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Masahiro Kyo
Motoaki Hatori
Shiro Takahara
Miyaji Kyakuno
Takayuki Nakamura
Masanao Okada
Yukito Kokado
Kiyohide Toki
Xiao-Q:lang Ding
Tuneharu Miki
Makoto Miyamoto
Akihiko Okuyama

Morphological findings in non-episode biopsies of kidney transplant allografts treated with FK506 or cyclosporine

M. Kyo (✉)
Sakurabashi Circulate Organ Clinic 1100,
1-3-1 Umeda, Kita-ku, Osaka 530, Japan
Tel. + 81-6-344-6611; Fax + 81-6-344-6631

M. Hatori
Department of Urology,
Gunma University School of Medicine,
3-39-15 Showa-machi, Maebashi city,
Gunma, Japan

S. Takahara · Y. Kokado · K. Toki ·
X.-Q. Ding · T. Miki · M. Miyamoto ·
A. Okuyama
Department of Urology and Pathology,
Osaka University School of Medicine,
2-2 Yamadaoka Suita-city, Osaka 565,
Japan

M. Kyakuno · T. Nakamura ·
M. Okada
Department of Urology and Pathology,
Osaka Senninhoken Hospital,
1-8-30 Chikkou, Minato-ku, Osaka 552,
Japan

Abstract We conducted an analysis of biopsy specimens of non-episode renal allografts from patients treated with tacrolimus (FK506) or cyclosporine (CsA) to evaluate chronic drug-induced nephropathy in stable allografts. A total of 38 biopsy specimens from stable functioning renal allografts were examined. The patients had been treated with FK506 (n = 16) or CsA (n = 18) as main immunosuppressant for 0.3 to 7.4 years. Of the 38 biopsy specimens, 15 showed mild drug-induced arteriolopathy (hyalinosis or insudative change of arterioles and small arteries) with striped-form interstitial fibrosis, 10 showed minimum interstitial cellular infiltration (borderline rejection), 2 showed IgA nephropathy, 4 showed evidence of chronic rejection (transplant nephropathy) and 12 showed no abnormal findings. Of 34 renal allograft biopsy specimens with stable function, 22 (65%) showed pathological evidence of drug-induced nephropathy. There were no significant qualitative or quantitative differences between FK506- and CsA-associated nephropathy.

Key words Non-episode biopsy · Cyclosporin · Tacrolimus · Drug-induced arteriolopathy

Introduction

FK506 has been successfully used in clinical organ transplantation since 1989 [1]. Graft and patient survival rates in short-term [2] and long-term studies [3] of renal allografts under FK506 treatment are similar to those under cyclosporine (CsA) treatment. Adverse events with FK506 are also similar to those with CsA [4], and of these, renal disorder has emerged as an especially serious problem in renal allografts.

It has been reported that subclinical rejection is apparent in protocol biopsies within 1 year of renal allograft [5, 6], but there have been no reports of histological confirmation of the incidence of subclinical drug-induced nephropathy, particularly FK506-associated nephropathy, by non-episode biopsy.

In this study, we analysed the clinical data and histopathological findings obtained from biopsies of renal allografts from patients who had been treated with FK506 or CsA continuously.

Materials and methods

A total of 34 biopsy specimens from 31 renal allografts were studied. These biopsy specimens were taken from stable functioning renal allografts (serum creatinine (S-Cr) < 2.0 mg/dl and urine protein negative or trace after) obtaining informed consent (for non-episode biopsy) from the patients. The patients had been treated

Table 1 Pathological findings from the non-episode biopsies from patients treated with FK506 (*FAA* FK506-associated arteriolopathy)

	Year after transplantation						Total
	0–1	1–2	2–3	3–4	4–5	5 +	
Number	3	0	3	4	3	3	16
Normal findings	1		1	3	1	1	7
Acute rejection (borderline)	1		2				3
Chronic rejection			1		2	1	4
IgA nephropathy			1				1
FAA (mild-type)	2		1	1		2	6

Table 2 Pathological findings from the non-episode biopsies from patients treated with CsA (*CAA* CsA-associated arteriolopathy)

	Year after transplantation						Total
	0–1	1–2	2–3	3–4	4–5	5 +	
Number	2	5	2	0	3	6	18
Normal findings		1	1		1	2	5
Acute rejection (borderline)	2	2	1		2		7
IgA nephropathy						1	1
CAA (mild-type)		3	1		2	3	9

with FK506 ($n = 13$) or CsA ($n = 18$) as main immunosuppressant (+ steroids) at the Department of Urology, Osaka University School of Medicine Hospital.

Also studied, for comparison, were 15 episode biopsies.

Biopsy samples were obtained using with a 16-gauge Bird biopsy needle and a biopsy gun under ultrasound guidance. For light microscopy, the biopsied materials were immediately fixed with 10% buffered formalin and processed for paraffin embedding. Each biopsy specimen was stained with haematoxylin and eosin (HE) stain, periodic acid schiff (PAS) stain and periodic acid methenamine silver (PAM) stain. If necessary, immunostaining was also carried out.

The chi-squared test with Yates' correction and the Mann-Whitney test were used to evaluate the significance of differences.

Results

Table 1 shows a summary of the histopathological diagnoses of the 16 non-episode graft biopsies treated with FK506 (overlapping diagnoses). Seven biopsies showed no abnormal findings. Three biopsies showed mild interstitial cellular infiltration, which was classified as borderline acute rejection (AR) according to the Banff working classification. Four showed grade 1 chronic rejection (CR), one showed silent IgA nephropathy, and six showed mild FK506-associated arteriolopathy (FAA) (Fig. 1). The histopathological diagnoses of the

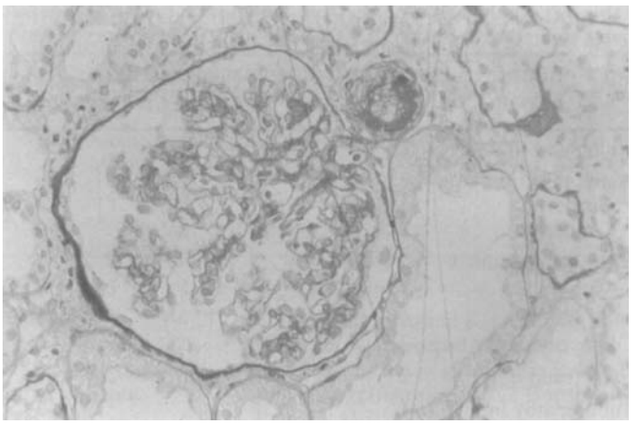

Fig. 1 FK506-associated arteriolopathy showing insudative change (PAS stain, × 400)

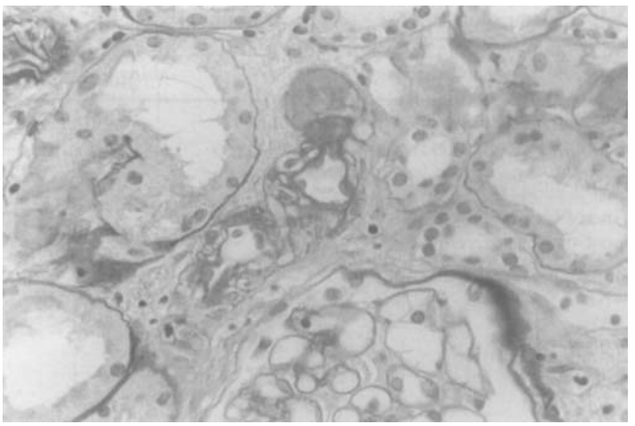

Fig. 2 CsA-associated arteriolopathy showing subendothelial and medial hyalinosis (PAS stain, × 800)

18 biopsies treated with CsA is (summarized in Table 2) one were as follows: no abnormal findings, five; silent IgA nephropathy, one; mild CsA-associated arteriolopathy (CAA) (Fig. 2), nine.

Drug-induced arteriolopathy was present in each stage after renal transplantation, and was confirmed mainly by the deposition of hyaline-like substance and the severity as well as the amount of destroyed vascular structure. The age of the patients and the findings from the 1-h or previous biopsy, if it had been performed, were also considered. Minimum arteriolar changes and vacuolization of proximal tubular cells were not classified as drug-induced lesions.

In total, 15 out of 34 biopsies (44%) included mild FAA or CAA, 11 (32%) showed no abnormal findings and 10 (29%) showed borderline AR that was observed in biopsies taken in comparatively early years after transplantation. No clinical rejection crisis was seen in

Table 3 Pathological findings from the episode biopsies from patients treated with FK506 (*FAA* FK506-associated arteriolopathy)

	Year after transplantation					Total
	1–2	2–3	3–4	4–5	5 +	
Number	3	5	2	3	2	15
Acute rejection						
Borderline	1	1	1		1	4
Grade 1	2	3	1	1		7
Chronic rejection						
Grade 1	1	5	2	1	1	10
Grade 2	1					1
Glomerulonephritis	3	2			1	6
FAA (mild-type)	2	3	1	1	2	9
Tubulopathy (mild)	1	1	1			3

Table 4 Clinical characteristics of all patients. Values are means ± SD (*CAA* CsA-associated arteriolopathy, *FAA* FK506-associated arteriolopathy, *S-Cr* serum creatinine)

	Control	CAA or FAA (mild-type)
Number	20	14
S-Cr (mg/dl)	1.29 ± 0.08*	1.60 ± 0.10*
Donor age (years)	53 ± 3	59 ± 2
Tine of biopsy (post-transplant year)	3.5 ± 0.6	3.5 ± 0.5
Anti-hypertensive therapy		
No	10	7
Yes	10	8
Diabetes mellitus		
No	17	13
Yes	3	2

* $P < 0.05$

these cases afterwards. Biopsies from two FK506-treated patients and one CsA-treated patient showed slight vacuolization of the proximal tubules.

Table 3 shows the results from the episode biopsies from patients treated with FK506. Episode biopsies were taken at the time of an increase in S-Cr and/or positive proteinuria. These cases included grade 1 AR, grade 2 CR and mild tubulopathy which the non-episode biopsies did not have.

Table 4 shows the clinical findings in the patients with mild arteriolopathy. S-Cr was significantly higher ($P < 0.05$) in the mild arteriolopathy group than in the control group without arteriolopathy. There were no significant differences between the two groups in terms of the age of the donors at the time of transplantation, biopsy timing, administration of hypotensive agents, or the presence or absence of diabetes mellitus.

Discussion

It has been reported that subclinical rejection is apparent in protocol biopsies within 1 year of renal allografting, but there have been no reports of histological confirmation of the incidence of subclinical FK506 nephropathy by non-episode biopsy. The histological changes in chronic FK506 nephropathy were mainly FAA and striped-form interstitial fibrosis. Various degrees of FAA were observed from the deposition of hyaline-like substance in lump form under the endothelial cells, to the replacement of all the vascular smooth muscle cells and destruction of the vascular wall structure, and these were also seen in CAA. In both non-episode and episode biopsy specimens, chronic FK506 nephropathy was observed histologically in 48.4% (6/16 non-episode, 7/15 episode), indicating a high incidence. On the other hand, the incidence of chronic CsA nephropathy in biopsies from those treated with long-term CsA was higher than that reported by Mihatsch et al. [7] (10/15 specimens; 66.7%) and also higher than the previously reported incidence of CAA (14.1–15.1%) [8].

Two cases of slight vacuolization of the proximal tubules were found in FK506-treated patients and one case in CsA-treated patients. This is an acute-type FK506 nephropathy frequently observed in the early stages of renal transplantation and which is also observed in acute CsA nephropathy.

It is still unclear how much the transplanted kidney function is influenced by chronic CsA renal disorder alone. Morozumi et al. [9] investigated transplanted kidney specimens which were obtained from episode biopsies conducted at the time of an increase in S-Cr, and found that the prognosis was poorer in the group in which rejection and chronic CsA nephropathy was observed than in the group in which rejection alone was noted, but that the function of the transplanted kidney was not influenced by a CAA lesion alone. It is reasonable to assume that a similar status exists in chronic FK506 nephropathy mainly observed as FAA and striped fibrosis. Based on this assumption, we have reduced the dosage of FK506 by concomitant use, or by increasing the dosage, of metabolic antagonists (e.g. azathioprine, mizoribine) in patients with mild chronic FK506 nephropathy. However, we do not think it appropriate to discontinue FK506 altogether because a higher incidence of rejection has been reported in renal allograft patients after the discontinuation of CsA.

CR was observed in many of the episode biopsies from patients treated with long-term FK506. Similar findings have been reported by Randhawa et al. [10], who found a high incidence of chronic FK506 nephropathy (11/15, 73.3%; grade 1 10/15, grade 2 1/15).

The following conclusions can be drawn from this study:

1. Non-episode biopsies may show mild interstitial cellular infiltration, mild drug induced arteriolopathy, evidence of CR and silent IgA nephropathy.
2. Chronic FK506 nephropathy is mediated mainly by arteriolopathy, confirmed by the deposition of hyaline-like substance and the destruction of vascular structure.
3. It is useful to obtain protocol biopsies or non-episode biopsies from renal allografts treated with FK506 or CsA to make an appropriate choice of immunosuppressant therapy.

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