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症 例

腎生検にて血栓性微小血管障害を認めた若年性加速型高血圧の1例

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A young case of kidney failure with thrombotic microangiopathy lesions in renal biopsy caused by accelerated hypertension

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要 旨

症例は19歳，男性。新生児期に髄膜炎とその後の脳波異常の既往があり，16歳で高血圧(200/100 mmHg)を指摘された。当時，腎動脈狭窄や内分泌異常を認めず，本態性高血圧と診断されたが，その後通院を自己中断していた。19歳で高血圧(210/140 mmHg)と血清クレアチニン 2.3 mg/dL, BUN 31 mg/dL の腎機能低下を指摘された。心肥大，高血圧性網膜症(Keith-Wagener III度)を認め，加速型高血圧(accelerated hypertension)と診断された。腎生検では縞状の間質の線維化があり，小動脈に内膜・中膜の肥厚と壊死を認め，細動脈領域にフィブリノイド変性，内皮細胞増殖を伴った多数の血栓閉塞像を認めた。電子顕微鏡にて糸球体に係蹄内皮細胞の膨化と血栓形成，基底膜の二重化や mesangial interposition を認めた。以上の所見から血栓性微小血管障害(thrombotic microangiopathy)と診断した。血小板減少，破砕赤血球や神経症状は認めず，抗リン脂質抗体は陰性であった。降圧治療と抗血小板薬投与で腎機能は改善を示した。この症例においては加速型の重症高血圧による血管内皮障害から多数の細動脈に血栓形成を生じ，腎機能が低下したと考えられた。

A 19-year-old male was admitted to our hospital for the treatment of severe hypertension with renal dysfunction. Two years before admission, his hypertension had been diagnosed as essential hypertension based on a series of examinations when his renal function was not impaired. Visits to his primary physician ended when he developed severe hypertension of 210/140 mmHg, at which time renal dysfunction and serum creatinine of 2.25 mg/dL were discovered. Renin and antidiuretic hormone were slightly elevated, but renal artery stenosis or other abnormalities were not detected by magnetic resonance imaging and computer tomography. After the hypertension was controlled by medication, a renal biopsy was performed to assess renal impairment. Histology demonstrated lesions compatible with thrombotic microangiopathy (TMA) and ischemic lesions, including fibrinoid necrosis, intimal thickening, occlusion in the small arteries, wrinkling and duplication of the glomerular basement membrane with microthrombi, and focal interstitial fibrosis. Renal function ameliorated after the hypertension was controlled. This case suggests that severe and accelerated hypertension can cause TMA with renal impairment even in young people.

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Key words：thrombotic microangipathy, accelerated hypertension, renal biopsy

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緒　言

従来，悪性高血圧は脳症，うっ血性心不全，あるいは腎不全が急速に進行し予後不良の疾患であるとされていた[1,2]。組織学的には，細動脈のフィブリノイド壊死や小動脈の内皮細胞増殖と内膜の線維化による肥厚，それによる内腔狭窄や閉塞を特徴とし，しばしばonion-skin lesionと呼ばれる病変を形成する。今回われわれは，古典的な悪性高血圧の基準に達する臨床症状は満たさなかったものの，腎生検にてフィブリノイド壊死や細動脈・糸球体毛細血管における血栓性微小血管障害所見を呈した加速型高血圧の若年発症例を経験したのでここに報告する。

症　例

患　者：19歳，男性

主　訴：高血圧と腎機能低下の精査希望

既往歴：生後直後に細菌性髄膜炎に罹患し，3歳まで脳波異常を認められ抗てんかん薬を投与されていた。6歳まで熱性痙攣を生じていた。14歳から夜尿症を自覚し，imipramine 25 mgが処方されていたが，16歳から通院を中断していた。

家族歴：祖父が高血圧

生活歴：喫煙歴10本/day 3年間，飲酒歴なし，卵アレルギーあり，現在無職

現病歴：16歳時に近医で高血圧(170～200/100 mmHg)を指摘され精査を受けた。レニン活性9.9 mg/mL/hrと上昇を認めたが，antidiuretic hormone(ADH)，コルチゾール，カテコラミン系の異常は認めず，レノグラムでも異常所見は認めなかった。当時血清クレアチニン(Cr)0.7 mg/dL，blood urea nitrogen(BUN)12.0 mg/dLと腎機能は正常範囲内であった。Ca拮抗薬による治療が開始されたが，その後通院を自己中断した。その後は医療機関を受診しておらず，19歳時に感冒様症状をきっかけに近医を受診し，高血圧(210/140 mmHg)と腎機能低下(Cr 2.25 mg/dL，BUN 23 mg/dL)を指摘され，amlodipine 10 mgの内服が開始された。夜尿症に対しsodium valproateも処方された。その後，精査のため紹介され入院となった。

日常生活において，食事については塩分の摂取過多の傾向があった。運動については犬と散歩をする程度であった。もともと肥満があり，最近の体重変化はない。入院の数日前より腹痛と食欲不振を認めていた。

入院時現症：身長164.5 cm，体重80 kg，BMI 29.8，血圧196/141 mmHg，体温36.2℃，脈拍102/分整，貧血・黄疸・浮腫なし。心音はIII音とIV音を聴取，雑音なし。肺音は清。腹部は右下腹部に圧痛あり。

Table.　Laboratory data

WBC	11,400/μL(3,300～9,000)	Na	139 mEq/L(135～147)
Neu	75.0 %	K	2.8 mEq/L(3.5～5.1)
Eos	3.5 %	Cl	99 mEq/L(98～108)
Bas	0.3 %	Ca	9.3 mg/dL(8.4～10.3)
Lym	15.3 %	P	3.0 mg/dL(2.5～4.5)
Mon	5.9 %	TP	7.0 g/dL(6.5～8.2)
Hb	13.8 g/dL(11.4～15.5)	Alb	4.2 g/dL(3.7～5.2)
Plt	299×10³/μL(140～360)	BUN	31.1 mg/dL(8.0～20.0)
		Cr	2.3 mg/dL(0.5～0.8)
		UA	8.0 mg/dL(<7.0)
PT	10.5 sec(11.0～14.0)	GOT	14 IU/L(10～40)
APTT	34.5 sec(30.0～45.0)	GPT	16 IU/L(5～45)
FBG	406 mg/dL(200～400)	LDH	310 IU/L(115～245)
D-dimer	3.9μg/mL(<1.0)	ALP	211 IU/L(110～350)
		T. Bil	0.72 mg/dL(0.2～1.2)
CRP	0.82 mg/dL(<0.1)	CK	57 IU/L(33～150)
haptoglobin	165 mg/dL(50～300)	T. Chol	68 mg/dL(130～219)
抗CL-β_2GPI	1.2 U/mL(<3.5)	HDL-C	40 mg/dL(40～96)
		TG	238 mg/dL(35～149)
		HbA_{1c}	3.5 %(4.3～5.8)
lupus anticoagulant	1.12(<1.3)	sOsm	286 mOsm/L(284～294)

Endocrine data		Urinalysis	
TSH	1.73μU/mL(0.35～3.73)	比重	1.019
fT3	2.49 pg/mL(2.2～4.1)	pH	6.0
fT4	1.21 ng/dL(0.88～1.81)	OB	(－)
BNP	9.8 pg/mL(<18.4)	Pro	(2＋), 0.7 g/day(<0.13)
PRA	9.9 mg/mL/hr(0.2～3.9)	Glu	(＋), 0.6 g/day(<0.1)
aldosterone	220 pg/mL(3～21)	Uro	(±)
adrenalin	0.01 ng/mL(<0.10)	Bil	(－)
noradrenalin	0.88 ng/mL(<0.50)	Ket	(－)
dopamine	0.04 ng/mL(<0.30)	RBC	<1/5F
ACTH	17.7 pg/mL(7.0～56.0)	WBC	1～4/F
cortisol	5.9μg/mL(4.0～23.3)	NAG	15.5 IU/L(<7.0)
ADH	8.4 pg/mL(0.3～3.5)	β_2MG	13,814μg/L(<230)
		Osm	500 mOsm/L

検査所見(Table)：尿検査では0.7 g/dayの蛋白尿を認めた。K 2.8 mEq/Lと低下を認め，BUN 31.1 mg/dL，Cr 2.3 mg/dL，UA 8.0 mg/dL，Creatinine clearance(CCr)43.0 mL/minと腎機能低下を認めた。肝・胆道系酵素の異常は認めなかった。WBC 11,400/μL，CRP 0.82 mg/dLと炎症反応の軽度増加を認めた。甲状腺機能，下垂体ホルモンの異常はなかったが，カテコラミンとアルドステロンが軽度上昇しており，レニン活性も9.9 mg/mL/hrと上昇していた。hap-

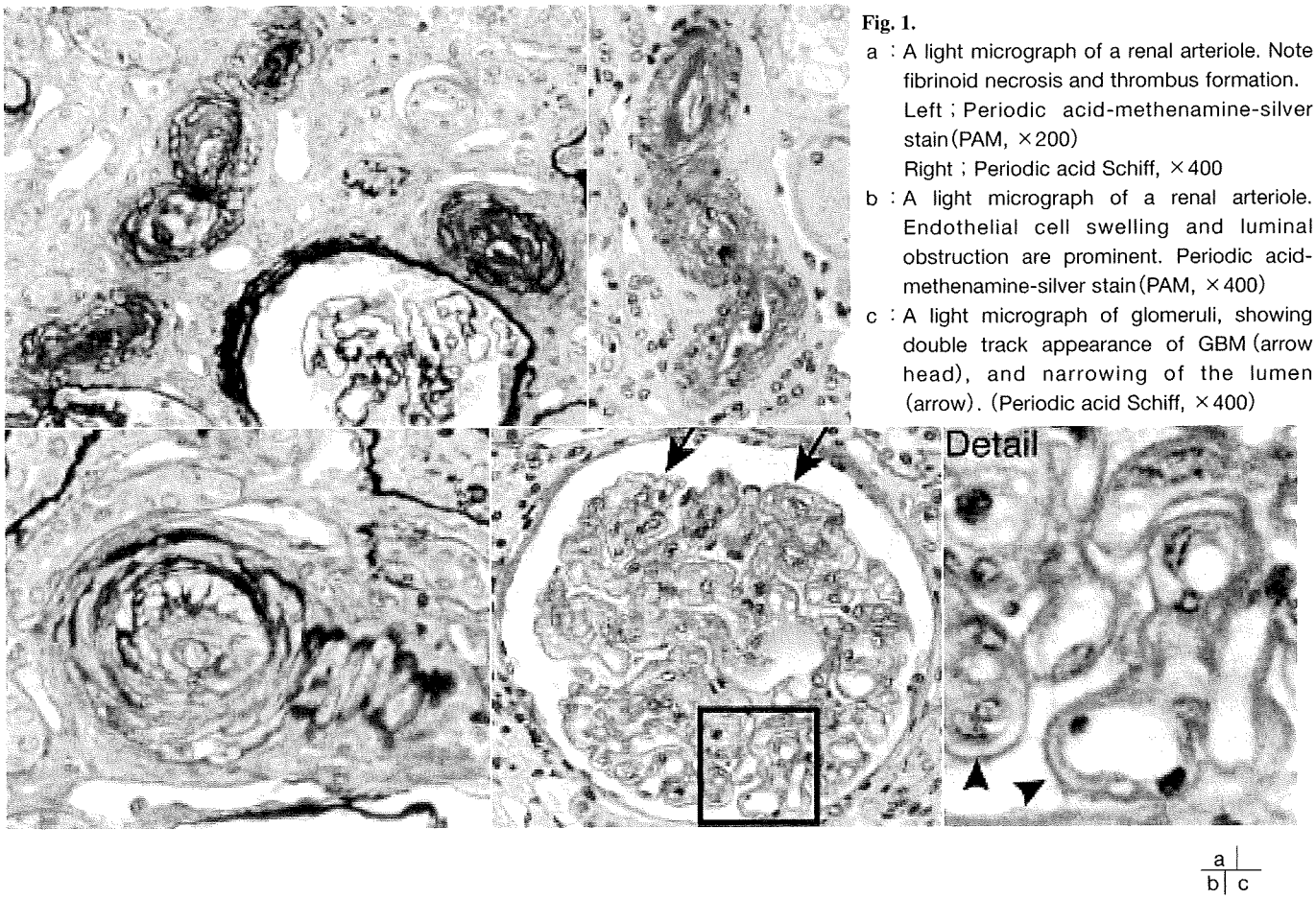

Fig. 1.
a：A light micrograph of a renal arteriole. Note fibrinoid necrosis and thrombus formation. Left；Periodic acid-methenamine-silver stain (PAM, ×200)
Right；Periodic acid Schiff, ×400
b：A light micrograph of a renal arteriole. Endothelial cell swelling and luminal obstruction are prominent. Periodic acid-methenamine-silver stain (PAM, ×400)
c：A light micrograph of glomeruli, showing double track appearance of GBM (arrow head), and narrowing of the lumen (arrow). (Periodic acid Schiff, ×400)

toglobin，抗 CL-β_2 GPI，lupus anticoagulant はいずれも異常を認めなかった。

胸部 X 線写真では心胸比 53 %，左第 3・4 弓が突出しており，心陰影の拡大を認めたがうっ血や胸水は認めなかった。心電図でも Ⅰ，Ⅱ，aVL，aVF，V4-6 で ST の低下を伴う左室肥大の所見を認めた。心エコーでは拡張期左房内径 43 mm，拡張期左室内径 51 mm と拡張しており，さらに求心性心肥大(心室中隔厚 15 mm，後壁厚 15 mm)を認め，駆出率 74 %と収縮能は保たれていたが，拡張能障害を認めた。眼底検査では Keith-Wagener(K-W)Ⅲ度の高血圧性網膜症を認めた。腎エコーでは左 101×58×64 mm，右 94×40×52 mm と左右差を認め，ともに軽度の表面不整を伴う萎縮所見を認めた。レノグラムでは両側腎機能低下のパターンを示し，右腎機能は左の 2/3 程度であった。血管相の立ち上がりの低下は認めなかった。腹部 computer tomography (CT)では副腎に腫瘤性病変は認めなかった。腸管リンパ節の軽度腫脹を認め，腸管リンパ節炎と考えられた。magnetic resonance(MR)angiography では腎動脈に狭窄は認めなかった。頭部 magnetic resonance imaging(MRI)でも下垂体に異常所見を認めなかった。

低カリウム血症と尿糖，β_2ミクログロブリンの異常高値を認めたが，入院時に認めた腸間膜リンパ節炎の改善とともに血清カリウム値は改善し尿糖は消失した。しかし蛋白尿は改善せず，腎機能低下や高血圧に関して慢性糸球体腎炎による腎実質性高血圧の可能性も考えられ，降圧を行った後に腎生検を施行した。

腎生検所見は，光顕では散在性に間質の線維化があり，小動脈に内膜・中膜の肥厚や壊死を認め(Fig. 1a)，細動脈領域に血管膜の肥厚を伴った閉塞を認めた(Fig. 1b)。糸球体は 4 個含まれ，1 個の糸球体は全硬化を認めた。それ以外の糸球体は毛細血管係蹄の二重化や内腔の狭小化(Fig. 1c)を認めた。一方，毛細血管係蹄の wrinkling が主体である糸球体もあり，糸球体によって所見が一様ではなかった。半月体は認めなかった。電顕では基底膜の蛇行，mesangial interposition と基底膜の新生，内皮細胞の膨化と(Fig. 2a)血栓による糸球体係蹄内腔の閉塞を認めた(Fig. 2b)。electron

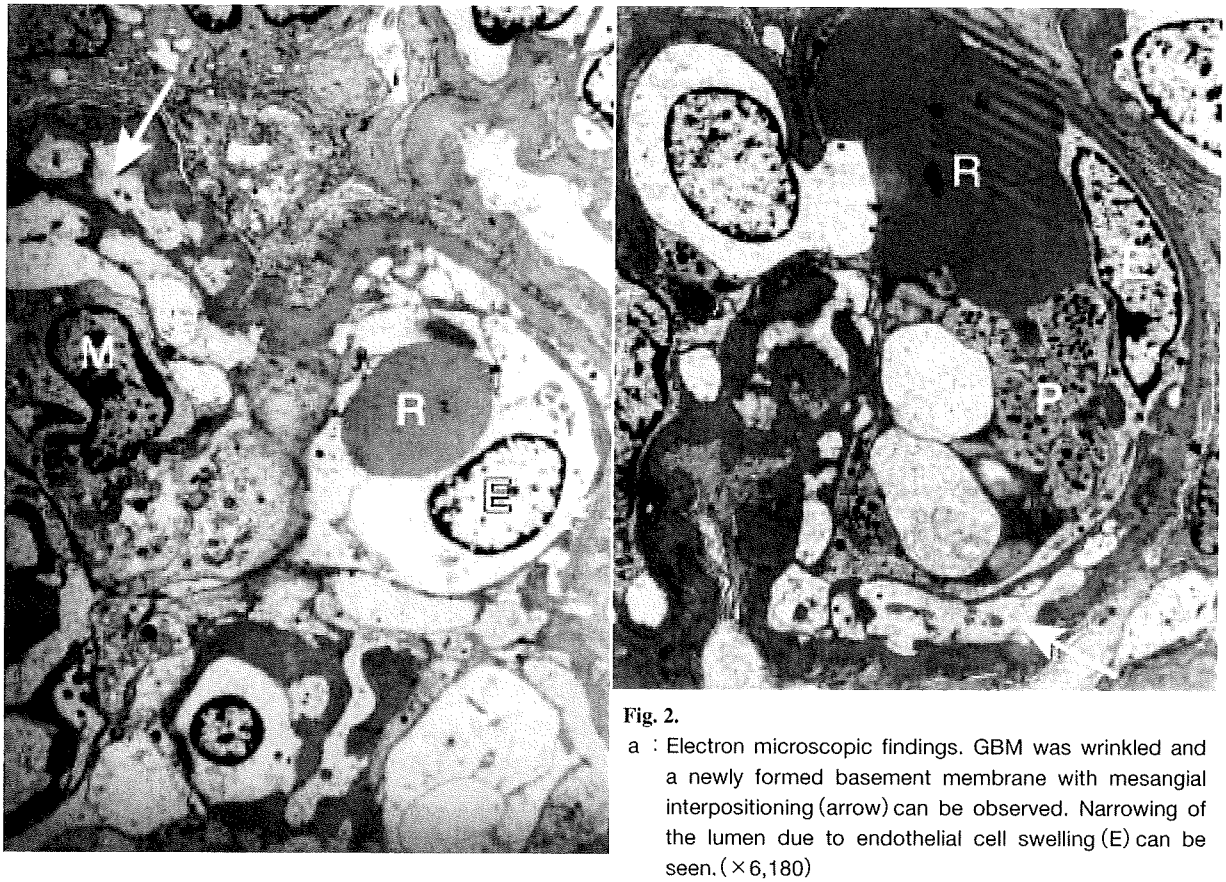

Fig. 2.
a：Electron microscopic findings. GBM was wrinkled and a newly formed basement membrane with mesangial interpositioning (arrow) can be observed. Narrowing of the lumen due to endothelial cell swelling (E) can be seen. (×6,180)
b：Thrombus in a glomerular capillary (×10,300)
arrow：mesangial interpositioning, E：endothelial cell, M：mesangial cell, P：platelets, R：red blood cell

dense deposit は認めなかった。蛍光染色のための新鮮凍結切片が小さく，そこに含まれている糸球体，細動脈には IgG，IgA，IgM，C3，C4，C1q，fibrinogen の有意な沈着は認めなかった。

臨床経過：上記の腎生検の結果より，著明な進行性の高血圧による血栓性微小血管障害（thrombotic microangiopathy：TMA）と診断した。安静，塩分制限，低たんぱく質食と Ca 拮抗薬の amlodipine，ACE 阻害薬（ACEI）の temocapril，アンジオテンシン受容体拮抗薬（ARB）の valsartan，抗アルドステロン薬の spironolactone を含む内服治療で血圧は 130〜140/80 mmHg に低下した。入院前より使用していた sodium valproate は入院後も続行した。なお，ACEI，ARB，抗アルドステロン薬は一連の内分泌検査終了後に開始した。抗アルドステロン薬により，経過中血中 K の上昇を認めたため trichlormethiazide へ変更した。たんぱく質制限食（50 g），塩分制限（7 g），運動，禁煙を指導し退院となった。退院後一時内服を自己中断しており，そのときは血圧が 182/132 mmHg と再上昇したが，腎機能の更なる低下は認めなかった。その後通院と内服を徹底することで血圧は 130/70 mmHg 程度を維持しており，腎機能も Cr 1.5〜1.7 mg/dL と安定している。

考　察

本症例では過去と今回の 2 度にわたり高血圧の検索が行われたが，二次性高血圧の所見を認めず，若年発症の本態性高血圧と考えられた。今回の入院時，カテコラミン系，ADH などが上昇していたが一次性のものではないと考えられた。

悪性高血圧（malignant hypertension）は重篤な高血圧によって血管障害と末梢組織の虚血が急速に進行する病態であり[1,2]，強皮症の crisis などがその典型例である[3]。（旧）厚生省の診断基準では A 群：1）治療前の拡張期血圧が 130 mmHg 以上，2）高血圧性網膜症 K-W Ⅳ度の乳頭浮腫，3）急速に進行し腎不全に至る腎機能障害，4）体重減少，脳症状，心不全などを伴う急速な全身症状の悪化。B 群：1）治

療前の拡張期血圧が120～130 mmHg，2）K-W Ⅲ度の眼底所見，3）腎不全に至らない腎機能障害，があげられ，そのうち，A群で3条件以上，B群では1)と3)のいずれかを満たすものを悪性高血圧と定めている。一方，歴史的にはK-W Ⅳ度を満たすものを悪性高血圧と定義し[1]，悪性高血圧と同様の重篤な臓器障害を呈し，眼底所見でK-W Ⅲ度を呈するものを加速型高血圧(accelerated hypertension)として区別してきた。降圧治療が発達した今日においてはK-W Ⅲ，Ⅳ度でも重症度や予後には差がないといわれている[4]。本症例では経過中に脳症や心不全は認めなかったが，高血圧(210/140 mmHg)と短期間に高血圧性網膜症(K-W Ⅲ度)，腎機能低下の進行を認め，加速型高血圧と診断した。

悪性高血圧のメカニズムは血管内皮障害によると考えられている[3,5～8]。血圧上昇によるshear stressの増加により力学的に血管内皮細胞に障害が生じるが[9,10]，同じ血圧でも悪性高血圧で認めるような血管障害を呈さないこともあり[3,6]，血圧以外にレニン・アンジオテンシン系の活性化[11,12]，プロスタグランジン[11,13]，カテコラミン[6]，グルココルチコイド[14,15]，免疫機序[16]，凝固異常[17]，ADH[6,18]などの関与も考えられている。内皮障害が細動脈のフィブリノイド壊死や葉間動脈の内皮細胞増生と内腔狭窄をきたすと同時に，血管内凝固を亢進させ，TMAの病態を引き起こすこともある[6]。しかしながら，今までこういった血管内皮障害は悪性高血圧と臨床診断され，いずれも急速な腎機能低下をきたした症例の腎生検の病理診断で報告されていることが多い。

しかし本症例では，神経症状などの臨床症状を認めず，検査所見でも血小板減少，破砕赤血球の出現やhaptoglobin値低下を認めなかったにもかかわらず，腎組織上ではTMA所見を認めた。具体的には，細・小動脈壁のフィブリノイド変性と血管内皮細胞の増殖・膨化による内腔閉塞，糸球体では毛細血管の内皮細胞の膨化と血栓形成，mesangial interpositionと新生基底膜などである。糸球体によって所見が一様でないことは，途中の小・細動脈の通過障害の違いによって高血圧による糸球体障害が糸球体ごとに異なるためと考えられた。またこのことから，糸球体障害は原発性糸球体疾患によるものではないと考えられた。同時に硬化糸球体や間質の線維化も進行しており，急性と慢性の混在した所見を認めた。

悪性高血圧以外にTMAを呈する病態として，溶血性尿毒症症候群(hemolytic uremic syndrome：HUS)，血栓性血小板減少性紫斑病(thrombotic thrombocytopenic purpura：TTP)，cyclosporinなど血管内皮障害を起こす免疫抑制薬やVEGF阻害薬の使用，臓器移植後，DIC，HELLP症候群，SLEなどの全身性血管炎が知られている[19]。本症例は薬剤の使用歴はなかった。入院後の精査では抗リン脂質抗体を含め自己抗体は陰性であり，自己免疫疾患は否定的であった。入院時は腸管リンパ節炎を起こしていたが，発熱下痢などは認めず，短期間に軽快したため，入院直前の消化管感染症によるHUSを合併したとは考えにくく，数年間続いた高血圧以外に血管内皮障害を起こす要因は認めなかった。高血圧や血管内皮障害に関与しうるその他の要因として肥満や喫煙の影響が考えられた。

近年，TTPの患者で血中ADAMTS13活性が減少しており，ADAMTS13活性が低位の患者では血漿交換が奏効することが報告されている[19]。本症例の入院当時はADAMTS13の測定は一般的でなかったため測定できなかった。前述のように病歴と検査所見より，重症高血圧による血管内皮障害が長期に続き，緩徐にTMAが進行し慢性腎不全に至ったと考え，ACEI・ARBを含めた降圧治療と抗血小板薬投与をまず開始した。その後の経過において腎機能は改善を示した。

結　語

悪性高血圧にみられる臨床症状や検査所見を認めなかったものの，腎生検組織で血管内皮細胞障害によるTMA所見を呈した若年性重症高血圧の1例を経験した。本例においては高血圧による腎障害のメカニズムとしてTMAの関与が考えられた。またこの症例の経験より，原因不明の腎機能低下患者では可能な限り積極的に腎生検を行い，病理診断すべきであると考えられた。

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CASE REPORT

Angio-Embolization of Renal Artery Pseudoaneurysm after Renal Biopsy: A Case Report

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Renal artery pseudoaneurysm is a rare clinical entity that has been reported after renal biopsy, percutaneous renal surgery, penetrating trauma, and rarely blunt renal trauma. We present the case of a 37-year-old man with ruptured renal artery pseudoaneurysm accompanied by massive gross hematuria, urinary clot retention, and bladder tamponade, which were the presenting signs seven hours after renal biopsy. Abdominal CT scan showed a large perinephric, intracapsular hematoma of left kidney. His angiogram revealed a left renal segmental artery pseudoaneurysm that measured 1 cm × 1 cm. He was successfully treated by selective embolization of the arterial branch supplying the pseudoaneurysm.

Keywords pseudoaneurysm, renal artery, renal biopsy, tamponade, coiling

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INTRODUCTION

Renal artery pseudoaneurysm is a rare clinical entity; however, it has great clinical significance when encountered because of its propensity for rupture.[4] It is a rare complication of renal biopsy percutaneous renal procedures, penetrating trauma and, rarely, blunt renal trauma.

The clinical manifestations of renal artery pseudoaneurysms may vary from incidental to causing hypertension, flank pain, hematuria, and rupture. The risk of rupture is estimated low, but it is associated with a mortality rate as high as 80%.[3] Aneurysms larger than 2 cm in diameter are considered to have a high risk of rupture, although ruptures have also been reported in smaller aneurysm.

Angiographic embolization is now considered a safe and effective treatment in patients with renal artery pseudoaneurysm. This treatment should be the procedure of choice due to its advantage of being minimally invasive and its selective treatment with maximal preservation of renal parenchyma.

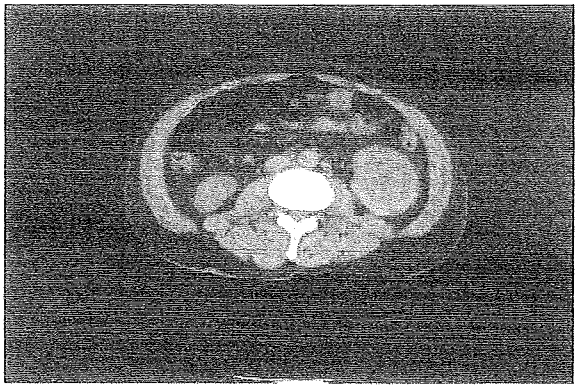
CASE REPORT

A 37-year-old was admitted to our rheumatology department of our hospital because of dyspnea and arthralgia. Systemic sclerosis was diagnosed on proximal scleroderma, Raynaud's phenomenon, and the lung abnormality of computed tomography as well as positive antinuclear antibody. Because of proteinuria and microscopic hematuria, he was moved to our department and had renal biopsy performed. After seven hours of biopsy, flank pain, severe gross hematuria, urinary clot retention, and bladder tamponade were recognized, and abdominal CT showed a large perinephric, intracapsular hematoma of the left kidney (see Figures 1a and 1b). Gross hematuria persisted the next day, so we decided to perform angiography. His angiogram revealed a left renal segmental artery pseudoaneurysm that measured 1 cm × 1 cm and its rupture, and then the subsequent coiling of this spontaneously ruptured left renal segmental artery pseudoaneurysm (see Figure 2).

DISCUSSION

Renal artery pseudoaneurysm is a rare complication of renal biopsy percutaneous renal procedures,[6] but when encountered, it is of great clinical significance because of propensity for rupture.[4] A pseudoaneurysm is the presence of arterial blood entering into adjoining tissue with continuous blood flow within this space. Symptoms may include abdominal tenderness, abdominal mass, hematuria, hypertension, and shock[8]; however, incidence for ruptured renal pseudoaneurysm and the mortality rate of pseudoaneurysm are difficult to establish due to the lack of reported cases in the literature.[1] When there is rupture, there are four spaces the blood can be redistributed (viz., retroperitoneal, intraperitoneal, intrarenal, and intrapelvic). Most intraparenchymal renal artery pseudoaneurysm ruptures are self-contained,

a



b

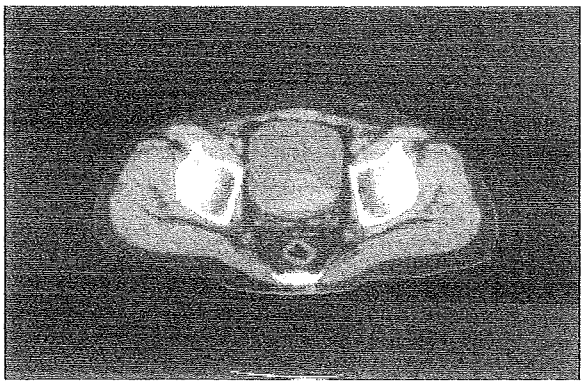


Figure 1. CT scan shows a large perinephric, intracapsular hematoma of left kidney.

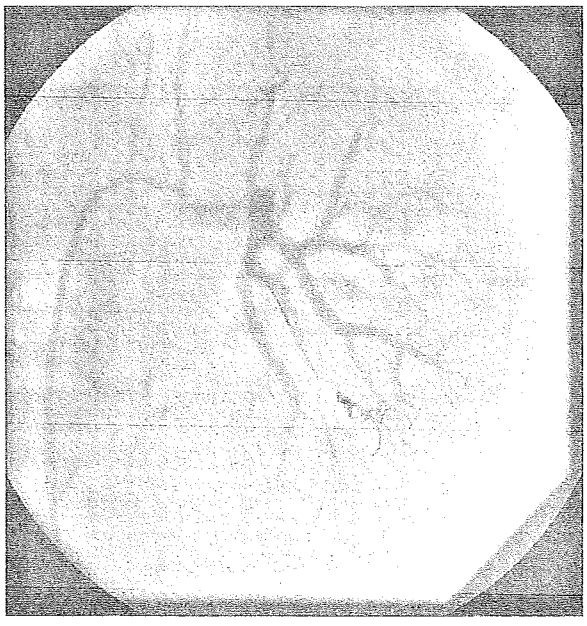


Figure 2. Selective angiogram shows a complete exclusion of the pseudoaneurysm in left renal artery.

leading to increased probability of tamponade and improved mortality.[7] The same principle may apply to extraparenchymal aneurysms that are contained in the retroperitoneum with concomitant tamponade.[5]

Early detection and embolization are important in treating this life-threatening injury with reported high success rates.[2] Treatment of renal pseudoaneurysm consists of nephrectomy, open vascular surgery, or angiographic embolization, depending on the patient's clinical condition. Angiographic embolization should be the procedure of choice due to its advantage of being minimally invasive and its selective treatment with maximal preservation of renal parenchyma. Surgical indications for repair include overt ruptures, aneurysm greater than 2 cm, renovascular hypertension, expansion of the aneurysm, and evidence of renal damage.[3]

We herein showed a case in which massive microhematuria, urinary clot retention, and bladder tamponade seven hours after renal biopsy were the presenting signs of renal pseudoaneurysm rupture, and demonstrated that it can be managed successfully with angiographic embolization.

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Case Report

Improvement of Renal Function after Opening Occluded Atherosclerotic Renal Arteries

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ABSTRACT: Percutaneous transluminal renal angioplasty (PTRA) with stenting has been effective in the control of hypertension, renal function and pulmonary edema caused by atherosclerotic renal artery stenosis (ARAS). However, concerning the viability of renal function, this procedure has not been fully established, especially in the presence of renal atrophy or severe renal parenchymal disease. We report a dramatically improved case of acute renal failure caused by acute worsening ARAS treated by stenting. A 72-year-old female was admitted for accelerated renal dysfunction (serum ceatinine; 1.2–2.3 mg/dl) and hypertension (190/100 mmHg). At 10 days after admission, the patient's serum ceatinine increased to 6.7 mg/dl, her pulmonary edema was exaggerated and hemodialysis was required. Ultrasonography showed bilateral high-echoic kidneys, but no apparent finding of renal artery stenosis (RAS). At day 15, computed tomographic angiography indicated bilateral ostial RAS. Renal angiography demonstrated total occlusion of the right and severe (90%) disease in the left. ARAS was diagnosed by intravascular ultrasonography. The guidewire was inserted in both renal arteries, PTRA with stenting was performed in the right and a stent was directly implanted in the left. Immediately, each kidney enlarged to almost normal size, leading to satisfactory urination. She was released from hemodialysis the next day since her serum creatinine was normal and the pulmonary edema was improved. Although there is still no reliable prognostic factor including resistive index or kidney size, it is important that PTRA with stenting in ARAS should be considered in a case of accelerated renal dysfunction because of the possible improvement.

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It is well known that renal artery stenosis causes refractory hypertension. Among the diseases that cause renal artery stenosis, including atherosclerotic renal artery stenosis (ARAS), fibromuscular dysplasia (FMD), aortic dissection, aortitis, and so on, ARAS is the most common underlying cause (approximately 90%).[1] Recently, noninvasive diagnostic techniques have been established for the examination of renal arteries including magnetic resonance angiography (MRA), computed tomographic angiography (CTA), and duplex ultrasonography, and ARAS has begun to draw attention as the cause of end-stage renal disease (ESRD).[2] It is reported that early identification and management of ARAS, especially percutaneous renal angioplasty (PTRA) followed by primary stenting, have a beneficial effect on the control of hypertension and renal function.[3] However, concerning the viability of renal function, this procedure has not been established, especially in the presence of renal atrophy or severe renal parenchymal disease.[4,5] Here we report a dramatically improved case of acute renal failure caused by possible acute worsening ARAS (total occlusion in the right renal artery and 90% stenosis in left) and treated by intravascular stent placement with or without PTRA. This case offers some clues to the appropriate indication for PTRA and stenting to treat ARAS.

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Case Description. *We present a case of acute renal failure with bilateral severe ARAS treated by PTRA followed by intravascular stent placement, leading to the discontinuation of hemodialysis (HD). A 72-year-old female presented with dizziness associated with hypertension (190/100 mmHg), and candesartan (8 mg) was administered. Laboratory findings showed renal dysfunction (sCr, 1.2 mg/dl). Twenty days later, the patient's serum creatinine had increased to 2.3 mg/dl and her hypertension had not improved. She was therefore admitted to our hospital for further examination. Since her renal functional decline appeared to be due to angiotensin receptor-blockers (ARB), which implied the existence of bilateral ARAS, nifedipine (40 mg) was administered as a substitute for candesartan on admission (day-0). Urine analysis showed no apparent abnormal finding. A bruit was heard beside the umbilicus. At day-10, the patient's urinary volume declined and her serum creatinine had increased to 6.7 mg/dl. Although furosemide was administered, her pulmonary edema was exaggerated (Figure 1A) and HD was required. The patient's plasma rennin activity (PRA) and serum aldosterone[6] level were revealed to be high (PRA 17.3 ng/ml/hour; Ald 402 pg/ml) (Table 1). Renal artery stenosis was suspected, however, no clear finding was confirmed with duplex ultrasonography (Table 1). Renal echography showed atrophic kidneys. These facts implied that both kidneys might not viable. However, we decided to perform an interventional study because the patient's clinical course was acute and there was a possibility of recovering renal function. At day-15, CT angiography showed bilateral ostial renal artery stenosis and atrophic kidneys (long-axis: right 74 mm; left 85 mm) (Figure 2). Renal angiography demonstrated total occlusion of the right renal artery and severe (90%) disease in the left renal artery (Figures 3A and 3E, respectively). ARAS was diagnosed for its plaque formation by intravascular ultrasonography (IVUS). The totally occluded lesion of right renal*

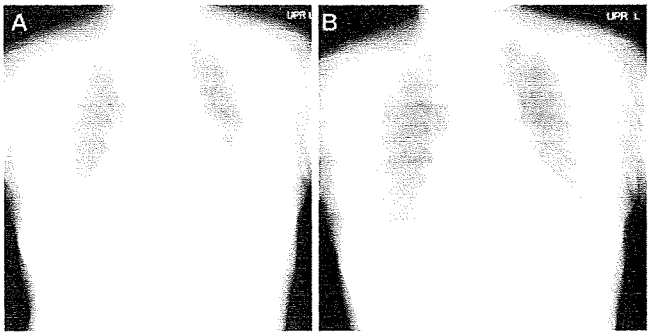

Figure 1. *Chest X-ray findings.* **(A)** *At day-10 (before the start of hemodialysis), pulmonary edema was apparent.* **(B)** *After percutaneous transluminal renal angioplasty with stenting, the patient's pulmonary edema had improved.*

Table 1. Laboratory findings at admission.

Hemogram and Coagulation		Immunological Examinations	
WBC	6,900/ L (2,800–9,300)	IgG	1,598 mg/dL (826–1840)
RBC	373 x 104/ L (319–482)	IgA	163.4 mg/dL (93–426)
Hb	11.7 g/dL (10.2–14.6)	IgM	147.5 mg/dL (54–333)
Ht	35.0% (29.8–43.4)	C3	114.6 mg/dL (70.5–125.6)
Plt	21.2 x 104/ L (12.3–34.3)	C4	28.4 mg/dL (10.6–33.0)
PT(INR)	0.86 (0.98–1.24)	CH50	54.8U/mL (28–51)
APTT	24.9 sec (26.2–39.3)	ASO	< 30 IU/mL
Blood Chemistry			
		ANA	< x 40
TP	7.4 g/dL (6.3–8.1)	RF	30.7 IU/mL (0–11.7)
Alb	3.8 g/dL (3.9–5.1)	MPO-ANCA	< 10 EU
T-Bil	0.5 g/dL (0.3–1.3)	PR3-ANCA	< 10 EU
ChE	198 IU/mL (201–436)	Metabolism	
GOT	49 IU/L (13–33)	Rennin	17. 3 ng/mL/hr (0.2–2.7)
GPT	46 IU/L (6–27)	Aldosteron	402 pg/mL (30–159)
ALP	357 IU/L (115–359)	Urinalysis	
LDH	225 IU/L (129–241)	Gravity	1.003
CPK	72 IU/L (35–141)	pH	6.0
BUN	44 mg/dL (8–22)	Protein	-- (0.1 g/day)
Cre	2.3 mg/dL (0.4–0.8)	Glucose	--
UA	9.5 mg/dL (2.6–6.2)	Occult blood	±
T-Cho	232 mg/dL (140–220)	Sediments	
TG	145 mg/dL (34–173)	RBC	1 >/HPF
AMY	240 IU/L(36–129)	Casts	--
Na	139 mmol/L (136–144)	Urine chemistry	
K	4.1 mmol/L (3.6–4.8)	u-NAG	4.9 U/L (0.5–9.1)
Cl	100 mmol/L (99–109)	Creatinine clearance (Ccr)	7 ml/min
Ca	8.0 mg/dL (8.5–9.9)		
P	3.9 mg/dL(2.6–4.5)	Ultrasonographic examination	
BS	87 mg/dL(78–110)	Peak systolic velocity (PSV)	
CRP	0.2 mg/dL (0–0.2)	Right 140 cm/sec, left 150 cm/sec	
HbA1c	5.4% (4.3–5.8)	Resistive index (RI)	
Infection		Right 0.48, left 0.42	
HBs-Ag	--		
HCV-Ab	+		

artery was successfully crossed and was dilated using a 2.0 balloon catheter and a Genesis 4.0 x 18 mm stent was implanted with IVUS guidance, followed by dilatation using 3.5 and 4.0 mm balloon catheters (Figures 3B and 3C). Final angiography showed 0% residual stenosis with normal flow (Figure 3D). A Genesis 5.0 x 18 mm stent was directly implanted in the left renal artery without predilatation (Figures 3 E and F). Immediately after the revascularization of the renal arteries, both kidneys were enlarged to almost normal size. Sufficient urination was noticed during the intervention. The patient was released from HD. Her serum creatinine and PRA normalized to 0.8 mg/dl and 0.7 ng/ml/hr, respectively. Her pulmonary edema was completely ameliorated (Figure 1B). The patient's hypertension also improved to 140/90 mmHg.

Discussion. ARAS is the most common underlying cause of renal artery stenosis.[1] Advanced age, hyperlipidemia, diabetes mellitus, smoking, heart disease and vascular disease are cited as risk factors.[6] Our case did not have any apparent risk factors except a slightly high level of serum total cholesterol and advanced age. However, severe atherosclerotic lesions in bilateral renal arteries were diagnosed by IVUS. The most crucial clinical findings associated with ARAS are hypertension and renal dysfunction. Hypertension is due to the activation of the rennin-angiotensin pathway,[7] which usually worsens rapidly refractory to antihypertensive agents. Renal dysfunction is caused by ischemic nephropathy, with renal parenchymal ischemia caused by a decrement of renal perfusion, often developing into end-stage renal disease (ESRD) and requiring dialysis therapy.[8]

Although angiography is historically the gold standard for diagnosing renal artery stenosis, it may cause atheroembolism and contrast nephropathy. Recently, various noninvasive methods such as MRA, CTA and duplex ultrasonography have been devised and developed. Although MRA and CTA are equal to angiography in terms of sensitivity and specificity (MRA: approximately 90–95%, CTA: approximately 95%), CTA poses a risk of contrast nephropathy, and MRA poses a risk of gadolinium-induced nephrogenic systemic fibrosis.[9] Taking those facts into consideration, duplex ultrasonography is the safest and most convenient on a cost/performance basis. Although the usefulness of duplex ultrasonography depends on the technical skill of the operator, it was recently reported that its sensitivity and specificity are 90–95%.[10,11] Duplex ultrasonography can provide information about the viability of kidneys with ARAS. According to Strandness et al, both a peak systolic velocity (PSV) of a renal artery > 180 cm/sec and a renal-to-aorta ratio (RAR) > 3.5 indicate renal artery stenosis > 60%.[12] It is also reported that a PSV > 200 cm/sec by ultrasonography is almost equal to a translesional pressure gradient > 20 mmHg by angiography.[13] In cases of a resistive index (RI) > 0.8, renal parenchymal dysfunction is estimated to be severe. Our patient's plasma renin activity (PRA) and serum aldosterone level were high, but duplex ultrasonography of the renal arteries did not reveal renal artery stenosis (Table 1).

Given this information and the atrophic finding in both kidneys, we hesitated to perform further studies. However, accelerated renal dysfunction, congestion (flush pulmonary edema) and hypertension that required HD led us to perform CTA (Figure 2).

In terms of treatment for renal artery stenosis, it is reported that angiotensin-converting enzyme inhibitors (ACE I) or angiotensin II receptor-blockers (ARBs) are effective in treating hypertension for 86–92% of patients.[14] Caution should be practiced because ACEIs or ARBs can cause the progression of renal dysfunction,[15] which was the case in our patient. Those agents are also contraindicated in cases of bilateral stenosis or functional unilateral stenosis. The indication for PTRA for ARAS is stated in the ACC/AHA 2005 guidelines.[4] These guidelines cite the following: "...percutaneous revascularization is reasonable for patients with hemodynamically significant RAS and accelerated hypertension, resistant hypertension, malignant hypertension, hypertension with an unexplained unilateral small kidney, and hypertension with intolerance to medication (Class IIa, LOB B), percutaneous revascularization is indicated for patients with hemodynamically significant RAS and recurrent, unexplained congestive heart failure or sudden, unexplained pulmonary edema (Class I, LOB B)."[4]

Van et al reported that in the treatment of ostial ARAS, the primary success rate employing PTRA with or without stenting was 88% and 57%, respectively, and that the restenosis rate after a successful primary procedure in patients who underwent PTRA with or without stenting was in 14% and 48%, respectively. The author concluded that PTRA with stenting is a better approach in the treatment of ostial ARAS.[16] However, concerning the recovery of renal function, it is still controversial.[5]

The resistive index (RI) has been said to predict the outcome in patients with renal artery stenosis who are undergo intervention. It is reported that among patients with renal artery stenosis > 50% of the luminal diameter and who underwent PTRA or surgery, a RI of at least 0.8 reliably identifies those who will not experience improved renal function.[17] On the contrary, it is also reported that among patients with ARAS > 70% of the luminal diameter, even if the RI is > 0.8, PTRA with stenting offers favorable acute and long-term clinical results for the preservation of renal function.[18] RI is currently controversial, with no reliable data on outcomes in patients with renal artery stenosis treated with PTRA.

There is no evidence (such as randomized, controlled studies) that dilating a totally occluded renal artery is beneficial. However, recanalization of chronic total occlusions (CTOs) has been shown to be feasible in the coronary circulation.[19] It is also reported that renal function was improved after opening a totally occluded renal artery with PTRA followed by stenting.[20,21] In our case, severe and even occluded ostial ARAS was treated by stent placement, leading to recovery of the kidneys' size, immediate satisfactory urination, and a normalized creatinine level and discontinuation of HD. At day-23 (8 days post intervention), a renogram showed that the right kidney functioned at nearly half the capacity as the left kidney (Figures 4A and B), which would

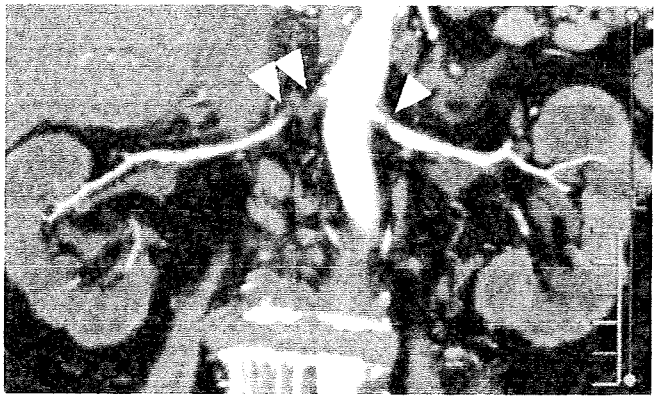

Figure 2. *Computed tomographic angiography finding. Bilateral severe ostial renal artery stenosis (arrowheads) and bilateral atrophic kidneys were seen. The kidney size (major axis) was 74 mm in the right and 85 mm in the left.*

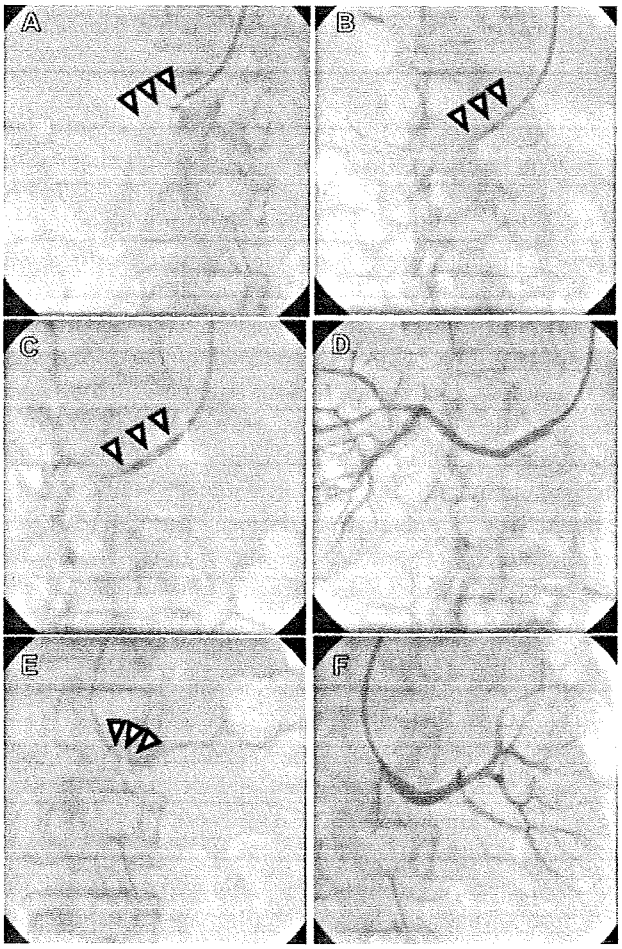

Figure 3. *Renal revascularization. Right renal artery* **(A–D)** *and left renal artery* **(E–F)**. **(A)** *Angiography of the right renal artery showed total occlusion (arrowheads).* **(B)** *The lesion was successfully crossed with a guidewire, dilated using a Trytop 2.0 mm balloon catheter, and a Genesis 4.0 x 18 mm stent was positioned (arrowheads).* **(C)** *The lesion was dilated with a Trytop 3.5 mm balloon catheter followed by a 4.0 mm stent balloon (arrowheads).* **(D)** *Final angiography showed no stenosis.* **(E)** *Angiography of the left renal artery showed 90% stenosis (arrowheads). At the lesion, a Genesis 5.0 x 18 mm stent was directly implanted without predilatation.* **(F)** *Final angiography showed 0% residual stenosis, with normal flow.*

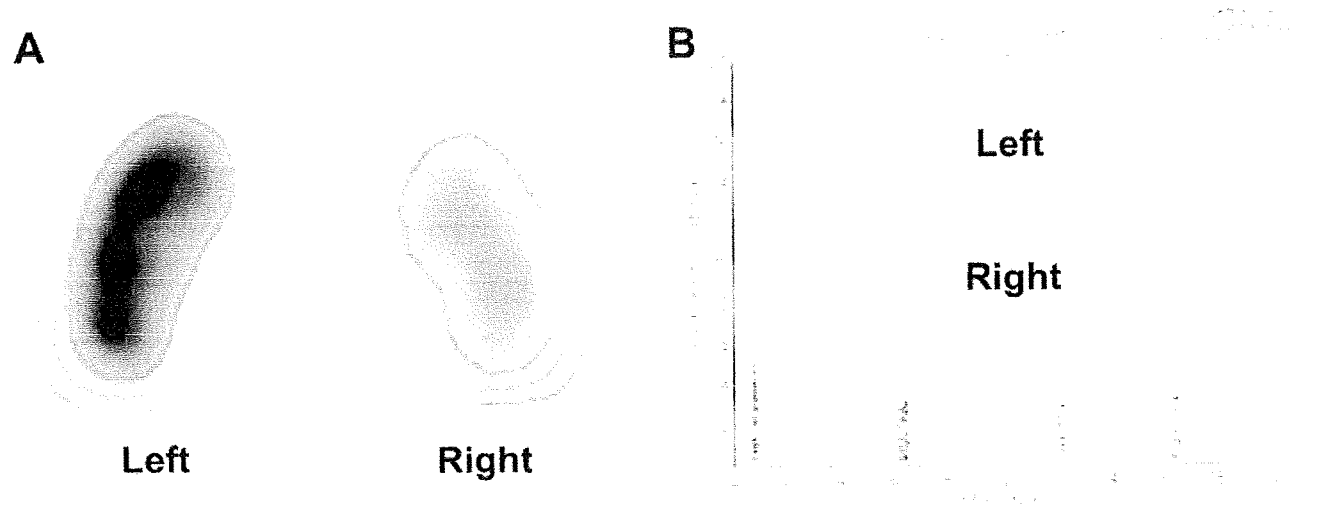

Figure 4. *Renogram (99 mTc-MAG3).* (A) *The uptake of 99 mTc-MAG3 was less in the right kidney than in the left kidney.* (B) *The effective renal plasma flow of the right and left kidneys was 63.8 mL/min and 142.1 mL/min, respectively.*

imply that opening the right occluded renal artery contributed to the improvement of renal function to some extent.

Our case provides new information regarding PTRA for ARAS and renal function prognosis due to this interventional approach. In our patient, the conditions implying negative indications and poor prognosis included: 1) small kidneys that looked atrophied and highly-echoic by ultrasound; 2) duplex ultrasonography did not show positive stenotic findings; 3) risk of contrast nephropathy; 4) total occlusion of the right renal artery. Conditions implying a favorable prognosis for our patient included: 1) acute process of renal functional decline; 2) HD was initiated, which meant no further progression of azotemia and congestion; 3) the guidewire was able to reach the totally occluded renal artery which was probably suspected of recent occlusion; 4) immediate recovery of our patient's kidney size and urine output.

Our case thus provided several insights: 1) an atrophic high-echoic appearance of the kidney does not always mean irreversible function; 2) duplex ultrasonography and the RI do not always provide the right information; 3) an acute process of renal dysfunction with ARAS should be treated as quickly as possible; 4) even a totally occluded artery can be treated with PTRA when the guidewire can cross the occlusion.

Acknowledgments. We wish to thank Jun-ichi Tasaki, Noriyuki Iehara, Takeshi Matsubara, Akira Mima, Misa Tanaka and Yoshinori Tanaka for consultation on the work-up and treatment of the patient.

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Clin Transplant 2009: 23 (Suppl. 20): 62–66 DOI: 10.1111/j.1399-0012.2009.00999.x

Clinical Transplantation

Case Report

A case of living-related renal transplant from the donor with membranous nephropathy

Akioka K, Okamoto M, Ushigome H, Nobori S, Suzuki T, Sakai K, Sakamoto S, Urasaki K, Yanagisawa A, Fukatsu A, Yoshimura N. A case of living-related renal transplant from the donor with membranous nephropathy.
Clin Transplant 2009: 23 (Suppl. 20): 62–66.

Abstract: Introduction: When a patient who had renal replacement therapy becomes older, an elder donor candidate may be considered as a potential donor for living-related transplantation. Elder donor candidate might have pre-existing disease including mild renal dysfunction, such as proteinuria. Marginally appropriate donors might be considered for renal graft because of the shortage of donors. A successful outcome after kidney transplantation from a living-related donor diagnosed as membranous nephropathy is reported.
Case report: A 38-yr-old male had been on continuous ambulatory peritoneal dialysis (CAPD) since the age of 37. His 63-yr-old father had mild proteinuria, and had been diagnosed with membranous nephropathy by needle biopsy at the age of 60. However, renal function of the father was found to be stable for three yr in a preoperative examination for donor; the father had normal renal function except for mild proteinuria. After adequate informed consent, we transplanted a kidney from the father, diagnosed with membranous nephropathy, to his son with a cyclosporine A-based immunosuppression regimen. In both the recipient and the donor, postoperative course was stable without complication such as rejection or infection. At 57 months after transplantation, the serum creatine level was 1.7 mg/dL in the recipient and 1.2 mg/dL in the donor. At 39 months after transplantation, allograft needle biopsy showed mild spike formation with partial thickening of the glomerular basement membrane (GBM). Decreases in electron-dense deposits and electron-lucent washout lesions with thickening of the GBM were observed using electron microscopy. This was diagnosed as Stage IV membranous nephropathy, showing clearance of the immune complexes and histological repair of the GBM.
Conclusion: Donation of the kidney did not affect the residual renal function of the father with membranous nephropathy. Pre-existing membranous nephropathy itself might show remission after transplantation in the recipient. However, long-term careful observation for both the donor and recipient is required.

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Key words: donor – kidney transplantation – membranous nephropathy

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Introduction

When the patient who had renal replacement therapy becomes older, elder donor candidate might be considered as a potential donor for living-related kidney transplantation. Elder donor candidate might have pre-existing disease including mild renal dysfunction, such as proteinuria. Because of the shortage of donors for renal transplantation, marginally appropriate kidney donors are also considered in an attempt to widen the donor criteria.

Some papers have reported successful outcomes after kidney transplantation from donors with pre-existing nephropathy. Here, we report a successful outcome after kidney transplantation from a living-related donor diagnosed with membranous nephropathy, citing appropriate references from the literature.

Case report

A 38-yr-old male who had proteinuria since the age of 22 yr has been on CAPD since the age of 37 because of end-stage renal failure caused by glomerulonephritis. His 63-yr-old father had mild proteinuria and had been diagnosed with membranous nephropathy by needle biopsy at the age of 60. Renal function of the father was stable for last three yr. The father wished to be a donor for living-related kidney transplantation to his son. In a preoperative examination for donor, the father was observed to have normal renal function excepting mild proteinuria. Serum creatinine and 24 h creatinine clearance were 0.96 mg/dL and 106 mL/min (167 cm/77 kg). Blood pressure was normalized by angiotensin receptor blocker. Urinary protein was − or 1+ and ranged about 400 mg/d, and did not increase during the clinical course.

Second needle biopsy of the kidney also had been performed as a final examination; there was no progressive change in histologic findings of membranous nephropathy. As the patient and the donor expressed willingness to have living-related kidney transplantation, after they were given adequate verbal instructions and written informed consent for the transplantation was obtained, we performed transplantation of kidney from the father with membranous nephropathy to his son.

Immunosuppressive treatment was started and maintained using cyclosporine A (CsA), FTY720, Fingolimod (FTY) and prednisolone (PSL). Shortly, the initial dose of CsA (7 mg/kg/d) was administered orally for two d before transplantation, and then CsA (3 mg/kg/d) was administered intravenously on the day of transplantation, followed thereafter by oral administration at 6–8 mg/kg/d. The dosage of CsA was adjusted by reference to the area under the blood concentration–time curve $(AUC)_{0-9\ h}$ level. A bolus dose of 500 mg of methyl prednisolone (MP) was administered on the day of transplantation, followed by 50 mg/d PSL on days 0–3. PSL was then reduced every week, from 40 to 30, 25, 20, 15 and finally 10 mg/d. On day 1, FTY (5 mg/d) was added. The postoperative course was good and stable; protocol allograft biopsy on postoperative day (POD) 23 showed no evidence of acute rejection and nephrotoxicity except pre-existing membranous nephropathy (Fig. 1).

The serum creatinine level had reached 1.6 mg/dL at the time of hospital discharge on POD33. At 57 months after transplantation, the serum creatinine level was 1.7 mg/dL in the recipient and 1.2 mg/dL in the donor. Their renal functions were stable and no proteinuria was evident in the recipient. Postoperation course is summarized in Fig. 2. Clinical trial use of FTY was over for initial two yr, FTY was converted to 1250 mg of mycophenolate mofetil (MMF). For three yr after the

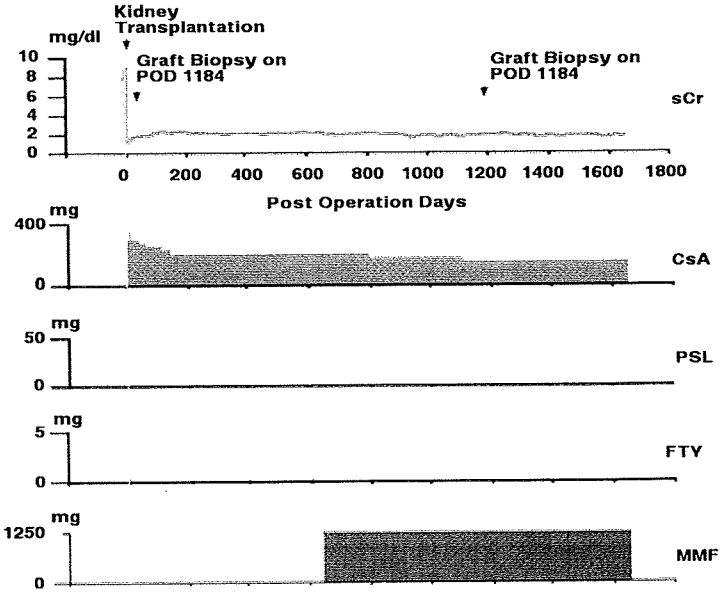

Fig. 1. Postoperative course, showing induction and maintenance of immunosuppression with time after kidney transplantation, and the levels of serum creatinine. Postoperative course, showing induction and maintenance of immunosuppression with time after kidney transplantation, and the levels of serum creatinine. Allograft biopsy was performed on POD 23 and 1184.

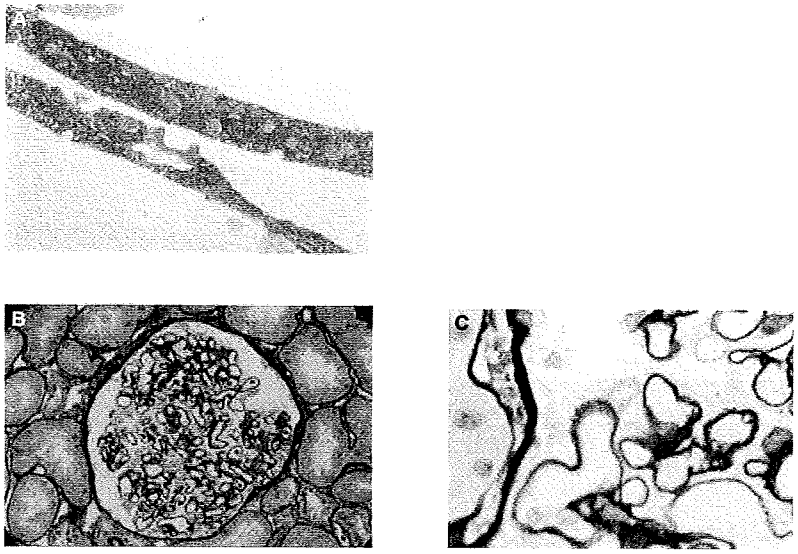

Fig. 2. Microscopic section of needle biopsy specimen obtained on postoperative day 23. (A) hematoxylin and eosin (HE) × 20, (B) Periodic acid-silver methenamine (PAM) × 400, (C) PAM × 1000. Spike formation, bubbling formation and partial thickening of the glomerular basement membrane (GBM) ware seen in PAM staining. Membranous glomerulonephritis was diagnosed. There was no evidence of acute rejection and tubulointerstitial injury.

transplantation, the graft function was stable and there was no evidence of adverse event such as rejection and infection. At 38 months after transplantation, protocol allograft needle biopsy for the recipient was performed and the specimen showed mild spike formation with partial thickening of the glomerular basement membrane (GBM) after staining with periodic acid-silver methenamine (PAM). Mild membranous glomerulonephritis was therefore diagnosed. There was no evidence of acute rejection, and focal segmental sclerotic change and tubulointerstitial injury, characteristic of chronic allograft change, were observed (Fig. 3).

Immunofluorescence staining study showed moderate deposition of IgG, C3d and weak deposition of IgA, IgM and C3c, which were observed on POD 23 in glomerulus, disappeared and only weak deposition of C3d was observed on POD 1184. Deposition of immune complexes disappeared from GBM during post-transplantation course (Fig. 4). Electron microscopy showed decreases in electron-dense deposits and electron-lucent washout lesions with thickening of the GBM. The finding was diagnosed as Stage IV membranous nephropathy, resulting from clearance of the immune complexes and histologic repair of the GBM (Fig. 5).

Discussion

Marginally appropriate kidney donors also are considered for renal transplantation in an attempt to extend the donor criteria. Two papers have described successful outcomes after cadaveric

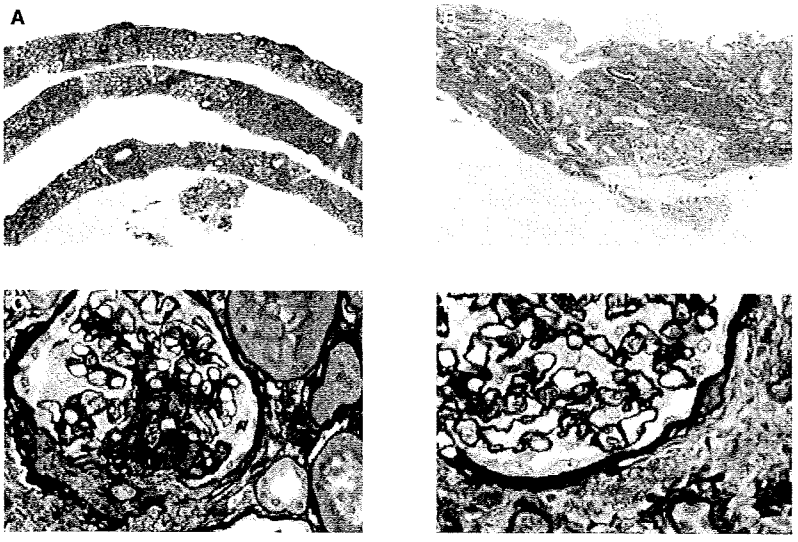

Fig. 3. Microscopic section of needle biopsy specimen obtained on postoperative day 1184. (A) Periodic acid-silver methenamine (PAM) × 20, (B) HE × 100, (C) PAM × 400, (D) PAM × 1000. Mild spike formation with partial thickening of the glomerular basement membrane (GBM) was seen in PAM staining. Mild membranous glomerulonephritis was therefore diagnosed. There was no evidence of acute rejection, and focal segmental sclerotic change and tubulointestinal injury, characteristic of chronic allograft change, were observed.

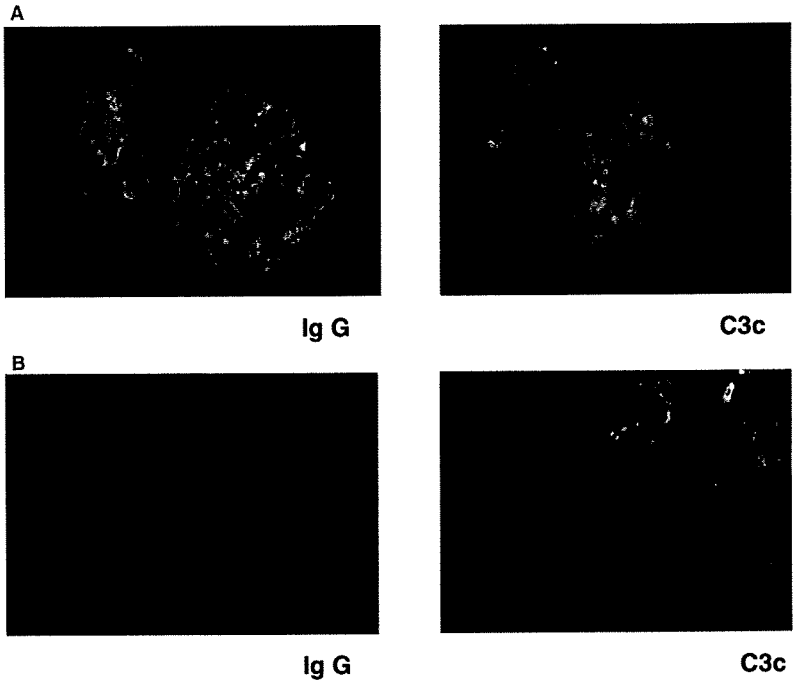

Fig. 4. Immunofluorescence staining section of needle biopsy specimen obtained on postoperative day 23 and 1184. (A) POD 23, (B) POD1184. Moderate deposition of IgG and weak deposition of C3c were observed on POD 23. Deposition of immune complexes disappeared from glomerular basement membrane (GBM) during post-transplantation course on POD 1184.

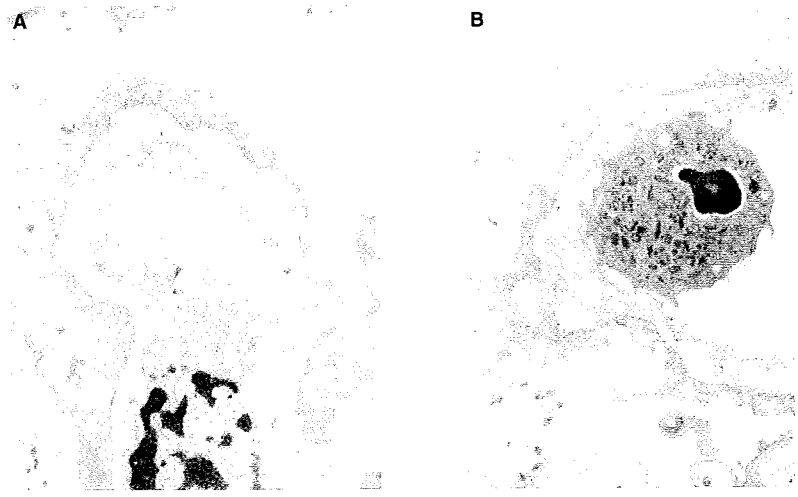

Fig. 5. Electron microscopic section of needle biopsy specimen obtained on postoperative day 1184. Electron microscopy showed decreases in electron-dense deposits and electron-lucent washout lesions with thickening of the glomerular basement membrane (GBM). This was diagnosed as Stage IV membranous nephropathy, resulting from clearance of the immune complexes and histologic repair of the GBM.

kidney transplantation from donors with pre-existing membranous nephropathy (1, 2). In these cases, from the finding of graft biopsies of the donor kidney performed at the time of transplantation, the donors were diagnosed to have pre-existing membranous nephropathy. These reports showed stable graft function after kidney transplantation for a couple of years, and histologic repair of the GBM was also observed. The report mentioned that membranous nephropathy itself, as well as IgA nephritis and diabetic nephropathy, resolves after kidney transplantation and deposition of IgG markedly decreases within a few months after transplantation, but that complete histologic restoration of the basement membrane needs at least a few years (2). Our histologic findings at 39 months after transplantation showed resolution and remission of membranous nephropathy. The natural history of the membranous nephropathy is variable; however, spontaneous remissions of proteinuria with stable renal function eventually occur in 40–50% of patients and the remainder slowly progress to end-stage renal disease or die of complications or of unrelated disease after 5–15 yr, whereas approximately one third of them progress towards renal insufficiency (3, 4). It

is difficult for us to find discriminately which case can enter remission of membranous nephropathy. It is said that outcome in non-nephrotic patients with membranous nephropathy invariably is good and 10-yr renal survival rate is reported approximating 100% (5). Other paper mentioned that the presence of focal segmental glomerulosclerosis (FSGS)-type glomerular lesions on membranous nephropathy is the prognostic factor, which portends a significantly worse outcome in terms of nephrotic syndrome and renal insufficiency (6). In our case, renal function of the father was stable for three yr, proteinuria was < 400 mg/d and there was no progressive change in histologic findings such as focal glomerulosclerosis (FGS)-type glomerular lesion from second needle biopsy. Then, we expected the favorable prognosis and stable residual kidney function after donation of the kidney. After obtaining adequate verbal and written informed consent, we decided kidney transplantation from the father with membranous nephropathy to his son. At that time of the transplantation, we did not have Amsterdam forum guidelines (7), which mention that proteinuria more than 300 mg/d is contraindication to donation. Karpinski et al. proposed slight relaxation of current rigid criteria. They defined that potentially acceptable proteinuria as 150–300 mg/dL (8). So we dared to qualify the father as marginally appropriate donor. Therefore, kidney transplantation from living donor with membranous nephropathy has never been reported in the literature; this might be the first case.

Here, we reported a favorable outcome of kidney transplantation from a donor with membranous nephropathy. For the present donor, donation of the graft did not affect his residual renal function. Pre-existing membranous nephropathy itself might show remission after transplantation and immunosuppression in the recipient. An attempt to extend the donor criteria for the family in this case would be an alternative choice for living-related transplantation. It was effective enough to achieve successful result; however, a report said prognosis for life and renal survival was worse in the older onset patients (> 60 yr) (9). It is also known that kidney donation results in small increases in urinary protein, but initial decrement in glomerular filtration rate (GFR) is not followed by accelerated losses over a subsequent span of 15 yr (10). Long-term careful observation for both the donor and recipient is required. Marginally appropriate donors could be considered to extend the donor criteria.

Conflict of interest

The authors have no conflict of interest to declare.

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Revised Equations for Estimated GFR From Serum Creatinine in Japan

Seiichi Matsuo, MD, PhD, Enyu Imai, MD, PhD, Masaru Horio, MD, PhD, Yoshinari Yasuda, MD, PhD, Kimio Tomita, MD, PhD, Kosaku Nitta, MD, PhD, Kunihiro Yamagata, MD, PhD, Yasuhiko Tomino, MD, PhD, Hitoshi Yokoyama, MD, PhD, and Akira Hishida, MD, PhD, on behalf of the collaborators developing the Japanese equation for estimated GFR

Background: Estimation of glomerular filtration rate (GFR) is limited by differences in creatinine generation among ethnicities. Our previously reported GFR-estimating equations for Japanese had limitations because all participants had a GFR less than 90 mL/min/1.73 m^2 and serum creatinine was assayed in different laboratories.

Study Design: Diagnostic test study using a prospective cross-sectional design. New equations were developed in 413 participants and validated in 350 participants. All samples were assayed in a central laboratory.

Setting & Participants: Hospitalized Japanese patients in 80 medical centers. Patients had not participated in the previous study.

Reference Test: Measured GFR (mGFR) computed from inulin clearance.

Index Test: Estimated GFR (eGFR) by using the modified isotope dilution mass spectrometry (IDMS)-traceable 4-variable Modification of Diet in Renal Disease (MDRD) Study equation using the previous Japanese Society of Nephrology Chronic Kidney Disease Initiative (JSN-CKDI) coefficient of 0.741 (equation 1), the previous JSN-CKDI equation (equation 2), and new equations derived in the development data set: modified MDRD Study using a new Japanese coefficient (equation 3), and a 3-variable Japanese equation (equation 4).

Measurements: Performance of equations was assessed by means of bias (eGFR − mGFR), accuracy (percentage of estimates within 15% or 30% of mGFR), root mean squared error, and correlation coefficient.

Results: In the development data set, the new Japanese coefficient was 0.808 (95% confidence interval, 0.728 to 0.829) for the IDMS–MDRD Study equation (equation 3), and the 3-variable Japanese equation (equation 4) was eGFR (mL/min/1.73 m^2) = 194 × Serum creatinine$^{-1.094}$ × Age$^{-0.287}$ × 0.739 (if female). In the validation data set, bias was −1.3 ± 19.4 versus −5.9 ± 19.0 mL/min/1.73 m^2 ($P = 0.002$), and accuracy within 30% of mGFR was 73% versus 72% ($P = 0.6$) for equation 3 versus equation 1 and −2.1 ± 19.0 versus −7.9 ± 18.7 mL/min/1.73 m^2 ($P < 0.001$) and 75% versus 73% ($P = 0.06$) for equation 4 versus equation 2 ($P = 0.06$), respectively.

Limitation: Most study participants had chronic kidney disease, and some may have had changing GFRs.

Conclusion: The new Japanese coefficient for the modified IDMS–MDRD Study equation and the new Japanese equation are more accurate for the Japanese population than the previously reported equations.

Am J Kidney Dis 53:982-992.

INDEX WORDS: Glomerular filtration rate; Japanese; inulin clearance; serum creatinine.

Editorial, p. 932

Glomerular filtration rate (GFR) is the most accurate index for assessing overall kidney function and an important tool for making diagnostic decisions in clinical practice.[1] GFR may be measured by using the clearance of an exogenous marker; inulin is the gold standard, but the method is not applicable to daily practice because it is time consuming, labor intensive, and expensive. Kidney function usually is assessed from serum creatinine (SCr) concentration alone, but SCr is affected by creatinine generation, including muscle mass and dietary intake, in addition to GFR.[2] GFR can be estimated from SCr level by using equations that include age, sex, race, and serum urea nitrogen (SUN) and albumin levels, as surrogates for creatinine generation, and are more accurate than estimates based on SCr level alone.[1,3,4]

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A list of the investigators who helped develop the Japanese equation for estimated GFR appears at the end of the article.

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The Modification of Diet in Renal Disease (MDRD) Study equation[5] and Cockcroft-Gault (CG) equation[6] are most commonly used for GFR estimation worldwide. Recently, the 4-variable MDRD Study equation was reexpressed by Levey et al[7] for use with isotope dilution mass spectrometry (IDMS)-standardized SCr values (the IDMS–MDRD Study equation). Several studies have validated the MDRD Study equation in whites and blacks.[8-14] In studies of more than 5,500 participants, Stevens et al[15,16] reported that GFR estimates using the IDMS–MDRD Study equation were unbiased and accurate for interpretations of GFR less than 60 mL/min/1.73 m^2, but warned that estimates just less than 60 mL/min/1.73 m^2 must be interpreted with caution to prevent misclassification of chronic kidney disease. The equation is less accurate for Asians, with greater bias at estimated GFR (eGFR) less than 60 mL/min/1.73 m^2.[17-19] Accordingly, both Ma et al[17] and our investigators[18,19] modified the MDRD Study equation by using separate "correction coefficients" for Chinese and Japanese. In both studies, the new equations were more accurate than the MDRD Study equation, but the correction coefficients were considerably different, with a Chinese coefficient of 1.233[17] and Japanese coefficient of 0.741.[19]

The difference in correction coefficients between Japanese and Chinese has not been explained. In our previous study, there may have been nonuniformity of creatinine assays because study samples for SCr were assayed in multiple laboratories and during different periods. Furthermore, data from participants with GFR greater than 90 mL/min/1.73 m^2 were not used for deriving the equation in the study. To verify results of our previous study, a new project was launched by the Japanese Society of Nephrology (JSN) with cooperation of nephrologists nationwide. The new study was conducted in 763 individuals to measure GFR and SCr by using inulin clearance (Cin) and standardized assays. A new Japanese correction coefficient was derived, as were new 3- and 5-variable Japanese equations.

METHODS

Inclusion and Exclusion Criteria

Inclusion criteria were: (1) age 18 years and older; (2) relatively stable kidney function, assessed by using SCr level; and (3) patient's agreement to have urinary Cin measured using a continuous infusion.

Exclusion criteria were: (1) acute kidney injury, (2) apparent malignancy, (3) problems in micturition, (4) pregnancy, (5) inulin allergy, (6) amputation, and (7) individuals for whom the investigator judged that measuring Cin was inappropriate. Although some study participants were hospitalized for diagnosis of rapidly progressive or acute glomerulonephritis, renal biopsies and Cin measurements were performed after their conditions became relatively stable. We did not record data for day-to-day SCr level changes.

Study Population of the Data Set

The study recruited participants from 80 medical centers throughout Japan between December 2006 and July 2007. Participants included mostly nephrology inpatients. Hospitalization of 5 to 14 days for kidney biopsy or education about lifestyle change was commonly practiced in Japan. Data for Cin and SCr were collected from 878 participants, mostly those with chronic kidney disease and a small number of healthy kidney donors. A total of 115 participants were excluded for the following reasons: 36 lacked data for urine volume, 11 were 17 years and younger, 2 had high serum inulin concentrations, 4 had lack of data for inulin blank, 51 had high values for inulin blank, 9 had a low volume of voided urine (<10 mL), and 2 had extraordinarily high GFRs. The final study population included 763 participants. Data collected from December 1, 2006, to April 20, 2007 (n = 413), were used as the development data set, and those obtained from April 21, 2007, to July 31, 2007 (n = 350), were used as the validation data set. The institutional review board at all the study institutions approved anonymous use of data for the present study. All patients signed written informed consent.

Cin and Creatinine Renal Clearance

Cin and creatinine clearance (Ccr) were measured simultaneously in 757 participants. In 6 participants, only Cin was measured. The method for measuring renal Cin was described elsewhere.[18] Briefly, Cin and Ccr were calculated from serum and urine concentrations and urine flow rate. Inulin (1%) was administered by means of a continuous intravenous infusion for 2 hours under overnight fasting, but hydrated, conditions. During the inulin infusion, serum samples were collected 4 times at 0 (blank), 45, 75, and 105 minutes for creatinine and inulin, and urine samples were collected between 30 and 60, 60 and 90, and 90 and 120 minutes for inulin and creatinine after completely emptying the bladder at 30 minutes from the start of the inulin infusion. Inulin samples were assayed by means of an enzymatic method using a kit (Diacolor Inulin; Toyobo Co, Osaka, Japan). The mean value of 3 measurements was used for the Cin and Ccr study.

SCr Measurement

Serum samples were assayed for creatinine in a central laboratory (Central Laboratory; SRL Co, Hachioji, Japan) by means of the enzymatic creatinine assay method using an