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Novel Complications with HTLV-1-associated Myelopathy/Tropical Spastic Paraparesis: Interstitial Cystitis and Persistent Prostatitis

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Lower urinary symptoms associated with HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) are common, but have been regarded as 'neurogenic' due to spinal involvements. However, in some cases, these symptoms are persistent, progressive, and not directly correlated with the severity of other neurologic symptoms of the lower spinal cord. These findings prompted us to locate organic lesions in the lower urinary tract and to correlate them with HTLV-1 infection. Among 35 HAM patients with lower urinary symptoms, we found 4 cases with the symptoms persistent and progressive: 3 with contracted bladder and another with persistent prostatitis. Histological or cytological examinations indicated local lymphocytic infiltrations in the lower urinary tract in all cases: 3 by the infiltration in the bladder and the other by a high concentration of lymphocytes in expressed prostatic secretions. Of 3 cases whose urinary samples were available, 2 showed significant increase in the concentration of urinary anti-HTLV-1 antibody of IgA class. The urinary IgA antibody of the third case was not elevated, but the sample had been obtained after resection of the affected bladder. None of the control cases showed significant anti-HTLV-1 IgA antibody in urine except for a case of gross hematuria due to chemotherapy directed against adult T-cell leukemia. We suggest inclusion of these processes into the spectrum of complications for HAM/TSP. The elevated excretion of anti-HTLV-1 of IgA class in urine may be an indicator of these complications.

Key words: HAM/TSP — HTLV-1 — Interstitial cystitis — Persistent prostatitis — Urinary antibody

Diseases closely associated with human T-lymphotropic virus type 1 (HTLV-1) include adult T-cell leukemia (ATL)[1,2] and HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP).[3,4] While ATL is a leukemia of CD4+ cells integrating HTLV-1 monoclonally, HAM/TSP is associated with infiltration of CD4+ and CD8+ lymphocytes including cells integrating HTLV-1 poly- or oligo-clonally.[5,6] Complications of HAM include bronchio-alveolitis,[7,8] uveitis,[9] arthritis,[10] skin disorders,[8,11] etc. Most of these complications are also associated with infiltration of polyclonal T cells infected with HTLV-1. We have experienced some 40 cases of HAM in our hospital. The majority of HAM/TSP patients presented lower urinary symptoms. These symptoms have been regarded as 'neurogenic' because they can be easily explained in terms of spinal lesions due to HAM/TSP.[12] Although infrequent, the urinary symptoms of HAM/TSP can be persistent and progressive, and their severity may be inconsistent with neurologic symptoms ascribed to the lower spinal cord. We report here that the lower urinary symptoms in some HAM/TSP patients are not simple 'neurogenic,' but are organic, due to lesions associated with HTLV-1 infection.

MATERIALS AND METHODS

Clinical cases and specimens The diagnosis of HAM/TSP was based on the criteria described by WHO.[12] Among 35 HAM/TSP patients we have experienced at our urology clinic since 1984, we found a case of persistent prostatitis (Case 1), and 3 cases of contracted bladder (Cases 2–4). As control cases, we included 3 neurogenic bladder patients with HAM/TSP (Cases 5–7), 2 neurogenic bladder patients with complications of prostatic carcinoma and multiple bone metastases who were anti-HTLV-1-negative (Cases 8 and 9), 3 healthy carriers (Cases 10–12), and 5 overt ATL patients without urinary symptoms (Cases 13–17). Urinary and serum specimens of these patients, and histological and cytological specimens from the first 3 groups were employed in this study.

Histological and cytological examinations Paraffin-embedded sections of operative and biopsy specimens

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were used for routine histological examinations, and urinary sediments for cytological examinations, after hematoxylin-eosin staining.

Concentration of antibody in urine Fresh urinary samples were centrifuged at 1500 rpm for 5 min. The supernatant was filtered through a 0.45 μm Millipore filter and concentrated to 1/10 volume by a Diaflo PM10 molecular sieve membrane (Amicon, UK). The sample was kept at -70°C until use.

Enzyme-linked immunoassay (EIA) to detect anti-HTLV-1 antibody Eitest-ATL kit (Eisai, Tokyo) is dependent on alkaline phosphatase enzyme reactions. To detect anti-HTLV-1 in IgG, IgM or IgA class separately, we replaced the tagged second antibody in the kit with anti-human IgG (Fc) monoclonal, anti-human IgA (α-chain specific) polyclonal, or anti-human IgM (μ-chain specific) polyclonal antibodies, respectively, each labeled with alkaline phosphatase (Sigma). Color signals were obtained with disodium *p*-nitrophenyl phosphate and optical density was determined at 405 nm.

Western blot analysis A western blot (WB) kit ED005 (Eisai) is programmed to detect anti-HTLV-1. Each strip received 50 μl of serum or urinary specimen. To detect the antibody subclasses separately, we used appropriate biotinylated second antibodies, anti-human IgG (Fc) monoclonal, anti-human IgA (α-chain specific) polyclonal, or anti-human IgM (μ-chain specific) polyclonal antibodies (Sigma). The strips were stained with streptavidin, biotinylated alkaline phosphatase, and *p*-nitrophenyl phosphate. Since we have not found any HTLV-2 carriers in Nagasaki (data not shown), we did not try further to discriminate the antibody activity against HTLV-1 or -2.

RESULTS

HAM/TSP cases with persistent and progressive urinary symptoms The diagnosis of the cases with urinary symptoms as well as availabilities of histological, cytological, urinary and serum specimens are summarized in Table I. The clinical profiles of HAM/TSP patients including the onset of HAM/TSP and urinary complications are summarized in Table II. The prevalence of patients with persistent and progressive lower urinary symptoms in HAM/TSP patients was 9% for the contracted bladder (Cases 2, 3 and 4) and 3% for the persistent prostatitis (Case 1). The severity of disease indicated cystectomies in 2 cases of the contracted bladder (Cases 3 and 4). Case 4 refused to cooperate in serum and urinary studies. Urinary symptoms developed concurrently with the diagnosis of HAM/TSP in most cases. Although abnormal cells were detected in Case 4, none of these cases was associated with other clinical signs to suggest smoldering or overt ATL up to date (Jan. '92). The clinical course of Cases 2 and 3 has been reported elsewhere.[13]

Pathological examinations Intensive clinical examinations, including radiological examination, cystoscopic tests, urinary sediments and bacteriological examinations of urine, did not reveal abnormalities in the lower urinary tract in 31 cases of HAM/TSP. Histological data for these cases are not shown. The patients with persistent and progressive urinary symptoms showed abnormal findings in the clinical tests, such as reduced bladder capacity and petechial hemorrhage in the cystoscopy (Cases 2, 3 and 4; data not shown). Biopsies were performed on these cases. The histological examinations of these bladder specimens invariably revealed sub-

Table I. Profiles of Patients with Urinary Symptoms

Case	Age/Sex[a]	Serum anti-HTLV-1 (IgG)	Diagnosis[b]		Specimens available		
			Primary	Complications	Biopsy	Serum	Urine
1	39/M	+	HAM/TSP	NB, Prostatitis	+	+	+
2	66/F	+	HAM/TSP	NB, CB	+	+	+
3	50/F	+	HAM/TSP	NB, CB, UD	+	+	+
4	33/M	+	HAM/TSP	NB, CB, UD	+	−	−
5	59/F	+	HAM/TSP	NB	−	+	+
6	70/F	+	HAM/TSP	NB	−	+	+
7	62/F	+	HAM/TSP	NB	−	+	+
8	80/M	−	PC	NB	−	+	+
9	68/M	−	PC	NB	−	+	+

a) Age at diagnosis of the primary disease. F, female; M, male.
b) NB, neurogenic bladder; CB, contracted bladder; UD, received urinary diversion; PC, prostatic carcinoma.

Table II. Clinical Profiles of HAM/TSP Patients

Case	HAM/TSP onset	Urinary complication		Hematology		Other ATL symp.[b]
		Major symptom	Onset	WBC counts	Abnormal cells[a]	
1	08/89	dysuria	11/89	7600	−	−
2	09/86	pollakisuria	01/87	4400	−	−
3	03/83	gross hematuria	01/83	3100	−	−
4	01/80	pollakisuria	01/79	5500	+	−
5	07/88	incontinence	07/88	5100	−	−
6	06/88	pollakisuria	06/88	6000	−	−
7	03/90	pollakisuria	03/90	7000	−	−

a) Lymphocytes with indented nuclei.
b) Other symptoms suggesting ATL.

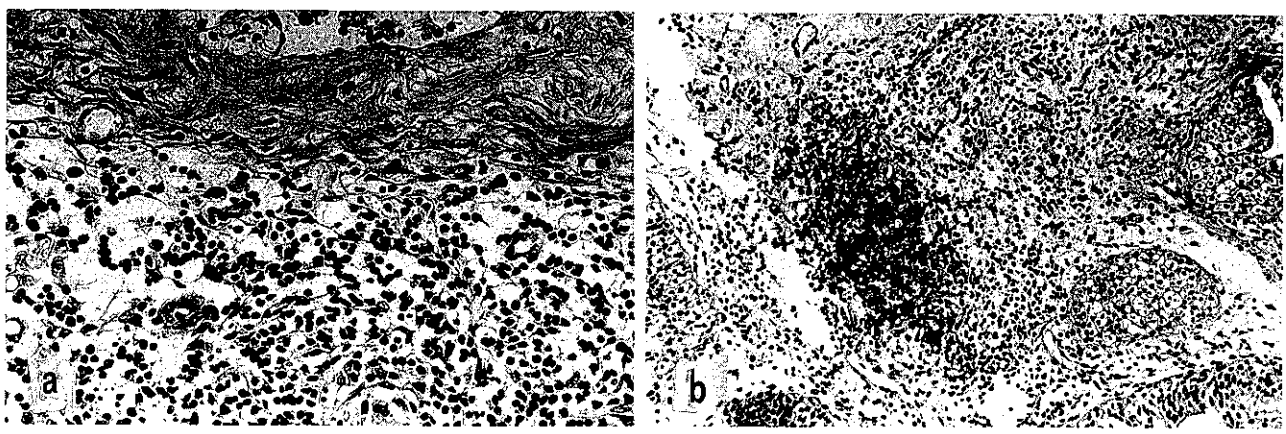

Fig. 1. Bladder specimens showing submucosal infiltration of mononuclear cells with dominant lymphocytes. a: a surgical specimen of Case 2 (hematoxylin-eosin staining, ×200); b: a biopsy specimen of Case 3 (hematoxylin-eosin staining, ×100).

mucosal infiltration of lymphocytes (Cases 2 and 3, Fig. 1; Case 4, data not shown). The findings were consistent with interstitial cystitis.[14] In Case 1 with persistent prostatitis, the biopsy specimen of the bladder did not show severe infiltration in the bladder. However, his expressed prostatic secretions (EPS) contained abnormally high concentrations of lymphocytes (direct examination of the EPS showed over 100 cells in a high power field; normally less than 5). The result strongly suggested that he had a similar inflammatory process on-going in the prostate. Biopsy of the prostate gland was not indicated. These histological examinations confirmed the presence of local pathological lesions in persistent and progressive cases, but there remain two alternative possibilities, i.e., either 'neurogenic' bladder induced these lesions non-specifically or these lesions induced the persistent and progressive lower urinary symptoms.

Class of anti-HTLV-1 in sera The levels of IgG, IgA and IgM were normal in HAM/TSP patients regardless of the presence or absence of chronic lower urinary tract symptoms (Table III). The anti-HTLV-1 IgG antibody in sera was positive in all HAM/TSP patients, healthy carriers, and ATL patients by both EIA and western blot analyses (Table IV, Fig. 2). IgA antibody was positive in most cases. Among HAM/TSP patients with urinary symptoms, 4 cases (Cases 1, 3, 5, and 6) showed strong reactivity in EIA and at least double bands (p24 and p19 of HTLV-1 antigens) in WB, whereas the other 2 cases (Case 2 and 7) were barely positive in both EIA and WB. Healthy carriers and ATL patients without urinary symptoms seem to be less reactive than HAM/TSP patients in EIA, and the healthy carriers than ATL patients in WB. IgM antibody was strongly positive in a case of HAM/TSP (Case 6) and a healthy carrier (Case 11).

Therefore, we could not find a significant correlation between each class of anti-HTLV-1 antibody, and the presence or absence of the persistent and progressive lower urinary symptoms.

Class of anti-HTLV-1 in urine The presence of anti-HTLV-1 IgG antibody in urine was common (Table V; Fig. 3a). On the other hand, IgM antibody in urine was not detectable in any case (Table V; Fig. 3c). IgA antibody was significantly elevated in Cases 1 and 2 (Table V; Fig. 3b). Both of these cases were associated with chronic and persistent lower urinary symptoms. Contamination of blood in urine in these samples was ruled out by the discordantly low level of IgM activity, and also by the urinary concentration of erythrocytes (data not shown), indicating that these anti-HTLV-1 antibodies were generated in the lower urinary tract rather than having originated from blood due to impaired filtration. The failure to detect urinary anti-HTLV-1 of IgA class in Case 3 can be explained by the urinary diversion which rerouted her urine away from the pathologic bladder wall. An exceptional case of ATL gave urine that was positive for anti-HTLV-1 of IgA class but showed no persistent urinary symptoms (Case 17). However, she had a relatively high level of serum IgA antibody and gross hematuria due to renal damage induced by the chemotherapy directed against ATL.

These results are consistent with the proposals that HAM/TSP patients with persistent and progressive urinary symptoms have organic changes in the lower urinary tract, that not all cysto-urinary disturbances associated with HAM/TSP are neurogenic, and that the elevation of urinary IgA antibody against HTLV-1 could be used as an indicator of the presence of pathological changes in the lower urinary tract directly associated with HTLV-1 infection.

Table III. Immunoglobulin Concentrations in Sera

Case	IgG	IgM	IgA
1	11.53[a)]	1.19	3.46
2	16.35	1.61	1.83
3	14.73	1.33	1.62
4	nd[b)]	nd	nd
5	14.17	1.87	2.37
6	14.91	1.72	2.04
7	12.10	0.36	2.60
8	14.86	1.70	1.67
9	13.20	0.62	3.74
AV[c)]	14.91	2.06	2.68
SD	5.19	1.53	1.77

a) Concentration: mg/ml.
b) nd: not done.
c) AV, SD: average and standard deviations of normal non-carrier controls in our hospital.

Table IV. Anti-HTLV-1 Antibody Subclasses in Sera by Enzyme Immunoassay and Western Blotting

Case No.	IgG class				IgA class				IgM class			
	OD	p19	p24	p28	OD	p19	p24	p28	OD	p19	p24	p28
1	1.289	+	+	+	0.270	+	+	+	0.032	−	−	−
2	1.092	+	+	±	0.031	−	+	−	0.033	−	−	−
3	1.434	+	+	+	0.163	+	+	−	0.060	−	+	−
5	1.402	+	+	+	0.163	+	+	−	0.052	−	+	−
6	1.320	+	+	+	0.155	+	+	−	0.439	+	+	−
7	1.031	+	+	+	0.042	±	±	−	0.005	−	−	−
10	0.654	+	+	+	0.020	−	−	−	0.030	−	−	−
11	1.559	+	+	+	0.017	−	+	+	0.104	+	+	+
12	1.582	+	+	+	0.025	−	−	−	0.043	+	+	−
13	1.041	+	+	+	0.014	+	+	−	0.022	−	−	−
14	1.816	+	+	+	0.016	+	+	+	0.019	+	+	−
15	1.218	+	+	+	0.016	+	+	+	0.022	+	+	−
16	1.531	+	+	+	0.026	+	+	±	0.048	+	+	+
17	1.686	+	+	+	0.062	+	+	+	0.038	+	+	+
CO[a)]	0.008				0.020				0.005			

a) Cut-off values for anti-HTLV-1 antibodies in class IgG, IgA and IgM were determined from the values of 10 control samples from non-carriers.

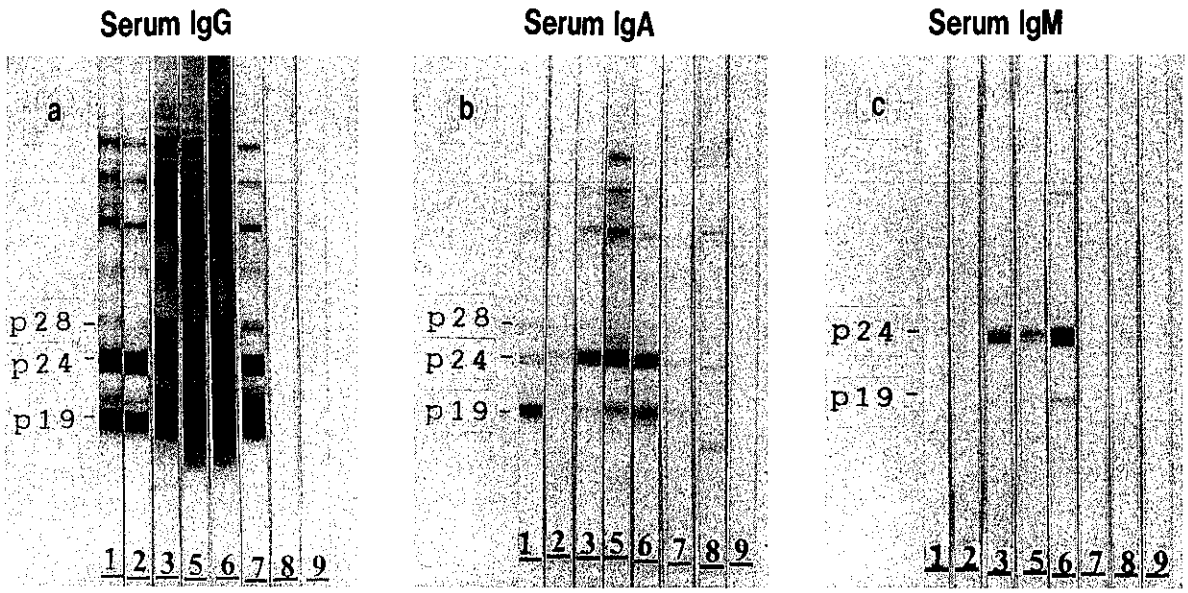

Fig. 2. Serum anti-HTLV-1 antibody in IgG (a), IgA (b), or IgM (c) subclass by western blot analysis. The number of each slot corresponds to the patient's number in Table I.

Table V. Anti-HTLV-1 Antibody Subclasses in Urine by Enzyme Immunoassay and Western Blotting

Case No.	IgG class				IgA class				IgM class			
	OD	p19	p24	p28	OD	p19	p24	p28	OD	p19	p24	p28
1	0.055	+	+	±	0.043	+	±	±	0.001	−	−	−
2	0.798	+	+	±	0.024	−	+	−	0.000	−	−	−
3	0.015	±	+	−	0.013	−	−	−	0.000	−	−	−
5	0.022	+	+	−	0.004	−	−	−	0.000	−	−	−
6	0.030	+	+	−	0.011	−	−	−	0.001	−	−	−
7	0.007	−	−	−	0.015	−	−	−	0.000	−	−	−
10	0.014	−	−	−	0.012	−	−	−	0.030	−	−	−
11	0.015	−	+	−	0.012	−	−	−	0.104	−	−	−
12	0.014	+	+	−	0.012	−	−	−	0.043	−	−	−
13	0.014	−	−	−	0.012	−	−	−	0.022	−	−	−
14	0.013	+	+	+	0.012	−	−	−	0.019	−	−	−
15	0.017	+	+	−	0.013	−	−	−	0.022	−	−	−
16	0.013	−	−	−	0.013	−	−	−	0.048	−	−	−
17	0.024	+	+	+	nt[a]	+	−	+	0.038	−	−	−
CO[b]	0.010				0.014				0.000			

a) Not tested.
b) Cut-off values for anti-HTLV-1 antibodies in class IgG, IgA and IgM in urine were determined from the values of 10 control samples from non-carriers.

DISCUSSION

The major pathological feature of HAM/TSP is a chronic inflammatory process located mainly in the spinal cord.[15] Histopathologically, it includes perivascular infiltration by mononuclear cells, marked destruction of myelin and axons, and astrocytic gliosis. The subarachnoid space of the spinal cord showed fibrosis and infiltration by lymphocytes.[15, 16] However, the central nervous system is not the sole organ or tissue suscep-

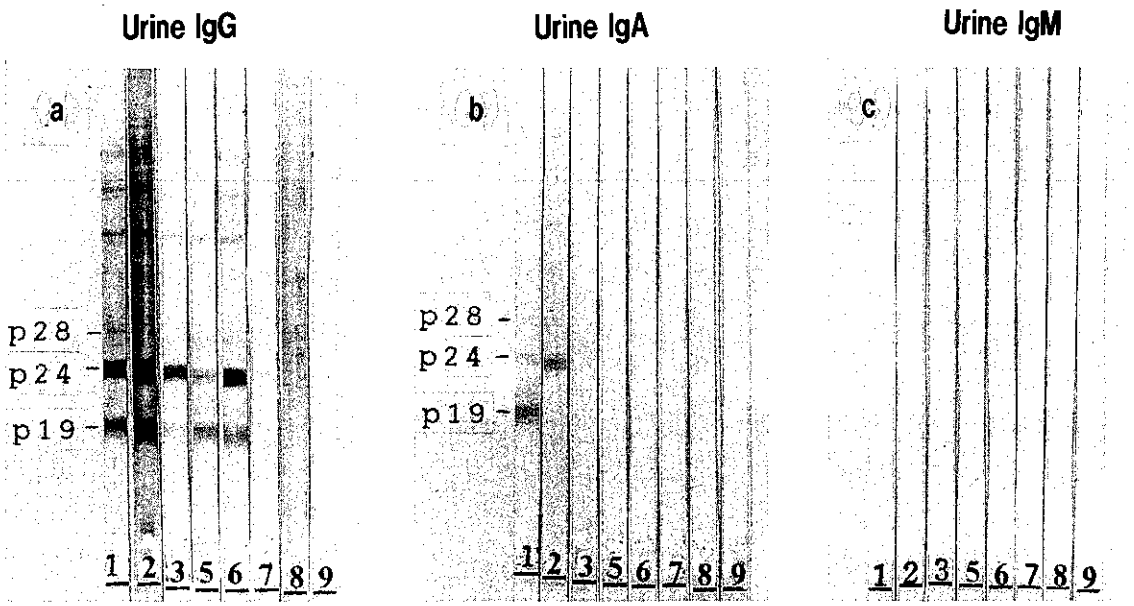

Fig. 3. Urinary anti-HTLV-1 antibody in IgG (a), IgA (b), or IgM (c) subclass by western blot analysis. The number of each slot corresponds to the patient's number in Table I.

tible to HAM/TSP. Complications of HAM/TSP outside of the central nervous systems are usually associated with interstitial infiltration of lymphocytes, including lung,[7,8] eye,[9] joints,[10] skin,[11] muscles,[17,18] etc. Actually, Case 2 was complicated with diffuse superficial keratitis.[13]

We found cystorectal disturbances in 35 of 40 cases of HAM/TSP. These disturbances are so common in HAM/TSP[12] that they have been simply regarded as 'neurogenic,' since the major pathological change of HAM/TSP is in the spinal cord. However, we noticed that the lower urinary symptoms of some HAM/TSP patients were persistent and progressive irrespective of neurologic dysfunctions of HAM/TSP. The profile of the usual neurogenic bladder is detrusor-sphincter dissociation (DSD) and uninhibited bladder[19] due to central and/or peripheral nerve destruction, in the absence of significant changes in the lower urinary tract. The cystoscopic and histological findings of bladder specimens of 3 patients with persistent and progressive courses showed organic changes in the bladder consistent with interstitial cystitis.[13] Furthermore, the cytological examination of the expressed prostatic secretion of the patient with persistent prostatitis showed a significant increase of lymphocytes, indicating the presence of an inflammatory process in the prostate gland. Our data demonstrated that chronic inflammatory infiltration by lymphocytes in the bladder or prostatic gland might cause the lower urinary symptoms in HAM/TSP patients, and the lower urinary symptoms of these patients might not be 'neurogenic.'

In order to shed light on the cause of these organic changes, and to find a marker to discriminate them from those of neurogenic origin, we looked for anti-HTLV-1 of IgG, IgA and IgM subclasses in sera and urinary samples. The inconsistently elevated urinary anti-HTLV-1 in patients with the lower urinary symptoms supported the view that the antibodies originated from the lower urinary organs rather than from blood via leakage or contamination. The abundance of IgA in urine and expressed prostatic secretions is consistent with the nature of IgA, as the major antibody in excretory fluid. It would be intriguing to look for possible involvement of cells infected with HTLV-1 in the locale using a technique such as *in situ* hybridization. Unfortunately, prospective sampling of urinary sediments or biopsy materials had not been performed in these cases. The data we have presented suggest that these lower urinary lesions are not a secondary process following a long history of lower urinary problems, but the cause of the latter. Furthermore, the presence of antibody directed to HTLV-1, pathogenic for HAM/TSP, indicated that HTLV-1 is closely associated with these lesions. Thus, we propose that the clinical spectrum of HAM/TSP includes contracted bladder and persistent chronic prostatitis with urinary anti-HTLV-1 IgA antibodies originating from the lower urinary tract.

HTLV-1 is peculiarly endemic in southwestern Japan, including Nagasaki Prefecture, where the average prevalence of HTLV-1 carriers is as high as 10% of residents over the age of 40.[20, 21] This striking endemicity is closely correlated with milk-borne transmission as the major route of HTLV-1 infection.[22, 23] Most HAM/TSP cases in Japan seem to occur in carriers infected by maternal transmission. Since HAM/TSP is known to develop also in horizontally infected carriers, the incidence of these urinary involvements in HAM/TSP may change in geographical areas where the values of the ratio of horizontally/maternally transmitted patients are different.

There is no clear evidence that viruses closely related to HTLV-1 cause any human disease.[24] However, the spread of HTLV-2 in drug abusers has been detected recently.[25] Since anti-HTLV-2 in urine could be tested without distress to patients, this may be a useful method to search for potential pathogenicity of HTLV-2. Another human retrovirus, human immunodeficiency virus (HIV), may cause lower urinary lesions, since there have been some reports that a small percentage of patients with AIDS suffer from significant urological manifestations.[26, 27] The same method may be used to survey such a possibility.

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