Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.0044-22
Intern Med 61: 3469-3471, 2022
http://internmed.jp

【 EDITORIAL 】

Determinants of the Pathological Features of Renal Adverse Effects Due to Vascular Endothelial Growth Factor Signaling Inhibition

Kiyoshi Mori [1,2]

Key words: vascular endothelial growth factor, cancer, proteinuria, glomerular microangiopathy, collapsing glomerulopathy

(Intern Med 61: 3469-3471, 2022)
(DOI: 10.2169/internalmedicine.0044-22)

Cancer Angiogenesis and VEGF

Cancer growth depends on an abundant supply of nutrients, oxygen and vessels. Vascular endothelial growth factors (VEGFs), especially VEGF-A, are important factors that support cancer neovascularization (1). Therefore, inhibition of VEGF signaling has been successfully used to treat various cancers (2, 3). Typical reagents used are inhibitory antibodies against VEGF-A (bevacizumab) or VEGF receptor 2 (VEGFR2, ramucirumab), soluble VEGFR1/VEGFR2 extracellular domains (aflibercept), or receptor tyrosine kinase inhibitors (RTKIs, such as sunitinib), which interfere with the signaling downstream of VEGFR2 (1). Treatment with such reagents often induces proteinuria and hypertension, which may make it difficult to continue treatment long-term (1-5).

Renal biopsies in cases with such renal side effects have shown that there are distinct types of renal lesions (6). In this issue of *Internal Medicine*, Yoshimura et al. report the second case to develop two types of renal lesions simultaneously immediately after ramucirumab administration in a cancer patient (7).

Role of VEGF in the Kidney

Glomerular visceral epithelial cells or podocytes are the primary source of VEGF in the kidney. An adequate (not too little and not too much) amount of VEGF secreted from podocytes towards glomerular vascular endothelial cells is essential for maintaining the structure and function of the glomeruli, which are the apparatus for urine production in the kidney (8). More than 100 L per day of plasma is filtered in the glomerular capillary from the endothelial/luminal side to the podocyte/outer side across the glomerular basement membrane (GBM). Therefore, it is difficult to believe that a retrograde flow of VEGF under normal conditions can play a physiologically essential role.

Direct evidence for such a concept was obtained using drug-inducible, podocyte-specific *Vegfa* knockout mice (5). Disruption of the *Vegfa* gene in podocytes after normal kidney development resulted in severe glomerular endothelial damage, proteinuria and hypertension resembling thrombotic microangiopathy (TMA) or preeclampsia (5). These observations have provided a rationale for the possibility that intravenously administered neutralizing antibody that binds to VEGF or VEGF receptor, without passing through the GBM, can inhibit VEGF signaling in glomerular endothelial cells.

Renal Biopsy Findings of Cases with Renal Adverse Effects by VEGF Inhibitors

Two major types of renal lesions have been reported based on renal biopsies of patients who developed renal adverse effects after treatment with VEGF signaling inhibitors (6). It is now recognized that bevacizumab may cause TMA-like lesions characterized by duplication (or double contour) of the GBM, endothelial swelling and mesangiolysis. Two groups in Europe found that pseudothrombi occluding the capillary lumen were stained positive by periodic acid-Schiff (PAS) or Azan (9) but did not contain platelets, indicating that they were actually not thrombi (10, 11). Pfister et al. and Person et al. hypothesized that subendothelial exudation would induce double contour of the GBM that

[1]Graduate School of Public Health, Shizuoka Graduate University of Public Health, Japan and [2]Department of Nephrology and Kidney Research, Shizuoka General Hospital, Japan
Received: March 28, 2022; Accepted: March 30, 2022; Advance Publication by J-STAGE: May 14, 2022
Correspondence to Kiyoshi Mori, kiyoshimori2001@gmail.com

might develop into hyaline pseudothrombi. Therefore, they proposed dubbing these lesions 'glomerular microangiopathy', instead of TMA (10, 11). As Yamada et al. and Ozawa et al. reported, ramucirumab may also cause glomerular microangiopathy (9, 12).

In 2014, Izzedine et al. reported a different type of renal lesion after RTKI administration (6). The pathological feature was collapsing glomerulopathy, characterized by shrinking of the glomerular capillary and GBM as well as massive podocyte proliferation (called a pseudocrescent). The authors analyzed 100 renal biopsy cases with renal adverse effects induced by anti-VEGF treatment (6). They found that 73 glomerular microangiopathy cases were mainly caused by bevacizumab or aflibercept, whereas 21 collapsing glomerulopathy or minimal change nephrotic syndrome-like cases were primarily the result of RTKI administration, with no overlap cases reported. In 2021, Nakano et al. reported the first case pathologically expressing both types of lesions after ramucirumab treatment (13).

Regarding the morphological features of glomerular microangiopathy, Goodship et al. proposed that endothelial swelling, red blood cell fragmentation and mesangiolysis were active lesions, whereas double contour of the GBM and widening of the subendothelial area were chronic lesions (14). Since ramucirumab is typically given as a second-line drug after repeated injection of bevacizumab, and ramucirumab-induced GMA occurs soon after initiation of ramucirumab therapy, it is likely that bevacizumab has already caused double contour of the GBM and predisposed a patient to develop overt proteinuria before ramucirumab is administered (9).

Of note, PAS staining-positive pseudothrombi in glomerular microangiopathy may stain positive for anti-immunoglobulin antibodies in an IgM-dominant manner. Staining intensities may be weaker in the fresh-frozen sections often used in Japan (9, 12) than in the fixed sections used in European countries (10-12).

Potential Factors Affecting Renal Pathology by VEGF Inhibition

The pathological features of renal adverse effects may be affected by differences in drug administration protocols. Bevacizumab and ramucirumab are given as intravenous intermittent injections, and the antibody concentration gradually decreases with the elimination from the blood. In contrast, sunitinib is orally administered by alternating on and off periods, resulting in rapid changes in the drug concentrations in the blood.

Not only VEGF-A but also VEGF-C is a ligand for VEGFR2 (15). Therefore, blocking both VEGF-A and VEGF-C by ramucirumab or RTKIs may exert stronger or qualitatively different effects compared to blocking only VEGF-A by bevacizumab (13).

Of note, in mice completely lacking the *Vegfa* gene expression in podocytes, not only glomerular microangiopathy lesions but also collapsing nephropathy lesions (containing pseudocrescents) were observed (Fig. 2Eb) (5). These findings suggest that strong suppression of VEGF signaling is required for the development of collapsing glomerulopathy.

Nadasdy et al. managed three cases of kidney allograft nephrectomy and reported that collapsing glomerulopathy lesions showed zonal distribution associated with obliterative vascular changes (16). These findings suggest that there is a certain possibility that collapsing glomerulopathy may be underdiagnosed in general. Consistently, Buob et al. carefully reviewed renal biopsy samples with TMA cases of various causes and found that as many as 36% of the 53 TMA cases showed collapsing glomerulopathy (17).

Taken together, these findings suggest that the type of renal lesion caused by VEGF signaling inhibition, either glomerular microangiopathy or collapsing glomerulopathy, may be affected by the target site of inhibitory drug, treatment protocol, preservation of VEGF-C signaling and thoroughness of searching for rare collapsing glomerulopathy lesions.

The author states that he has no Conflict of Interest (COI).

References

1. Cosmai L, Gallieni M, Liguigli W, Porta C. Renal toxicity of anticancer agents targeting vascular endothelial growth factor (VEGF) and its receptors (VEGFRs). J Nephrol **30**: 171-180, 2017.
2. Soria JC, Mauguen A, Reck M, et al.; the meta-analysis of bevacizumab in advanced NSCLC collaborative group. Systematic review and meta-analysis of randomised, phase II/III trials adding bevacizumab to platinum-based chemotherapy as first-line treatment in patients with advanced non-small-cell lung cancer. Ann Oncol **24**: 20-30, 2013.
3. Arnold D, Fuchs CS, Tabernero J, et al. Meta-analysis of individual patient safety data from six randomized, placebo-controlled trials with the antiangiogenic VEGFR2-binding monoclonal antibody ramucirumab. Ann Oncol **28**: 2932-2942, 2017.
4. Zhu X, Wu S, Dahut WL, Parikh CR. Risks of proteinuria and hypertension with bevacizumab, an antibody against vascular endothelial growth factor: systematic review and meta-analysis. Am J Kidney Dis **49**: 186-193, 2007.
5. Eremina V, Jefferson JA, Kowalewska J, Hochster H, Haas M, Weisstuch J, et al. VEGF inhibition and renal thrombotic microangiopathy. N Engl J Med **358**: 1129-1136, 2008.
6. Izzedine H, Escudier B, Lhomme C, et al. Kidney diseases associated with anti-vascular endothelial growth factor (VEGF): an 8-year observational study at a single center. Medicine (Baltimore) **93**: 333-339, 2014.
7. Yoshimura Y, Sawa N, Matsuoka S, et al. Glomerular microangiopathy with cellular crescent-like formation and endotheliopathy due to ramucirumab treatment for metastatic sigmoid colon cancer. Intern Med **61**: 3547-3552, 2022.
8. Eremina V, Sood M, Haigh J, et al. Glomerular-specific alterations of VEGF-A expression lead to distinct congenital and acquired renal diseases. J Clin Invest **111**: 707-716, 2003.
9. Yamada R, Okawa T, Matsuo K, Suzuki M, Mori N, Mori K. Renal-limited thrombotic microangiopathy after switching from bevacizumab to ramucirumab: a case report. BMC Nephrol **20**: 14, 2019.
10. Pfister F, Amann K, Daniel C, Klewer M, Buttner A,

Buttner-Herold M. Characteristic morphological changes in anti-VEGF therapy-induced glomerular microangiopathy. Histopathology **73**: 990-1001, 2018.

11. Person F, Rinschen MM, Brix SR, et al. Bevacizumab-associated glomerular microangiopathy. Mod Pathol **32**: 684-700, 2019.

12. Ozawa M, Ohtani H, Komatsuda A, Wakui H, Takahashi N. VEGF-VEGFR2 inhibitor-associated hyaline occlusive glomerular microangiopathy: a Japanese single-center experience. Clin Exp Nephrol **25**: 1193-1202, 2021.

13. Nakano Y, Kumagai J, Nagahama K, Fujisawa H. A case of ramucirumab-induced renal failure with nephrotic-range proteinuria and its pathological findings. BMJ Case Rep **14**: 2021.

14. Goodship TH, Cook HT, Fakhouri F, et al. Atypical hemolytic uremic syndrome and C3 glomerulopathy: conclusions from a "Kidney Disease: Improving Global Outcomes" (KDIGO) Controversies Conference. Kidney Int **91**: 539-551, 2017.

15. Michaelsen SR, Staberg M, Pedersen H, et al. VEGF-C sustains VEGFR2 activation under bevacizumab therapy and promotes glioblastoma maintenance. Neuro Oncol **20**: 1462-1474, 2018.

16. Nadasdy T, Allen C, Zand MS. Zonal distribution of glomerular collapse in renal allografts: possible role of vascular changes. Hum Pathol **33**: 437-441, 2002.

17. Buob D, Decambron M, Gnemmi V, et al. Collapsing glomerulopathy is common in the setting of thrombotic microangiopathy of the native kidney. Kidney Int **90**: 1321-1331, 2016.