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Single Case

A Case of Rapidly Progressive Diabetic Nephropathy Induced by Osimertinib

Kazunori Karasawa   Ken-ichi Akiyama   Taro Akihisa   Yoei Miyabe
Kosaku Nitta   Junichi Hoshino

Department of Nephrology, Tokyo Women's Medical University, Tokyo, Japan

Abstract

The number of patients with diabetic nephropathy is increasing worldwide and it is important to understand the underlying pathological mechanisms of the disease. In early stage diabetic nephropathy, the hyperglycemic environment leads to vascular endothelial cell damage, resulting in overexpression of vascular endothelial growth factor (VEGF) in podocytes and renal pathology of glomerular hypertrophy, glomerular basement membrane thickening, and mesangial hyperplasia. In diabetic nephropathy, renal thrombotic microangiopathy (TMA) develops and the nephropathy progressively worsens in some cases of severe glomerular podocyte damage. Further, receptor tyrosine kinase inhibitors (RTKIs) may suppress VEGF secretion via VEGF receptor-2 tyrosine kinase inhibition in podocytes, which results in renal TMA and rapid deterioration of diabetic nephropathy. Osimertinib, a third-generation irreversible epidermal growth factor receptor (EGFR)-TKI, is approved as a first-line treatment agent for metastatic or locally advanced EGFR mutation-positive non-small cell lung cancer. We encountered a case of a patient with diabetic nephropathy with lung adenocarcinoma treated with osimertinib, whose condition deteriorated from early nephropathy to end-stage renal disease in approximately 4 months. The patient had early diabetic nephropathy, but the use of a RTKI suppressed VEGF expression in podocytes, resulting in the induction of renal TMA and the development of rapidly progressive diabetic nephropathy.

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Correspondence to:
Ken-ichi Akiyama, akiyama.kenichi @ twmu.ac.jp

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Introduction

The number of patients with diabetic nephropathy (DN) is increasing worldwide; DN is the leading cause of end-stage renal disease (ESRD) and requires dialysis. Vascular endothelial growth factor (VEGF) is a paracrine secreted product of podocytes under physiological conditions and is involved in endothelial cell homeostasis [1]; however, pathological conditions such as DN induce paracrine and autocrine hypersecretion from podocytes [2]. This results in the typical renal pathology of glomerular hypertrophy, glomerular basement membrane (GBM) thickening, mesangial matrix enlargement, slit membrane loss, and podocyte loss [2]. The etiology of DN is thought to be decreased endothelial nitric oxide synthase (eNOS) production in vascular endothelial cells and increased VEGF production in podocytes (uncoupling of VEGF and endothelial monoxide) due to endothelial cell damage from reactive oxygen species and advanced glycation end products produced in the hyperglycemic environment caused by diabetes mellitus (DM) [3, 4]. In early stage DN, excessive VEGF production induces abnormal renal pathology, but as the disease progresses and podocyte necrosis and glomerulosclerosis prevent VEGF production, renal TMA is thought to develop, leading to further endothelial cell damage and ESRD. DN complicated with renal TMA lesions deteriorates more rapidly than uncomplicated cases, and decreased VEGF expression in the glomeruli is correlated with decreased estimated glomerular filtration rate (eGFR) [5, 6].

While it is well known that the use of anti-VEGF agents is associated with TMA, a rare case of drug-induced renal TMA in a patient with early stage DN resulting in rapidly progressive diabetic nephropathy (RPDN) has been reported [7].

Osimertinib potently and selectively inhibits epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) activity, suppressing tumor growth. Recently, a rare case of crescent formation, IgA deposition in the glomerulus, and renal tubular damage in a patient with lung cancer treated with osimertinib was reported, but the detailed pathogenesis was unknown [8]. We report a case of DN in which a patient with lung adenocarcinoma was treated with osimertinib, whose condition deteriorated from early DN to ESRD in approximately 4 months.

Case Report

The patient was a 77-year-old man. Type II DM was diagnosed 16 years ago, and the patient was started on oral hypoglycemic agents. Later, his glycosylated hemoglobin A1c (HbA1c) level worsened to ~9%, and insulin therapy was introduced 6 years ago. One year ago (December), he was diagnosed with lung adenocarcinoma positive for *EGFR* mutations (S768I). The patient was started on osimertinib in January, at which time, his laboratory findings showed urine protein 2+, glucose 3+, occult blood ±, no abnormalities in sediment, serum creatinine (Cre) 0.83 mg/dL, eGFR 68.4 mL/min/1.73 m^2, and HbA1c 7.5%. He had no complications of retinopathy and no deterioration in blood Cre level for more than 10 years. In February, his systolic blood pressure was elevated at 150/mm Hg, and microscopic hematuria with dysmorphic erythrocytes was noted for the first time. In March, the Cre level worsened to 1.81 mg/dL, and osimertinib was discontinued. In April, Cre further worsened to 2.38 mg/dL, and the patient was admitted to our institution. The following were recorded on admission: height 162.1 cm, weight 59.9 kg, body mass index 22.9 kg/m^2, blood pressure 167/68 mm Hg, pulse rate 90 beats/min, body temperature 35.7°C; head and neck; eyelid conjunctiva pallor; extremities: edema of lower legs; nerves: thermal hypoalgesia and pallanesthesia in the lower limbs. There were no other notable findings. Urine qualitative analysis showed protein 2+,

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Table 1. Laboratory data on admission

	Result	Reference range
Blood tests		
Hemoglobin, g/dL	9.4	14.0–18.0
White blood cell count, $\times10^3/\mu L$	7.67	4.00–8.60
Platelets, $\times10^4/\mu L$	18.1	15.0–35.0
Serum creatinine, mg/dL	3.77	0.69–1.06
eGFR, mL/min/1.73 m^2	13.1	>90
Sodium, mEq/L	142	135–145
Potassium, mEq/L	4.4	3.4–4.9
Chlorine, mEq/L	108	98–108
Calcium, mg/dL	7.9	8.5–9.9
Phosphorus, mg/dL	4.2	2.5–4.3
Bicarbonate, mmol/L	22.5	21.0–28.0
Uric acid, mg/dL	5.6	3.7–6.9
Serum total protein, g/dL	6.4	6.5–8.2
Serum albumin, g/dL	3.3	3.8–5.1
Lactate dehydrogenase, IU/L	265	119–229
Aspartate aminotransferase, IU/L	14	13–33
Alanine aminotransferase, IU/L	8	6–30
Low-density cholesterol, mg/dL	109	61–139
High-density cholesterol, mg/dL	57	40–149
Triglycerides, mg/dL	123	42–67
Antinuclear antibody	1:80, homogenous type 1:80, speckled type 1:80	
Autoantibodies and viral testing[a]	Negative	
IgG, mg/dL	1,075	870–1,700
IgA, mg/dL	301	110–410
IgM, mg/dL	49	33–190
Serum C3, mg/dL	107.3	65.0–135.0
Serum C4, mg/dL	31.4	13.0–35.0
Total hemolytic complement, U/mL	>60	30.0–46.0
Cryoglobulins, mg/L	Negative	
Serum protein electrophoresis	Hypoalbuminemia, hyper-α1 globulinemia, hyper-α2 globulinemia, hyper-β2 globulinemia	
Serum immunofixation	Negative	
Serum VEGF (ELISA), pg/mL	326	143.1–658.8
Urine studies		
Erythrocytes/HPF	≧ 100	≦ 4
Leukocytes/HPF	1–4	≦ 4
Protein-creatinine ratio, g/gCr	4.55	<0.15
Bence-Jones protein (spot)	Negative	

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Table 1 (continued)

	Result	Reference range
Urine immunofixation	Negative	
Urine eosinophils, %[b]	5.0	less than 1–5%
β2MG, μg/L	10,575	$\leqq$ 230
NAG, U/L	4.3	2.6–6.8

eGFR, estimated glomerular filtration rate (as calculated based on the paper by 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 Jun; 53(6):982–92. doi: 10.1053/j.ajkd.2008.12.034). Ig, immunoglobulin; sFLC, serum free light chains (assay obtained from binding site); VEGF, vascular endothelial growth factor; ELISA, enzyme-linked immunosorbent assay; HPF, high power field; β2MG, β2 microglobulin; NAG, N-acetyl-beta-D-glucosaminidase.

Conversion factors for units: Serum creatinine in mg/dL to μmol/L, ×88.4; serum calcium in mg/dL to mmol/L, ×0.2495; serum phosphorus in mg/dL to mmol/L, ×0.3229; serum low-density cholesterol in mg/dL to mmol/L, ×0.02586; serum high-density cholesterol in mg/dL to mmol/L, ×0.02586.

[a]Antineutrophil cytoplasmic antibody (ANCA), anti-glomerular basement membrane antibody (GBM), lupus anticoagulant (LAC), anticardiolipin antibody (ACL), β2-glycoprotein 1 antibody (β2GP-1), hepatitis B surface antigen; hepatitis C antibody; human immunodeficiency virus antibody; syphilis reaction qualitative; lipid antibody qualitative.

[b]Muriithi AK, Nasr SH, Leung N. Utility of urine eosinophils in the diagnosis of acute interstitial nephritis. Clin J Am Soc Nephrol. 2013;11:1857–1862. doi: 10.2215/CJN.01330213.

4.55 g/gCre, occult blood 3+; sugar−, urine sedimentation analysis showed red blood cell ≥100/high power field (HF), white blood cell 1–4/HF, vitreous cylinder 1–4/HF, granular cylinder 1/20 low power field (LF), fat cast 1/50 LF, oval fat body 1/20 HF, and few dysmorphic red blood cells. Blood sample results showed mildly elevated lactate dehydrogenase (265 IU/L), renal impairment (Cre: 3.77 mg/dL, eGFR: 13.1 mL/min/1.73 m^2), hypoalbuminemia (3.3 g/dL), and anemia. Other laboratory examination findings on admission are shown in Table 1.

Table 2 shows the characteristics of the cases used as DN controls and normal controls in the renal pathology analysis in comparison to RPDN. Renal biopsy was performed; DN class IIb, glomerular and peritubular capillary (PTC) microangiopathy, diffuse tubular injury, and inactive IgA nephropathy were diagnosed. Light microscopy showed mild mesangial expansion (Fig. 1a: periodic acid-Schiff stain [PAS], Fig. 1b, c: periodic acid-methenamine-silver stain [PAM]) and neovascularization at the glomerular vascular pole (Fig. 1a, arrow), but no lesions of nodular sclerosis were observed. Electron microscopy revealed thickening of the GBM, although the results are not shown. Based on these results, a diagnosis of DN class IIb was made. Despite the absence of thrombotic findings, pathologic TMA findings such as glomerular and PTC endothelial enlargement (Fig. 1b, asterisk), mesangiolysis (Fig. 1b, arrow), and GBM doubling (Fig. 1c, arrow head) were observed. Fluorescent antibody results were positive for IgG in granular form on the GBM (Fig. 1d), a finding consistent with DN. IgA (Fig. 1e) and C3 (Fig. 1f) deposits were found in the mesangial area, suggesting IgA nephropathy, but the absence of mesangial cell proliferation suggested that the disease was inactive. Immunohistochemical staining results showed markedly decreased VEGF expression only in glomeruli (Fig. 2d, h) and markedly increased heparin-binding epidermal growth factor-like growth factor (HB-EGF) expression in mesangial regions (Fig. 2k) in the RPDN case compared to DN class IIb (Fig. 2b, c, f, g) and normal (Fig. 2a, e) controls. In DN class IIb controls, VEGF expression in the glomerular (Fig. 2b, c) and tubular interstitium (Fig. 2f, g) was markedly upregulated compared to that in the normal controls (Fig. 2a, e), and

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Table 2. Characteristics of each patient

Biopsy group	Sex	Age, years	Histology diagnosis	Creatinine, mg/dL	eGFR, mL/min/1.73 m²	Interstitial fibrosis, %	Proteinuria, g/day	HbA1c, %	Hypertension	Retinopathy	DM type	Urinary 8-OHdG, ng/mg Cr
RPDN	Male	77	Class IIb	3.77	13.1	5	2.93	6.4	Yes	No	II	11.7
DN control 1	Male	49	Class IIb	0.93	69.6	30	1.80	7.1	Yes	Yes	II	5.4
DN control 2	Female	27	Class IIb	1.17	46.9	50	0.80	5.4	Yes	Yes	I	5.4
DN control 3	Male	68	Class IIa	1.39	40.3	5	1.60	6.2	Yes	No	II	7.1
DN control 4	Male	71	Class IIa	0.75	78.2	5	0.14	7	Yes	No	II	10.8
DN control 5	Male	71	Class IIa	0.75	78.2	30	1.28	6.1	Yes	No	II	4.8
Normal 1	Male	51	–	0.82	78.0	–	–	5.6	No	–	–	–
Normal 2	Male	54	–	0.83	75.7	–	–	5.7	Yes	–	–	–

Characteristics of RPDN, 5 DN control cases, and normal cases are shown. RPDN and three DN class IIa (diabetic controls 3, 4, 5) cases had no complications of diabetic retinopathy. Two class IIb DN controls (1, 2) had diabetic retinopathy. 8-OHdG, an oxidative stress marker in the kidney, was highest in the RPDN case. DN, diabetic nephropathy; Normal, normal control; RPDN, rapidly progressive diabetic nephropathy.
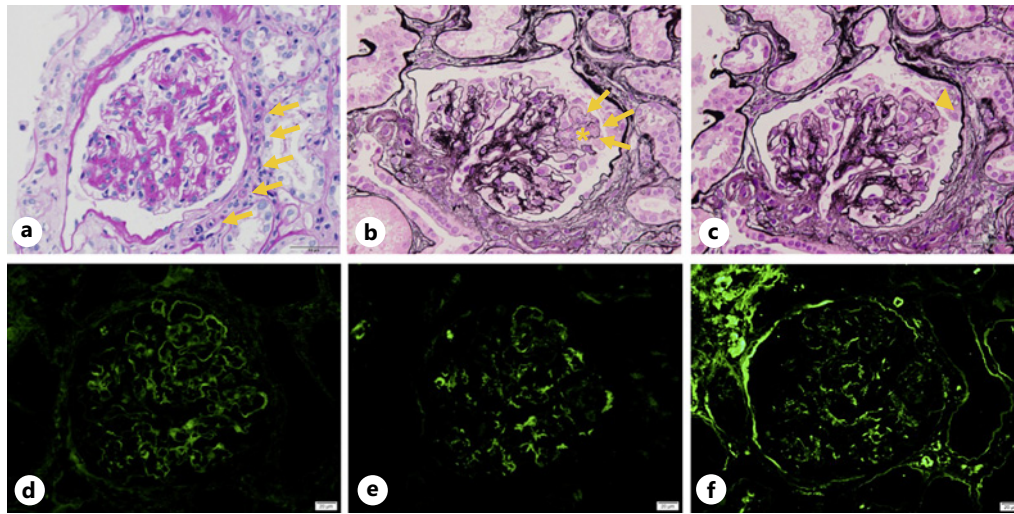
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Fig. 1. Renal histopathology of RPDN. **a**: PAS, **b, c**: PAM, **d**: IgG, **e**: IgA, **f**: C3, magnification, ×400. Light microscopy revealing endothelial enlargement and inflammatory cell infiltration in the glomeruli and PTCs and a moderately enlarged mesangial area (**a**). Mesangiolysis, and some GBM doubling were observed (**b, c**). Immunofluorescent staining of paraffin-embedded kidney tissue showing that IgG was 1+ to 2+ in granular form on the GBM (**d**), a finding consistent with DN, IgA was 1+ to 2+ in the mesangium (**e**) and C3 was 1+ in the mesangium (**f**), suggesting a complication of IgA nephropathy, but the increase in mesangial cells was not noticeable on light microscopy.

HB-EGF expression in the mesangial region was slightly enhanced (Fig. 2j). Moreover, HB-EGF expression was not observed in the normal control (Fig. 2i). Despite the discontinuation of the suspected drug, the Cre level increased to 5.30 mg/dL in approximately 1 month. Hemodialysis treatment was introduced as alternative chemotherapy for lung adenocarcinoma.

Discussion

Clinically, there is a case report of an early stage DN patient with rapidly progressing diabetic kidney disease due to previously developed advanced rectal cancer, treated with a tegafur/gimeracil/oteracil [7], and a case series in which the appearance of renal TMA lesions and decreased VEGF expression in the glomeruli was associated with progressive worsening of DN [5, 6]. Hyperplasia of the mesangial matrix, a hallmark of early DN, involves accelerated HB-EGF production in the mesangial cells and its downstream EGFR-mediated transforming growth factor-β1 expression [9]. Furthermore, in DN, decreased eNOS expression and increased HB-EGF expression are associated with worsening of the disease [10]. In a mouse model of type I diabetes-induced DN, treatment with podocyte-specific *EGFR* knockout or EGFR-TKI (erlotinib) was reported to have a nephroprotective effect by decreasing albuminuria, transforming growth factor-β1 expression, and fibronectin deposition in the kidney compared to controls [11]. HB-EGF staining was performed to validate the previously reported findings. The results showed that HB-EGF expression in the mesangial region was enhanced in the RPDN case (Fig. 2g) compared to the DN class IIb control case (Fig. 2f), and no renoprotective effect of EGFR-TKI was observed. To the best of our knowledge, this is the first case of HB-EGF staining in human DN tissues.
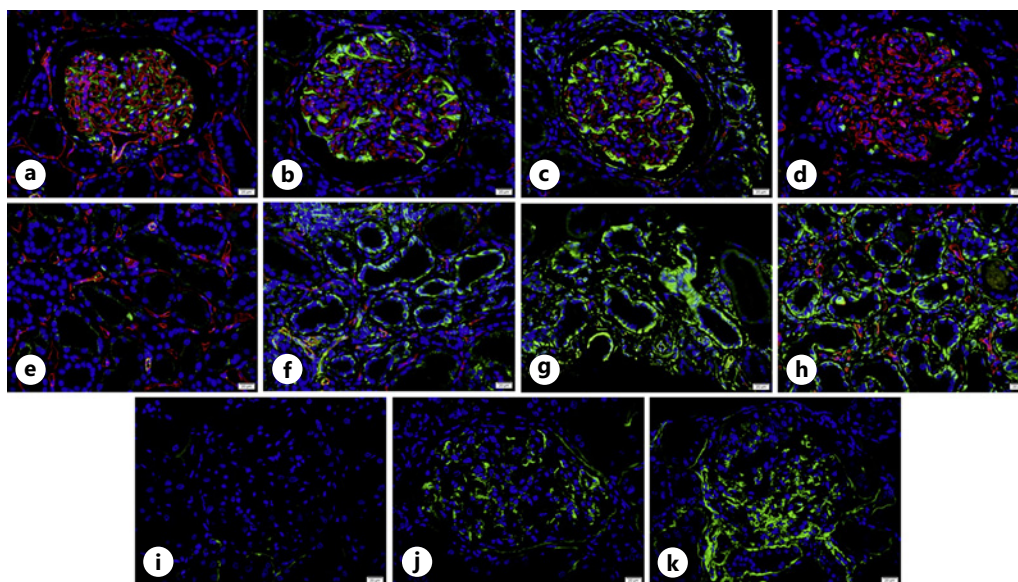
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Fig. 2. VEGF staining results (**a**: normal kidney glomerulus, **b, c**: DN control glomerulus, **d**: RPDN glomerulus, **e** normal kidney interstitium, **f, g**: DN control interstitium, **h**: RPDN interstitium, magnification, ×400) and HB-EGF staining results (**i**: normal kidney, **j**: DN control, **k**: RPDN, magnification, ×400). Immunohistological examination results showing VEGF staining on the glomerular epithelial cells and CD31 staining on the vascular endothelial cells and PTCs in the normal control (Normal 1) (**a**). VEGF is rarely expressed in the tubular interstitium (**a**). In the DN controls (DN 1, 2), there is a marked expression of VEGF in the glomeruli and tubulointerstitium and a decrease in the number of CD31-positive endothelial cells in the glomerular and tubulointerstitium (**b, c**). In the RPDN case, a marked decrease in VEGF expression was only present in the glomerular epithelial cells, and the expression of VEGF in the tubulointerstitium was higher than that in the normal control (Normal 1) (**d**). HB-EGF immunostaining showing high expression in mesangium in the RPDN case (**g**), weak positivity in the DN control (DN 2) (**f**), and no expression in the normal control (Normal 2) (**e**). VEGF and HB-EGF are stained green, CD31-positive vascular endothelium is stained red, and nuclei are stained blue with DAPI. PAS, periodic acid-Schiff stain; PAM, periodic acid-methenamine-silver stain; PTCs, peritubular capillaries; DN, diabetic nephropathy; GBM, glomerular basement membrane; RPDN, rapidly progressive diabetic nephropathy; VEGF, vascular endothelial growth factor; HB-EGF, heparin-binding epidermal growth factor-like growth factor; GBM, glomerular basement membrane.

Receptor tyrosine kinase inhibitors (RTKIs) are known to cause development of minimal change disease (MCD) and focal segmental glomerulosclerosis (FSGS). It is believed that RelA cannot remain in the nucleus in podocytes, resulting in increased expression of c-mip in the cytoplasm and impaired phosphorylation of nephrin, leading to MCD and FSGS [12]. Although this study did not examine the expression of RelA and c-mip in the renal glomeruli, there were no findings suggestive of MCD or FSGS, such as diffuse global podocyte effacement or FSGS lesions on light and electron microscopy (data not shown). It was anticipated that excessive VEGF autocrine and paracrine signaling via VEGF receptor-2 tyrosine kinase activation in podocytes, possibly caused by the lack of a negative feedback mechanism [13] due to eNOS deficiency in the endothelium, was suddenly inhibited by the RTKI, osimertinib. In conclusion, RPDN was considered to have developed from renal TMA due to RTKI use. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000531015.

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Statement of Ethics

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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