

Case Report

# Thrombotic Microangiopathy with Severe Proteinuria Induced by Lenvatinib for Radioactive Iodine-Refractory Papillary Thyroid Carcinoma

Yasuko Hyogo<sup>a</sup> Naomi Kiyota<sup>a, b</sup> Naoki Otsuki<sup>c</sup> Shunsuke Goto<sup>d</sup>  
Yoshinori Imamura<sup>a</sup> Naoko Chayahara<sup>a</sup> Masanori Toyoda<sup>a</sup>  
Ken-ichi Nibu<sup>c</sup> Toshiki Hyodo<sup>e</sup> Shigeo Hara<sup>f</sup> Hiroo Masuoka<sup>g</sup>  
Toshihiko Kasahara<sup>h</sup> Yasuhiro Ito<sup>g</sup> Akihiro Miya<sup>g</sup>  
Mitsuyoshi Hirokawa<sup>i</sup> Akira Miyauchi<sup>g</sup> Hironobu Minami<sup>a, b</sup>

<sup>a</sup>Division of Medical Oncology/Hematology, Department of Medicine, Kobe University Graduate School of Medicine, Kobe, Japan; <sup>b</sup>Kobe University Hospital Cancer Center, Kobe, Japan; <sup>c</sup>Department of Otolaryngology-Head and Neck Surgery, Kobe University Graduate School of Medicine, Kobe, Japan; <sup>d</sup>Division of Nephrology and Kidney Center, Kobe University Graduate School of Medicine, Kobe, Japan; <sup>e</sup>Department of Diagnostic Pathology, Kakogawa Medical Center, Kakogawa, Japan; <sup>f</sup>Department of Diagnostic Pathology, Kobe City Medical Center General Hospital, Kobe, Japan; <sup>g</sup>Department of Surgery, Kuma Hospital, Kobe, Japan; <sup>h</sup>Department of Internal Medicine, Kuma Hospital, Kobe, Japan; <sup>i</sup>Department of Diagnostic Pathology, Kuma Hospital, Kobe, Japan

## Keywords

Lenvatinib · Thrombotic microangiopathy · Proteinuria · Radioactive iodine- refractory differentiated thyroid cancer

## Abstract

Standard therapy for radioactive iodine (RAI)-refractory differentiated thyroid cancer (DTC) is multi-targeted kinase inhibitors (m-TKIs), represented by sorafenib and lenvatinib. One of the main target molecules of m-TKIs is vascular endothelial growth factor receptor (VEGF-R). m-TKIs are known to cause adverse reactions such as hypertension and proteinuria as a class effect. In particular, proteinuria is thought to result from vascular endothelial damage and

podocytopathy in glomeruli, and the development of thrombotic microangiopathy (TMA) has been reported for VEGF inhibitors. We encountered a patient with RAI-refractory (RR) papillary thyroid carcinoma (PTC) who developed proteinuria and renal dysfunction due to lenvatinib. Renal biopsy demonstrated that these changes were caused by TMA. To our knowledge, this is the first reported case of TMA due to lenvatinib in a Japanese patient with RR-PTC. A 70-year-old woman developed proteinuria, renal impairment and hypertension while receiving lenvatinib for RR-PTC. Her proteinuria and renal damage continued to worsen despite dose reductions and dose interruptions. Renal biopsy was consistent with the chronic type of TMA. These findings indicate that TMA is a possible cause of proteinuria due to lenvatinib, as has been reported for the VEGF inhibitors.

© 2018 The Author(s)  
Published by S. Karger AG, Basel

## Introduction

Standard therapy for radioactive iodine (RAI)-refractory differentiated thyroid cancer (DTC) is multi-targeted kinase inhibitors (m-TKIs), represented by lenvatinib and sorafenib [1, 2]. An important target molecule of these m-TKIs is vascular endothelial growth factor receptor (VEGF-R). m-TKIs cause hypertension and proteinuria as a class effect [3]. In particular, the mechanisms of proteinuria due to m-TKIs are vascular endothelial damage and podocytopathy in glomeruli. Various pathological conditions have been reported, including thrombotic microangiopathy (TMA) and other glomerular nephropathies [3–5]. The development of TMA has been reported for VEGF inhibitors [5–10].

Lenvatinib is an m-TKI that inhibits VEGF-R1–3, fibroblast growth factor receptor (FGFR) 1–4, platelet-derived growth factor receptor (PDGFR $\alpha$ ), RET, and KIT. Characteristic adverse reactions include hypertension and proteinuria [1]. Subgroup analysis of Japanese RAI-refractory (RR)-DTC patients from the randomized controlled trial (RCT) SELECT trial showed hypertension in 87% of subjects (grade 3 or higher in 80%) and proteinuria in 63% (grade 3 or higher in 20%) [11].

We recently encountered a patient with RR-papillary thyroid carcinoma (PTC) who developed proteinuria and renal impairment due to lenvatinib. Renal biopsy demonstrated that these changes were caused by TMA. To our knowledge, this is the first case of histologically proven TMA due to lenvatinib in a Japanese patient with RR-PTC.

## Case Report

A 70-year-old woman with metastatic RR-PTC diagnosed 40 years previously was started on treatment with lenvatinib (Fig. 1A, B). Left lobectomy of the thyroid gland and left cervical lymph node dissection were performed 5 years later as initial treatment, followed 26 years later by total thyroidectomy and left cervical lymph node dissection as salvage therapy for recurrence in left cervical lymph nodes. After repeated salvage lymph node dissection for recurrence, pulmonary metastases were detected. I-131 RAI therapy was performed at 100 mCi three times to treat residual lymph node metastases and pulmonary metastases. Because RAI did not accumulate in pulmonary metastases and the recurrent lesions grew, she was diagnosed with RR-PTC.

Comorbidities included concomitant type 2 diabetes arising 3 years ago, which was well-controlled with oral metformin 500 mg, with an HbA1c of 5.8%. No abnormal findings related

to diabetic nephropathy were detected. Hypertension was controlled at about 130/70 mm Hg at baseline with candesartan 8 mg and carvedilol 10 mg/day.

Blood and biochemical test findings at baseline were serum creatinine (sCr) 0.56 mg/dL, BUN 10 mg/dL, estimate glomerular filtration rate (eGFR) 81.6 mL/min/1.73 m<sup>2</sup>, total protein 7.4 g/dL, albumin 4.6 g/dL, free-T4 2.13 ng/dL and TSH 0.047 μU/mL, while urine findings at baseline were negative.

She was started on lenvatinib at 24 mg/day. Hypertension arising after one week was controlled with candesartan 12 mg/day. Two weeks after the start of lenvatinib, a grade 3 asymptomatic increase in pancreatic enzymes required a 10-day interruption followed by a reduction in lenvatinib to 20 mg/day. After repeated interruptions and reductions due to hypertension and leg edema, lenvatinib was eventually reduced to 14 mg/day at approximately 3 months. Hypertension was controllable with carvedilol 10 mg, candesartan 12 mg and amlodipine 5 mg. At seven months, she achieved a partial response (PR) with a 38% reduction by the Response Evaluation Criteria In Solid Tumors (RECIST) ver 1.1 criteria [12].

With regard to the progression of proteinuria, qualitative testing first detected urine protein at 1+ at 4 months after starting lenvatinib, increasing to 2+ and 0.83 g/day on quantification of pooled urine at 5 months. After a 7-day interruption, lenvatinib was then resumed at the reduced dose of 10 mg/day and continued at this level with repeated interruptions. At 1 year after the start of treatment, however, urine protein remained at 2+ in qualitative testing even with repetitive interruptions of lenvatinib. Twenty-six months after the start of treatment, urine protein was 4+ and leg edema was observed. After dose interruption, lenvatinib was eventually reduced to 8 mg. During the clinical course, eGFR gradually decreased (Fig. 2), and proteinuria continued at 904–3,568 mg/day on quantitation of pooled urine. Fifty-six months after the start of treatment, sCr was 1.12 mg/dL, eGFR was 37.4 mL/min/1.73 m<sup>2</sup>, and albumin was 2.9 g/dL, indicating that renal impairment had worsened. In urinary sediment findings, white blood cells were <1 cell/HPF, red blood cells were 5–9 cells/HPF, hyaline casts were 1+, and epithelial cell casts were 1+. Because of the persistent severe proteinuria and deterioration of renal function, we performed renal biopsy.

#### Findings of renal biopsy and clinical course after renal biopsy

Light microscopic findings (Fig. 3A) revealed double contouring of the loop walls in many glomeruli, and exudate and infiltration of foamy histiocytes in expanded, saccular glomerular tufts accompanied by mesangiolytic. Severe intimal thickening was observed in the arcuate arteries, mild intimal thickening in the interlobular arteries, and mild to moderate hyalinosis in the arterioles. No vasculitis was detected. These findings indicated severe endothelial cell damage accompanied by the remodeling of glomerular tufts (double contouring of the loop walls), consistent with the chronic type of TMA. Although the patient was diagnosed with diabetes about 8 years previously, no diabetic glomerular lesions were observed.

On electron microscopy (Fig. 3B), overall findings showed a marked edematous expansion of subendothelium, as well as new glomerular basement membrane formation, hypertrophy of endothelial cell cytoplasm and loss of fenestrae were also detected. Chronic endothelial cell damage and remodeling were also detected, which is also compatible with the chronic type of TMA.

Because renal biopsy revealed that TMA was a plausible cause of her proteinuria and renal impairment, lenvatinib was discontinued. Renal function gradually improved, and showed partial recovery at approximately 2 months after discontinuation of the drug (Fig. 2).

## Discussion

Proteinuria and hypertension are well-known class effects of VEGF-targeted therapy. In this case, severe proteinuria was prolonged despite repeated dose interruptions and dose reductions, resulting in renal impairment with an eGFR below 40 mL/min/1.73m<sup>2</sup> and discontinuation of lenvatinib. Pathological findings from renal biopsy revealed that these sequelae were due to the chronic type of TMA.

The pivotal RCT of the SELECT trial for RR-DTC showed proteinuria in 31% (grade 3 or higher in 10.0%) of patients [1]. Frequency was higher still in Japanese patients, at 63.3% (grade 3 or higher in 20.0%) [11]. In a study of metastatic renal cell carcinoma (mRCC) patients using sunitinib or pazopanib, 30% of patients with Asian ethnicity had on-therapy proteinuria compared with 8% with white ethnicity (adjusted HR 4.1,  $p < 0.001$ ). In addition to Asian ethnicity, other independent predictors of on-therapy proteinuria were diabetes, baseline hypertension, pre-existing proteinuria and prior nephrectomy [13].

Previous reports of renal biopsies to explore the pathophysiology of the proteinuria and renal impairment induced by VEGF inhibitors, such as anti-VEGF antibody, have reported that VEGF trap and m-TKIs can cause TMA [5–10]. While anti-VEGF antibody tends to cause TMA, a variety of renal histopathologies, including TMA and other glomerular nephropathies have been reported for m-TKIs [3, 5, 9, 10]. Proteinuria is caused by vascular endothelial damage and podocytopathy in glomeruli, which are also due to VEGF inhibition [3]. Glomerular vascular permeability is regulated by the interaction between glomerular endothelial cells and podocytes via the podocyte-derived VEGF pathway. On this basis, VEGF inhibition may cause proteinuria [5, 9]. Typical TMA is accompanied by platelet thrombus in the microvasculature, thrombocytopenia, and microangiopathic hemolytic anemia. TMA due to VEGF inhibitors is considered to differ from that induced by cytotoxic anticancer drugs such as Mitomycin C since it tends to be dose-independent and reversible by stopping administration, and the lesions are localized in glomeruli [14]. One mechanism by which VEGF inhibitors induce TMA involves a deficiency in VEGF derived from podocytes in glomeruli. VEGF is constantly produced by podocytes and binds to VEGF receptor 2 (VEGF-R2) on endothelial cells to exert a paracrine effect, which maintains the function and structure of fenestrations in endothelial cells. Moreover, it has been reported that VEGF secreted by podocytes binds back to VEGF-R2 and soluble fms-like tyrosine kinase-1 (sFlt-1) on podocytes to exert an autocrine action, namely regulation of the cytoskeleton and slit membranes between the foot processes. Accordingly, this demonstrates the importance of VEGF in maintaining the homeostasis of the filtration barrier in the glomerular vasculature [9].

In our present patient, pathological findings from renal biopsy showed the same severe endothelial cell damage as seen in previous reports of TMA due to VEGF inhibitors. However, the proteinuria and renal impairment in this patient partially recovered with the discontinuation of lenvatinib. TMA due to VEGF inhibitors is often reversible, and the recovery of renal function can be expected by early discontinuation of the drug and blood pressure control. However, plasmapheresis or dialysis may be required in advanced cases [3, 5]. Moreover, given a report that the continuation or re-administration of the causal VEGF inhibitor for TMA resulted in more severe and irreversible TMA, discontinuation should be continued for as long as possible [3]. However, switching treatment to other m-TKIs might also be a treatment option [15].

## Conclusions

We report the first case of lenvatinib-induced TMA in an Asian patient, which caused severe proteinuria and renal impairment. Given previous studies showing a higher incidence of proteinuria due to m-TKI in Asian patients, close monitoring and renal biopsy should be considered if patients on m-TKI experience severe proteinuria accompanied by renal impairment. These can help in elucidating the pathophysiology of this adverse reaction and aid in determining a suitable treatment strategy.

## Statement of Ethics

Approval for this study was provided by the Research Ethics Board of Kobe University (authorization number: 1481), and the patient provided written informed consent to participate.

## Disclosure Statement

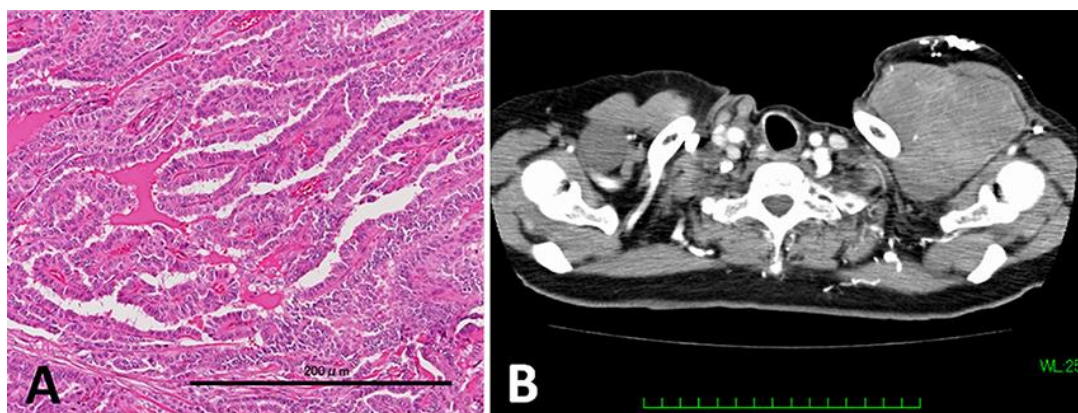
Naomi Kiyota has received honoraria from Bayer C.C. and honoraria and a research grant from Eisai Inc.

Hironobu Minami has received a research grant from Bayer C.C.

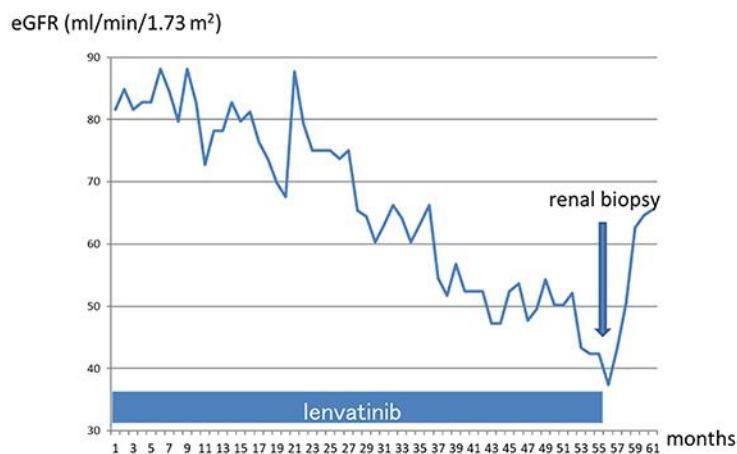
## References

- Schlumberger M, Tahara M, Wirth LJ, Robinson B, Brose MS, Elisei R, et al. Lenvatinib versus placebo in radioiodine-refractory thyroid cancer. *N Engl J Med*. 2015 Feb;372(7):621–30.
- Brose MS, Nutting CM, Jarzab B, Elisei R, Siena S, Bastholt L, et al.; DECISION investigators. Sorafenib in radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, phase 3 trial. *Lancet*. 2014 Jul;384(9940):319–28.
- Izzedine H, Escudier B, Lhomme C, Pautier P, Rouvier P, Gueutin V, et al. Kidney diseases associated with anti-vascular endothelial growth factor (VEGF): an 8-year observational study at a single center. *Medicine (Baltimore)*. 2014 Nov;93(24):333–9.
- Perazella MA, Izzedine H. New drug toxicities in the onco-nephrology world. *Kidney Int*. 2015 May;87(5):909–17.
- Usui J, Glezerman IG, Salvatore SP, Chandran CB, Flombaum CD, Seshan SV. Clinicopathological spectrum of kidney diseases in cancer patients treated with vascular endothelial growth factor inhibitors: a report of 5 cases and review of literature. *Hum Pathol*. 2014 Sep;45(9):1918–27.
- Bollée G, Patey N, Cazajous G, Robert C, Goujon JM, Fakhouri F, et al. Thrombotic microangiopathy secondary to VEGF pathway inhibition by sunitinib. *Nephrol Dial Transplant*. 2009 Feb;24(2):682–5.
- Okuno Y, Kume H, Hosoda C, Homma Y. Development of nephrotic syndrome after administration of sorafenib in a case of metastatic renal cell carcinoma. *Case Rep Med*. 2011;2011:710216.
- Wallace E, Lyndon W, Chumley P, Jaimes EA, Fatima H. Dasatinib-induced nephrotic-range proteinuria. *Am J Kidney Dis*. 2013 Jun;61(6):1026–31.
- Ollero M, Sahali D. Inhibition of the VEGF signalling pathway and glomerular disorders. *Nephrol Dial Transplant*. 2015 Sep;30(9):1449–55.
- Cavaliere S, Cosmai L, Genderini A, Nebuloni M, Tosoni A, Favales F, et al. Lenvatinib-induced renal failure: two first-time case reports and review of literature. *Expert Opin Drug Metab Toxicol*. 2018 Apr;14(4):379–85.
- Kiyota N, Schlumberger M, Muro K, Ando Y, Takahashi S, Kawai Y, et al. Subgroup analysis of Japanese patients in a phase 3 study of lenvatinib in radioiodine-refractory differentiated thyroid cancer. *Cancer Sci*. 2015 Dec;106(12):1714–21.
- Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009 Jan;45(2):228–47.

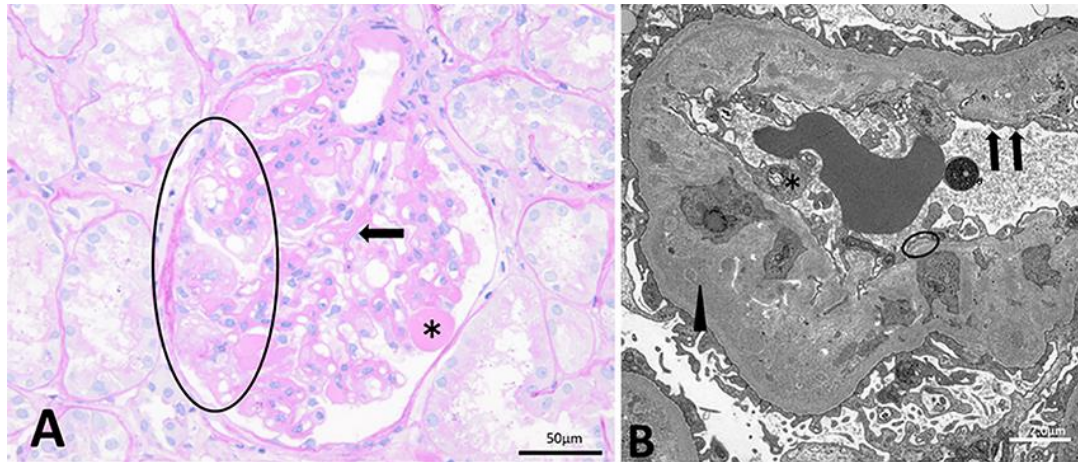
- 13 Sorich MJ, Rowland A, Kichenadasse G, Woodman RJ, Mangoni AA. Risk factors of proteinuria in renal cell carcinoma patients treated with VEGF inhibitors: a secondary analysis of pooled clinical trial data. *Br J Cancer*. 2016 Jun;114(12):1313–7.
- 14 Izzedine H, Perazella MA. Thrombotic microangiopathy, cancer, and cancer drugs. *Am J Kidney Dis*. 2015 Nov;66(5):857–68.
- 15 Goto H, Kiyota N, Otsuki N, Imamura Y, Chayahara N, Suto H, et al. Successful treatment switch from lenvatinib to sorafenib in a patient with radioactive iodine-refractory differentiated thyroid cancer intolerant to lenvatinib due to severe proteinuria. *Auris Nasus Larynx*. 2018 Dec;45(6):1249–52.



**Fig. 1.** Light microscopic finding of surgical specimens of cervical lymph nodes excision, hematoxylin-eosin staining, metastatic lesion of the papillary carcinoma of thyroid. The scale bar indicates 200  $\mu\text{m}$ . Coronal sections of the axillary lymph nodes metastases before treatment with lenvatinib.



**Fig. 2.** Time course of change in eGFR (mL/min/1.73 m<sup>2</sup>) during treatment with lenvatinib.



**Fig. 3.** Histological findings of renal biopsy. Light microscopic findings under Periodic acid-Schiff staining included double contouring of the loop walls in many glomeruli (arrow), exudative change (\*) and mesangiolysis (circle). The scale bar indicates 50  $\mu\text{m}$ . Electron microscopic findings showed edematous expansion of the sub-endothelium (arrowhead), new glomerular basement membrane formation (circle), hypertrophy of endothelial cell cytoplasm (\*) and loss of fenestrae (arrows). The scale bar indicates 2  $\mu\text{m}$ .