Acta Med Okayama 43 (6) 317-321(1989)

— Review —

Immune Suppression in HTLV-I Carriers : A Predictive Sign of Adult T-Cell Leukemia

Hirokuni Taguchi* and Isao Miyoshi

Department of Internal Medicine, Kochi Medical School, Nankoku, Kochi 781-51, Japan

Suppression of the cellular immune system appears to be a prerequisite for the manifestation of adult T-cell leukemia (ATL). In other words, ATL will develop when impairment of the immune system is caused by the infection of human T-lymphotropic virus type I (HTLV-I). This defect of immune surveillance against virus-infected cells may be a result of the impairment of the function of cytotoxic T-cells (CTLs) specific for the HTLV-I-infected cells. The manifestation of ATL could be predicted by examining the function of CTLs in HTLV-I carriers. A new strategy of prevention and therapy for ATL would include an attempt to restore and fortify the CTL function of the host.

Key words : immunodeficiency, ATL, HTLV-I carrier, opportunistic infection, malignancy

In the chronic wasting syndrome of cats, mice and birds infected with type C leukemia viruses, the animals are immunodeficient before developing tumors (1). Human T-lymphotropic virus type I (HTLV-I) is thought to be closely related to the pathogenesis of adult T-cell leukemia (ATL). A severe immunological defect is universally seen in patients with ATL, resulting in the frequent association of opportunistic infections such as *Pneumocystis carinii* pneumonia (PCP) (2, 3). The immunodeficiency in ATL is often regarded as a condition resulting from malignant transformation of helper T cells. We experienced a case in which PCP preceded the onset of ATL by one and a half year (4, 5). Several similar cases have been reported in Japan recently (6-8). These cases show that immunodeficiency is present before the manifestation of ATL. Our hypothesis is that impairment of cellular immune responses caused by HTLV-I infection may be a prerequisite of the development of ATL.

Immunodeficiencies in ATL. In acquired immunodeficiency syndrome, human immunodeficiency virus infection causes severe impairment of immune function by destroying helper T-cells. In ATL, immunodeficiency is usually explained as a result of dysfunction of malignant helper T cells. Various opportunistic infections such as PCP, herpes zoster and cryptococcal meningitis are frequently associated with ATL, indicating severe impairment of cellular immune functions (2, 3). The suppressive nature of ATL cells on the immunoglobulin synthesis of normal B cells was reported (9, 10). Other studies demonstrated loss of cytotoxic function after infection of T cells with HTLV-I (11, 12). Two reports revealed the presence of immunosuppressive factors derived from ATL

* To whom correspondence should be addressed.

Table 1 Cases of opportunistic infections in human T-lymphotropic virus type I carriers

Case no.	Age/Sex	Opportunistic infection	Outcome	Anti-HTLV-I antibody	WBC $\times 10^9$/L	Abnormal cell %	PPD	PHA	ConA	Immuno-globulin	Reference no.
1	37/F	PCP	D, ATL (after 18 mo.)	× 20 (IF)	9.8	0	−	N	N	N	4, 5
2	36/M	PCP	Recovered	+ (?)	9.3	0	?	?	?	?	16
3	44/M	Toxoplasmosis	D, cerebral bleeding (after 3 mo.)	× 40 (IF)	5.9	A few	?	?	?	?	17
4	79/M	Cryp. Men.	?	× 320 (IF)	N	8	?	?	?	?	18
5	35/M	PCP	D, GI bleeding Pneumothorax (after 1 mo.)	× 40 (IF)	9.2	6	−	↓ ↓	↓ ↓	?	19
6	35/M	PCP	D, ATL (after 6 mo.)	× 8192 (PA)	5.3	0	−	N	N	N	6
7	70/F	Cryp. Men.	Recovered	× 40 (IF)	6.7	0	−	↓	↓	N	15
8	45/F	Cryp. Men.	D (after 7 mo.)	＃ (PA) 31.8 (EIA)	5.3	2	−	?	?	N	20
9	34/F	PCP	D, ATL (after 12 mo.)	× 160 (IF)	30.5	3	−	↓ ↓	↓ ↓	?	7
10	56/M	PCP	D, ATL (after 15 mo.)	× 160 (IF)	8.6	0	−	?	?	?	8
11	70/M	PCP	D (after 10 days)	× 512 (IF)	32.0	0.5	−	?	?	↓	21
12	39/M	PCP	D (after 24 days)	× 126 (PA)	13.6	5	−	↓	↓	?	22
13	30/M	PCP	D, atypical mycobacteria (after 12 mo.)	× 256 (PA)	13.8	0.1	−	N	↓	↓	22

Abbreviations : HTLV-I, human T-lymphotropic virus, type I ; M, male ; F, female ; PCP, *Pneumocystis carinii* pneumonia ; Crip. Men., *Cryptococcus* meningitis ; D, dead ; ATL, adult T-cell leukemia ; mo., months ; +, positive ; ＃, strongly positive ; GI, gastrointestinal ; IF, immunofluorescence ; PA, particle agglutination ; EIA, enzyme immunosorbent assay ; WBC, white blood cell ; PHA, phytohemaggulutinin lymphocyte blastogenesis ; ConA, Concanavalin A ; N, normal ; ↓, slightly depressed ; ↓ ↓, depressed.

cells (13, 14).

Immunodeficiencies in HTLV-I carriers. We reported cases of PCP (4, 5) and cryptococcal meningitis with no underlying disease except positive serum anti-HTLV-I antibody tests (15). Among 13 similar cases in recent Japanese literature (Table 1) (6–8, 16–22), 9 were PCP, 3 were cryptococcal meningitis and one was toxoplasmosis. Although the association of opportunistic infections strongly suggests the existence of immunodeficiencies in these patients, T-cell functions examined were not always abnormal. One consistent finding was a negative purified protein derivative skin test. Responses of lymphocytes to phytohemagglutinin and concanavalin A were not invariably depressed. Studies on immune functions in healthy HTLV-I carriers in Japan (23–26) suggested the presence of subclinical impairment. Immune suppression in HTLV-I carriers is also suggested by the high association of *Strongyloides stercoralis* infection in Okinawa where ATL is highly endemic (27). Another interesting fact indicating immunosuppression in HTLV-I carriers is an increased risk of malignancy (28) and the existence of a case of HTLV-I carrier with disseminated metastasis of early uterine cancer (29). Some defects in immune surveillance against malignancy are conceivable.

Hypothesis. ATL develops in only a portion of HTLV-I-infected persons. It may be that other factors such as age at the time of exposure, route of infection, virus dose or the host immune response are important in disease manifestation. Among them we propose here the impairment of host immune function as a prerequisite for malignant proliferation of HTLV-I-infected T-cells.

We still do not know the mechanism of transformation by HTLV-I. Roles of the product of the HTLV-I pX gene (30) and abnormally expressed interleukin 2 receptor (31) have been proposed. Both theories require initial activation and proliferation of HTLV-I-infected T-cells. In most healthy carriers, abnormal cells are infrequently seen in the blood, indicating that some regulatory process controls the proliferation of HTLV-I-infected cells. We speculate that this control function is performed by normal cytotoxic T-cells (CTLs) (probably CD8 positive self-HLA restricted T-cells). It is well known that CTLs are one of the primary immune defenses of the host against viral infections and virus-induced tumors (32). In most HTLV-I carriers, occasionally activated HTLV-I-expressing cells may be effectively eradicated by CTLs specifically induced for HTLV-I antigen-bearing cells (33). If the CTL function is impaired in HTLV-I carriers, persistence and proliferation of HTLV-I-infected cells will continue, leading to malignant transformation.

Can we predict those who will develop ATL among HTLV-I carriers? Association of opportunistic infection is probably an early predictive sign as illustrated in 3 cases of PCP (6–8) as well as ours (4, 5). If impairment of CTL function specific for HTLV-I-infected self cells can be examined, it also may be a predictive sign of ATL. Prevention of the development of ATL may be possible if restorement and fortification of CTL function is achieved. Spontaneous remission of ATL has been reported (34). Long-term remission of ATL is also known (35). CTL functions in these cases may have been restored. If so, we should try a completely different treatment from chemotherapy, namely, a strategy to restore and fortify specific CTL function against HTLV-I-infected malignant cells. A successful report in murine leukemia (36) suggests the plausibility of this strategy.

References

1. Levy JA : The multifaceted retroviruses. Cancer Res (1986) **46**, 5457–5468.
2. Matsumoto M, Nomura K, Matsumoto T, Nishioka K, Hanada S, Furusho H, Kikuchi Y, Kato A, Utsunomiya A, Uematsu T, Iwahashi M, Hashimoto S and Yunoki K : T-cell leukemia lymphoma in Kagoshima district, south western Japan. Jpn J Clin Oncol (1979) **9** (Suppl 1) 325–336.
3. Taguchi H, Niiya K, Yorimitsu Y, Machida K, Yoshimoto S, Takaoka M, Shiomi F and Ueda N : Seven cases of adult

T-cell leukemia in the south part of Shikoku district. Jpn J Clin Hematol (1980) **21**, 80–85 (in Japanese).
4. Kobayashi M, Miyoshi I, Sonobe H, Taguchi H and Kubonishi I : Association of *Pneumocystis carinii* pneumonia and scabies. JAMA (J Am Med Assoc) (1982) **248**, 1973.
5. Kobayashi M, Yoshimoto S, Fujishita M, Yano S, Niiya K, Kubonishi I, Taguchi H and Miyoshi I : HTLV-I positive T-cell lymphoma/leukemia in an AIDS patient. Lancet (1984) i, 1361–1362.
6. Ko M, Nakagawa J, Hamagami S, Itakura N, Miyagawa T and Ochi N : A case of adult T-cell leukemia/lymphoma preceded by *Pneumocystis carinii* pneumonia. Jpn J Thoracic Dis (1987) **25**, 605 (in Japanese).
7. Suzuki F, Hayakawa T, Matsumoto M, Kishimoto H, Wada R, Murakami M, Iwata M and Sato A : A case of *Pneumocystis carinii* pneumonia without underlying disease. Jpn J Thoracic Dis (1988) **26**, 304 (in Japanese).
8. Kuwazuru Y, Hanada S, Uematsu T, Saito T, Makino T, Uozumi K and Hashimoto S : *Pneumocystis carinii* pneumonia in a HTLV-I carrier terminating with acute type of adult T-cell leukemia. Jpn J Clin Hematol (1988) **29**, 2132–2135 (in Japanese).
9. Uchiyama T, Sagawa K, Takatsuki K and Uchino H : Effect of adult T-cell leukemia cells on pokeweed mitogen-induced normal B-cell differentiation. Clin Immunol Immunopathol (1978) **10**, 24–34.
10. Hattori T, Uchiyama T, Toibana T, Takatsuki K and Uchino H : Surface phenotype of Japanese ATL cells characterized by monoclonal antibodies. Blood (1981) **58**, 645–647.
11. Popovic M, Flomenberg N, Volkman DJ, Mann D, Fauci S, Dupont B and Gallo RC : Alteration of T-cell function by infection with HTLV-I and HTLV-II. Science (1984) **26**, 459–462.
12. Yarchoan R, Guo H-G, Reitz M, Mauluish A, Mitsuya H and Broder S : Alterations in cytotoxic and helper T-cell function after infection of T cell clones with human T cell leukemia virus type I. J Clin Invest (1986) **77**, 1466–1473.
13. Shirakawa F, Tanaka Y, Oda S, Chiba S, Suzuki H, Eto S and Yamashita U : Immunosuppressive factors from adult T-cell leukemia cells. Cancer Res (1986) **46**, 4458–4462.
14. Cinciolo GJ, Copeland TP, Oroszlan S and Snyderman R : Inhibition of lymphocyte proliferation by a synthetic peptide homologous to retroviral envelope proteins. Science (1985) **230**, 453–455.
15. Hirose S, Iwahara Y, Taguchi H and Miyoshi I : Cryptococcal meningitis in a human T-cell leukemia virus type I carrier : Report of a case. J Jpn Soc Int Med (1987) **76**, 1868–1879 (in Japanese).
16. Hori A, Yano T, Inoue H, Yamaguchi K, Yoshimura H, Koyama T, Sonoda T, Ito Y and Shinohara S : A case of primary *Pneumocystis carinii* pneumonia. Jpn J Chest Dis (1983) **42**, 766–769 (in Japanese).
17. Furukawa T, Harada K, Nobuoka T, Kobayashi Y, Matsuoka Y and Fukuda J : A case of toxoplasmosis presenting similar clinical symptoms as adult T cell leukemia (ATL). J Jpn Soc Int Med (1985) **74**, 656 (in Japanese).
18. Murai K, Yamamura Y, Tsuruta K, Kurihara T and Matsukura S : Successful intrathecal miconazole treatment for cryptococcal meningitis associated with adult T cell leukemia. Neurol Med (1986) **25**, 366–370 (in Japanese).
19. Koreishi S, Tamura K, Kiyota M, Yuda T, Chosa N and Hika A : Lung abnormalities associated with adult T cell leukemia. J Soc Physician Miyazaki Prefecture (1986) 44–47 (in Japanese).
20. Matsumuro K, Machigashira K, Abe H and Nagamatsu K : An autopsy case of cryptococcal meningitis associated with smoldering adult T cell leukemia. Clin Neurol (1988) **28**, 670–673 (in Japanese).
21. Nakamura H, Kusajima K, Nakamura N, Ooishi F, Nagasaka M and Kawabata Y : A case of adult T cell leukemia initiated with *Pneumocystis carinii* pneumonia. J Jpn Soc Int Med (1987) **76**, 474 (in Japanese).
22. Moriyama K, Muranishi H, Nishimura J, Tanaka K, Asayama R and Takita A : Immunodeficiency in preclinical smoldering adult T-cell leukemia. Jpn J Clin Oncol (1988) **18**, 313–319.
23. Imai J and Hinuma Y : Epstein-Barr virus-specific antibodies in patients with adult T-cell leukemia (ATL) and healthy ATL virus-carriers. Int J Cancer (1983) **31**, 197–200.
24. Katsuki T, Katsuki K, Imai J and Hinuma Y : Immune suppression in healthy carriers of adult T-cell leukemia retrovirus (HTLV-I) : Impairment of T-cell control of Epstein-Barr virus infected B-cells. Jpn J Cancer Res (1987) **78**, 639–642.
25. Morishima Y, Ohya K, Morishima T, Nishikawa K and Fukuda T : Immunological studies on adult T cell leukemia virus (ATLV) carriers. Clin Exp Immunol (1986) **64**, 457–464.
26. Tachibana N, Okayama A, Ishizaki J, Yokota T, Shishime E, Murai K, Shioiri S, Tsuda K, Essex M and Mueller N : Suppression of tuberculin skin reaction in healthy HTLV-I carriers from Japan. Int J Cancer (1988) **42**, 829–831.
27. Nakada K, Kohakura M, Komoda H and Hinuma Y : High incidence of HTLV-I antibody in carriers of *Strongyloides stercoralis*. Lancet (1984) i, 633.
28. Asou N, Kumagai T, Uekihara S, Ishii M, Sato M, Sakai K, Nishimura H, Yamaguchi K and Takatsuki K : HTLV-I seroprevalence in patients with malignancy. Cancer (1986) **58**, 903–907.
29. Taguchi H, Daibata M, Kitagawa K, Kubonishi I, Asai M, Sagara Y, Enzan H, Hara H and Miyoshi I : Generalized lymph node metastasis of early uterine cancer in an HTLV-I carrier. Cancer (1988) **62**, 2614–2617.
30. Yoshida M : Expression of the HTLV-I genome and its association with a unique T-cell malignancy. Biochim Biophys Acta (1987) **907**, 145–161.
31. Uchiyama T, Wano R, Tsudo M, Umadome H, Hori T, Tamori S, Uchino H, Yodoi J, Maeda M, Kobayashi N and Hatanaka M : Abnormal expression of interleukin-2 receptor (Tac antigen) in adult T-cell leukemia ; in Retroviruses in Human Lymphoma/Leukemia, Miwa, Sugano, Sugamura, and Weiss eds, Scientific Societies Press, Tokyo (1985) pp

253–258.
32. Berke G : Cytotoxic T-lymphocytes. How do they function? Immunol Rev (1983) **72**, 5–42.
33. Kannagi M, Sugamura K, Kinoshita K, Uchino H and Hinuma Y : Specific cytolysis of fresh tumor cells by an autologous killer T cell line derived from an adult T cell leukemia/lymphoma patient. J Immunol (1984) **133**, 1037–1041.
34. Kimura I, Tsubota T, Hayashi K and Ohnoshi T : Spontaneous complete remission in adult T-cell leukemia : A case report. Jpn J Clin Oncol (1983) **13** (Suppl 2) 231–236.
35. Fujii H, Maekawa T, Seki S, Hatanaka M, Kita K and Miwa K : Long-term remission in a case of acute adult T cell leukemia. Jpn J Clin Hematol (1987) **28**, 1481–1486 (in Japanese).
36. Plata F, Langlade-Demoyen P, Abastado JP, Berbar T and Kourilsky P : Retrovirus antigens recognized by cytotoxic T lymphocytes activate tumor rejection *in vivo*. Cell (1987) **48**, 231–240.

Received June 29, 1989 ; accepted August 10, 1989