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ORIGINAL ARTICLE

The renal pathological findings in Japanese HIV-infected individuals with CKD: a clinical case series from a single center

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Abstract
Background Chronic kidney diseases (CKD) have emerged as a significant cause of morbidity and mortality in patients infected with human immunodeficiency virus (HIV). However, the detailed study of renal pathological findings currently remains unclear in these Japanese patients.
Methods A retrospective cohort study was undertaken to investigate renal pathological findings between January 1996 and July 2016. Our study included 20 Japanese HIV-infected patients with CKD; 10 cases had undergone renal biopsies, and 10 cases had undergone autopsies, respectively. Moreover, in the 10 biopsied patients, their clinical courses as well as renal outcomes after renal biopsy were also reviewed.
Results All of the patients had received combination antiretroviral therapy (cART). The 10 biopsy cases (mean age, 54 ± 14 years and duration of cART, 8 ± 5 years) included three cases of diabetic nephropathy (DMN), two of IgA nephropathy, two of cART-induced tubulointerstitial nephritis (TIN), one of minimal change disease, one case of only finding intrarenal arterioles, and one case without abnormal findings. Among those patients, their clinical courses were preferable except for in the DMN cases. In the autopsy cases (mean age, 52 ± 10 years and duration of cART, 5 ± 5 years), no distinct mesangial or membranous abnormalities were detected. Mild to moderate tubulointerstitial atrophies were observed in six cases. Intrarenal arteriosclerosis was identified in nine cases, and the proportion of global glomerulosclerosis seen was 8.4 ± 12.5%/100 glomeruli.
Conclusion DMN and cART-induced TIN was noted in the biopsy cases. In the autopsy cases, renal arteriosclerosis, global glomerulosclerosis, and tubulointerstitial atrophy were remarkable. Early diagnosis of kidney diseases should be crucial to introduce optimal management, including controlling rigorous comorbidities and appropriate use of cART, to prevent further progression of CKD.

Keywords Autopsy · Chronic kidney disease · Combination antiretroviral therapy · Human immune deficiency virus · Renal biopsy

Introduction

Since 1996, the longevity of patients infected with human immunodeficiency virus (HIV) has been increased by combination antiretroviral therapy (cART), and kidney diseases have emerged as a significant cause of morbidity and mortality [1]. In particular, in resource-rich settings, with increased survival and continued exposure to cART, a greater number of HIV-positive individuals are developing comorbid chronic kidney disease (CKD) risk factors, such as diabetes mellitus (DM), dyslipidemia (DL), and hypertension (HT) [1–5]. The prevalence of CKD was previously reported to be 9.7% among HIV-infected patients in Japan [CKD being defined as estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2] [1]. This has been considered relatively high prevalence compared with those in China (5.6%) [6], Europe (3.5%) [7], and the United States

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(5.0–9.7%) [8, 9]. Therefore, in Japan, the high prevalence of CKD in HIV-infected patients is a high burden of clinical issue. Before 1996, in the pre-cART era, the main cause of renal impairment was known to be HIV-associated nephropathy (HIVAN), which is characterized by collapsing focal segmental glomerulosclerosis (FSGS) in histological findings [10]. HIVAN usually occurs in states of advanced immunosuppression and in young African–Americans, while HIV immune complex kidney disease (HIVICK), which is characterized histologically by immune complex deposits in the capillary loops and mesangium, mesangial cell expansion, tubulointerstitial inflammation, and comorbidities such as DM, HT, and atherosclerosis, and various drugs including cART now complicate the landscape of kidney disease in HIV [11]. Moreover, there are different racial disparities and geographical locations in the spectrum of glomerulonephritis [11]; it may be difficult to hold consistent discussions across multiple countries. Therefore, the analysis of a Japanese cohort of HIV patients should be important to discuss the above questions. However, there are no reports of either detailed studies of the causes of renal impairment or renal pathological findings in Japanese HIV patients with CKD. We herein examined renal pathological findings on renal biopsy and autopsy specimens to assess the causes of renal impairment among Japanese HIV-infected individuals with CKD.

Materials and methods

Subjects and definitions

A retrospective cohort study was undertaken to investigate renal pathological findings between January 1996 and July 2016. Our study included 10 Japanese HIV-infected patients with CKD who had undergone renal biopsies to evaluate the causes of renal impairment. In addition, 127 cases of autopsied HIV-infected patients were extracted from our hospital in the same period. Of these, 10 cases were eligible for a pathological analysis because they had been diagnosed with CKD on cART. This study was approved by the Institutional Review Board of Tokyo Metropolitan Komagome Hospital (approval certificate no. 1864) and was conducted in accordance with the Declaration of Helsinki Principles on Human Experimentations. The electronic medical records of all patients in the cohort were reviewed to evaluate characteristics and laboratory data. We evaluated age, gender, race, cART use, urinary findings, blood tests, and the presence or absence of HT, DM, DL, hepatitis B virus (HBV), and hepatitis C virus (HCV) at the time of execution of either the renal biopsy or autopsy. CKD was defined as an eGFR <60 mL/min/1.73 m^2, sustained for at least 3 months. Nephrotic syndrome was defined as both a urinary protein creatinine ratio (UPCR) of more than 3.5 g/g and serum albumin of less than 3 g/dL. In autopsy cases, CKD was defined as being sustained for at least 3 months before death. HT was defined as a systolic blood pressure of 140 mmHg and/or a diastolic blood pressure of 90 mmHg or the use of antihypertensive agents. DM was defined as a diagnosis of DM prior to baseline or both HbA1c $\geq$6.5% and casual plasma glucose $\geq$200 mg/dL or the use of oral anti-diabetic agents or insulin. DL was defined as a total cholesterol (TC) $\geq$220 mg/dL and/or triglyceride (TG) $\geq$150 mg/dL and/or low-density lipoprotein (LDL)-cholesterol (C) $\geq$140 mg/dL and/or the use of oral hypolipidemic agents. HCV and HBV infections were defined as a positive/reactive HCV antibody test and a positive/reactive HBV antibody test, respectively. If renal impairment coincided with the time when HIV infection control had deteriorated, we regarded this finding as relevant to the HIV infection. If metabolic abnormalities that are considered to be due to cART affected renal pathological changes, or if administration of cART was directly involved with renal impairment, we regarded these findings as relevant to the cART. All renal biopsy specimens were diagnosed by a single pathologist who had prior information about the HIV status and clinical background in these patients. Definition of HIVICK was as follows: both pathologic findings consistent with lupus-like glomerulonephritis, membranous nephropathy (MN), membranoproliferative glomerulonephritis (MPGN), IgA nephropathy, postinfectious glomerulonephritis, cryoglobulinemia, and immune complex renal disease not otherwise specified and HIV infection control was deteriorating at the execution of biopsy [12, 13]. Moreover, in patients who had undergone renal biopsy, we reviewed the clinical course as well as renal outcome after renal biopsy.

Measurements

All patients provided blood and urine samples for analysis when admitted to the nephrology ward. In autopsy cases, blood and urine samples were evaluated at the time of death. Blood cell count and routine laboratory data were measured using standard methods with the automated analyzer SF-3000 Sysmex (Hitachi, Tokyo, Japan). Serum Cr was measured by an enzymatic method (N-assay L Creatinine Kit; Nittobo Medical Co. Ltd., Tokyo, Japan). eGFR was calculated based on serum Cr concentrations, using the following equation: GFR (mL/min/1.73 m^{2-}) $= 194 \times Cr^{-1.094} \times Age^{-0.287} \times 0.739$ (if female), which was developed for Japanese individuals by the Japanese Society of Nephrology due to inaccuracies in the modification of diet in renal disease (MDRD) equation for

Asian people, including the Japanese [14]. Urinary protein and occult hematuria were assessed by a dipstick test. Urinary total protein was measured using a turbidimetric method, and urine Cr was assayed using an enzymatic method. Concentrations of urinary total protein were standardized to urinary Cr of 1 g/L and denoted as UPCR. CD4 cell counts were determined using a specific monoclonal antibody and flow cytometry analysis. HIV-RNA levels were measured using the Roche Amplicor HIV Monitor assay based on the reverse transcription–polymerase chain reaction (Roche Molecular Systems, Tokyo, Japan; the lower detection limit was 50 copies/mL). Both anti-HCV antibodies and anti-HBV antibodies were measured using an enzyme immunoassay test (Abbott Laboratories, Tokyo, Japan).

After being fixed in 10% buffered formalin, obtained renal tissue was dehydrated and defatted in alcohol and benzene, and it was paraffin-embedded. Hematoxylin–Eosin (HE) staining, Periodic acid-Schiff (PAS) staining, and periodic acid-silver methenamine (PAM) staining were performed following a procedure where 2 to 3-μm thin sections were produced by microtome from the obtained kidney tissue. The sections were observed by light microscope. Immunofluorescent study and electron microscope analysis were also performed in patients who had undergone renal biopsy. The number of sclerotic glomeruli was counted per 100 glomeruli which were randomly selected, and the proportion was expressed as a percentage. The proportion of inflammatory cell infiltrations and fibrosis in tubulointerstitial lesions were evaluated according to the following definition: 0, none; 1, mild (0–25%); 2, moderate (25–50%); and 3, severe (>50%). The presence or absence of arteriosclerosis lesions was evaluated and shown as a 0 or 1. All statistical analyses were performed using JMP version 12 (SAS Institute, Cary, NC, USA). Data are shown mean ± standard deviation, unless otherwise stated.

Results

Demographics and laboratory characteristics of HIV-infected patients

The demographics and clinical characteristics of HIV-infected participants who had undergone renal biopsy or autopsy are shown in Table 1. All patients were Japanese, and they had CKD on cART. The mean age was

Table 1 Demographics and laboratory characteristics of HIV-infected patients

	HIV-infected patients who underwent renal biopsy ($n = 10$)	HIV-infected patients who underwent autopsy ($n = 10$)
Age (years)	54 ± 14	52 ± 10
Men, no. (%)	9 (90.0)	10 (100.0)
Japanese, no. (%)	10 (100)	10 (100)
Prevalence of HT, no. (%)	5 (50.0)	2 (20.0)
Prevalence of DM, no. (%)	4 (40.0)	2 (20.0)
Prevalence of DL, no. (%)	7 (70.0)	6 (60.0)
cART use, no. (%)	10 (100)	10 (100)
Prevalence of HCV infection, no. (%)	2 (20.0)	1 (10.0)
Prevalence of HBV infection, no. (%)	2 (20.0)	1 (10.0)
Duration of cART use (years)	8 ± 5	5 ± 5
Proteinuria ≥ 1+, no. (%)	6 (60.0)	6 (60.0)
Occult hematuria ≥ 1+, no. (%)	7 (70.0)	4 (40.0)
UPCR (g/g)	4.20 ± 6.00	NA
Hb (g/dL)	12.9 ± 2.59	9.20 ± 2.90
Alb (g/dL)	3.46 ± 0.95	2.63 ± 0.78
Cr (mg/dL)	1.56 ± 0.48	2.40 ± 1.51
eGFR (mL/min/1.73 m^2)	40.1 ± 16.0	40.1 ± 19.8
CD4 cell count (cells/μL)	460 ± 250	135 ± 80.0
HIV viral load (<50 copies/mL), no. (%)	5 (50.0)	5 (50.0)

Data are expressed as the mean ± standard deviation

HIV human immunodeficiency virus; *No.* number; *HT* hypertension; *DM* diabetes mellitus; *DL* dyslipidemia; *cART* combination antiretroviral therapy; *HCV* hepatitis C virus; *HBV* hepatitis B virus; *UPCR* urinary protein creatinine ratio; *Hb* hemoglobin; *alb* albumin; *Cr* creatinine; *eGFR* estimated glomerular filtration rate; *NA* not available

Table 2 Demographics of renal pathological findings in HIV-infected patients who underwent renal biopsy

Case	Comorbidity	Age (y)/gender	CD4 (cells/μL)/HIV-RNA (copies/mL)	eGFR (mL/min/1.73 m^2)	Proteinuria (dipstick test)	UPCR (g/g)	Occult hematuria (dipstick test)	Pathological diagnosis	Relevance of HIV infection	Relevance of cART
1	HBV	27/M	35/850,000	42.2	–	0.06	–	NOS	NA	NA
2	DL	40/M	633/51	75.7	4+	17.9	2+	MCNS	−	−
3	DL	66/M	463/120	35.0	±	0.34	3+	GIN	−	+
4	–	72/M	289/–	24.0	±	0.17	1+	AIN	−	+
5	HCV	55/F	237/87	41.1	±	0.13	2+	IgA nephropathy	+	−
6	DL, HT	45/M	644/–	28.9	2+	0.89	1+	Only atherosclerotic lesion	−	+
7	DL, HT, DM	66/M	414/–	27.4	4+	9.61	1+	DM nephropathy	−	−
8	DL, HT, DM	49/M	487/29,000	31.5	4+	8.86	±	DM nephropathy	−	−
9	DL, HT, DM	59/M	527/–	37.5	2+	0.80	3+	IgA nephropathy	−	−
10	DL, HT, DM, HCV, HBV	64/M	944/–	57.8	3+	3.00	–	DM nephropathy	−	+

HIV human immunodeficiency virus; *y* year; *eGFR* estimated glomerular filtration rate; *UPCR* urinary protein creatinine ratio; *cART* combination antiretroviral therapy; *DL* dyslipidemia; *HT* hypertension; *DM* diabetes mellitus; *HBV* hepatitis B virus; *HCV* hepatitis C virus; *M* male; *F* female; *NOS* not otherwise specified; *MCNS* minimal change nephrotic syndrome; *GIN* granulomatous interstitial nephritis; *AIN* acute interstitial nephritis; *NA* not available

54 ± 14 years, and 9 men were included in the biopsy cases; in the autopsy cases, the mean age was 52 ± 10 years, and all of them were men. In the biopsy cases, the prevalences of HT, DM, DL, and HCV co-infection were 50% ($n = 5$), 40% ($n = 4$), 70% ($n = 7$), and 20% ($n = 2$), respectively. In the autopsy cases, the prevalences of those comorbidities were 20% ($n = 2$), 20% ($n = 2$), 60% ($n = 6$), and 10% ($n = 1$), respectively. The prevalence of proteinuria greater than 1+ by dipstick test was 60% ($n = 6$) in both biopsy and autopsy cases. The mean duration of cART use was 8 years in the biopsy cases and 5 years in the autopsy cases, respectively. The mean UPCR was 4.20 ± 6.00 g/g in the biopsy cases. The mean eGFR value was 40.1 ± 16.0 mL/min/1.73 m^2 in the biopsy cases and 40.1 ± 19.8 mL/min/1.73 m^2 in the autopsy cases. The mean CD4 cell count was 460 ± 250 cells/μL in the biopsy cases and 135 ± 80.0 cells/μL in the autopsy cases. The proportion of HIV-RNA <50 copies/mL was 50.0% in both cases.

Renal pathological findings in biopsy and autopsy patients

Renal pathology in biopsy

Renal pathologies were reviewed in 10 biopsied HIV-infected CKD patients receiving cART (Table 2). There were three cases of diabetic nephropathy (DMN), two of IgA nephropathy, two of drug-induced tubulointerstitial nephritis (TIN), one of minimal change disease (MCD), one case of only finding intrarenal arterioles, and one case without abnormal findings. Further, the results of these pathological findings were stratified by reason [due to nephrotic syndrome (NS) or worsening renal function (WRF)] for execution of the biopsy. According to this, the three cases of DMN and one of MCD were included in the NS group. The two cases of IgA nephropathy (Fig. 1a, b), two of drug-induced TIN (Figs. 1c, 2), one case of intrarenal arterioles (Fig. 1d), and one case without abnormal findings were included in the WRF group. We defined IgA nephropathy in the WRF group as HIVICK. In the drug-induced TIN, we considered atazanavir (ATV), which is one of the protease inhibitors that causes TIN. The pathological findings of ATV-induced granulomatous interstitial nephritis (GIN) (Case #3 in Tables 2, 4) are shown in Fig. 2. Interstitial nephritis, accompanied by diffuse inflammatory infiltrates consisting of lymphocytes and plasma cells, was noted. Moreover, needle-shaped crystalline precipitation, likely in the epithelia of the tubule, surrounded by multinuclear giant cells, was very characteristic (Fig. 2a). Electron microscopy showed no electron-dense deposits in the glomeruli; however, crystalline precipitation was confirmed within the tubular

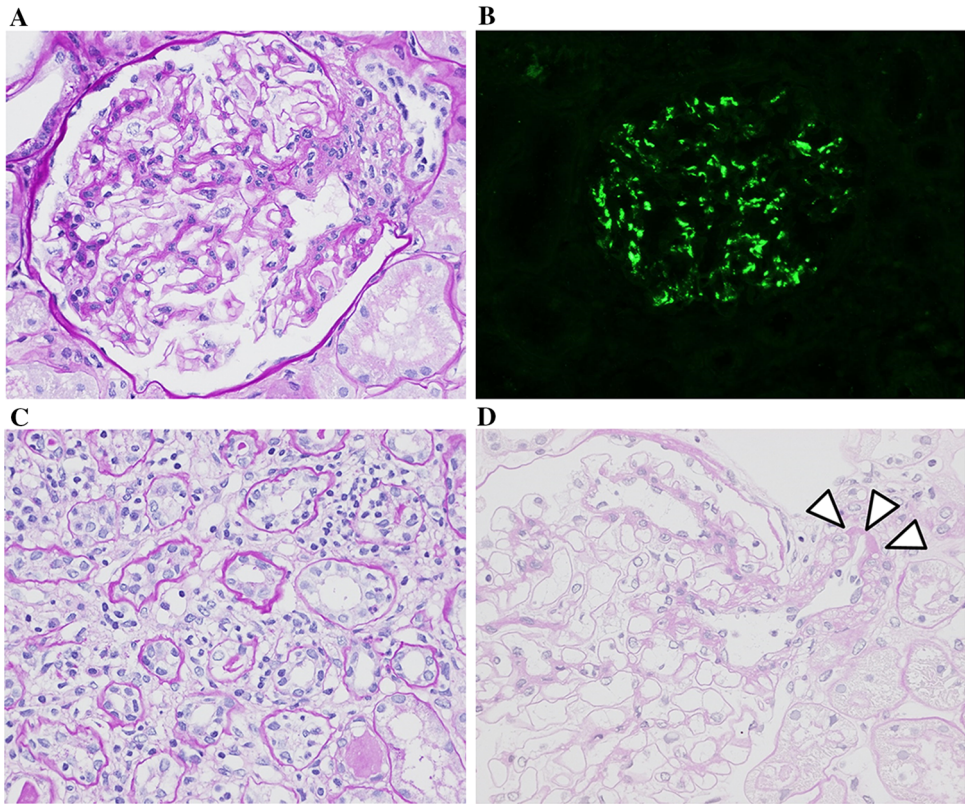

Fig. 1 **a** Periodic Acid-Schiff (PAS) stain of a glomerulus: the glomerulus has slight mesangial cellular and matrix proliferation (Patients #5 who is described in Tables 2, 4). **b** Immunofluorescence staining of a glomerulus: granular depositions of IgA were shown in the mesangial matrix area (Patients #5 who is described in Tables 2, 4). **c** PAS stain of tubulointerstitial area: infiltration of inflammatory cells (lymphocytes and neutrophils) were shown in tubules and interstitium (Patients #4 who is described in Tables 2, 4). **d** PAS stain of a glomerulus: arteriolar thickening was shown in a glomerulus (arrowheads) (Patients #6 who is described in Tables 2, 4)

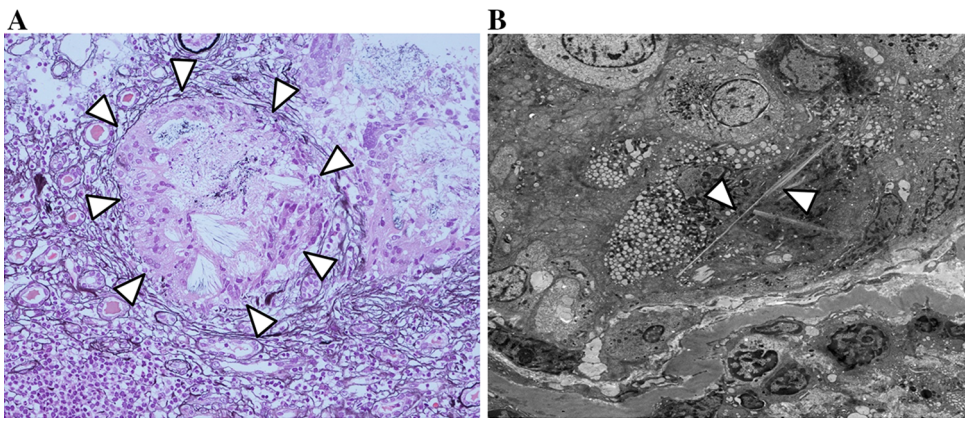

Fig. 2 Renal pathological findings on Patient #3 who is described in Tables 2 and 4. **a** Needle-shaped crystals surrounded by multinuclear giant cells in the tubular epithelium (*arrowheads*) (Periodic Acid-Methenamine-Silver stain). **b** Needle-shaped crystalline precipitation is seen within the tubular epithelial cells (*arrowheads*) (electron microscopy)

epithelial cells (Fig. 2b). In this case, we identified ATV crystals by infrared spectroscopic analysis of the urinary specimen. Therefore, we concluded the crystalline precipitation that could be detected in the pathological specimen consisted of ATV crystals.

Renal pathology in autopsy

Renal pathologies were also reviewed in 10 autopsied Japanese HIV-infected CKD patients receiving cART (Table 3). All of them received cART. The most frequent cause of death was infection ($n = 5$, 50%). No distinct mesangial or membranous abnormalities were detected. Mild to moderate tubulointerstitial atrophy was observed in six cases (60%). Intrarenal arteriosclerosis was identified in nine cases (90.0%), and the average proportion of global glomerulosclerosis was 8.4 ± 12.5%.

Clinical courses and treatments of the patients who had undergone renal biopsy

The clinical courses and treatments of the 10 HIV-infected patients are shown in Table 4. The mean follow-up period was 3.7 years [interquartile range (IQR): 1.7–4.7 years]. All patients had been receiving cART. Two out of the three DMN cases had been receiving angiotensin receptor

Table 3 Autopsied patient characteristics and renal pathologies

Case	Comorbidity	Age (y)/gender	cART	Cause of death	eGFR (mL/min/1.73 m^2)	CD4 (cells/μL)/HIV-RNA (copies/mL)	Glomerulus			Tubules and interstitia	Intrarenal arterioles
							Mesangial abnormalities	Membrane abnormalities	Proportion of global glomerulosclerosis, no. (%)		Arteriosclerosis
1	–	35/M	+	Lymphoma	5.9	<200/39,000	–	–	1 (1)	0	0
2	DL	46/M	+	Lymphoma	55.9	<200/<400	–	–	2 (2)	0	1
3	–	40/M	+	Sepsis	57.2	<200/< 400	–	–	0 (0)	0	1
4	–	58/M	+	Lymphoma	49.3	<200/14,000	–	–	10 (10)	1	1
5	DL, HT	51/M	+	PCP	56.6	<200/<400	–	–	12 (12)	2	1
6	DL	57/M	+	Sepsis	53.0	<200/<400	–	–	1 (1)	0	1
7	DL, DM	59/M	+	Sepsis	32.8	<200/<400	–	–	16 (16)	2	1
8	–	45/M	+	PCP	54.8	<200/63,0000	–	–	2 (2)	1	1
9	DL	62/M	+	IP	20.9	<200/69,000	–	–	0 (0)	2	1
10	DL, DM, HT	66/M	+	CI	14.8	281/300	–	–	40 (40)	2	1

y year; *cART* combination antiretroviral therapy; *eGFR* estimated glomerular filtration rate; *HIV* human immunodeficiency virus; *DL* dyslipidemia; *HT* hypertension; *DM* diabetes mellitus; *M* male; *PCP* pneumocystis jirovecii pneumonia; *IP* interstitial pneumoniae; *CI* cerebral infarction

blockers (ARB) or angiotensin-converting enzyme inhibitor (ACE-I) agents. In those patients, one patient started hemodialysis 2 years and 4 months after renal biopsy (Case #7 in Tables 2, 4), while in the other case, renal function had deteriorated (serum creatinine levels of more than two times normal) 2 years after renal biopsy (Case #8 in Tables 2, 4). One IgA nephropathy case, defined as HIVICK, did not have any deterioration in renal function with only conventional therapy and tight HIV infection control by continuous treatment with cART (Case #5 in Tables 2, 4). In the other case of IgA nephropathy, the patient had received prednisolone (PSL) therapy following a tonsillectomy due to a moderate histological grade and had a good clinical course where proteinuria and occult hematuria disappeared and the serum creatinine level was stable for 8 months after commencement of PSL therapy (Case #9 in Tables 2, 4). In the patients with ATV-induced TIN, one case had renal function improved only after the cessation of ATV (Case #4 in Tables 2, 4). The other case with ATV-induced TIN also had improved renal function by the combination therapy of ATV cessation and administration of PSL (Case #3 in Tables 2, 4). The MCD patient had intractable nephrotic syndrome, though he received a combination therapy with PSL, cyclosporine, and tacrolimus. Therefore, he received rituximab after the administration of these immunosuppressive therapies. Following administration of rituximab, his nephrotic syndrome went into complete remission (CR) (Case #2 in Tables 2, 4).

Discussion

We showed the first case series of renal pathological findings in Japanese HIV-infected individuals with CKD. In our study, DMN was the most common, and two cases of ATV-induced TIN and a case of IgA nephropathy, defined as HIVICK, were involved in the biopsy cases. Among those patients, the clinical courses of renal function were preferable except for in the DMN cases. On the other hand, there were no cases of glomerulonephritis in the autopsy cases, while findings of arteriosclerosis and tubulointerstitial damages were noted in these patients.

In the renal biopsy cases, there were no HIVAN cases. The most common pathological finding was DMN. Two cases of ATV-induced TIN and one of IgA nephropathy as HIVICK were also included. HIVAN is characterized by collapsing focal segmental glomerulosclerosis (FSGS), microcystically dilated tubules, and tubulointerstitial inflammation [10, 11]. Genetic susceptibility to HIVAN had originally been attributed to genetic variations within non-muscle MYH9 and is now considered to be due to APOL1. An association has been shown between the

Table 4 Treatment and clinical course of HIV-infected patients who underwent renal biopsy

Case	Age (y)/gender	Follow-up period (y)	Indication of renal biopsy (NS or WRF)	Pathological diagnosis	Treatment	Clinical course
1	27/M	4.8	WRF	NOS	None	Both Cre and urinary findings were unchanged
2	40/M	5	NS	MCNS	PSL, CyA, TAC, and rituximab	CR
3	66/M	4.3	WRF	GIN	Cessation of ATV and PSL daily for 4 weeks	Both Cre and urinary findings were unchanged (Cre 1.7–1.6 mg/dL, Pro trace, and OB 3+)
4	72/M	4.1	WRF	AIN	Cessation of ATV	Both Cre and urinary findings were improved (Cre 2.2–1.6 mg/dL, disappearance of Pro, OB)
5	55/F	4.7	WRF	IgA nephropathy	None	Both Cre and urinary findings were unchanged (Cre 1.1–1.2 mg/dL, Pro 2+ , and OB 1+)
6	45/M	3.3	WRF	Only atherosclerotic lesion	None	Both Cre and urinary findings were improved (Cre 2.1–1.2 mg/dL, Pro 2+ to 1+ , and OB 1+ to trace)
7	66/M	2.4	NS	DM nephropathy	None	Commencement of HD
8	49/M	2	NS	DM nephropathy	Administration of ARB	Urinary findings were unchanged, Cre was exacerbated (1.9–4.3 mg/dL)
9	59/M	1	WRF	IgA nephropathy	PSL therapy following tonsillectomy	Both Cre and urinary findings were improved (Cre 1.7–1.2 mg/dL, Pro 2+ to trace, OB 3+ to trace)
10	64/M	0.8	NS	DM nephropathy	Administration of ACE inhibitor	Both Cre and urinary findings were unchanged (Cre 1.0–1.1 mg/dL, Pro 2+ , and OB−)

HIV human immunodeficiency virus; *y* year; *M* male; *F* female; *WRF* worsening renal function; *NS* nephrotic syndrome; *NOS* not otherwise specified; *MCNS* minimal change nephrotic syndrome; *GIN* granulomatous interstitial nephritis; *AIN* acute interstitial nephritis; *DM* diabetes mellitus; *PSL* prednisolone; *CyA* cyclosporine; *TAC* tacrolimus; *ATV* atazanavir; *ARB* angiotensin receptor blocker; *ACE* angiotensin-converting enzyme; *Cre* creatinine; *CR* complete remission; *Pro* proteinuria; *OB* occult blood; *HD* hemodialysis

APOL1 gene on chromosome 22 (seen in African-Americans) that expresses on podocytes and FSGS [15, 16]. Moreover, the percentage of glomerulonephritis had been determined mainly by ratios of African-American and Caucasian patients in past studies [13–15]. Thus, the former category of patients has a much higher prevalence of HIVAN. On the other hand, a lower proportion of African-Americans leads to lower ratios of glomerulonephritis. This finding suggested that HIVAN is a more common histological pattern in African-Americans than in other races. We showed summary of clinical characteristics of previously reported study of both biopsy and autopsy in HIV-infected patients in Table 5. According to this, there were no cases of HIVAN in the reports of India [17] and Thailand [18]. Moreover, there were several case reports in Japanese HIV-infected individuals (one case of Henoch–Schönlein purpura nephritis [19], three cases of acute interstitial nephritis (AIN) [20–22], and one case of GIN [23]). In addition, HIVAN cases were not observed among these reports. We considered that these results consistent with our results. Therefore, HIVAN may not have been prioritized as a differential diagnosis in Japanese HIV patients with renal impairment. On the other hand, HIVICK is characterized histologically by immune complex glomerular disease, including MN, MPGN, IgA nephropathy, and lupus-like glomerulonephritis. The direct role of HIV infection in its pathogenesis is not clear [24]. Several reports have showed that more than half of the pathological findings in HIV patients were HIVICK regardless of race. Therefore, HIVICK may be a crucial pathogenesis of renal impairment in HIV patients [11, 25]. Indeed, IgA nephropathy, which was considered HIVICK, was included in our study. We may have the opportunity to meet such patients in clinical settings in Japan. No comparative studies have reported on the treatment methods and therapeutic effects between HIVICK and non-HIVICK glomerulonephritis. The case of IgA nephropathy (Case #5 in Tables 2, 4) had a good renal outcome for about 4.5 years through both good HIV infection control and conventional therapies. Booth et al. demonstrated that HIVICK was associated with lower rates of progression to end stage renal disease (ESRD) compared with HIVAN in a multicenter study (included 65 HIVICK and 70 HIVAN patients) during a median follow-up period of 3.5 years [26]. We consider HIVICK may have good renal outcome, after taking the above past study's results and the good

Table 5 Summary of clinical characteristics of previously-reported study that biopsy and autopsy in HIV-infected patients from 1996 to 2016

References	Country	Patients number (n)	Mean age (y)	Gender, male (%)	Proportion of African-American (%)	Proportion of HIVAN in renal pathological findings (%)
Praditpornsilpa et al. [18]	Thailand	26	31	58	0	0
Winston et al. [32]	USA	20	24–58 (range)	NA	53	50
Ahuja et al. [33]	USA	14	37	79	75	64
Szczech et al. [34]	USA	89	42	82	89	47
Han et al. [35]	South Africa	30	35	40	97	83
Gerntholtz et al. [36]	South Africa	99	35	87	100	27
Berliner et al. [37]	USA	152	43	66	91	35
Nebuloni et al. [38]	Italy	73	31	56	78	12
Gupta et al. [17]	India	26	37	81	0	0
Foy et al. [12]	USA	267	42 (median)	59	96	21
Booth et al. [26]	UK	162	40	62	99	43
Present study[a]	Japan	20	53	95	0	0

HIV human immunodeficiency virus; *n* number; *y* years; *HIVAN* HIV-associated nephropathy; *NA* not available; *USA* United States of America; *UK* United Kingdom

[a] Inclusion of autopsy data. Study of autopsy was not founded except for our report

renal outcome in our case into consideration. On the other hand, in DMN patients, there is no effective treatment other than renin angiotensin system inhibitors, such as ARB and ACE-I. Additionally, the progression of renal impairment may be faster due to comorbidities that may induce cART, such as DL, HT, and even DM itself. Indeed, in two out of three patients, their renal function worsened, and one patient needed hemodialysis. Therefore, we consider that DM and DMN are crucial part of HIV treatment-related kidney disease. Early management of DM and comorbidities is necessary to prevent renal impairment in HIV-infected DMN patients.

It has been well known that some cART agents are related to renal impairment. In cART, Tenofovir (TDF), which could induce TIN, has been famous for its adverse effects [27, 28]. There were no patients taking TDF at the start of the study; however, four patients ($n = 4$, 40%) had been receiving TDF before the initiation of this study (mean administration period was 2.2 ± 1.7 years), though there were no patients with tubulointerstitial impairments. On the other hand, the patients with ATV-induced TIN (Case #4 in Tables 2, 4) and GIN (Case #3 in Tables 2, 4) were included, and this was very interesting. ATV is a widely used protease inhibitor for the treatment of patients infected with HIV. Brewster and Perazella first described acute interstitial nephritis associated with ATV in 2004 [29]. There are nine case reports showing an association between ATV and TIN including GIN [30]. In our study, both cases (Case #3, 4 in Tables 2, 4) had improved renal impairment by only cessation of ATV in one case and PSL therapy following cessation of ATV in the other case. We should be recognized this drug-induced glomerulonephritis as one of the important factors of renal impairment under administration of cART.

There were also no patients with HIVAN in the autopsy study. Glomerulosclerosis, intrarenal arteriosclerosis, and TIN were noted. The fact that HIVAN is rarely diagnosed in Japanese patients because it is thought to occur in the context of the geographical and genetic backgrounds that are mentioned above are consistent with the results in this study. Hailemariam et al. reported that the most common glomerular findings were ischemic changes, vascular scars, and glomerulosclerosis in 239 Caucasian HIV autopsied patients before the cART era [31]. This result resembles ours in the findings of glomerular lesions. It has been shown that upregulation of many genes that mediate the inflammatory response in renal epithelial cells, such as chemokines, cytokines, and adhesion molecules, occurs in HIV-infected patients. In addition, there were high prevalence of comorbidities (two cases had DM, two cases had HT, and six cases had DL in our study). These mechanisms and results may lead to intrarenal arteriosclerosis and TIN. As to the difference in the findings of renal pathology between the biopsy and autopsy cases, the pathological findings in the autopsy patients were evaluated just at the time of death following the usual HIV clinical treatment, while the pathological findings in the biopsy patients were evaluated when nephrologists desired examination for pathological study due to nephrotic syndrome, and drug-induced renal impairment. Therefore, we consider these differences of renal pathological findings between the autopsy cases and biopsy cases.

There were several limitations in this study. First, because this was a single center study, only 20 HIV-

infected individuals with CKD were included. However, there were no reports of similar previous research in Japan, and the number of HIV patients in Japan are only about 0.02% of the general population (the United States has twenty times the number of HIV-infected patients); therefore, our study population may not be considered small in Japan. Second, because the participants in this study were collected after 1996, it is difficult to assess the direct relationship between HIV infection and renal dysfunction because of the influence of comorbidities such as HT, DM, and DL that occurred by cART and cART itself. However, cART was used in most clinical treatments of HIV patients in Japan. Therefore, the results of the present study are considered to be more suitable for the clinical settings in Japan. Third, selection bias might be existed in biopsy cases because examinations for pathological study were decided at the discretion of each nephrologists according to presence or absence of nephrotic syndrome and/or worsening renal function.

In conclusion, DMN and cART-induced TIN were noted; however, there were no HIV-infected individuals with HIVAN. In autopsy cases, renal arteriosclerosis, global glomerulosclerosis, and tubulointerstitial atrophy were remarkable. According to these results, we consider that renal impairment caused by comorbidities such as DM, HT, DL is common in Japanese HIV-infected individuals. Therefore, early diagnosis of kidney diseases by screening of HIV-positive individuals is critical to introduce prompt optimal management, including management of the comorbidities of these patients.

Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interest.

Informed consent Informed consent was obtained from all participants prior to enrollment.

Research involving human participants This study was approved by the Institutional Review Board of Tokyo Metropolitan Komagome Hospital (approval certificate no. 1864) and was conducted in accordance with the Declaration of Helsinki Principles on Human Experimentations.

References

1. Yanagisawa N, Ando M, Ajisawa A, Imamura A, Suganuma A, Tsuchiya K, Nitta K. Clinical characteristics of kidney disease in Japanese HIV-infected patients. Nephron Clin Pract. 2011;118:c285–91.
2. Horberg M, Tang B, Towner W, Silverberg M, Bersoff-Matcha S, Hurley L, Chang J, Blank J, Quesenberry C Jr, Klein D. Impact of tenofovir on renal function in HIV-infected, antiretroviral-naive patients. J Acquir Immune Defic Syndr. 2010;53:62–9.
3. Mocroft A, Kirk O, Reiss P, De Wit S, Sedlacek D, Beniowski M, Gatell J, Phillips AN, Ledergerber B, Lundgren JD, EuroSIDA Study Group. Estimated glomerular filtration rate, chronic kidney disease and antiretroviral drug use in HIV-positive patients. AIDS. 2010;24:1667–78.
4. Mocroft A, Lundgren J, Ross M, Law M, Reiss P, Kirk O, Smith C, Wentworth D, Heuhaus J, Fux C, Moranne O, Morlat P, Johnson M, Ryom L, Data on Adverse Events (D:A:D) study group, the Royal Free Hospital Clinic Cohort and the INSIGHT study group. A clinically useful risk-score for chronic kidney disease in HIV infection. J Int AIDS Soc. 2014;17:19514.
5. Young J, Schafer J, Fux CA, Furrer H, Bernasconi E, Vernazza P, Calmy A, Cavassini M, Weber R, Battegay M, Bucher HC, Swiss HIV Cohort Study. Renal function in patients with HIV starting therapy with tenofovir and either efavirenz, lopinavir or atazanavir. AIDS. 2012;26:567–75.
6. Cheung CY, Wong KM, Lee MP, Liu YL, Kwok H, Chung R, Chau KF, Li CK, Li CS. Prevalence of chronic kidney disease in Chinese HIV-infected patients. Nephrol Dial Ttransplant. 2007;22:3186–90.
7. Mocroft A, Kirk O, Gatell J, Reiss P, Gargalianos P, Zilmer K, Beniowski M, Viard JP, Staszewski S, Lundgren JD. Chronic renal failure among HIV-1-infected patients. AIDS. 2007;21:1119–27.
8. Estrella MM, Parekh RS, Astor BC, Bolan R, Evans RW, Palella FJ Jr, Jacobson LP. Chronic kidney disease and estimates of kidney function in HIV infection: a cross-sectional study in the multicenter AIDS cohort study. J Acquir Immune Defic Syndr. 2011;57:380–6.
9. Fernando SK, Finkelstein FO, Moore BA, Weissman S. Prevalence of chronic kidney disease in an urban HIV infected population. Am J Med Sci. 2008;335:89–94.
10. D'Agati V, Suh JI, Carbone L, Cheng JT, Appel G. Pathology of HIV-associated nephropathy: a detailed morphologic and comparative study. Kidney Int. 1989;35:1358–70.
11. Diana NE, Naicker S. Update on current management of chronic kidney disease in patients with HIV infection. Int J Nephrol Renovascular Dis. 2016;9:223–34.
12. Foy MC, Estrella MM, Lucas GM, Tahir F, Fine DM, Moore RD, Atta MG. Comparison of risk factors and outcomes in HIV immune complex kidney disease and HIV-associated nephropathy. Clin J Am Soc Nephrol. 2013;8:1524–32.
13. Couser WG. Basic and translational concepts of immune-mediated glomerular diseases. J Am Soc Nephrol. 2012;23:381–99.
14. Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, Yamagata K, Tomino Y, Yokoyama H, Hishida A, Collaborators developing the Japanese equation for estimated GFR. Revised equations for estimated GFR from serum creatinine in Japan. Am J Kidney Dis. 2009;53:982–92.
15. Genovese G, Friedman DJ, Ross MD, Lecordier L, Uzureau P, Freedman BI, Bowden DW, Langefeld CD, Oleksyk TK, Uscinski Knob AL, Bernhardy AJ, Hicks PJ, Nelson GW, Vanhollebeke B, Winkler CA, Kopp JB, Pays E, Pollak MR. Association of trypanolytic ApoL1 variants with kidney disease in African Americans. Science. 2010;329:841–5.
16. Kopp JB, Smith MW, Nelson GW, Johnson RC, Freedman BI, Bowden DW, Oleksyk T, McKenzie LM, Kajiyama H, Ahuja TS, Berns JS, Briggs W, Cho ME, Dart RA, Kimmel PL, Korbet SM, Michel DM, Mokrzycki MH, Schelling JR, Simon E, Trachtman H, Vlahov D, Winkler CA. MYH9 is a major-effect risk gene for focal segmental glomerulosclerosis. Nat Genet. 2008;40:1175–84.
17. Gupta V, Gupta S, Sinha S, Sharma SK, Dinda AK, Agarwal SK, Tiwari SC, Ekka M. HIV associated renal disease: a pilot study from north India. Indian J Med Res. 2013;137:950–6.
18. Praditpornsilpa K, Napathorn S, Yenrudi S, Wankrairot P, Tungsaga K, Sitprija V. Renal pathology and HIV infection in Thailand. Am J Kidney Dis. 1999;33:282–6.

19. Hidaka H, Okada T, Matsumoto H, Yoshino M, Nagaoka Y, Takeguchi F, Iwasawa H, Tomaru R, Wada T, Shimizu T, Ohtani M, Yamanaka K, Fukutake K, Nakao T. Henoch–Schönlein purpura nephritis in a patient infected with the human immunodeficiency virus. Nihon Jinzo Gakkai Shi. 2003;45:387–92.
20. Nishijima T, Yazaki H, Hinoshita F, Tasato D, Hoshimoto K, Teruya K, Gatanaga H, Kikuchi Y, Oka S. Drug-induced acute interstitial nephritis mimicking acute tubular necrosis after initiation of tenofovir-containing antiretroviral therapy in patient with HIV-1 infection. Intern Med. 2012;51:2469–71.
21. Tajima K, Kohno K, Shiono Y, Suzuki I, Kato Y, Hiroshima Y, Yamamoto M, Ohtake H, Iwaba A, Yamakawa M, Kato T. Acute kidney injury and inflammatory immune reconstitution syndrome in mixed genotype (A/E) hepatitis B virus co-infection in HIV-associated lymphoma. Int J Clin Exp Pathol. 2013;6:536–42.
22. Doi A, Iwata K, Hara S, Imai Y, Hasuike T, Nishioka H. Interstitial nephritis caused by HIV infection by itself: a case report. Int J Gen Med. 2016;9:311–4.
23. Kanzaki G, Tsuboi N, Miyazaki Y, Yokoo T, Utsunomiya Y, Hosoya T. Diffuse tubulointerstitial nephritis accompanied by renal crystal formation in an HIV-infected patient undergoing highly active antiretroviral therapy. Intern Med. 2012;51:1543–8.
24. Ando M, Yanagisawa N. Epidemiology, clinical characteristics, and management of chronic kidney disease in human immunodeficiency virus-infected patients. World J Nephrol. 2015;4:388–95.
25. Nochy D, Glotz D, Dosquet P, Pruna A, Guettier C, Weiss L, Hinglais N, Idatte JM, Méry JP, Kazatchkine M, et al. Renal disease associated with HIV infection: a multicentric study of 60 patients from Paris hospitals. Nephrol Dial Transplant. 1993;8:11–9.
26. Booth JW, Hamzah L, Jose S, Horsfield C, O'Donnell P, McAdoo S, Kumar EA, Turner-Stokes T, Khatib N, Das P, Naftalin C, Mackie N, Kingdon E, Williams D, Hendry BM, Sabin C, Jones R, Levy J, Hilton R, Connolly J, Post FA; HIV/CKD Study and the UK CHIC Study. Clinical characteristics and outcomes of HIV-associated immune complex kidney disease. Nephrol Dial Transplant. 2016;31:2099–107.
27. Izzedine H, Harris M, Perazella MA. The nephrotoxic effects of HAART. Nat Rev Nephrol. 2009;5:563–73.
28. Izzedine H, Hulot JS, Vittecoq D, Gallant JE, Staszewski S, Launay-Vacher V, Cheng A, Deray G, Study 903 Team. Long-term renal safety of tenofovir disoproxil fumarate in antiretroviral-naive HIV-1-infected patients. Data from a double-blind randomized active-controlled multicentre study. Nephrol Dial Transplant. 2005;20:743–6.
29. Brewster UC, Perazella MA. Acute interstitial nephritis associated with atazanavir, a new protease inhibitor. Am J Kidney Dis. 2004;44:e81–4.
30. Hara M, Suganuma A, Yanagisawa N, Imamura A, Hishima T, Ando M. Atazanavir nephrotoxicity. Clin Kidney J. 2015;8:137–42.
31. Hailemariam S, Walder M, Burger HR, Cathomas G, Mihatsch M, Binswanger U, Ambühl PM. Renal pathology and premortem clinical presentation of Caucasian patients with AIDS: an autopsy study from the era prior to antiretroviral therapy. Swiss Med Wkly. 2001;131:412–7.
32. Winston JA, Klotman ME, Klotman PE. HIV-associated nephropathy is a late, not early, manifestation of HIV-1 infection. Kidney Int. 1999;55:1036–40.
33. Ahuja TS, Borucki M, Funtanilla M, Shahinian V, Hollander M, Rajaraman S. Is the prevalence of HIV-associated nephropathy decreasing? Am J Nephrol. 1999;19:655–9.
34. Szczech LA, Gupta SK, Habash R, Guasch A, Kalayjian R, Appel R, Fields TA, Svetkey LP, Flanagan KH, Klotman PE, Winston JA. The clinical epidemiology and course of the spectrum of renal diseases associated with HIV infection. Kidney Int. 2004;66:1145–52.
35. Han TM, Naicker S, Ramdial PK, Assounga AG. A cross-sectional study of HIV-seropositive patients with varying degrees of proteinuria in South Africa. Kidney Int. 2006;69:2243–50.
36. Gerntholtz TE, Goetsch SJ, Katz I. HIV-related nephropathy: a South African perspective. Kidney Int. 2006;69:1885–91.
37. Berliner AR, Fine DM, Lucas GM, Rahman MH, Racusen LC, Scheel PJ, Atta MG. Observations on a cohort of HIV-infected patients undergoing native renal biopsy. Am J Nephrol. 2008;28:478–86.
38. Nebuloni M, Barbiano di Belgiojoso G, Genderini A, Tosoni A, Riani LN, Heidempergher M, Zerbi P, Vago L. Glomerular lesions in HIV-positive patients: a 20-year biopsy experience from Northern Italy. Clin Nephrol. 2009;72:38–45.