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Case Report

Everolimus Reduces the Size of Tuberous Sclerosis Complex-Related Huge Renal Angiomyolipomas Exceeding 20 cm in the Longest Diameter

Naoya Toriu[a] Hiroki Mizuno[a] Naoki Sawa[a] Keiichi Sumida[a] Tatsuya Suwabe[a] Noriko Hayami[a] Akinari Sekine[a] Masayuki Yamanouchi[a] Junichi Hoshino[a, b] Kenmei Takaichi[a, b] Motoko Yanagita[c] Takuya Fujimaru[d] Takayasu Mori[d] Eisei Sohara[d] Shinichi Uchida[d] Yoshifumi Ubara[a, b]

[a]Nephrology Center, Toranomon Hospital, Tokyo, Japan; [b]Okinaka Memorial Institute for Medical Research, Tokyo, Japan; [c]Department of Nephrology, Kyoto University Graduate School of Medicine, Kyoto, Japan; [d]Department of Nephrology, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Tokyo, Japan

Keywords
Everolimus · Angiomyolipoma · Tuberous sclerosis complex

Abstract
We evaluated the efficacy of everolimus in 3 patients who had huge renal angiomyolipomas associated with tuberous sclerosis complex. Two patients with large lipid-rich angiomyolipomas had a history of renal transarterial embolization for renal bleeding, but the effect had only been temporary and the embolized kidneys had continued to enlarge. In case 1, case 2, and case 3, total renal volume was respectively 3,891, 4,035, and 1,179 cm^3 before admin-

Yoshifumi Ubara, MD, and Naoya Toriu, MD
Nephrology Center, Toranomon Hospital Kajigaya
1-3-1, Takatsu
Kawasaki, Kanagawa 212-0015 (Japan)
E-Mail ubara@toranomon.gr.jp and ntoriu@kuhp.kyoto-u.ac.jp

istration of everolimus, decreasing to 3,016 (77%), 3,043 (75%), and 1,051 (89%) cm^3 after 1 year of everolimus therapy and to 2,832 (73%), 3,209 (80%), and 1,102 (93%) cm^3 after 3 years. New renal bleeding did not occur, but elevation of serum creatinine and urinary protein were noted in 2 patients. While previous reports have largely assessed the effect of everolimus for angiomyolipomas of <10 cm in the longest diameter, our findings suggest that this drug might also be effective for huge lesions of >20 cm in diameter. However, total renal volume still exceeds 2,000 cm^3 in 2 of our patients, suggesting limited size reduction of lipid-rich angiomyolipomas. In addition, occurrence of everolimus-related nephropathy needs to be monitored carefully.

Introduction

Renal angiomyolipoma (RAML) is a benign tumor composed of fat, smooth muscle, and disorganized vascular elements, which is a common renal manifestation in patients with tuberous sclerosis complex (TSC). RAML is associated with spontaneous bleeding and potentially life-threatening hemorrhage if the lesion is >4 cm in diameter [1]. In the past, renal transarterial embolization (TAE), surgery (nephrectomy and partial nephrectomy), and ablation procedures (percutaneous or laparoscopic radiofrequency ablation, microwave ablation, and cryoablation) have been recommended to manage symptoms due to a mass effect or bleeding, while more recently everolimus has become the first-line medical treatment for RAML in patients with TSC [2]. Everolimus is effective for noninvasively reducing the size of many RAMLs, but its activity and limitations in patients with huge RAMLs of >20 cm in the longest diameter are unknown.

Here we report 3 TSC patients with huge RAMLs who were treated with everolimus and discuss the effect of this drug on their massive lesions.

Case Reports

Case 1

In 2013, a 48-year-old Japanese woman who had a huge RAML associated with TSC was admitted to our hospital because of abdominal distention. She had developed RAML-associated renal hemorrhage 6 times between the ages of 20 and 42 years, and selective TAE had been performed repeatedly to treat hemorrhage according to our previous method [3]. At the age of 41 years, her renal volume was calculated to be 3,112 cm^3 by the previous method [4], but her kidneys continued to enlarge thereafter. This patient hoped to receive treatment with everolimus as a medical therapy covered by the national health insurance scheme.

On admission, she was 158.9 cm tall and weighed 53.0 kg, with a blood pressure of 150/78 mm Hg and a temperature of 35.8°C. Perinasal angiofibromas (adenoma sebaceum) were evident. Laboratory tests showed that serum creatinine was 0.85 mg/dL, the estimated glomerular filtration rate (eGFR) was 57.1 mL/min/1.73 m^3, and proteinuria was 0.14 g/day (Table 1). Computed tomography (CT) showed huge lipid-rich RAMLs, with the total volume

of both kidneys being 3,896 cm^3 and the maximum RAML diameter being 21.8 cm (Fig. 1). Genetic testing revealed a large deletion of TSC2. TSC was diagnosed according to the clinical diagnostic criteria because more than two major features were present (Table 2) [5].

Clinical Course

Treatment with everolimus was initiated at a dose of 10 mg/day. After 1 year, total renal size decreased to 3,016 cm^3 (77% of baseline), and then decreased further to 2,832 cm^3 (73%) after 3 years (Fig. 1). RAML-associated hemorrhage has not occurred since everolimus therapy was initiated, but serum creatinine and proteinuria have respectively increased to 1.16 mg/dL and 0.81 g/day after 3 years.

Case 2

In 2014, a 29-year-old Japanese woman who had RAML associated with TSC was admitted to our hospital due to abdominal distention. She had a history of RAML-associated hemorrhage at 21 and 24 years of age, which had been treated by selective renal TAE. At the age of 21 years, her total renal volume had been calculated as 986 cm^3, but it continued to increase thereafter.

On admission, she was 162.9 cm tall and weighed 58.1 kg, with a blood pressure of 105/68 mm Hg and a temperature of 36.7°C. Laboratory tests revealed that serum creatinine was 0.55 mg/dL, eGFR was 106.0 mL/min/1.73 m^3, and proteinuria was 0.04 g/day (Table 1). CT showed huge lipid-rich RAML, with the total renal volume being 4,035 mL and the maximum RAML diameter being 28.0 cm (Fig. 2). Genetic testing was negative for abnormalities of TSC1 and TSC2, but TSC was diagnosed according to clinical criteria because she had more than two major features (Table 2).

Clinical Course

Everolimus was initiated at 10 mg/day. After 1 year, her total renal size was reduced to 3,043 cm^3 (75%), while it was 3,246 cm^3 after 3 years (80%). Solid lesions decreased in size, but lipid-rich lesions persisted (Fig. 2). RAML-associated hemorrhage has not occurred since everolimus was initiated. In addition, renal function is unchanged and proteinuria has not been detected.

Case 3

In 2014, a 36-year-old Japanese woman was admitted to our hospital due to enlargement of TSC-related RAML (12.7 cm in the longest diameter).

On admission, she was 156.0 cm tall and weighed 54.3 kg, with a blood pressure of 128/83 mm Hg and a temperature of 37.0°C. She had perinasal angiofibromas. Laboratory tests demonstrated that serum creatinine was 0.87 mg/dL, eGFR was 59.7 mL/min/1.73 m^3, and proteinuria was 0.07 g/day (Table 1). CT showed huge solid and lipid-rich RAMLs, with a total renal volume of 1,179 cm^3 and maximum kidney diameter of 12.7 cm (Fig. 3). Genetic testing revealed a large deletion of TSC2. TSC was diagnosed according to clinical criteria because she had more than two major features (Table 2).

Clinical course

This patient did not have a history of renal bleeding. Everolimus was initiated at 10 mg/day. After 1 year, her total renal size was reduced to 1,051 cm^3 (89%), while it was 1,102 cm^3 (93%) after 3 years (Fig. 3). RAML-associated hemorrhage has not occurred after everolimus was initiated, but serum creatinine and proteinuria have respectively increased to 1.01 mg/dL and 0.32 g/day after 3 years.

Discussion

Two important clinical issues were suggested by the response of our 3 patients to everolimus therapy. First, everolimus can be effective for huge RAML, even after renal TAE had been performed. Second, patients should be monitored carefully during treatment with everolimus because it may induce nephropathy with deterioration of renal function and development of proteinuria.

In 2 clinical trials of everolimus for RAML, statistically significant reduction of lesion volume was seen with everolimus treatment compared to placebo [6, 7]. Bissler et al. [6] treated 79 patients with everolimus, whose maximum renal size and median total renal total volume were 1,602 and 85 cm^3, respectively. After 24 weeks of everolimus treatment, at least 50% reduction of RAML volume from baseline was achieved in over half of the patients [3]. Kingswood et al. [7] treated 30 patients with everolimus, whose maximum renal size and median total renal volume were 198 and 10.9 cm^3, respectively. After 12, 24, and 48 weeks of treatment, 56.5, 78.3, and 80.0% of the patients, respectively, showed ≥50% reduction in the total volume of target RAMLs [4]. In addition, Hatano et al. [8] reported the effect of everolimus therapy in 40 RAML patients with a maximum renal diameter of 4–10 cm (n = 32) or >10 cm (n = 8). After 6 months, the mean percent reduction of lipid-rich lesions was 24%, whereas it was 68% for solid lesions ($p < 0.001$). They concluded that everolimus could reduce the size of RAML mainly consisting of angiomatous and leiomyomatous tissue, but had a relatively poor effect on lipomatous RAML [8]. As far as we could determine, there has been no report in the English literature about the effect of everolimus on huge RAML >20 cm in the longest diameter, like the lesions in 2 of our cases.

TSC is an autosomal dominant disorder in which benign tumors develop in multiple organs, including the skin, brain, and kidneys [9]. In TSC patients, mutation of the TSC1 or TSC2 gene leads to unregulated activation of mTOR pathway. mTOR inhibitors like everolimus reduce phosphorylation of downstream effectors of mTOR, resulting in a decrease in DNA synthesis and cell proliferation that reduces the size of RAML associated with TSC [10]. Because mTOR inhibitor therapy is noninvasive as well as being effective, it is recommended as the first-line treatment for RAML, while selective embolization, kidney-sparing resection, or ablation therapy are acceptable as second-line modalities [2].

Everolimus can cause deterioration of renal function. In kidney transplant recipients, everolimus treatment has been associated with an increase in proteinuria [11, 12]. The proteinuria associated with everolimus was of mixed glomerular and tubular origin, and occasionally reached the nephrotic range [13]. In a rat model, glomerular repair was inhibited by everolimus, leading to an increase in proteinuria, glomerulosclerosis, interstitial fibrosis, and glomerular inflammation, as well as a decline in creatinine clearance [14]. On the other hand,

renal events (including proteinuria, elevation of serum creatinine, and transient acute renal failure) were not more frequent in the everolimus group compared with the placebo group in a clinical trial of everolimus for RAML [6]. While the precise association of everolimus with renal adverse events has not been established, cessation of this drug is recommended if proteinuria increases to >1 g/day (or especially to >3 g/day) or if eGFR declines to <30 mL/min [15].

In conclusion, we reported 3 TSC patients with huge RAMLs. In 2 patients with lipid-rich RAMLs, the total renal volume was >3,000 cm^3 and the longest RAML diameter was >20 cm even after repeated renal TAE. Treatment with everolimus improved even such huge RAMLs, and the effect persisted during long-term administration. However, total renal volume was still >2,000 cm^3 in 2 patients, suggesting limited size reduction for lipid-rich lesions, which is also supported by Hatano et al. [5]. In addition, serum creatinine and proteinuria increased in 2 patients after everolimus therapy was started, suggesting that everolimus-related nephropathy should be monitored carefully.

Statement of Ethics

The present study adhered to the Declaration of Helsinki, and all 3 patients gave consent for the details of their cases to be published.

Disclosure Statement

The authors declare no competing financial interests. The authors also declare that they have no conflicts of interest.

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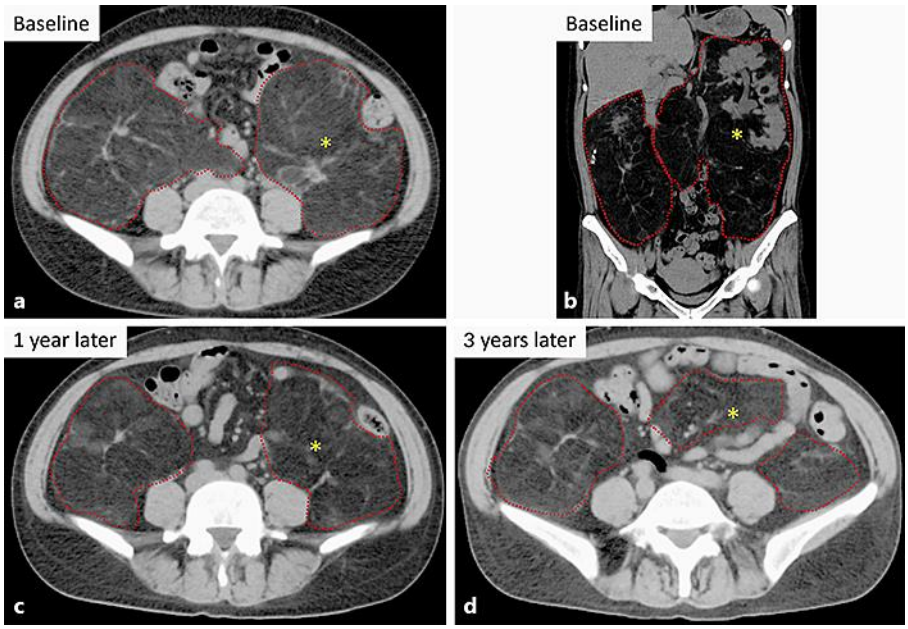

Fig. 1. Case 1. **a**, **b** Computed tomography (CT) reveals huge RAMLs before initiation of everolimus therapy. The maximum diameter of the biggest RAML (asterisk) is 21.8 cm. **c** CT shows huge RAMLs at 1 year after initiation of everolimus therapy. The maximum diameter of the biggest RAML (asterisk) is 18.5 cm. **d** CT shows huge RAMLs at 3 years after initiation of everolimus therapy. The maximum diameter of the biggest RAML (asterisk) is 17.3 cm.

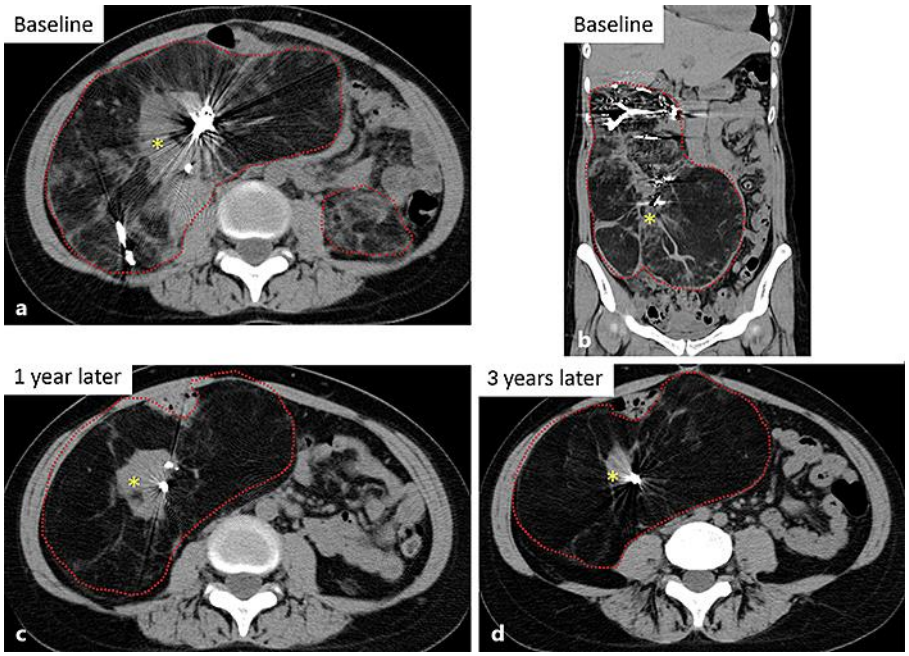

Fig. 2. Case 2. **a**, **b** Computed tomography (CT) reveals huge RAMLs before initiation of everolimus therapy. The maximum diameter of the biggest RAML (asterisk) is 28 cm. **c** CT shows huge RAMLs at 1 year after initiation of everolimus therapy. The maximum diameter of the biggest RAML (asterisk) is 22.1 cm. **d** CT shows huge RAMLs at 3 years after initiation of everolimus therapy. The maximum diameter of the biggest RAML (asterisk) is 23.1 cm.

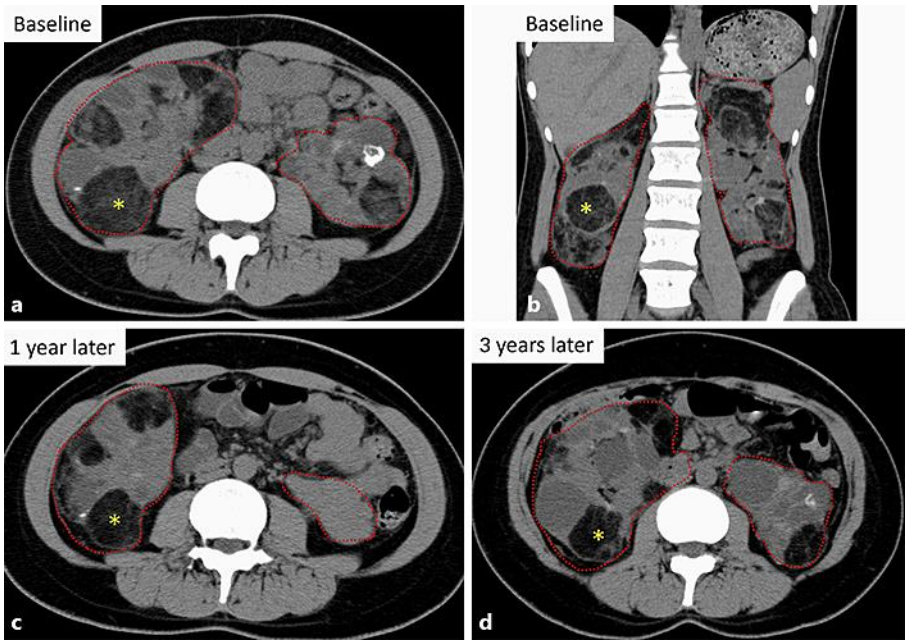

Fig. 3. Case 3. **a**, **b** Computed tomography (CT) reveals huge RAMLs before initiation of everolimus therapy. The maximum diameter of the biggest RAML (asterisk) is 12.7 cm. **c** CT shows huge RAMLs at 1 year after initiation of everolimus therapy. The maximum diameter of the biggest RAML (asterisk) is 11.5 cm. **d** CT shows huge RAMLs at 3 years after initiation of everolimus therapy. The maximum diameter of the biggest RAML (asterisk) is 12.1 cm.

Table 1. Clinical findings

	Case 1					Case 2				Case 3				Normal range
	2013 baseline	2014 1 year later	2015 2 years later	2016 3 years later	2017 4 years later	2014 baseline	2015 1 year later	2016 2 years later	2017 3 years later	2014 baseline	2015 1 year later	2016 2 years later	2017 3 years later	
White blood cell count/μL	7,300	4,300	5,400	5,300	5,800	4,900	4,200	4,500	4,600	6,800	5,300	5,700	7,300	3,200–7,900
Hemoglobin, g/dL	10	11.5	11.4	11.1	12.2	11.2	12.8	11.9	11.4	12.3	13.1	12.3	12.8	11.3–15.0
Platelet, ×1,000/μL	272	237	165	179	126	315	298	342	31	275	351	284	319	155–350
Total protein, g/dL	7.5	7.8	7.9	7.8	7.8	7.7	7.6	7.5	7.3	7.3	7.5	7.1	7.0	6.9–8.4
Albumin, g/dL	3.3	3.4	4.1	4.0	4.2	4.0	3.8	4.4	4.4	3.8	3.8	4.1	4.1	3.9–5.2
Urea nitrogen, mg/dL	11	15	18	17	23	15	12	11	15	16	15	16	15	8–21
Creatinine, mg/dL	0.85	0.94	1.27	1.16	1.27	0.55	0.54	0.55	0.59	0.87	1.04	1.03	1.01	0.46–0.78
eGFR, mL/min/1.73 m^2	57.1	50.8	36.1	39.9	35.9	106.0	107	102.9	95.3	59.7	48.7	48.5	49.2	>90
Urinary														
RBC per high-power field	<1	11–30	1–4	1–4	1–4	1–4	5–10	5–10	1–4	<1	1–4	1–4	1–4	<1
Proteinuria, g/day	0.14	0.71	0.98	0.81	0.73	0.04	0.78	0.04	0.06	0.12	0.38	0.42	0.32	<0.1
NAG, IU/gCr	5.7	n/a	3.9	n/a	n/a	n/a	3.5	n/a	n/a	14.7	n/a	n/a	n/a	0.8–5.0
α1MG, mg/L	12.4	n/a	13.79	n/a	n/a	n/a	6.19	6.1	5.9	7.0	4.0	14.6	10.3	0.6–8.8
β2MG, mg/L	1.4	n/a	1.0	n/a	n/a	n/a	0.2	0.0	0.1	n/a	0.4	1.5	0.6	0.1–1.9
Maximum diameter of RAML, cm	21.8	18.5	17.3	18.8	18.5	28.0	22.1	23.1	23.9	12.7	11.5	11.8	120.6	
Total volume of RAML, cm^3	3,891	3,016	2,651	2,832	2,674	4,035	3,043	3,209	3,246	1,179	1,051	1,043	1,102	
Total volume/baseline volume ×100, %	100	77	68	73	69	100	75	80	80	100	89	88	93	

Table 2. Baseline patients' characteristics

	Case 1	Case 2	Case 3
Age, years	48	29	36
Sex	female	female	female
ECOG performance states	2	2	0
Mental retardation	negative	negative	negative
Skin	positive (facial angiofibromas)	positive (facial angiofibromas)	positive (facial angiofibromas)
Brain	negative	positive (epilepsy)	positive (SEN)
Lung lymphangioleiomyomatosis	positive	positive	positive
Retinal hamartoma	positive	positive	positive
Liver angiomyolipoma	positive	negative	positive
Cardiac rhabdomyoma	negative	negative	negative
Genetic analysis	TSC2	negative	TSC2

ECOG, Eastern Cooperative Oncology Group; SEN, subependymal nodule.