RAPID COMMUNICATION Jpn. J. Cancer Res. 80, 401–404, May 1989

Adult T-cell Leukemia in Spouses

Isao Sanada,[1,5] Kazunari Yamaguchi,[2] Mitsuaki Yoshida.[3] Toshinori Ishii,[4] Atsuko Tsukamoto,[1] Masahiko Sato,[1] Shin-ichiro Obata[1] and Tadahiro Shido[1]

[1]Department of Internal Medicine, Kumamoto National Hospital, 1-5 Ninomaru, Kumamoto 860, [2]Blood Transfusion Service, Kumamoto University Medical School, Honjo 1-1-1, Kumamoto 860, [3]Department of Viral Oncology, Cancer Institute, Kami-Ikebukuro 1-37-1, Toshima-ku, Tokyo 170 and [4]Department of Medical Technology, College of Medical Science, Kumamoto University, Kuhonji 4-24-1, Kumamoto 862

A married couple who developed adult T-cell leukemia (ATL) is described. The husband presented with acute ATL and died soon after admission in spite of aggressive chemotherapy, and his wife, who is diagnosed as smoldering ATL, has been followed in the out-patient clinic. The couple had serum antibodies against human T-cell leukemia virus type I (HTLV-I) and the monoclonal integration of HTLV-I proviral DNA in their lymphocytes. The patients described represent the first reported example of ATL in a married couple.

Key words: Adult T-cell leukemia — Familial occurrence — Horizontal transmission of HTLV-I — HTLV-I

Human T-cell leukemia virus type I (HTLV-I) has been isolated from ATL cell line[1] and serum antibodies against HTLV-I[2] have been detected in all patients with ATL. Further, not only the geographic clustering of ATL patients[3] but also the familial occurrence of ATL[4–10] and the prevalence of HTLV-I infection within the family members of patients[4–12] have been pointed out. However, as far as we know, no examples of husband-wife familial ATL have been reported, though the positive rate of anti HTLV-I antibodies in the spouses of patients with ATL, is higher than those in siblings and/or children of patients.[4,5] The case report presented here describes new findings between the time of HTLV-I infection and the occurrence of ATL.

Case 1. A 55-year-old man, who had been born in Ushibuka city, Kumamoto prefecture, Kyushu, Japan and had moved to Minamata city in the same prefecture at the age of 20 and there had married a woman from Minamata at the age of 22. It was not an intermarriage. He was admitted to our hospital on May 19, 1988 because of general fatigue and left hypochondralgia lasting about one month. He had no history of blood transfusion. On physical examination, he had moderate hepatosplenomegaly and slight icteric bulbar conjunctiva. Hematologic examinations demonstrated a white blood cell count (WBC) of 91.1×10^9/liter, Hb of 12.2 g/dl and platelet count of 33.0×10^9/liter. The differential analysis of WBC demonstrated 90% of ATL cells having the typical flower-like nuclei (Fig. 1A). Anti HTLV-I antibodies were positive, more than 1:8162 by means of the particle agglutination test (PA test) (Serdia-ATLA, Fujirebio, Inc., Tokyo), and HTLV-I proviral DNA in lymphocytes was proved to be monoclonal (Fig. 2). Blood chemistry showed total bilirubin of 2.8 mg/dl, GOT 955 U, GPT 371 U and LDH 619 IU/liter. The lymphocyte surface marker study (Table I) revealed OKT4+, OKT8−, OKT11+, mean channel of OKT3 FI (fluorescence intensity of OKT3-positive cells) of 38.5 and HLA-DR in OKT4 of 18.0%, characteristic of acute-type ATL.[13] He received combined chemotherapy including epi-adriamycin, cyclophosphamide, vincristine and prednisolone. White blood cell count decreased abruptly. Jaundice, however, increased to total bilirubin of 32.6 mg/dl while the titer of other liver enzymes improved. The patient died on July 17, 1988. Necropsy of the liver revealed submassive necrosis but no infiltration of ATL cells. On admission, a family study was also performed (Fig. 3). His wife, son and daughter were positive for anti HTLV-I antibody, 1:256, 1:256 and 1:512 by PA test, respectively. The third son of his daughter was also positive; the origin might have been his mother's serum, because he was just 4 months old and had been fed only with artificial milk.

Case 2. A 55-year-old woman, the wife of case 1, had WBC of $9.2–10.2\times10^9$/liter with 43–39% lymphocytes, of which less than 1% were judged as characteristic abnormal lymphocytes of smoldering ATL[14,15] (Fig. 1B). Her lymphocytes phenotypically showed a mean channel of OKT3 FI of 83.1, and HLA-DR in OKT4 of 18.0%.[13] She had been suffering from hypertension and diabetes mellitus, but had never received any blood transfusion. Blood chemistry showed hyperlipemia and hyper-

[5] To whom correspondence should be addressed.

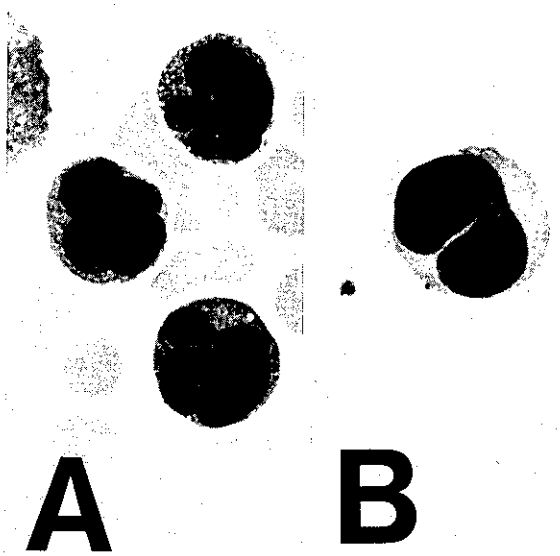

Fig. 1. A. Peripheral blood of case 1, showing typical acute ATL cells with multilobulated nuclear contour (Wright stain, ×1000). B. An abnormal lymphoid cell in the peripheral blood of case 2, showing mature nucleus with convolution and lobulation (Wright stain, ×1000).

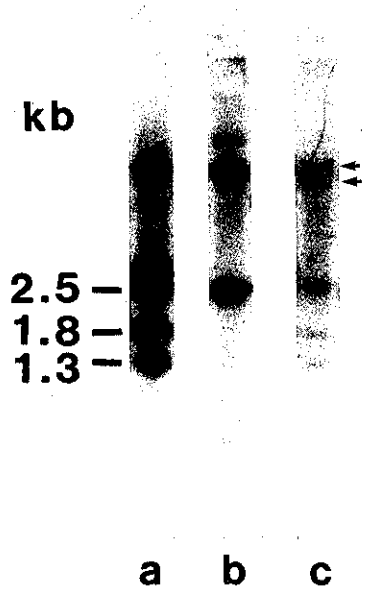

Fig. 2. Monoclonal integration of HTLV-I proviral DNA. DNA samples from fresh peripheral lymphocytes were digested with *Pst* I and subjected to Southern blot analysis using representative proviral ^{32}P-DNA as the probe. When the cellular DNA was digested with *Pst* I, which cleaves several sites in the HTLV-I provirus genome, lane a (typical ATL sample as a control) showed two clear bands containing viral-cellular DNA in addition to the three internal fragments 2.5, 1.8 and 1.3 kb (monoclonal and complete). Lane b (acute ATL, case 1) shows the monoclonal integration of HTLV-I proviral DNA of defective type with no detection of 1.8 and 1.3 kb internal fragments. Lane c (smoldering ATL, case 2) showed two bands (indicated by two arrows) other than the three internal fragments (monoclonal and probably complete).

uricemia suggestive of her past history and hypergammaglobulinemia (25.5% of total protein, 2.01 g/dl) of undetermined cause. Blot analysis of DNA from peripheral blood lymphocytes is shown in Fig. 2. The presence of two bands over 2.5 kb indicates a monoclonal expansion of an infected cell. These bands with high molecular weight should not be due to partial digestion with *Pst* I or mutation at one of the *Pst* I sites, because increasing doses of *Pst* I gave essentially the same results and a mutation at a single *Pst* I site can not explain the presence of two bands over 2.5 kb together with two bands of 1.8 and 1.3 kb. Thus, the diagnosis of smoldering ATL was confirmed.[16,17] She has been strictly followed up in the out-patient clinic.

Familial ATL has been reported in the southwestern district of Japan[4–9] as well as in the United States.[10] Ichimaru *et al.*,[4] who reviewed a large number of cases with familial ATL, found that the intrafamilial aggregation of ATL was limited to siblings and/or parent-child; no case of hasband-wife ATL had been reported. Therefore, they concluded it was unlikely that an individual, who suffered from HTLV-I infection during adulthood, would develop ATL. Seroepidemiological studies revealed two natural routes of HTLV-I transmission: the first, from mothers to children (vertical transmission via breast milk),[18] the second, from husband to wife (horizontal transmission),[3] or, though less likely, from wife to husband. Thus, it appears most likely that this husband, who had been infected with HTLV-I in his childhood, may have transmitted the virus to his wife sexually during marriage and after a long latent period, possibly involving the effects of promoter(s) through the intermediate stage,[19] the husband may have developed acute ATL, and his wife's lymphocytes infected with the virus may have acquired the monoclonality. The second possibility is that the transmission of HTLV-I may have occurred from wife to husband. Therefore, even individuals horizontally infected with HTLV-I by blood transfusion[20] or sexual contact,[3] must be strictly followed up for the possible development of ATL after a long period. However, we cannot exclude the possibility that this couple may have already been independently infected

with HTLV-I in their childhood before marriage, because they were both from the endemic areas of ATL (the positive rates of anti HTLV-I antibody among adult inhabitants in Ushibuka and Minamata are 7.1% and 2.7%, respectively[21]). That is to say, statistically it is possible to find ATL in both wife and husband who had been independently infected by HTLV-I. However, this possibility should be very low (0.0025 to 0.01%), since only 0.5 to 1% of HTLV-I carriers will get ATL in their lifetime. And, since more than 80% of wives with anti HTLV-I antibody-positive husbands over age 40 were infected with HTLV-I,[22] it follows that there are more wives infected with HTLV-I after marriage who are likely to get ATL in old age, if the development of ATL depends merely on the length of the incubation period of HTLV-I infection. Therefore, in the case of this couple, the possibility that the wife had been infected with HTLV-I after marriage from the anti HTLV-I antibody-positive husband should be about 30 times more probable than that she had already been positive for anti HTLV-I antibody before marriage. Further studies on familial ATL, for example, determination of the DNA sequences of HTLV-I proviral DNA, are needed to rule out the third possibility mentioned above.

Table I. Phenotypic Analysis of Peripheral Blood Mononuclear Cells from Two Patients

Antigens	Case 1	Case 2	Healthy control[h]
OKT3(CD3)[a]	NT[g]	75.1%	67.1±2.4%(74)
OKT4(CD4)[a]	94.8%	55.9%	40.6±1.7%(74)
OKT8(CD8)[a]	2.3%	19.7%	28.1±1.7%(74)
OKT11(CD2)[a]	98.9%	87.8%	79.2±1.7%(74)
B1(CD20)[b]	NT	5.3%	9.4±1.1%(33)
HLA-DR[c]	11.7%	27.2%	22.2±2.5%(33)
Tac(CD25)[d]	76.1%	11.3%	4.8±1.2%(17)
MC of OKT3·FI[e]	38.5%	83.1%	106.5±4.4%(74)
HLA-DR in OKT4[f]	8.3%	18.0%	12.8±2.0%(26)

Cells were analyzed for fluorescence staining by laser flow cytometry (Spectrum III, Ortho Diagnostics). The results were expressed as percentage of positive cells.
Reagents were obtained from: *a*) Ortho Diagnostics, Westwood, MA; *b*) Coulter Immunology, Hialeath, FL; *c*) Becton-Dickinson, Mountain View, CA; *d*) Dr. T. Uchiyama.
e) Mean channel of fluorescence intensity of OKT3-positive cells.
f) Percentage of HLA-DR-positive cells in OKT4-positive cells.
g) Not tested.
h) Mean±2 SEM (number of samples).

This work was supported by Grants-in-Aid for Cancer Research from the Ministry of Education, Science and Culture, Japan and the Ministry of Health and Welfare, Japan. The authors are grateful to Prof. K. Takatsuki, the Second Department of Internal Medicine, Kumamoto University Medical School, for his helpful criticism during the preparation of the manuscript and to Mr. T. Murakami, Mr. R. Tominaga, Mr. H. Jyogo and Ms. M. Yoshikawa for their excellent technical assistance.

(Received January 5, 1989/Accepted March 25, 1989)

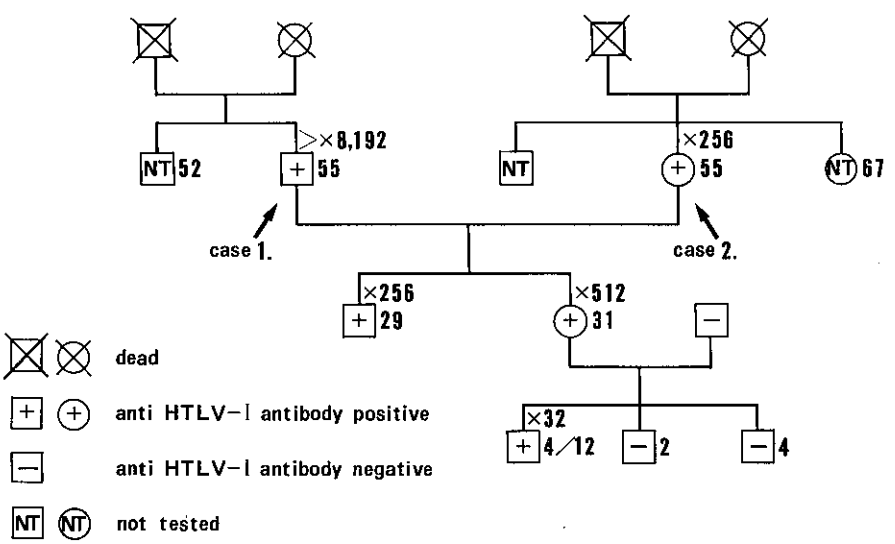

Fig. 3. Pedigree of the family and anti HTLV-I antibody titer. The numbers above and to the upper right indicate the antibody titer value and the numbers to the right indicate the age of the individuals.

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