Mini Review

Natural history of human T-lymphotropic virus type 1 infection and immune system imbalances

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The human T-lymphotropic virus type 1 (HTLV-1) is the causative agent of adult T-cell leukemia/lymphoma (ATL) and HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP). In addition, increased incidences of infectious diseases, autoimmune diseases, chronic inflammatory diseases and virus-associated malignancies have been reported in HTLV-1 carriers. HTLV-1 infection causes the continuous activation and clonal expansion of T cells. The levels of regulatory T cells and naïve T-cells are decreased in the peripheral blood of asymptomatic carriers. Spontaneous proliferation of peripheral blood mononuclear cells and subclinical deficiencies in both type 1 and type 2 immunity are also observed. It is possible that the immune system imbalances seen in HTLV-1 infection account for the disease manifestations described above, although the precise mechanism remains unclear.

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Introduction

The human T-lymphotropic virus type 1 (HTLV-1) has been shown to be a causative agent of adult T-cell leukemia/lymphoma (ATL), one of the most aggressive hematological malignant diseases[1,2]. The mechanism of leukemogenesis has not yet been determined; however, monoclonal expansion of T-cells with the provirus integrated into the genome is essential. HTLV-1 also causes the progressive neurological disease known as HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP)[3]. Infiltration of mononuclear cells into the spinal cord with an increased level of proviral loads in the peripheral load is observed in patients with HAM/TSP. Polyclonal expansion of HTLV-1 positive cells in the peripheral blood is also seen. Therefore, HTLV-1 causes two different types of disease in humans; namely, lymphocytic malignancy and non-malignant disease. In addition, there is evidence that HTLV-1 infection contributes to a broader spectrum of diseases, such as uveitis, arthropathy, polymyositis, pneumonitis, and infective dermatitis in children

Table 1 Diseases reported to be associated with HTLV-1 infection

Adult T-cell leukemia/lymphoma
HTLV-1-associated myelopathy/tropical spastic paraparesis
HTLV-1-associated uveitis
Infectious diseases
Infective dermatitis (children)
Strongyloidiasis
Autoimmune diseases/Chronic inflammatory diseases
Polymiositis
Sjogren's syndrome
Arthropathy
Pneumonitis
Virus-associated malignancies
Hepatitis C virus infection-associated hepatocellular carcinoma

(Table 1)[4-9]. HTLV-1 infection also increases the risk of Strongyloides stercoralis infection and hepatocellular carcinoma due to hepatitis C virus infection[10,11]. In this mini-review, immune abnormality due to HTLV-1 infection and its possible connection to the development of HTLV-1-associated diseases among asymptomatic carriers are discussed.

HTLV-1 infection

HTLV-1 transmission is mediated by live cells and not via cell-free body fluids[12]. The RNA genome undergoes reverse transcription into a DNA provirus that is integrated into the host genome[13]. HTLV-1 growth and propagation are supported primarily by CD4+ cells. One of the key regulatory elements of HTLV-1 replication is the Tax protein, which activates transcription of the viral genome[14]. HTLV-1 Tax protein has also been shown to promote the proliferation of infected cells and to be a good target for the host cellular immune response to the virus[14,15].

The major natural routes of infection of HTLV-1 are from mother to infant and sexual contact[16]. Blood transfusion was once a route of HTLV-1 infection; however, the efficient screening of blood products has prevented new infection thus far[17]. Therefore, when we find a middle-aged person who tests positive for HTLV-1, he or she may have been infected from his/her mother while in infancy or from his/her spouse or blood products after reaching adulthood. Identifying the infection route is important because ATL appears to develop primarily in persons who acquire HTLV-1 perinatally, whereas HAM/TSP is associated with exposure to HTLV-I later in life[18].

Asymptomatic carriers are positive for HTLV-1 antibody. The peripheral blood mononuclear cells (PBMCs), primarily CD4 positive T-cells, harbor HTLV-1 provirus[19]. The level of proviral load is likely determined within a year of infection[20]. The development of a humoral and, probably, cellular immune response to virus occurs during this period. The nature of the host immune response may affect the burden of HTLV-1, which varies widely among asymptomatic carriers[21]. Most individuals infected with HTLV-1 develop into asymptomatic carriers with low proviral loads; however, some develop into carriers with high proviral loads[20]. Proviral load appears to remain stable, once a set point has been achieved[20, 22]. The maintenance of the level of proviral load seems largely due to the relationship between the clonal expansion of HTLV-1-infected cells and the immune response to them[22-24].

Phenotypic change of T cells and immune dysfunction in HTLV-1 infection

The phenotypic changes of T-cells, which have been reported thus far, are described in Table 2. HTLV-1 infection has been shown to cause the expression of activation markers, such as interleukin-2 (IL-2) receptor, in T-cells[14]. HTLV-1 Tax has been reported to activate the promoter for IL-2 and IL-2 receptor[14]. Proliferation of unstimulated PBMCs in cell culture without interleukin 2 is observed in the HTLV-1 carriers (spontaneous proliferation)[25]. Spontaneous proliferation of PBMCs from HTLV-1 carriers is due to the polyclonal expansion of cells and correlates directly with the expression of viral genes such as Tax[26]. Activated T cells infected with HTLV-1 may subsequently activate resting T-cells through interaction among T cells.

Changes in circulating leukocytes, specifically an increase in the percentage of lymphocytes and a decrease in the percentage of eosinophils and basophils, have been reported in asymptomatic HTLV-1 carriers[27]. CD4+ and CD25+ cell levels were also shown to be increased among asymptomatic carriers[28]. The largest increase was seen in asymptomatic carriers whose peripheral blood smears were positive for atypical lymphocytes.

Recently, CD4+CD25+ cells were reported to be the surface phenotype of regulatory T-cells (Treg)[29]. The majority of CD4+ CD25+T cells were positive for Foxp3, a master gene for Treg, in normal individuals[30]. Increased expression of Foxp3 was reported in ATL cells[31]. However, not all CD4+CD25+T cells in the asymptomatic HTLV-1carriers were reported to be positive for the expression of Foxp3. In another words, CD4+ CD25+T cells in HTLV-1 carriers were inconsistently composed of the

Table 2 Abnormalities of immune system reported in HTLV-1 asymptomatic carriers

Continuous activation of T-cells
Clonal expansion of certain population of T-cells
Change of the level of regulatory T-cells
Decreased level of naïve T-cells
Spontaneous proliferation of peripheral blood mononuclear cells
Increased level of CD4+CD25+T-cells
Decreased reaction to recall antigen
Decreased level of serum IgE

two populations with and without Foxp3, suggesting that the former are Treg and that the latter are either activated T cells or aberrant Treg downregulating Foxp3 expression. Foxp3 expression in CD4+CD25+T cells from HAM/TSP patients was reported to be lower than that from HTLV-1 negative individuals[32]. Moreover, HTLV-1 Tax was shown to have a direct inhibitory effect on Foxp3 expression and the function of CD4+CD25+T cells. It was suggested that the imbalance of CD25 and Foxp3 expression in asymptomatic carriers is closely related to HTLV-1 infection. This modulation of Foxp3 in asymptomatic carriers may be causatively implicated in the autoimmune-like diseases in HTLV-1 infection.

In addition to HTLV-1 Tax, expression of HTLV-1 HBZ, which is transcribed from 3'LTR, has been shown to promote the proliferation of infected cells[33]. It has been postulated that clonal proliferation of HTLV-1-infected cells is likely responsible for maintaining proviral loads in carriers. Expansion of certain clones of HTLV-1-infected cells is frequently observed in asymptomatic carriers[34]. In a particular case, only one clone of HTLV-1 infected cells occupied almost 1% of the total PBMCs in the asymptomatic carrier[35]. This abnormal growth of certain T-cells due to HTLV-1 infection, especially in asymptomatic carriers with high proviral loads, may cause the immune system imbalance. In addition, the number of naïve T cells was reported to be low in the HTLV-1 carriers[36]. It was suggested that the low number of naïve T-cells was due to the suppressed production of T-cells in the thymus, which may account for the immunodeficiency observed in HTLV-1 infection.

HTLV-1 carriers have been shown to have a reduced response to recall antigens. For example, we previously showed that asymptomatic carriers had a significantly reduced delayed-type hypersensitivity response to purified protein derivative skin testing[37]. The reduced response to recall antigens was shown to be more evident in the HTLV-1 carriers who show a spontaneous proliferation of PBMCs[38]. HTLV-1 carriers were also shown to have lower levels of IgE and may have subclinical deficiencies in both type 1 and type 2 immunity[39]. Indeed, when the relationship between strongyloidiasis and HTLV-1 infection was evaluated in Okinawa, Japan, serum IgE levels and peripheral eosinophil counts were significantly lower in HTLV-1 co-infected patients compared with patients without HTLV-1 infection[40]. A low frequency of atopy among HTLV-1 carriers was also reported in Brazil[41].

The natural history of HTLV-1 infection and disease manifestations

A hypothesis for the natural history of HTLV-1 infection and its association of disease manifestations is shown in Figure 1. The major infection routes of HTLV-1 are breast feeding by the mother during the child's infancy and between spouses after reaching adulthood. The level of HTLV-1 proviral load is likely determined within a year of infection and varies widely among asymptomatic carriers. The balance between the proliferation of HTLV-1-infected cells and the host immune response to them determines the proviral load, which remains stable, once a set point has been achieved. HTLV-1 carriers with low proviral loads may remain in an asymptomatic state for their entire lives. In case of the carriers with high proviral loads, continuous activation and clonal expansion of T cells due to HTLV-1 infection may occur frequently. Escape from the immune system and accumulation of genetic abnormalities may lead the clonally expanded T cells infected with HTLV-1 to the initial stage of ATL. Even in HTLV-1 carriers who do not develop ATL, decreased levels of regulatory T cells and naïve T-cells are observed in the peripheral blood. Spontaneous proliferation of PBMCs and subclinical deficiencies in both type 1 and type 2 immunity are also observed. These immune system imbalances may result in an increased incidence of opportunistic infections, autoimmune diseases, chronic inflammatory diseases and virus-associated malignancies in HTLV-1 infection.

However, there has been no direct evidence to connect HTLV-1 infection and opportunistic infections, autoimmune diseases, chronic inflammatory diseases and virus-associated malignancies. T-cell dysfunction may not be the only factor involved in the process of the immune deficiencies seen in HTLV-1 infection. Indeed, impairment of antigen-presenting cells or inability of PBMC from HTLV-1-infected individuals to respond to interleukin-12 might also account for the immunodeficiency

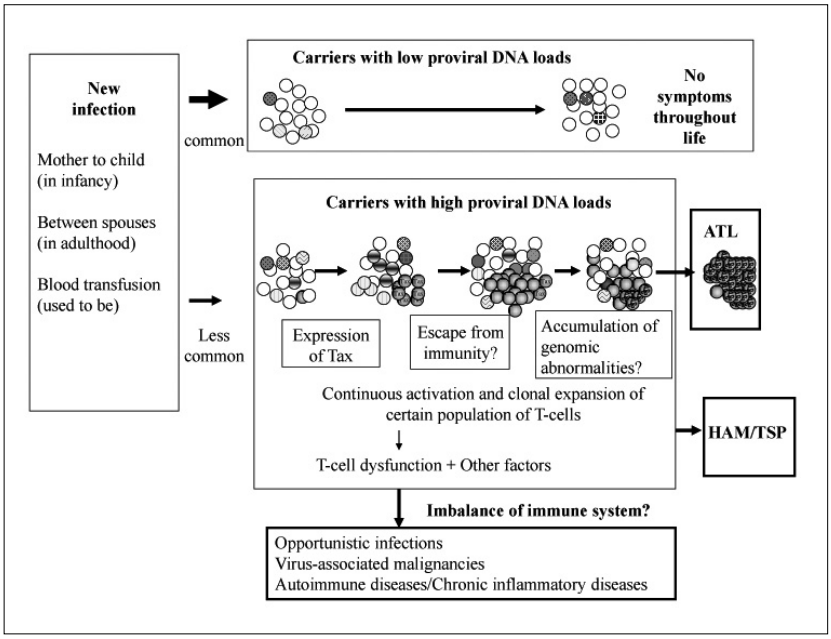

Fig.1 Natural history of human T-cell lymphotropic virus type 1 infection and possible association with the disease manifestations (hypothesis)

observed in HTLV-1 infection[42]. In addition, the natural history of HTLV-1 has been shown to differ markedly by geographic area, due in part to the host response to infection. For example, HTLV-1 infection was associated with diminished T-cell-mediated immunity in Japanese persons and with activated T-cell immunity in Jamaicans[43]. Markers of immune activation correlated more strongly with anti-HTLV-1 titers and provirus load in Jamaican than in Japanese individuals. Therefore, further studies are needed to clarify the mechanism of HTLV-1's contribution to the disease manifestations described above.

References

1) Poiesz BJ, Ruscetti FW, Gazdar AF, Bunn PA, Minna JD, Gallo RC: Detection and isolation of type-C retrovirus particles from fresh and cultured lymphocytes of patient with cutaneous T-cell lymphoma. Proc Natl Acad Sci USA, 7: 7415-7419, 1980.
2) Hinuma Y, Nagata K, Hanaoka M, et al: Adult T-cell leukemia: antigen in an ATL cell line and detection of antibodies to the antigen in human sera. Proc Natl Acad Sci USA, 78: 6476-6480, 1981.
3) Osame M, Usuku K, Izumo S, et al: HTLV-1 associated myelopathy, a new clinical entity. Lancet, 1: 1031-1032, 1986.
4) Mochizuki M, Yamaguchi K, Takatsuki K, Watanabe T, Mori S, Tajima K: HTLV-I and uveitis. Lancet, 339: 1110, 1992.
5) Ijichi, S, Matsuda T, Maruyama I, et al: Arthritis in a human T lymphotropic virus type I (HTLV-I) carrier. Ann Rheum Dis, 49: 718-721, 1990.
6) Nishioka K: HTLV-I arthropathy and Sjogren syndrome. J Acquir Immune Defic Syndr Hum Retrovirol, 13(Suppl 1): S57-S62, 1996.
7) Morgan OS, Rodgers-Johnson P, Mora C, Char G: HTLV-1 and polymyositis in Jamaica. Lancet, ii: 1184-1187, 1989.
8) Setoguchi, Y, Takahashi S, Nukiwa T, Kira S: Detection of human T-cell lymphotropic virus type I-related antibodies in patients with lymphocytic interstitial pneumonia. Am Rev Respir Dis, 144: 1361-1365, 1991.
9) LaGrenade L, Hanchard B, Fletcher V, Cranston B, Blattner W: Infective dermatitis of Jamaican children: a marker for HTLV-I infection. Lancet, 336: 1345-1347, 1990.
10) Robinson RD, Lindo JF, Neva FA, Gam AA, Vogel P, Terry SI, CooperES: Immunoepidemiologic studies of Strongyloides stercoralis and human T lymphotropic virus type I infections in Jamaica. J Infect Dis, 169: 692-696, 1994.
11) Okayama A, Maruyama T, Tachibana N, et al: Increased prevalence of HTLV-I infection in patients with hepatocellular carcinoma associated with hepatitis C virus. Jpn J Cancer Res, 86: 1-4, 1995.

12) Ishizaki J, Okayama A, Kuroki M, Tsubouchi H: Detection of human T-lymphotropic virus type I (HTLV-I) infection during coculture of HTLV-I infected and uninfected cells using inverse long PCR. Intervirology, 45: 164-71, 2002.
13) Yoshida M, Miyoshi I, Hinuma Y: Isolation and characterization of retrovirus from cell lines of human adult T-cell leukemia and its imolication in the disease. Proc Natl Acad Sci USA, 79: 2031-2035, 1982.
14) Yoshida M: Multiple viral strategies of HTLV-1 for dysregulation of cell growth control. Annu Rev Immunol, 19: 475-496, 2001.
15) Kannagi M, Matsushita S, Harada S: Expression of the target antigen for cytotoxic T lymphocytes on adult T-cell-leukemia cells. Int J Cancer, 54: 582-588, 1993.
16) Tajima K, Cartier L: Epidemiological features of HTLV-I and adult T cell leukemia. Intervirology, 38: 238-246, 1995.
17) Inaba S, Sato H, Okochi K, et al: Prevention of transmission of human T-lymphotropic virus type 1 (HTLV-1) through transfusion, by donor screening with antibody to the virus. One-year experience. Transfusion, 29: 7-11, 1989.
18) Bartholomew C, Jack N, Edwards J, et al: HTLV-I serostatus of mothers of patients with adult T-cell leukemia and HTLV-I-associated myelopathy/tropical spastic paraparesis. J Hum Virol, 302-305, 1998.
19) Uchiyama T: Human T cell leukemia virus type I (HTLV-I) and human diseases. Ann Rev Immunol, 15: 15-37, 1997.
20) Okayama A, Stuver S, Iga M, et al: Sequential change of viral markers in seroconverters with community-acquired infection of human T-lymphotropic virus type 1. J Infect Dis, 183: 1031-1037, 2001.
21) Etoh K, Yamaguchi K, Tokudome S, et al: Rapid quantification of HTLV-I provirus load: detection of monoclonal proliferation of HTLV-1 infected cells among blood donors. Int J Cancer, 81: 859-864, 1999.
22) Etoh K, Tamiya S, Yamaguchi K et al: Persistent clonal proliferation of human T-lymphotropic virus type I-infected cells in vivo. Cancer Res, 57: 4862-4867, 1997.
23) Cavrois M, Leclercq I, Gout O, et al: Persistent oligoclonal expansion of human T-cell leukemia virus type 1-infected circulating cells in patients with Tropical spastic paraparesis/HTLV-1 associated myelopathy. Oncogene, 17: 77-82, 1998.
24) Shimizu Y, Takamori A, Utsunomiya A, et al: Impaired Tax-specific T-cell responses with insufficient control of HTLV-1 in a subgroup of individuals at asymptomatic and smoldering stages. Cancer Sci, 100: 481-489, 2009.
25) Prince HE, York J, Owen SM, Lal RB: Spontaneous proliferation of memory (CD45RO+) and naive (CD45RO-) subsets of CD4 cells and CD8 cells in human T lymphotropic virus (HTLV) infection: distinctive patterns for HTLV-I versus HTLV-II. Clin Exp Immunol, 102:256-261, 1995.
26) Richardson JH, Höllsberg P, Windhagen A, Child LA, Hafler DA, Lever AM: Variable immortalizing potential and frequent virus latency in blood-derived T-cell clones infected with human T-cell leukemia virus type I. Blood, 89: 3303-3314, 1997.
27) Welles SL, Tachibana N, Orav EJ, Okayama A, Ishizaki J, Mueller NE: Changes in hematologic parameters among Japanese HTLV-I carriers. J Acquir Immune Defic Syndr, 7: 92-97, 1994.
28) Welles SL, Tachibana N, Okayama A et al: The distribution of T-cell subsets among HTLV-I carriers in Japan. J Acquir Immune Defic Syndr, 7: 509-516, 1994.
29) Sakaguchi S: Regulatory T cells: key controllers of immunologic self-tolerance. Cell, 101: 455-458, 2000.
30) Abe M, Uchihashi K, Kazuto T, et al: Foxp3 expression on normal and leukemic CD4+CD25+ T cells implicated in human T-cell leukemia virus type-1 is inconsistent with Treg cells. Eur J Haematol, 81: 209-217, 2008.
31) Kohno T, Yamada Y, Akamatsu N, et al: Possible origin of adult T-cell leukemia/lymphoma cells from human T lymphotropic virus type-1-infected regulatory T cells. Cancer Sci, 96: 527-533, 2005.
32) Yamano Y, Takenouchi N, Li HC, et al: Virus-induced dysfunction of CD4+CD25+ T cells in patients with HTLV-I-associated neuroimmunological disease. J Clin Invest, 115: 1361-1368, 2005.
33) Matsuoka M, Jeang KT: Human T-cell leukaemia virus type 1 (HTLV-1) infectivity and cellular transformation. Nat Rev Cancer, 7: 270-280, 2007
34) Tanaka G, Okayama A, Watanabe T et al: The clonal expansion of human T lymphotropic virus type 1-infected T cells: a comparison between seroconverters and long-term carriers. J Infect Dis, 191: 1140-1147, 2005.
35) Umeki K, Hisada M, Maloney ME, Hanchard B, Okayama A: Proviral, loads and clonal expansion of HTLV-1 infected cells following vertical transmission: A 10-year follow-up of children in Jamaica. Intervirology, 52: 115-122, 2009.
36) Yasunaga Ji, Sakai T, Nosaka K, et al: Impaired production of naive T lymphocytes in human T-cell leukemia virus type I-infected individuals: its implications in the immunodeficient state. Blood, 97: 3177-3183, 2001.

37) Murai K, Tachibana N, Shioiri S et al: Suppression of delayed-type hypersensitivity to PPD and PHA in elderly HTLV-I carriers. J Acquir Immune Defic Syndr, 3: 1006-1009, 1990.
38) Mascarenhas RE, Brodskyn C, Barbosa G, et al: Peripheral blood mononuclear cells from individuals infected with human T-cell lymphotropic virus type 1 have a reduced capacity to respond to recall antigens. Clin Vaccine Immunol, 13: 547-552, 2006.
39) Birmann BM, Mueller NE, Okayama A, et al: Patterns of serum type 1 and type 2 immune markers in healthy carriers of HTLV-I. J Med Virol, 78: 847-852, 2006.
40) Hirata T, Uchima N, Kishimoto K, et al: Impairment of host immune response against strongyloides stercoralis by human T cell lymphotropic virus type 1 infection. Am J Trop Med Hyg, 74: 246-249, 2006.
41) Souza-Machado A, Galvão TS, Porto A, Figueiredo J, Cruz AA: Skin reactivity to aeroallergens is reduced in human T-lymphotropic virus type I-infected healthy blood-donors (asymptomatic carriers). Allergy, 60: 379-384, 2005.
42) Suzuki M, Dezzutti CS, Okayama A, et al: Modulation of T-cell responses to a recall antigen in human T-cell leukemia virus type 1-infected individuals. Clin Diagn Lab Immunol, 6: 713-717, 1999.
43) Birmann BM, Breen EC, Stuver S, et al: Population differences in immune marker profiles associated with human T-lymphotropic virus type I infection in Japan and Jamaica. Int J Cancer, 124: 614-621, 2009.