ CD8-) phenotype confirm the post-thymic nature of the ATLL cells. The majority of cases exhibit positive expression of CD25, which corresponds to the α -peptide chain of the interleukin-2 receptor (IL2-R).⁶

Typical cytogenetic abnormalities include trisomy 3, 6q- (Fig. 1), trisomy 7 and chromosome 14 elongation with breaks at bands q11 and q32.

The diagnosis of ATLL is made from the characteristic clinical findings, the detection of serum antibodies to HTLV-I, and when necessary, the confirmation of monoclonal integration of HTLV-I proviral DNA in cellular DNA of ATLL cells.

Diagnostic criteria for HTLV-I associated ATLL have been defined as follows:^{7,8}

1. Histologically and/or cytologically proven lymphoid malignancy with T-cell surface antigens (mostly CD2, CD3 and CD4 positive).
2. Abnormal T-lymphocytes consistently present in the peripheral blood, except in the lymphoma type. These abnormal T-lymphocytes include not only typical ATLL cells, the so-called flower cells, but also the small mature T-lymphocytes with incised or lobulated nuclei that are characteristic of the chronic or smouldering type.
3. Serum specimens for all patients with ATLL have anti-HTLV-I antibodies. There is no difference in the pattern of serum antibodies between ATLL patients and HTLV-I carriers.
4. Demonstration of clonality of HTLV-I proviral DNA is essential to diagnosis of ATLL. Southern blot analysis may be used for this purpose by using inverse polymerase chain reaction to detect clonality of HTLV-I proviral DNA.

ATLL patients are classified into four subtypes according to the clinical picture: acute, chronic, smouldering, and lymphoma type. Recently, the Lymphoma Study Group in Japan proposed diagnostic criteria for clinical subtypes of ATLL (Table I).⁸ They are the smouldering type with mainly histologically-proven skin involvement with no lymphocytosis (albeit $\geq 5\%$ abnormal T lymphocytes), the chronic type with mainly lymphocytosis, the lymphoma type with mainly lymph node involvement and the acute type with prominent circulating "flower cells" often with multi-organ and lymph node involvement.

In a study of more than 800 patients, the Lymphoma Study Group determined that five features were predictive of shortened survival.⁵ These were:

1. Poor performance status
2. High lactate dehydrogenase
3. Age >40 years
4. Increased tumour bulk
5. Hypercalcaemia

Treatment can usually be withheld in early smouldering disease (as the patient probably had initially when he presented with the recurrent skin lesions) until the disease changes to the acute phase (as the patient had later with lymph node, blood and lung involvement).

Combination chemotherapy gives an initial response rate of 70% but complete remission (CR) rates $<10\%$ without anthracyclines^{5,8} and 17% to 22% with the addition of anthracyclines.⁹ Early relapse is also common, after which the disease tends to be unresponsive to treatment. The use of cyclophosphamide, adriamycin, vincristine and prednisolone or CHOP, followed by etoposide, vindesine, ranimustine and mitoxantrone, and supported by granulocyte colony-stimulating factor (G-CSF), resulted in a 36% CR and a median survival of 8.5 months, with those going into CR having longer survival.¹⁰ In view of the high frequency of central nervous system involvement (9/19

TABLE I: DIAGNOSTIC CRITERIA FOR CLINICAL SUBTYPES OF ATLL⁸

	Smouldering	Chronic	Lymphoma	Acute
Lymphocytes ($\times 10^9/l$)	<4	≥ 4	<4	+/-
Abnormal T lymphocytes	$\geq 5\%$	+	$\leq 1\%$	+
"Flower" cells	Occasionally	Occasionally	No	Yes
Calcium level	Normal	Normal	Normal/raised	Normal/raised
Lactate dehydrogenase	< 1.5 times of normal	< 2 times of normal	Normal/raised	Normal/raised
Lymph nodes	No	+/-	Yes	+/-
Hepato/splenomegaly	No	+/-	+/-	+/-
Skin	+/-*	+/-	+/-	+/-
Bone lesions	No	No	+/-	+/-
Marrow involvement	No	No	+/-	i-f-

* Histologically-proven malignant lesion required.
Anti HTLV-I antibody required in all groups for diagnosis.

ATLL: adult T-cell leukaemia/lymphoma

patients at relapse), intrathecal chemotherapy should be given in all cases and the cerebrospinal fluid sent for analysis.¹¹

As infectious complications are the most frequent cause of death, prophylactic use of cotrimoxazole is now routine, though anti-fungal and anti-viral agents should be considered.

As the tumour expresses the IL-2 receptor, anti-IL-2 receptor antibodies have been tried with some long-term responses but an overall survival of only 50% at 5 months; the radio-labelled form may be more effective.¹²

In view of the implication of retrovirus (HTLV-I) in the aetiology, anti-retroviral therapy (azidothymidine, AZT) has been tried alone or in combination with interferon. Interferon may induce the expression of viral or major histocompatibility antigens at the cell surface while AZT can exert cytostatic effects by terminating DNA replication. With the combination, there was major response in 66% including some response inpatients with refractory disease.¹³

While autologous bone marrow transplantation in ATLL may be precluded by the frequent marrow involvement, peripheral blood stem cell (PBSC) transplantation may be an attractive option for the patient in remission. This is especially so since CD34+ haemopoietic progenitor cells, which may be selected for before reinfusion, have been found to be free from HTLV-I infection.¹⁴

The combination of conventional chemotherapy with antiretroviral therapy and interferon or monoclonal antibodies to IL-2R, followed by a CD34 selected PBSC transplant may be the way ahead for the treatment of this interesting but resistant disease.

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