Lupus nephritis class I accompanied by tubulointerstitial nephritis with marked T-lymphocyte infiltration in an HTLV-1 positive patient

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Abstract We herein describe the case of a 40-year-old Japanese male who was admitted to our hospital because of a continuous remittent fever lasting 1 month. He fulfilled the items of the classification criteria for the diagnosis of systemic lupus erythematosus (SLE). The administration of 20 mg per day of oral prednisolone completely diminished his clinical symptoms. However, his renal biopsy performed 1 day after the admission showed marked pathognomonic characteristics. Not only did his glomeruli show class I lupus nephritis with mesangial depositions of IgG, IgA, C3, and C1q, but also tubulointerstitial nephritis with marked T-lymphocyte infiltration. These infiltrated T cells partly had nuclear atypia. The patient was positive for human T cell leukemia virus type 1 (HTLV-1) antibodies. Furthermore, clonal rearrangements of T cell receptor-gamma chain gene was detected in the DNA extracted from his kidney sections by the polymerase chain reaction (PCR) method. A second renal biopsy 6 months after the prednisolone treatment showed that the infiltrating T lymphocytes had markedly diminished. This is the first case report

of lupus nephritis class I with tubulointerstitial nephritis, which might include oncogenic T lymphocytes, in an HTLV-1 positive patient.

Keywords Systemic lupus erythematosus · Human T cell leukemia virus type 1 · T lymphocytes · Lupus nephritis

Introduction

Human T cell leukemia virus type 1 (HTLV-1) is a member of a group of mammalian C-type retroviruses and is endemic in southern Japan, the Caribbean, and parts of South America, Africa, and the Middle East [1]. It is well known that HTLV-1 causes adult T cell lymphoma (ATL) [2, 3] and HTLV-1 associated myelopathy (HAM)/tropical spastic paraparesis (TSP) [4, 5]. Interestingly, it was shown that the transgenic expression of HTLV-1 in mice was associated with autoimmunity [10]. In humans, HTLV-1 infection has also been hypothesized to play an important role in the pathogenesis of various autoimmune diseases, such as Sjögren's syndrome and rheumatoid arthritis [6–9]. In particular, an association between systemic lupus erythematosus (SLE) and C-type retrovirus has been suspected not only in humans [11–14] but also in mice [15, 16]. The mechanism underlying how HTLV-1 causes SLE remains elusive, but the postulated roles for such retroviruses in the etiopathogenesis of SLE are considered to include intrinsic effects, mimicry of antigens, and/or effects as stimulators of autoimmunity [17, 18]. In fact, there have been previous case reports of patients with SLE and ATL [19, 20], SLE and HAM [21, 22], and SLE and the persistent carrier state of HTLV-1 infection [23]. We herein report the first case in which a kidney biopsy revealed lupus nephritis with interstitial nephritis that might partly include oncogenic T

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lymphocytes in an HTLV-1 positive patient. This case again suggests the involvement of HTLV-1 infection in the pathogenesis of SLE.

Case report

The patient was a 40-year-old Japanese male who was admitted to our hospital because of a remittent fever, which lasted for approximately 1 month. The patient was born in Osaka prefecture and then moved to Chiba prefecture in Japan. These areas do not have endemic HTLV-1. No abnormalities had ever been detected in the patient's annual examinations, and his past history was noncontributory. Before admission to our hospital, he continuously received cefazolin intravenously for 7 days at another hospital, but his remittent fever continued. At that time, the patient had

specific abnormalities in his laboratory data, such as anti-nuclear antibody (ANA) positivity, double-strand DNA antibody (dsDNA Ab) positivity, and decreasing complement hemolytic activity. At that point, the patient was referred and admitted to our hospital. At admission, he was severely debilitated because of a sustained loss of appetite. The physical examination showed: height 175.6 cm; body weight 82.0 kg (BMI 26.6), which was 8 kg less than 1 month before; blood pressure 97/61 mmHg; and SpO₂ 98 %, with a regular heart rate of 76/min. No crackles or murmurs were detected on chest auscultation. The patient's abdomen was normal. Costovertebral angle tenderness was not detected. There was a tattoo, which he had received at age 20, on his back. There were no other abnormalities on his skin. A neurological examination did not reveal any abnormalities. No superficial lymph node swelling was detectable. Ophthalmological abnormalities were also not detected.

Table 1 Laboratory tests on admission

Urinalysis		Blood chemistry		Immunology	
Gravity	1.007	TP	5.7 g/dl	CRP	2.94 mg/dl
pH	7	Albumin	2.5 g/dl	HBs-Ag	(–)
RBC	0–1/HPF	AST	186 IU/l	HCV-Ab	(–)
WBC	0–1/HPF	ALT	106 IU/l	HIV-Ab	(–)
Protein	0.52 g/gCre	LDH	797 IU/l	ASO	67 IU/ml
NAG	13.9 U/l	ALP	266 IU/l	RF	(–)
β2-MG	1172 μg/l	Tbil	0.3 mg/dl	Anti-nuclear-Ab	1:80
BJP	(–)	Na	128 mEq/l	Anti dsDNA	53 IU/ml
		K	3.9 mEq/l	Anti SS-A	83.5 U/ml
		Cl	93 mEq/l	Anti SS-B	<7.0 U/ml
Blood cell count					
WBC	3300/μl	BUN	10.5 mg/dl	CH50	19 U/ml
Stab	2 %	Cre	1.0 mg/dl	C3	34.8 mg/dl
Seg	84 %	UA	4.1 mg/dl	C4	15.5 mg/dl
Lymphocyte	7 %	Ca	7.8 mg/dl	IgG	1410 mg/dl
Mono	4 %	P	3.0 mg/dl	IgG1	54.5 %
Eosino	3 %	Tcho	146 mg/dl	IgG2	40.6 %
RBC	4.55 × 10 ⁶ /μl	BS	93 mg/dl	IgG3	3.2 %
Hemoglobin	12.6 g/dl	HbA1c (NGSP)	6.9 %	IgG4	1.7 %
Hematocrit	36.5 %			IgA	221 mg/dl
MCV	80 fl			IgM	90 mg/dl
Platelet	16.5 × 10 ⁴ /μL			IgE	83.5 IU/ml
Reticulocyte	0.3 %			sIR-2R	2770 U/ml
				M protein	(–)

To convert Hb, TP, and Albumin in g/dl to g/l, multiply by 10; Tbil in mg/dl to μmol/l, multiply by 17.1; BUN in mg/dl to mmol/l, multiply by 0.357; Cr in mg/dl to μmol/l, multiply by 88.4; UA in mg/dl to μmol/l, multiply by 59.48; Ca in mg/dl to mmol/l, multiply by 0.2945; Tcho in mg/dl to mmol/l, multiply by 0.02586; C3, C4, IgG, IgA, and IgM in mg/dl to g/l, multiply by 0.01

RBC red blood cells, HPF high-power field, WBC white blood cells, NAG N-acetylglutamate, MG microglobulin, Stab stab cell, Seg segmented neutrophils, Mono monocytes, Eosino eosinophilic cells, MCV mean corpuscular volume, TP total protein, AST aspartate aminotransferase, ALT alanine aminotransferase, LDH lactate dehydrogenase, ALP alkaline phosphatase, Tbil total bilirubin, BUN blood urea nitrogen, Cr creatinine, UA uric acid, Tcho total cholesterol, BS blood sugar, HbA1c hemoglobin A1c, CRP C-reactive protein, ASO antistreptolysin-O, C3 complement 3, IgG immunoglobulin G, RF rheumatoid factor, ANA antinuclear antibody, HBs hepatitis B surface, HCV hepatitis C virus, M protein monoclonal protein

Table 2 The changes in the clinical data

	Normal range	Day 1	Day 9	Day 51	Day 71	Day 99	Day 135	Day 176	Day 197
Proteinuria (g/gCre)	<0.15	0.52	0.14	0.1	0.07	0.06	0.05	0.07	0.06
NAG (U/l)	<7	13.1	3.3	nd	nd	nd	nd	nd	1.8
β 2-MG (μ g/l)	<230	1172	2215	nd	nd	nd	nd	nd	640
WBC (/ μ l)	3500–9200	3300	9000	10800	11300	7800	10100	8200	8900
Lymphocytes (%)	30–45	7.0	8.7	9.8	21.0	23.0	13.0	16.0	13.5
eGFR (ml/min)		67.3	85.9	102.6	101.0	94.3	92.9	91.5	90.2
Albumin (serum) (g/dl)	3.8–5.3	2.5	2.8	3.8	3.5	3.6	3.6	3.7	3.5
AST (IU/l)	13–33	186	19	20	35	40	38	28	22
CH50 (U/ml)	30–50	19	nd	41.1	37.4	38.8	39.7	38.3	38.3
Anti-dsDNA Ab (IU/ml)	<20	53	nd	192	nd	123	nd	122	104
Anti-nuclear Ab (titer)	<1:40	1:80	nd	1:80	nd	1:80	nd	1:80	1:160
sIL-2R (U/ml)	145–519	2770	nd	746	nd	817	nd	623	657
Major axis of the left kidney (mm)		137.3	nd	nd	nd	nd	nd	nd	121.6
Major axis of the right kidney (mm)		134.8	nd	nd	nd	nd	nd	nd	127.6

Kidney sizes were measured by ultrasonography

The results of the laboratory tests on admission are summarized in Table 1. No atypical cells were observed in the patient's peripheral blood. He fulfilled four items of classification criteria for the diagnosis of SLE, i.e. lymphocytopenia (231/ μ l), proteinuria (0.52 g/gCre), ANA positivity, and dsDNA Abs. Thus, he was diagnosed to have SLE. We started the patient on 20 mg of oral prednisolone on the day of the admission. As a result, he never experienced the fever again and recovered his appetite promptly. His elevated ALT and AST also started to decrease soon after starting this treatment (Table 2). His condition continued to improve, and he was discharged from our hospital 8 days after the admission.

However, we thought that lymphoproliferative disease could not be ruled out completely. The patient's serum

level of soluble IL-2 receptor was elevated (Table 1). Furthermore, a computed tomography (CT) scan revealed abdominal para-aortic lymph node swelling (approximately 1 cm in diameter) (Fig. 1). The CT scan also revealed swelling of bilateral kidneys, suggesting infiltration or accumulation of something in the kidney. Therefore, we performed a kidney biopsy to define the etiology of the proteinuria and to determine the cause of the swelling of the kidney 1 day after the admission (day 2).

First renal biopsy

We could observe 20 glomeruli. All glomeruli appeared normal upon examination by light microscopy (Fig. 2a). On the other hand, immunofluorescent staining revealed that IgG, IgA, C3, and C1q, but not IgM, were positive in the mesangial area (Fig. 2c–f). These pathological findings in glomeruli were compatible with class I lupus nephritis [24]. However, it should be noted that the interstitium had marked changes. Approximately 30 % of the area of the interstitium had been occupied by infiltrating small to medium sized lymphoid cells partly with nuclear atypia (Fig. 3a, b). We also detected tubulitis with breaks of the tubular basement membrane. Most populations of the infiltrated cells were positive for CD3 (Fig. 3c), a part of which had enlarged or notched nuclei (Fig. 3d). On the other hand, there were minor populations of CD20-positive cells (Fig. 3e). In addition, these cells were positive for CD4, CD5, and CD8, and negative for CD10, CD21, CD56, MPO, and LMP-1. The Ki-67 labeling index was 49.1 % (Fig. 3f). These findings might suggest the oncogenic proliferation of T lymphocytes in the interstitium in the kidney.

Fig. 1 A CT scan image taken on admission. The abdominal paraaortic lymph nodes were swollen (approximately 1 cm in diameter). Enlarged kidneys were also observed

Fig. 2 Representative photos from the first kidney biopsy (1). **a** No apparent abnormalities were detected in any of the glomeruli. This glomerulus was slightly enlarged (major axis; 252 μ m) possibly because of obesity (periodic acid-Schiff stain). **b** IgG stain. **c** IgA stain. **d** IgM stain. **e** C3 stain. **f** C1q stain (**a–f** $\times 200$)

Analysis for HTLV-1

The finding of infiltrating T lymphocytes in the interstitium in the first biopsy prompted us to screen the patient for HTLV-1 infection. The chemical luminescence enzyme immunoassay (CLEIA) for serum showed positive results for the HTLV-1 antibody. On the other hand, integration of the HTLV-1 provirus genome was not detected in the DNA of peripheral blood cells by a Southern blot analysis 2 months after the admission to our hospital. Furthermore, we also checked the integration of the HTLV-1 provirus genome in the biopsied frozen kidney tissues by a Southern blot analysis. However, the sample volume was not large enough to obtain DNA for the analysis. Therefore, we performed polymerase chain reaction (PCR)-based clonality assessment according to the method reported previously [25] to investigate whether there were clonal rearrangements of the T cell receptor γ (TCR γ) chain gene by using paraffin-embedded kidney sections. As a consequence,

apparent clonal bands of TCR γ rearrangement were detected (Fig. 4). The patient's mother was negative for HTLV-1 antibody in the serum.

Follow-up and second renal biopsy

After the discharge, the patient's condition remained good, without any symptoms. His prednisolone treatment was decreased to 15 mg a day after 3 months. The changes in laboratory data after 3 months are summarized in Table 2. While the CH50 values were within the normal range, the dsDNA levels were still high. The proteinuria had disappeared. In the abdominal CT scans, the para-aortic lymphadenopathy had markedly diminished 1 month after the treatment (data not shown). The kidney size was slightly decreased compared with that at the first biopsy (major axis of the left kidney: 121.6 vs. 137.3 mm, major axis of the right kidney: 127.6 vs. 134.8 mm). Because the specific pathological manifestation of this patient was observed in

Fig. 3 Representative photos from the first kidney biopsy (2). **a** Inflammatory cells were spread throughout approximately 30 % of the area of the interstitium (H&E stain). **b** The nuclei of some infiltrating cells were enlarged with notched shapes (*arrows*) (H&E stain). **c** Most of the infiltrating cells were positive for CD3. **d** The CD3-positive cells had notched nuclei. **e** CD20-positive cells were minor populations in the interstitium. **f** These infiltrating cells were also positive for Ki-67 (**a** $\times 40$, **b** $\times 600$, **c** $\times 100$, **d** $\times 600$, **e** $\times 100$, **f** $\times 100$)

the kidney, a second percutaneous renal biopsy was performed to confirm the efficacy of the treatment 6 months after the first biopsy, and another 20 glomeruli were obtained. All of the glomeruli, except for one collapsed glomerulus, showed an almost normal appearance (Fig. 5a). Furthermore, an immunofluorescent study showed that all deposits had completely disappeared (Fig. 5b–f). In addition, the infiltrating cells in the interstitium were also markedly decreased (Fig. 6a, b).

Discussion

An association between HTLV-1 and SLE has been discussed for more than 3 decades. Both in humans [12–14, 18] and in mice [15, 16], the results of previous research have suggested the involvement of C-type retroviruses,

including HTLV-1, in the pathogenesis of SLE. While SLE with ATL or HAM is rare in the clinical setting, several reports have described these comorbidities [19–22, 26]. Compared with the previous cases, the most pathognomonic features of this patient are that his renal pathology showed lupus nephritis and marked T-lymphocyte infiltration into the interstitium (Figs. 2, 3) and that these T cells had abnormal nuclei (Fig. 4). There were no previous reports of such infiltration of T cells into the renal interstitium in HTLV-1 carriers.

Indeed, tubulointerstitial nephritis may be encountered in lupus nephritis. But, such tubulointerstitial disease is most commonly encountered in class III or IV [27]. Immunofluorescent analysis never showed deposits of immunoglobulin within their tubular basement membranes and interstitium. In addition, T cells had atypical nuclei and the Ki-67 labeling index was 49.1 %. Therefore, we cannot

Fig. 4 PCR-based clonality assessment for detecting clonal rearrangements of TCR γ chain. The paraffin-embedded kidney section at the first biopsy was used for this analysis to investigate whether there were clonal rearrangements of TCR γ chain. Two apparent peaks of

clonal bands (*blue*) from 140 to 180 bp were detected, which indicated that the kidney section should include oncogenic T lymphocytes. The 300-bp band (*black*) was an internal positive control

easily explain the reason for the T-lymphocyte infiltration into the interstitium only by lupus nephritis. Given the patient's laboratory data, we had to consider the presence of Sjögren's syndrome, in which interstitial nephritis occurs predominantly with CD4-positive T lymphocytes. However, the patient had neither dry eyes nor dry mouth. Although his anti SS-A antibody titer was positive, his anti SS-B antibody results were negative, and hypergammaglobulinemia was not detected. Therefore, we ruled out Sjögren's syndrome.

We could not conclusively diagnose this patient with ATL because we could not confirm the presence of integrated HTLV-1 provirus in the DNA of his peripheral blood sample. However, the blood samples were obtained 2 months after the treatment. If we had used the blood sample before the treatment, the band of HTLV-1 might have been detected. In addition, there was not a sufficient volume of DNA available from his kidney sample to analyze it for the presence of integrated HTLV-1 provirus in the renal interstitium. However, PCR using kidney sections revealed apparent clonal bands of TCR γ rearrangement (Fig. 4). This result should suggest that some of the infiltrating T lymphocytes were oncogenic. In addition, at this point we could not conclude that these oncogenic T cells were infected by HTLV-1. Although *in situ* PCR for HTLV-1 can answer this question, the analysis cannot be performed at our hospital. In this case, a considerable number of CD8-positive cells was also detected in the interstitium. Therefore, these T cells in the interstitium should not originate exclusively from oncogenic proliferation of T cells infected by HTLV-1. In fact, 20 mg of oral

prednisolone per day could completely diminish all clinical symptoms and pathological findings in the kidney. Such effectiveness of 20 mg of prednisolone would be unusual in cases of ATL.

In retrospect, we are not confident that our treatment was the best choice for this patient. The PSL did completely diminish all of his clinical symptoms, and the patient is still stable. In addition, the second renal biopsy revealed that the infiltrating T lymphocytes had markedly diminished (Fig. 6). Therefore, we decided to continue the same treatment in this situation. However, this treatment would have been insufficient if the patient had been diagnosed with ATL. The patient's AST and ALT, which were elevated on admission, were dramatically decreased by PSL. If a liver biopsy had been performed, it might have shown that oncogenic T lymphocytes had infiltrated into the liver. In addition, small abdominal paraaortic lymphadenopathies (Fig. 1), which also diminished soon after treatment, might have been caused by oncogenic proliferation of lymphocytes infected by HTLV-1. However, these are now obscure. We will need to take care to rule out the presence of ATL in the future as some reports described that ATL occurred after the treatment of SLE with HTLV-1-positive patients [20, 26].

This is the first case report of lupus nephritis class I with marked interstitial infiltration of T lymphocytes, which should partly consist of oncogenic ones in an HTLV-1 patient. This case provides evidence further suggesting the involvement of HTLV-1 infection in the pathogenesis of SLE.

Fig. 5 Representative photos from the second kidney biopsy (1). **a** No apparent abnormalities were detected in the glomeruli from the second biopsy (periodic acid-Schiff stain). **b** IgG stain. **c** IgA stain. **d** IgM stain. **e** C3 stain. **f** C1q stain (**a–f** $\times 200$)

Fig. 6 Representative photos from the second kidney biopsy (2). **a** Few inflammatory cells were in the interstitium (H&E stain). **b** Few CD3-positive cells were in the interstitium

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