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Original Article

A Family Predisposition to Adult T-Cell Leukemia

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We report here the rare case of a family predisposed to adult T-cell leukemia (ATL). Six of seven siblings developed ATL with ages of onset of 77, 48, 60, 64, 72, and 62 years old. Although virological tests for human T-lymphotropic virus type 1 were unavailable for two of the six patients, all were diagnosed with ATL based on their clinical, hematological, and histopathological features. Two of the six patients were tested for HLA haplotypes using fresh blood samples, and both were carriers of the HLA-A*26 allele known in the southern Japanese population to be susceptible to ATL. This series of genetic traits may help explain the familial predisposition to ATL. 〔*J Clin Exp Hematopathol 46(2) : 67-71, 2006*〕

Keywords: adult T-cell leukemia, familial ATL, HTLV-1, HLA allele

INTRODUCTION

Adult T-cell leukemia (ATL) is a T-cell neoplasia with specific clinical and epidemiological features, such as circulating leukemia cells with peculiar nuclear polymorphisms (convoluted or lobulated nuclei), lymphadenopathy, hepatosplenomegaly, skin manifestation, hypercalcemia, and a specific geographic distribution[1-3]. Human T-lymphotropic virus type 1 (HTLV-1) is the causative of ATL[4-6] and is transmitted within families from mothers to infants via breast-feeding and between spouses via sexual intercourse[7]. The infection rate of children of HTLV-1 carrier mothers is estimated at 10-30%[8], and the HTLV-1 seropositivity rate is as high as 65% in ATL related siblings[9,10]. Although a high incidence of familial clusters of ATL would therefore be expected, few family pedigrees of ATL have been discovered in which 2 of 4-7 siblings from a single family developed ATL[11-13]. We report here a rare case of highly accumulated familial ATL that exhibits the HLA alleles and haplotypes conferring susceptibility to ATL.

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DIAGNOSTIC CRITERIA FOR ATL

ATL was diagnosed according to the criteria of the Japanese Lymphoma Study Group organized by Shimoyama *et al*[14]. These criteria were the following : (i) histologically and/or cytologically proven lymphoid malignancy with T-cell surface antigens ; (ii) abnormal T-lymphocytes present in the peripheral blood, except lymphoma type. Abnormal T-lymphocytes include both typical ATL called "flower cells," and the small and mature T-lymphocytes with incised nuclei that are characteristic of chronic and smoldering type ATL ; (iii) antibodies to HTLV-1 present in the sera at the time of diagnosis. ATL clinical subtypes were also classified according to the criteria of the Japanese Lymphoma Study Group[14].

CASE REPORT

Case 1 (Sibling 1, the proband) was a 77-year-old woman who developed swelling of the peripheral lymph nodes (LNs) and skin lesions in November 1989. Her white blood cell count (WBC) was 100 x 10^9/L and 95% of these were abnormal lymphocytes ($CD3^+CD4^+CD8^-$) with convoluted or lobulated nuclei (Fig. 1A). Examination of her LNs revealed diffuse, pleomorphic type non-Hodgkin's lymphoma (NHL). The lymphoma cells were positive for CD2, CD3, CD4, CD25, and CD30, but not CD8. A serological test for anti-HTLV-1 antibodies was positive and the antibody titer was useful at greater than a 40-fold dilution in an immunofluorescence (IF) assay. Based on these results, she was diagnosed with ATL and treated with cyclophosphamide, vindesine, and prednisolone. She went into partial remission but

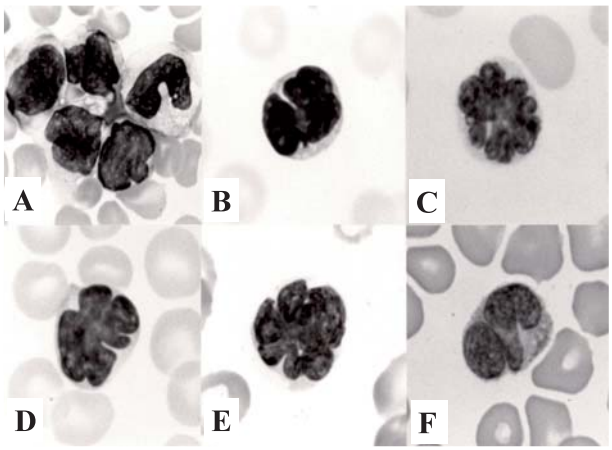

Fig. 1. Abnormal circulating lymphocytes with convoluted or lobulated nuclei. A, Sibling 1 (Case 1) ; B, Sibling 2 (Case 5) ; C, Sibling 4 (Case 3) ; D, Sibling 5 (Case 4) ; E, Sibling 6 (Case 6) ; F, Sibling 7 (Case 2). All images are of May-Giemsa stains, x1000.

later died of tumor progression. Her survival period was 17 months after beginning chemotherapy. According to her family history, five of her six siblings had hematological malignancies diagnosed as either lymphoma or leukemia. Hematological malignancies containing ATL, however, were not recognized in the other relatives.

Case 2 (Sibling 7) was a 48-year-old man admitted to our hospital in 1978 due to coughing and dyspnea. He had lymphadenopathy and a WBC count of 49.6 x 10^9/L, 90% of which were abnormal lymphocytes with convoluted nuclei (Fig. 1F). As the concept of ATL was unknown in 1978, he was diagnosed with leukemic reticulosarcoma. The typical morphological features of ATL cells found during our review of his peripheral blood specimen caused us to strongly suspect ATL. However, he was treated with combination chemotherapy and died three months after diagnosis. His cause of death was listed as unknown.

Case 3 (Sibling 4) was a 60-year-old woman with swelling of her peripheral LNs and a large number of abnormal lymphocytes with convoluted nuclei in her blood in 1982 (Fig. 1C). Examination of her LNs revealed NHL of diffuse, medium cell type. The surface phenotype of her lymphoma cells was found to be that of T cells by immunohistochemical staining with monoclonal antibodies for UCHL-1, MT-1, and DF-T1. A test for anti-HTLV-1 antibodies was not performed, and her survival period after chemotherapy was three months. Her cause of death was also unknown.

Case 4 (Sibling 5) was a 64-year-old woman with swelling of her cervical LNs in February 1988. She developed multiple skin tumors throughout her clinical course. Her WBC count was 7.7 x 10^9/L, of which 33% were abnormal lymphocytes with convoluted nuclei (Fig. 1D). Examination of the skin tumors revealed NHL of diffuse, pleomorphic type. The lymphoma cells stained positively for CD2, CD4, CD25, and CD30. A serological test for HTLV-1 antibodies was positive. She died of septicemia, and her survival period after chemotherapy was nine months.

Case 5 (Sibling 2) was a 72-year-old woman who noticed swelling of her cervical and inguinal LNs in July 1988. Her WBC count was 3.2 x 10^9/L, 10% of which were abnormal lymphocytes with indented nuclei (Fig. 1B). Examination of her LNs showed diffuse, pleomorphic type NHL. The surface phenotype of the lymphoma cells was that of T cells, according to immunohistochemical staining with monoclonal antibodies against UCHL-1, MT-1, and DF-T1. A serological test for HTLV-1 antibodies was positive, and the antibody titer was useful in an IF test at greater than an 80-fold dilution. She was diagnosed with ATL and treated with combination chemotherapy, but she died from tumor progression ten months after beginning chemotherapy.

Case 6 (Sibling 6) was a 62-year-old man with abdominal lymphadenopathy, ascites, and hypercalcemia in 1989. His WBC count was 68.7 x 10^9/L and 84% of these were abnormal lymphocytes with convoluted nuclei (Fig. 1E). Examination of his LNs showed NHL of diffuse, large cell type. The lymphoma cells had a T-cell phenotype, and he tested positively for anti-HTLV-1 antibodies in his serum. He was diagnosed with ATL and survived only three months after beginning chemotherapy. The cause of his death was unknown.

Sibling 3 had died during World War II at the age of 22.

The clinical signs and symptoms and the hematological and pathological findings of the six patients are summarized in Table 1.

Hematological and pathological examination of biopsy specimens

Abnormal circulating lymphocytes from the six cases are shown in Figure 1 (A to F). Convoluted and/or lobulated nuclei were present in all six cases.

The pathological findings of five cases showed diffuse proliferation of lymphoma cells. The surface phenotype of these lymphoma cells was found by immunohistochemical staining to be that of T cells (Table 1).

HLA allele types and haplotypes

The HLA alleles and haplotypes were examined in two (Siblings 1 and 5) of the seven siblings and in three blood relatives (one son and two grandchildren of Sibling 1). The HLA-A*, HLA-C*, HLA-B*, HLA-DRB1*, and HLA-DQB1* alleles were determined by the PCR-SSO method as previously described[15,16]. The patients' HLA haplotypes were inferred based on known patterns of linkage disequilibrium at five loci[17,18]. According to pattern analysis of the HLA alleles

of the ATL family members, specific allele types relating to ATL predisposition (HLA-A*26, B*4002, and B*4006)[16] were found in the ATL-affected patients (Fig. 2).

DISCUSSION

We report here a very rare familial predisposition to ATL. Although HTLV-1 tests for Siblings 4 and 7 and surface phenotyping for leukemia cells in Sibling 7 were not performed, we were able to diagnose ATL in all six patients, including Siblings 4 and 7, based on their specific clinical characteristics and blood cytologies. HTLV-1 is the causative agent of ATL[4-6], and vertical transmission from mother to child via HTLV-1-infected lymphocytes in breast milk is a major route of infection[19-21]. The overall infection rate of children by HTLV-1 carrier mothers in Southern Japan is estimated at 10-30%[8]. Furthermore, the HTLV-1 seropositivity rate of family members of ATL sufferers is about 50%[9], and the rate for their siblings is as high as 65%[9,10]. This evidence suggests that the mother of siblings reported here was probably infected by HTLV-1 and that the virus transmitted vertically to the siblings. The high rate of HTLV-1 infection in this family might have related to a high viral load in the breast milk, or an HLA allele-based susceptibility to

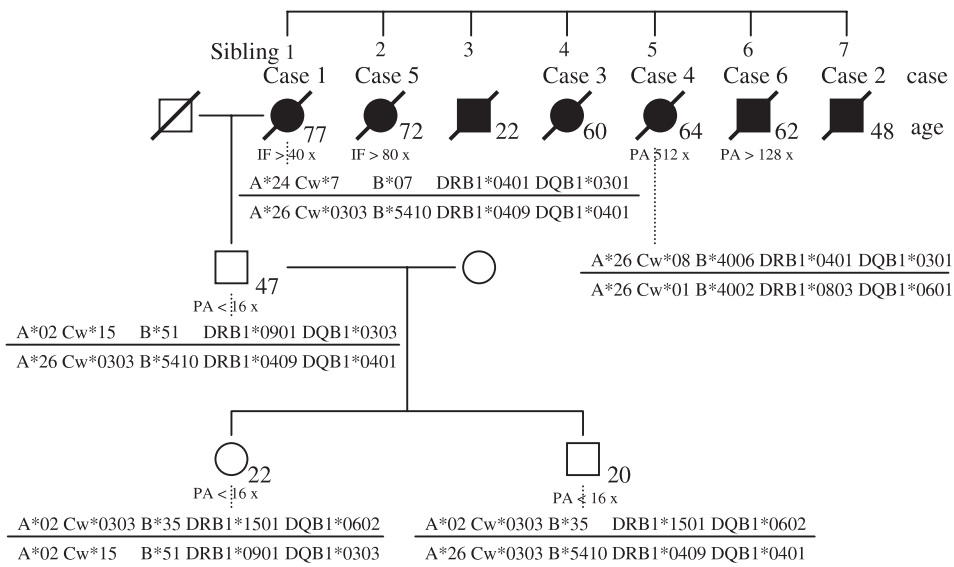

Fig. 2. Family pedigree showing HLA haplotypes predisposed to ATL. Siblings 1, 2, 4, 5, 6, and 7 died of ATL, while Sibling 3 died in World War II. IF, immunofluorescence ; PA, gelatin particle agglutination.

Table 1. Hematological and pathological findings of familial ATL cases

Order of siblings	WBC (× 10^9/ L)	Abnormal lymphocyte (%)	Age at onset	Sex	Subtype of ATL	Pathological diagnosis (LN)	Surface phenotype	anti-HTLV-1
1 (case 1)	100	95	77	F	Acute	Diffuse, pleomorphic	CD3(+) CD4(+), CD25(+)(PB, LN)	> 40 × (IF)
2 (case 5)	3.3	10	72	F	Acute	Diffuse, pleomorphic	UCHL-1(+) MT-1(+), DF-T1(+) (LN)	> 80 × (IF)
4 (case 3)	LOI	LOI	60	F	Acute	Diffuse, pleomorphic	UCHL-1(+), MT-1(+), DF-T1(+) (LN)	NT
5 (case 4)	7.7	33	64	F	Acute	Diffuse, pleomorphic	CD4(+), CD25(+) (skin)	512 × (PA)
6 (case 6)	68.7	84	62	M	Acute	Diffuse, pleomorphic	UCHL-1(+) (LN)	> 128 × (PA)
7 (case 2)	49.6	90	48	M	Acute	NT	NT	NT

LOI : lack of information, NT : not tested, PB : peripheral blood, LN : lymph node, IF : immunofluorescence method, PA : gelatin particle agglutination method

HTLV-1 in all six siblings. We previously reported that the annual incidence of ATL in Kyusyu was 0.60, based on studies of 1,000 HTLV-1 carriers over 20 years old[8]. Hisada *et al*. reported that HTLV-1 carriers with a higher anti-HTLV-1 titer and a lower anti-Tax reactivity might be at an increased risk for ATL[22]. We could not, of course, examine the anti-HTLV-1 titers or anti-Tax reactivities in our patients before the onset of ATL. In regard to the genetic risk for ATL, we also reported a relationship between specific HLA alleles and a predisposition to ATL[16]. We demonstrated that lower reactivity of anti-Tax cytotoxic T lymphocytes is associated with the HLA-A*26, B*4002, and B*4006 alleles, and higher reactivity is associated with the HLA-A*24 alleles[16]. Although HLA haplotypes were examined in only two cases of this family (Siblings 1 and 5), they both had HLA-A*26 alleles. The haplotypes of Siblings 1 and 5 are exclusive, as Sibling 1 has one A*26+haplotype and Sibling 5 has two A*26+haplotypes. From this distribution of HLA haplotypes, one of their parents should be homozygous for A*26+/A*26+, as 50% of the children had homozygous A*26+haplotypes. The A*26+haplotype carriers are low responders against HTLV-1-Tax antigen and are susceptible to HTLV-1 infection and ATL manifestation. This rare family, with six of seven siblings diagnosed with ATL, is predisposed by the ATL-susceptible HLA-A*26 gene, and consequently the risk of ATL was extremely high.

On the other hand, the HTLV-1 viral factor might relate to the incidence of ATL in the patients reported here. Furukawa *et al*. reported that the phylogenetic subgroup of HTLV-1 in the *tax* gene was associated with the occurrence of HTLV-1-associated myelopathy/ tropical spastic paraparesis, but not with the incidence of ATL[23]. We could not examine the *tax* sequence in our ATL patients, so there might be a relationship between HTLV-1 subgroup, *tax* mutation, deletion, and the incidence of ATL.

In conclusion, immunogenetic features—including specific HLA alleles—may be related to this family's high predisposition to ATL. To our knowledge, this is the most significant ATL cluster in a single family yet reported - a cluster in which six of seven siblings developed ATL.

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