Clinical Manifestations of Human T Lymphotropic Virus Type I-Infected Patients with Systemic Lupus Erythematosus

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ABSTRACT. *Objective.* Human T lymphotropic virus type I (HTLV-I) may be associated with some connective tissue autoimmune diseases, including systemic lupus erythematosus (SLE). To determine the relationship between HTLV-I infection and SLE, we examined the clinical manifestations of SLE patients with HTLV-I infection.

Methods. Eighty-nine patients with SLE were screened for antibodies to HTLV-I by electrochemiluminescence immunoassay. The presence of HTLV-I proviral sequences in peripheral blood mononuclear cells (PBMC) was determined by real-time polymerase chain reaction (PCR) quantification and Southern blotting analysis. The differences in clinical manifestations between HTLV-I-seropositive and seronegative patients with SLE were analyzed statistically.

Results. Fourteen of 89 (15.7%) patients were HTLV-I seropositive. All PBMC samples from 11 patients tested by PCR and 3 samples from 10 patients tested by Southern blotting analysis were positive for HTLV-I-related sequences. The age of HTLV-I-seropositive patients with SLE was significantly higher than that of seronegative patients (median 60 vs 42 yrs; p < 0.0005). The age at onset of SLE in HTLV-I-seropositive patients was also significantly higher than that of seronegative patients (median 45.5 vs 30 yrs; p < 0.0005). The lymphocyte count in HTLV-I-seropositive SLE patients was significantly higher than that of seronegative patients (median 1740 vs 1066/µl; p = 0.027). The maintenance dose of prednisolone in HTLV-I-seropositive patients with SLE was significantly lower than that in seronegative patients (median 5 vs 9 mg/day; p = 0.012).

Conclusion. This is the first report of the differences in clinical manifestations between SLE patients with and without HTLV-I infection. Our results suggest some involvement of HTLV-I in the pathogenesis of SLE. (First Release August 1 2007; J Rheumatol 2007;34:1841–8)

Key Indexing Terms:
HUMAN T LYMPHOTROPIC VIRUS TYPE I   SYSTEMIC LUPUS ERYTHEMATOSUS

Human T lymphotropic virus type I (HTLV-I) has long been thought to play a role in the etiology of connective tissue autoimmune diseases based on the pathogenic mechanisms of action of the retrovirus, as well as on the roles of some animal retroviruses as the etiological agents in animal autoimmune diseases. Natural infection with caprine arthritis encephalitis virus in goats results in an arthropathy that mimics human rheumatoid arthritis (RA)[1]. Endogenous murine retroviruses are involved in systemic lupus erythematosus (SLE)-like disease in specific inbred strains of mice[2]. Transgenic mice carrying retrovirus-specific genes, including HTLV *tax*, showed autoimmune-like pathology, suggesting that these viruses have the potential to induce autoimmune disorders[3,4]. In addition, HTLV-I has been shown to be associated with polyarthritis and proliferative synovitis, designated HTLV-I associated chronic inflammatory arthropathy in some HTLV-I-seropositive individuals[5,6]. Further, there is additional serological evidence linking HTLV-I to Sjögren's syndrome (SS). In the Nagasaki region of Japan, where HTLV-I is endemic, there is a high prevalence of anti-HTLV-I antibodies, with 13 of 36 (36%) patients with SS positive for these antibodies[7]. In another study in the same region, 17 of 74 (23%) SS patients showed serum reactivity to HTLV-I, as compared with only 3% of the general population[8].

A great deal of research has been directed toward determining the possible roles of human retroviruses in the etiology of SLE. A study using Western blotting analyses indicated that a significant proportion of SLE patient sera were reactive

with capsid antigen p24, the major group antigen (Gag) protein of human immunodeficiency virus type 1 (HIV-1)[9], although epidemiological studies indicated that HIV infection and SLE are rarely seen in the same patient[10]. There has also been speculation that human endogenous retroviruses (HERV) are associated with the pathogenesis of SLE, and HERV have been implicated in SLE[11]. On the other hand, investigations of HTLV-I infection in patients with SLE have indicated both the presence and absence of viral related antigens/antibodies[12-24]. In addition, studies of integrated HTLV-I proviral sequences have provided evidence of the absence of these sequences even in patients possessing antibodies reactive with HTLV-I[20-23]. The contradictory results published to date made it impossible to determine whether HTLV-I is involved in SLE. We have analyzed 89 SLE patients with or without HTLV-I infection. Here, we describe the differences in clinical manifestations between HTLV-I-infected and uninfected patients. Our results suggest a possible role of HTLV-I in the etiology of SLE in virus-infected patients, although the seroprevalence rate was not significantly elevated in this patient population.

MATERIALS AND METHODS

Subjects. Sera were obtained from 89 patients with SLE attending the Department of Hematology and Immunology, Kagoshima University Hospital, Kagoshima, Japan. Details of the patients are given in Table 1. All the patients had SLE as defined by the revised criteria of the American College of Rheumatology[25]. The median duration of disease for SLE was 11 years. Patients received various treatments, including prednisolone and immunosuppressants. Sera were also obtained from 409 patients with cardiovascular diseases attending the Department of Cardiovascular Medicine, Kagoshima University Hospital, as controls. The approval of the Medical Ethical Committee of Kagoshima University and informed consent of all patients were obtained for collection of additional venous blood during routine clinical management of patients. All samples were coded and tested in a blind manner.

Serology. Sera were screened by electrochemiluminescence immunoassay (ECLIA) for antibodies against purified HTLV-I antigen and synthetic Env peptides (Picolumi® HTLV-I; Eisai, Tokyo, Japan)[26]. Cutoff values for positivity were selected as directed in the specification protocols. A fluorescent antibody method was used for detection of antinuclear antibodies (ANA). Passive hemagglutination or radioimmunoassay was used for detection of anti-DNA antibodies. Enzyme linked immunosorbent assay or the Ouchterlony method was used for detection of anti-double-stranded DNA (dsDNA), anti-cardiolipin, anti-U1 RNP, anti-Sm, anti-Ro/SSA, and anti-La/SSB antibodies. Russell's viper venom test was used for detection of lupus anticoagulant.

Polymerase chain reaction (PCR). Peripheral blood mononuclear cells (PBMC) were separated from heparinized whole blood by centrifugation on Ficoll/Hypaque (Pharmacia, Uppsala, Sweden). The standard HTLV-I DNA was prepared from MT-2 cells[27]. The real-time PCR quantification of HTLV-I DNA was performed in a Light-Cycler System (Roche Diagnostics, Mannheim, Germany) by intra-assay using a series of duplicate measurements of 12 test samples with standard DNA for each assay. The HTLV-I primer set corresponded to the highly conserved HTLV-I pX region, SK43, and SK44[28]. The HTLV-I pX probe set was designed to correspond to 2 adjacent parts of the pX region and labeled with different fluorophores[29]. The HTLV-I proviral load was expressed as number of copies per 1000 cells using the following formula: HTLV-I proviral load = [(HTLV-I pX copy number)/(ß-globin copy number/2)] × 1000. The limit of detection of this method was 0.2 copies of HTLV-I provirus/1000 cells.

Southern blotting. Integrated proviral HTLV-I DNA was detected by Southern blotting analysis, as described with some modifications[30]. Briefly, extracted DNA was digested with *Eco*RI or *Pst*I. Then, DNA was electrophoresed on 1% agarose gels, and transferred onto nylon membranes. These blots were hybridized with fluorescently labeled whole HTLV-I proviral DNA.

Statistical evaluation. Statistical analysis was carried out using Mantel-Haenszel statistics test, chi-square test, and the Mann-Whitney test. P < 0.05 was considered significant.

RESULTS

Evaluation of HTLV-I infection in SLE patients. Evaluation of sera for the presence of antibodies to HTLV-I. Based on the results of HTLV-I ECLIA, 14 of 89 (15.7%) sera were considered positive, giving optical density values greater than the cutoff value; one was from a man and the others were from women. In the disease control group, 45 of 409 patients (11.0%; 22 men and 23 women) were considered positive. Overall, the data indicated no significant prevalence of HTLV-I ECLIA positivity in SLE patients compared with the disease control group by Mantel-Haenszel test controlling for age (in decades) and sex (p = 0.125; Table 2).

PCR detection of HTLV-I. To determine whether the SLE samples considered positive for HTLV-I ECLIA possessed integrated provirus, DNA was extracted from PBMC. However, in 3 of the 14 samples PBMC had not been reserved and could not be obtained. In all SLE samples, PCR using HTLV-I pX primers succeeded in quantification of HTLV-I DNA — the proviral load varied from 0.4 to 592.4 copies (Table 3).

Southern blotting. PBMC of only 10 of the 14 patients considered positive by HTLV-I ECLIA were examined by Southern blot hybridization. Cellular DNA from PBMC of 3 patients were positive for HTLV-I or HTLV-I-related

Table 1. Patient details.

	SLE	Control*
Number	89	409
Male:female	10:79	261:148
Age, yrs		
Mean (SD)	46.6 (14.8)	60 (15.3)
Range	21–77	16–85

* Patients with cardiovascular diseases. SLE: systemic lupus erythematosus.

Table 2. Prevalence of antibodies to HTLV-I in SLE as determined by ECLIA.

	HTLV-I ECLIA		
	Positive (%)	Negative	Mantel-Haenszel Test
SLE, n = 89	14 (15.7)	75	
CG, n = 409	45 (11.0)	364	0.125

ECLIA: electrochemiluminescence immunoassay.

Table 3. SLE patients considered positive in HTLV-I ECLIA.

Case	Sex	Age, yrs	Age at Onset yrs	PCR of HTLV-I*,	Southern Blotting	Complications and Prognosis
1	M	77	70	30.6	—	
2	F	71	47	350.7	Mono	sATL
3	F	55	35	19.4	—	
4	F	68	60	0.4	ND	
5	F	51	46	128.7	—	Hashimoto
6	F	45	19	ND	ND	
7	F	55	43	0.9	—	AOSD
8	F	47	42	8.8	—	SSc
9	F	65	46	ND	ND	NTM, Dead
10	F	53	43	592.4	—	Graves
11	F	43	40	314.7	Oligo	SS, Cryo
12	F	69	67	ND	ND	Hashimoto
13	F	72	62	22.4	—	
14	F	66	45	25.1	Oligo	

* Real-time PCR quantification of HTLV-I DNA (/1000 copies). ND: not determined; Mono: monoclonal; Oligo: oligoclonal; sATL: smoldering adult T-cell leukemia; Hashimoto: Hashimoto's disease; AOSD: adult-onset Still's disease; SSc: systemic sclerosis; NTM: nontuberculous mycobacteria; Graves: Graves' disease; SS: Sjögren's syndrome; Cryo: cryoglobulinemia.

sequences (1 monoclonal, 2 oligoclonal). The other 7 patients were classified as negative using this method (Table 3).

Clinical evaluation of SLE patients with HTLV-I infection. Complications. Complications arising in the 14 patients with SLE positive for HTLV-I by ECLIA (seropositive SLE patients) are shown in Table 3. Case 2 was diagnosed with smoldering adult T-cell leukemia (sATL) 20 years after the onset of SLE. Nontuberculous mycobacterial infection occurred in Case 9 and the patient died. Six patients were diagnosed as having autoimmune diseases other than SLE. A high prevalence of HTLV-I infection among patients with SS was reported in Japan, and complication by SS may affect the seroprevalence rate in this patient population. However, only one patient was diagnosed with SS, and there was no difference in prevalence of SS between seropositive and seronegative SLE patients (7.1% vs 10.7%; p = 1.000; Table 4).

Age and age at onset. As shown in Figure 1, the age of HTLV-I-seropositive patients with SLE was significantly higher than that of seronegative patients (median 60 vs 42 yrs; p <

0.0005). The age at onset of SLE in seropositive SLE patients was also significantly higher than that in seronegative patients (median 45.5 vs 30 yrs; p < 0.0005).

Clinical symptoms. There were no differences in clinical symptoms of SLE between the groups (Table 4).

Hematological disorders. Most of the first laboratory examinations of seronegative patients with SLE showed lymphocytopenia (median 1066/µl, range 231–4440/µl). However, the lymphocyte count in seropositive patients with SLE was significantly higher than that of seronegative patients (median 1740 vs 1066/µl; p = 0.027; Figure 2B). The platelet count in seropositive patients with SLE was slightly lower than that in seronegative patients (median 1.57×10^5 vs 1.97×10^5; p = 0.094; Figure 2C). In addition, the incidence of thrombocytopenia (platelet count < 10^5) in seropositive patients with SLE during the disease period was slightly higher than that of seronegative patients (42.9% vs 18.7%; p = 0.076; Table 5). There were no significant differences in leukocyte count (median 3800 vs 4350/µl; p = 0.539; Figure 2A) or abnormal

Table 4. Comparison of clinical symptoms between HTLV-I-seropositive and seronegative SLE patients.

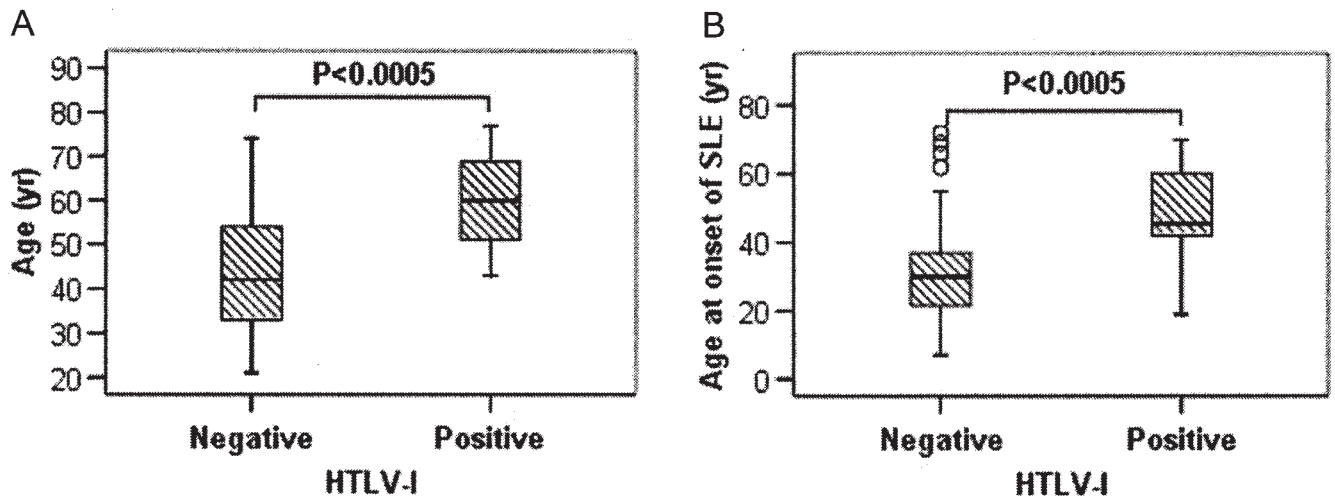|	HTLV-I-Seropositive SLE Patients (%)	HTLV-I-Seronegative SLE Patients (%)	Chi-square Test
Sjögren's syndrome	1/14 (7.1)	8/75 (10.7)	1.000
Malar rash	6/14 (42.9)	46/74 (62.2)	0.293
Discoid rash	1/14 (7.1)	11/74 (14.9)	0.682
Photosensitivity	8/14 (57.1)	43/74 (58.1)	1.000
Oral ulcers	2/14 (14.3)	14/74 (18.9)	1.000
Arthritis	9/14 (64.3)	50/74 (67.6)	1.000
Serositis	2/14 (14.3)	19/74 (25.7)	0.504
Renal disorder	5/14 (35.7)	36/75 (48.0)	0.579
Neurological disorder	2/14 (14.3)	15/74 (20.3)	1.000

Figure 1. Comparison of age and age at onset of SLE between HTLV-I-seropositive and seronegative patients. A. The age of HTLV-I-seropositive SLE patients was significantly higher than that of seronegative patients (median 60 vs 42 yrs; p < 0.0005). B. The age at onset of SLE in HTLV-I-positive patients was also significantly higher than that of seronegative patients (median 45.5 vs 30yrs; p < 0.0005).
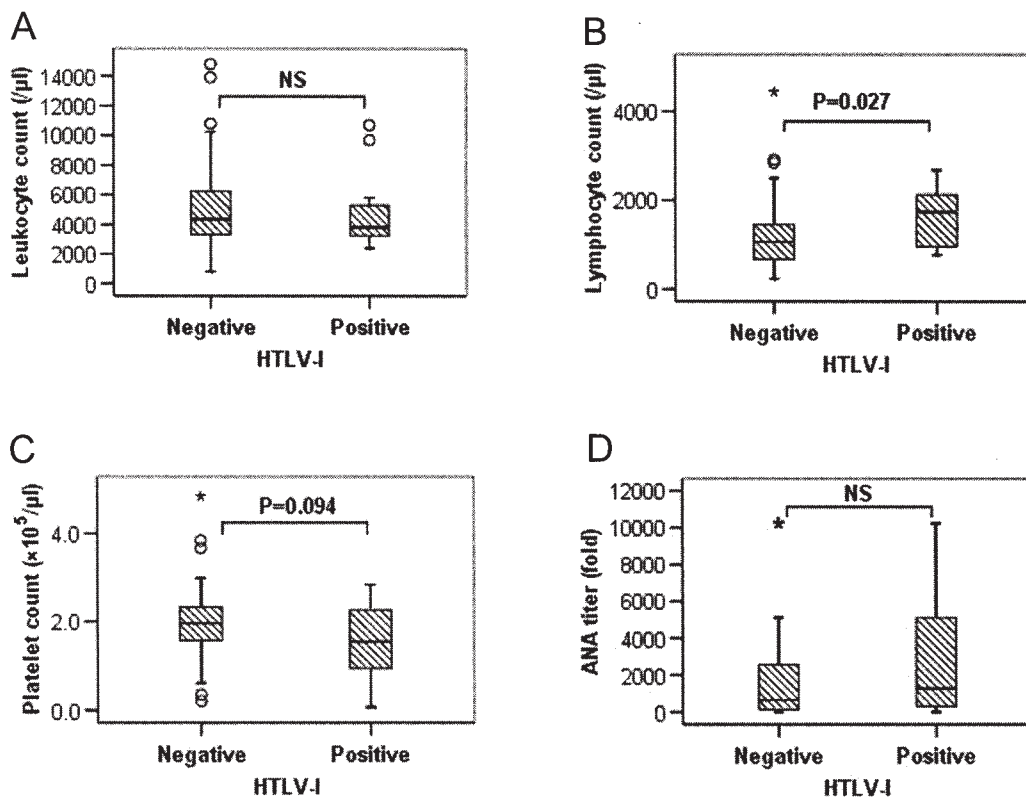

Figure 2. Comparison of laboratory data between seropositive and seronegative SLE patients. A. There were no significant differences in leukocyte count between seropositive and seronegative patients with SLE (median 3800 vs 4350/μl; p = 0.539). B. The lymphocyte count in HTLV-I-seropositive patients with SLE was significantly higher than that in seronegative patients (median 1740 vs 1066/μl; p = 0.027). C. The platelet count in seropositive patients with SLE was slightly lower than that in seronegative patients (median 1.57×10^5 vs 1.97×10^5/μl; p = 0.094). D. There was no difference in ANA titer between the groups (median 1280 vs 640-fold; p = 0.518). * Extreme values.

lymphocyte count (median 0.0 vs 0.0/μl; p = 0.173) between the groups (data not shown).

Autoantibodies. There were no differences between the groups in ANA titer (median 1280-fold vs 640-fold; p = 0.518; Figure 2D) or ANA pattern (data not shown). There were no significant differences in prevalence of the other autoantibodies between the 2 groups (Table 5).

Treatments. There were no differences between the 2 groups

Table 5. Comparison of laboratory data between HTLV-I-seropositive and seronegative SLE patients.

	HTLV-I-Seropositive SLE Patients (%)	HTLV-I-Seronegative SLE Patients (%)	Chi-square Test
Thrombocytopenia*	6/14 (42.9)	14/75 (18.7)	0.076
Anti-DNA/dsDNA**	12/14 (85.7)	57/74 (77.0)	0.725
Anti-Sm	4/14 (28.6)	33/71 (46.5)	0.347
Antiphospholipid	2/13 (15.4)	19/66 (28.8)	0.496
Anti-U1 RNP	7/14 (50.0)	35/71 (49.3)	1.000
Anti-Ro/SSA	3/10 (30.0)	37/59 (62.7)	0.082
Anti-La/SSB	1/10 (10.0)	13/58 (22.4)	0.674

* Platelets $< 10^5/\mu l$. ** Positive for either anti-DNA or anti-dsDNA antibody.

in the maximum dose of oral prednisolone (median 35 vs 30 mg/day; p = 0.900; Figure 3A) or the frequencies of use of intravenous pulse methylprednisolone and immunosuppressants (Table 6). However, the maintenance dose of prednisolone in seropositive patients with SLE was significantly lower than that in seronegative patients (median 5 vs 9 mg/day; p = 0.012; Figure 3B), whereas there was no difference in disease duration between the 2 groups (median 10 vs 12 yrs; p = 0.978; data not shown).

Prognosis. Death and exacerbation, such as irreversible renal failure, were considered an indication of poor prognosis in our study. There was no difference in the incidence of poor prognosis between the 2 groups (Table 6).

DISCUSSION

HTLV-I has been postulated as the etiological agent in human autoimmune diseases. Some previous investigations detected seroreactivity to HTLV-I in patients with SLE[16,18,21,22]. However, to date there have been only a few reports regarding the detection of HTLV-I in SLE using direct molecular biological approaches, such as PCR[21-24]. In these studies, HTLV-I infection was precluded as a causative agent of SLE by molecular biological methods, although a minority of patients possessed antibodies cross-reactive with retroviral antigens. These results may be explained by molecular mimicry[31]. However, in our study, PCR analysis detected HTLV-I in all patients seropositive for HTLV-I from whom PBMC were available (11/14 patients). Therefore, the seropositivity for HTLV-I in our study cannot be explained by molecular mimicry.

If HTLV-I is associated with SLE, a significantly higher seroprevalence rate in this patient population would be expected. However, our seroprevalence rate of 14/89 (15.7%) in this patient population was only slightly higher than the rate of 45/409 (11.0%) in the disease control group, and suggested that this patient population was not at increased risk of HTLV-I infection.

However, comparisons of clinical manifestations between seropositive and seronegative patients with SLE provided meaningful results suggesting a role of this retrovirus in autoimmunity in SLE. As the prevalence of seropositivity increases with age in both men and women in general[32], it
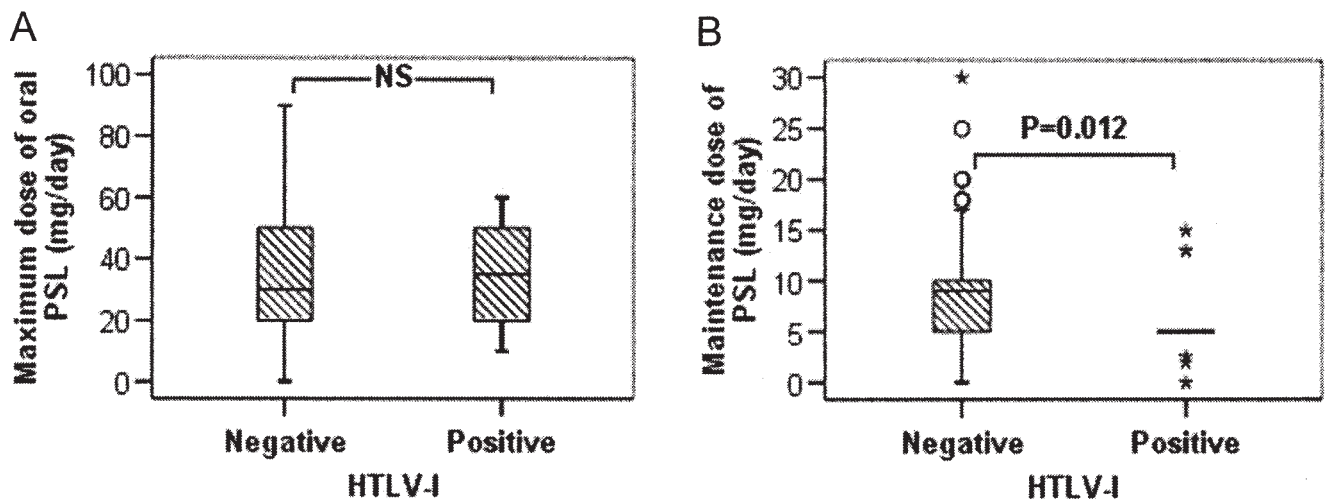

Figure 3. Comparison of prednisolone dose between seropositive and seronegative patients with SLE. A. There was no difference in maximum dose of oral prednisolone between the 2 groups (median 35 vs 30 mg/day; p = 0.900). B. The maintenance dose of prednisolone in seropositive patients with SLE was significantly lower than that of seronegative patients (median 5 vs 9 mg/day; p = 0.012). * Extreme values.

Table 6. Comparison of treatments and prognosis between HTLV-I-seropositive and seronegative SLE patients.

	HTLV-I-Seropositive SLE Patients (%)	HTLV-I-Seronegative SLE Patients (%)	Chi-square Test
Pulse methylprednisolone	2/14 (14.3)	18/72 (25.0)	0.505
Immunosuppressants	3/14 (21.4)	26/74 (35.1)	0.372
Poor prognosis*	1/14 (7.1)	8/71 (11.3)	1.000

* Death or exacerbation.

seems natural that the age of seropositive patients with SLE was higher than that of seronegative patients. However, we also found that the age at onset of SLE in seropositive patients was significantly higher than that in seronegative patients. It may be argued that HTLV-I may induce a unique autoimmune disease resembling SLE, many decades after initial infection, or that previous HTLV-I infection may delay onset of SLE, as it has been reported that many HTLV-I-infected individuals show chronic immunosuppression, even in the absence of malignant disease[33-38].

We detected some hematological disorders in seropositive patients with SLE. For example, the lymphocyte count in seropositive patients with SLE was significantly higher than that in seronegative patients. However, this observation is not specific to SLE, because HTLV-I infection of a CD4+ T cell also rapidly induces activation and proliferation of the cell in healthy carriers[39]. On the other hand, the platelet count was lower, and the incidence of thrombocytopenia was higher in HTLV-I-seropositive patients with SLE than in seronegative patients, although the difference was not statistically significant. HIV causes thrombocytopenia in 10% of patients with active HIV disease[40,41]. The etiologies of HIV thrombocytopenia are considered to be as follows: escalated destruction of platelets by the immune system, damage to megakaryocytes by HIV infection, and inhibition of thrombopoiesis by some antiviral drugs. In our previous study, we showed that the prevalence of HTLV-I infection among patients with idiopathic thrombocytopenic purpura (ITP) was higher than that in healthy carriers[42]. Further, the ITP patients with HTLV-I infection were older than those without HTLV-I infection, and the ITP patients with HTLV-I infection showed poor responses to prednisolone therapy. In the case of ITP patients with HTLV-I infection, the main etiology may be the increased destruction of platelets by the immune system, although the possibility of a role of infection of the megakaryocytes by HTLV-I in the disease etiology has not been examined. The etiology may also be the same as that of ITP with HTLV-I in the case of SLE patients with HTLV-I infection.

The lower maintenance dose of prednisolone in seropositive patients with SLE suggests that this patient group is not at risk for severe complications of SLE, and is controllable by prednisolone therapy. These patients may have had mild SLE activity because they were older than seronegative patients with SLE, or they may show chronic immunosuppression due to HTLV-I infection, as mentioned above. One female SLE patient with HTLV-I infection was affected with smoldering ATL after onset of SLE. However, we cannot draw any conclusions regarding the incidence of ATL among seropositive patients with SLE, as she may have been affected with the disease incidentally.

From the data in our study it is not possible to distinguish whether HTLV-I is involved with the pathogenesis, or affects the manifestations, of SLE. However, one of the mechanisms may be explained by the limited sequence homology between this retrovirus and cellular antigens, including endogenous retroviral sequences (ERS). In the case of HTLV-I *gag*, there is a high degree of homology to HTLV-related endogenous sequence (HRES-1)[43-45]. Polymorphic alleles of HRES-1, mapped to human chromosome 1 at q42[46], have been associated with SLE[47]. HRES-1 is centrally located at 1q42 with respect to microsatellite markers associated with susceptibility to SLE[48]. Antibodies to 28-kDa protein encoded by HRES-1 (HRES-1/p28) were detected in 21–50% of patients with SLE and overlap syndromes in various laboratories[45,47,49-51]. In contrast, 3.6% (4/111) of normal donors and none of 42 patients with acquired immune deficiency syndrome (AIDS) or 50 asymptomatic HIV-infected patients had HRES-1 antibodies[50]. This suggested that HRES-1 is an autoantigen for patients with autoimmune diseases, such as SLE. There may be molecular mimicry for generation of HRES-1-specific autoantibodies. That is, infection by an exogenous retrovirus with cross-reactive epitopes, such as HTLV-I, may trigger HRES-1 antibodies[52-54], which may lead to an autoimmune response against HRES-1. Unfortunately, we did not determine HRES-1 antibodies in patients with SLE in the present study.

Three consecutive highly charged amino acid residues, Arg-Arg-Glu (RRE), present in both HRES-1/p28 and HTLV-I *gag* p24[43] may be responsible for the cross-reactivity. This RRE triplet is also repeated 3 times in the retroviral *Gag*-like region of 70 K U1 snRNP lupus autoantigen[45,50,55]. Therefore, cross-reactivity of HTLV-I *gag* p24 and HRES-1/p28 may contribute to generation of anti-U1 RNP antibody. However, there was no significant difference in prevalence of anti-U1 RNP antibody between HTLV-I-seropositive and seronegative patients with SLE in our study (50.0% vs 49.3%; p = 1.000; Table 5). This suggests that the RRE triplet is not responsible for the cross-reactivity in HTLV-I-seropositive patients with SLE. However, HTLV-I *Gag* and HRES-1/p28 may contain other cross-reactive epitopes[43,45]. These epitopes may also

lead to molecular mimicry between the 2 proteins in HTLV-I-infected patients with SLE.

To our knowledge, this is the first report describing the difference in clinical manifestations between SLE patients with and those without HTLV-I infection. These observations suggest that HTLV-I infection may be associated with SLE in virus-infected individuals.

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