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Clinical Features of Adult T-cell Leukemia and its Problems

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Peripheral mature T-cell malignancy with HTLV-I (Human T-cell lymphotropic virus I) infection are designated as adult T-cell leukemia (ATL). ATL is devided to leukemic type and lymphoma type. Leukemic type is classified into at least two subgroups : acute and chronic types according to clinical course, and former being more common. Lymphoma type ATL is equal to T-cell non Hodgkin's lymphoma in clinical aspect, and acute ATL (leukemic) have some characteristic clinical features. I would like to describe mainly about clinical features of acute type ATL and some epidemiological aspects of HTLV-I.

How HTLV-I act for occurring ATL ? From first infection of HTLV-I to occurring ATL in human body, how HTLV-I act to T-cell?

At first, HTLV-I infect to body by cell to cell infection from HTLV-I carrier or ATL patient. This virus infect to CD4＋Tcell and is integrated to cell DNA as provirus.

Although this infected T-cell may be transformed to tumor cell and increase gradually in infected body and become disease of ATL finally, there may be some steps in this duration.

It is suspected that it takes 30-40 years from first infection to occurring ATL by the observation of epidemiological aspects, and the definitive mechanism how HTLV-I change T4 cell to tumor cell is obscure.

Anyway, lymphnode seems to be suitable area for proliferation of transformed T-cells.

We can see many ^{3} H-TdR labelled big cells or dividing cells in lymphnode tissue of ATL [1]. And, only large cells are labelled by ^{3} H-TdR (Fig. 1) in the peripheral blood abnormal T-cells of ATL. And small cells are dominant usually in the peripheral blood of acute leukemic ATL.

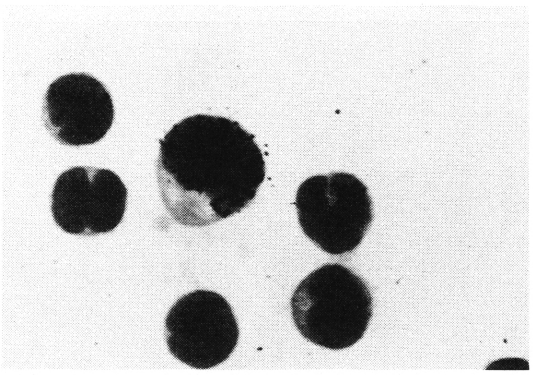

Fig. 1. Labell by ^{3}H-TdR of ATL cells

According to these facts, to study cell kinetics of large cells in lymphnode or tumor making tissue seems to be important to clarify the feature of ATL.

The clinical characteristics of acute ATL are the appearance of abnormal T-cells with loburated nuclei in the peripheral blood, (Fig. 2) generalized lymphnode swellings, (90%) hepatosplenomegaly with liver function disturbance, (hepatomegaly : 60%) skin involvement (50%), hypercalcemia (50%) and various infection diseases especially opportunistic infections like carinii pneumonia.

Although leucocyte count increase in high level in chronic type ATL, nuclear indentations of ATL cells are not remarkable, constitutional symptoms like fever, weight loss, and general malaise are also slight, and hypercalcemia is rare. Skin involvement is common in chronic ATL. Usually, level of serum LDH (lactete dehydrogenase) is high in acute ATL. In generally,

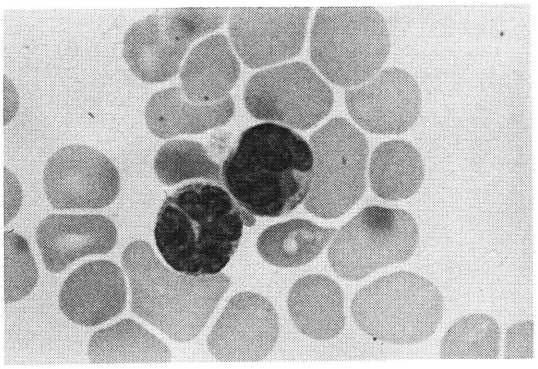

Fig. 2. ATL cells in peripheral blood

ATL has various features of T-cell lymphoproliferative disorders. Changes from chronic type to acute, from lymphoma type to acute ATL and from acute type to tumor making type have been observed.

DIAGNOSIS OF ATL

With the clinical signs mentioned above, to detect the infection of HTLV-I is necessary for diagnosis of ATL.

Cell surface marker of ATL cell : Immunological surface marker of helper T-cell is common in ATL cell. ATL cells react for monoclonal antibodies of OKT4 or Leu 3a. However, many ATL cells show suppressor function for immunoglobulin production of B cell. (Tab. 1)

Table 1. Function for B-cells of ATL cells

function	case
suppressor	24
non function	8
helper	2
total	34

or the detection of anti-HTLV-I antibody, rect immunofluorescence method (IF) is t reliable, using pt's sera and antigen posi- cultured cells. Gelatin particle agglutina- method (PA) or enzyme immunoassay A) are available for screening of many erials. Western blot method is valuable confirmation of positive sera by PA or assays.

urthermore, the detection of ATLA (ATL associated antigen-virus antigen) on the tumor cells by the IF method and the detection of proviral integration of HTLV-I for DNA of tumor cells by the southern blot method are desirable.

Monoclonal integration pattern of provival DNA using EcoR-I is observed in ATL or preATL as a rule. (Fig. 3)

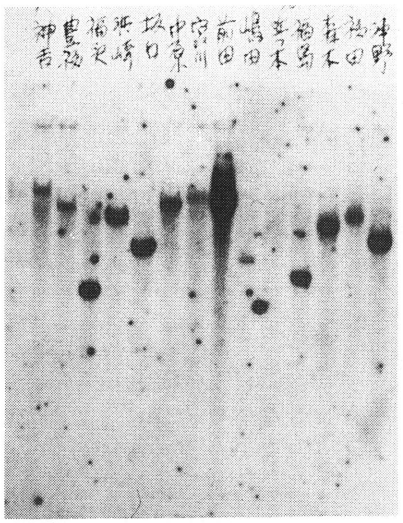

Fig. 3. Monoclonal pattern of HTLV-I provival DNA by southern blotting method

The pathohistological examination of biopsied lymphnode of ATL patient is useful to assist the diagnosis and to select therapy. The diffuse pleomorphic type by JLSG (Japanese lymphoma study group) classification is most characteristic as ATL. (Fig. 4) However, the various type of histology of non Hodgkin lymphoma can be seen in ATL lymphnodes.

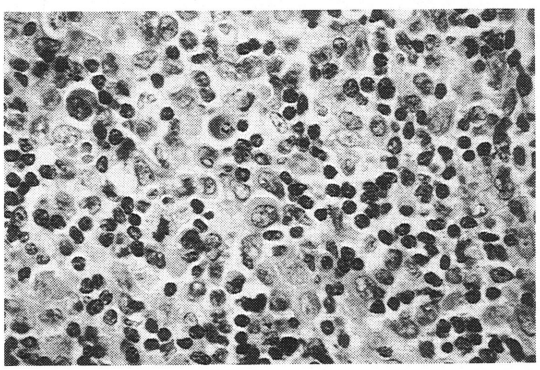

Fig. 4. Pleomorphic type in tissue of ATL

There is some dissociation in ATL cells morphologically between the ATL cells in lymphnode with the ATL cells in the peripheral blood. Small cells are common in peripheral blood, and large cells are dominant in lymphnode in the ATL cases with the histology of pleomorphic type or large cell type.

Chromosome study of ATL revealed many kinds of abnormalities. The break of 14q32, 6q21, 14q11, 6q15 and 10q11-13 are reported as the aberrations not rarely seen. Among these aberrations, Sadamori et al[2] reported 11 cases of ATL with 14q11 break. (Fig. 5) The break of 14q11 seems important to search the mechanism of carcinogenesis of ATL. Croce et al[3] reported the locus of the α-chain of the T-cell receptor is at band q11,2 of the chromosome 14.

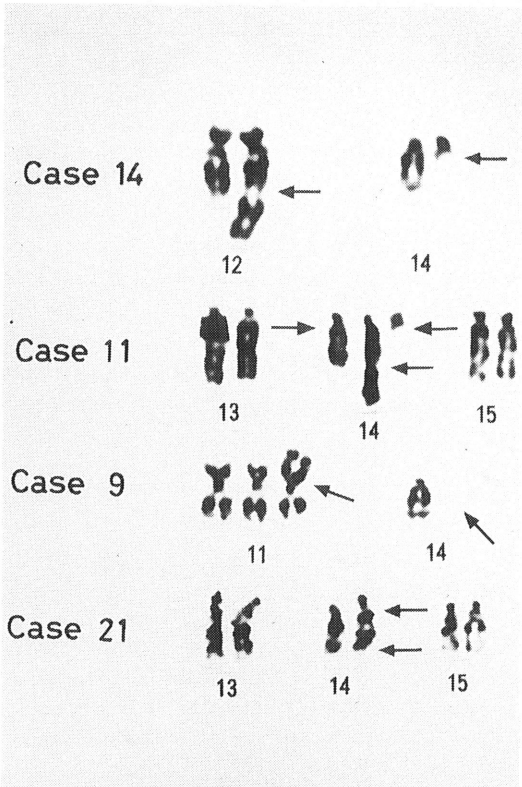

Fig. 5. Various 14q11 break in ATL

EPIDEMIOLOGY OF HTLV-I

Transmission of HTLV-I is established by the cell to cell infection due to the transmission of HTLV-I infected T-cells.

Three possible routes for the transmission of the virus have been reported. These are HTLV-I carrier mothers milk-born infection, blood transfusion from HTLV-I carrier and infection due to sexual intercourse. Two routes among them, mother milk-born transmission and due to blood transfusion are presented here.

Mother milk born transmission [4, 5] : Blood samples obtained from 5015 pregnant woman in Nagasaki city and its surrounding area were tested for anti HTLV-I antibody by IF assay. 187 pregnant woman were found to be positive for anti HTLV-I antibody.

The expression of HTLV-I antigen was confirmed by IF assay in PHA-cultured mononuclear cells of milk samples from 22 sero-positive mothers after delivery.

Next, concentrated fresh human milk cells obtained from carrier mothers were inoculated into the oral cavity of a common marmoset. The marmoset was found to be seroconverted 2.5 months after the first inoculation of the milk (3.5×10^8 total cells) (Fig. 6) and was confirmed to be infected with HTLV-I by the detection of viral antigen expression in short-term culture of its peripheral blood T lymphocytes.

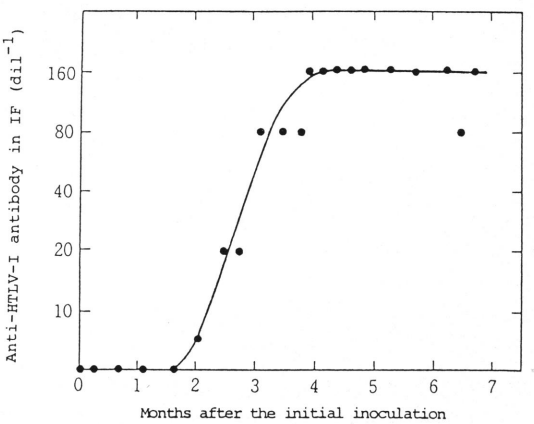

Fig. 6. Anti-HTLV-I antibody titers of the marmoset inoculated with fresh human milk from carrier mothers.

Furthermore, in human experience, positive rate of anti-HTLV-I antibody in mothers blood of HTLV-I carrier children showed very high rate as shown in table 2.

These facts strongly suggest that mothers milk-born infection is one of the important

Table 2. Positive rate of anti-HTLV-I antibody in mothers of carrier children

positives/tested (%)
12/13 (93%)

rout of HTLV-I infection.

Of 187 antibody-positive pregnant women, heparinized cord blood samples were obtained from 115 deliveries. All but two were positive for anti-HTLV-I antibody of IgG class. None of the cord blood samples showed antibody activity of IgM class, and ATLA (antigen)-bearing lymphocytes after shrot-term culture up to 4 weeks. Therefore, infection via cord blood was deniable.

Infection due to blood transfusion. :The anti-HTLV-I antibody positive rate in acute myelogenous leukemia and aplastic anemia was relatively high in Nagasaki district, and the positive rate was much higher in those with a history of blood transfusion.

Analysis of sera from the patient who changed to positive anti-HTLV-I antibody by blood transfusion revealed transient developement of the IgM antibody and then a gradual increase of the IgG antibody titer after transfusion [8]. (Fig. 7)

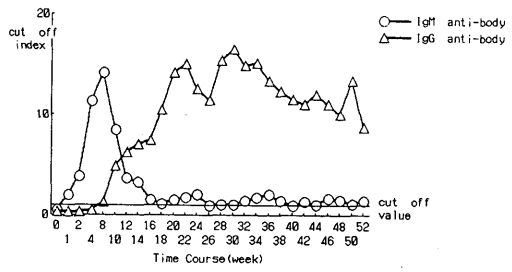

Fig. 7. The time course of development of IgG and IgM anti-ATLA antibodies in a recipient transfused unscreened blood products.

These data showed blood transfusion from H TLV-I carrier is another rout of HTLV-I infection.

Epidemiological study of HTLV-I carrier revealed 5-10% of the adult in Nagasaki prefecture are positive for anti-HTLV-I antibody [6].

Seroconversion following transfusion of random blood products before screening was observed in 45 of 84 recipients (53.6%) in Nagasaki. However, transfusion of selected blood products after screening of HTLV-I resulted in seroconversion in only 1 out of 148 recipients (0.9%)[7]. (Tab. 3)

Table 3. Seroconversion before and after screening by the PA test

	Number of follow-up patients	Seroconversive patients	
		n	%
Mass screening			
Before	84	45	53.6
After	108	1	0.9

On the other hand, we have begun a campaign to stop giving carrier mothers milk to their children for prevention of mother milk-born infection.

TREATMENT OF ATL

ATL is a malignancy of helper T-cell. Therefore, combination chemotherapy for lymphoid malignancy is first choice. Usually, acute ATL is treated with VEPA (vincristine, cyclophosphamide, prednisolone, adriamicin) therapy. Interferon- α, VP-16, cis-platinum and deoxycoformysin have showed responce in some cases. Various infections esp, opportunistic infection and hypercalcemia are unpleasant complications.

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