Kidney Diseases Associated With Anti-Vascular Endothelial Growth Factor (VEGF)

An 8-year Observational Study at a Single Center

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Abstract: Expanded clinical experience with patients taking antiangiogenic compounds has come with increasing recognition of the renal adverse effects. Because renal histology is rarely sought in those patients, the renal consequences are underestimated. Antiangiogenic-treated-cancer patients, who had a renal biopsy for renal adverse effects from 2006 to 2013, were included in the current study. Clinical features and renal histologic findings were reviewed. Our cohort was 100 patients (58 women) with biopsy-proven kidney disease using anti-vascular endothelial growth factor (VEGF) therapy with a mean age of 59.8 years (range, 20–85 yr). Patients were referred for proteinuria, hypertension, and/or renal insufficiency. Kidney biopsy was performed 6.87 ± 7.18 months after the beginning of treatment. Seventy-three patients experienced renal thrombotic microangiopathy (TMA) and 27 patients had variable glomerulopathies, mainly minimal change disease and/or collapsing-like focal segmental glomerulosclerosis (MCN/cFSGS). MCN/cFSGS-like lesions developed mainly with tyrosine-kinase inhibitors, whereas TMA complicated anti-VEGF ligand. Thirty-one percent of TMA patients had proteinuria up to 1 g/24 h. Half of TMA cases are exclusively renal localized. Pathologic TMA features are intraglomerular exclusively. MCN/cFSGS glomeruli displayed a high abundance of KI-67, but synaptopodin was not detected. Conversely, TMA glomeruli exhibited a normal abundance of synaptopodin-like control, whereas KI-67 was absent. Median follow-up was 12 months (range, 1–80 mo). Fifty-four patients died due to cancer progression. Hypertension and proteinuria resolved following drug discontinuation and antihypertensive agents. No patient developed severe renal failure requiring dialysis. Drug continuation or reintroduction resulted in a more severe recurrence of TMA in 3 out of 4 patients requiring maintenance of anti-VEGF agents despite renal TMA. In conclusion, TMA and MCN/cFSGS are the most frequent forms of renal involvement under anti-VEGF therapy. Careful risk-benefit assessment for individual patients should take into account risk factors related to the host and the tumor.

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Abbreviations: CG = collapsing glomerulopathy, c-kit = stem cell factor receptor, c-mip = c-maf-inducing protein, Flt-3 = FMS-like tyrosine kinase-3, GFR = glomerular filtration rate, HIVAN = HIV-associated nephropathy, MCN/cFSGS = minimal change disease and/or collapsing-like focal segmental glomerulosclerosis, MDRD = modification of diet in renal disease, PDGFRs = platelet-derived growth factor PDGF receptors, TKI = tyrosine-kinase inhibitor, TMA = thrombotic microangiopathy, VEGF = vascular endothelial growth factor, VEGFR = vascular endothelial growth factor receptor.

INTRODUCTION

Angiogenesis is a key physiologic process for growth and development.[4,8] In the renal glomeruli, podocytes express vascular endothelial growth factor (VEGF), whereas VEGF receptor (VEGFR) tyrosine kinases are expressed by both podocytes and glomerular endothelial cells.[23] The biological functions of VEGF are mediated by its binding to 1 of the VEGF receptor tyrosine kinases, which include VEGFR-1 (Flt-1), VEGFR-2 (KDR/Flk-1), and VEGFR-3 (Flt-4). A major regulator of angiogenesis is VEGF and its cognate receptor VEGFR2. Antiangiogenic compounds are among the most commonly used anticancer agents in clinical practice today. These agents target either the VEGF ligand (bevacizumab [anti-VEGF monoclonal antibody], aflibercept [VEGF Trap]) or the tyrosine kinase receptors (sunitinib, sorafenib, pazopanib, axitinib, regorafenib, vandetanib). Tyrosine-kinase inhibitors (TKIs) interfere with the activity of VEGFR and other growth factor receptors, such as PDGF receptors (PDGFRs), stem cell factor receptor (c-kit), FMS-like tyrosine kinase-3 (Flt-3), b-raf, and Bcl-Abl. They are, thus, commonly called multitargeted TKIs.

The filtration barrier of the renal glomeruli is formed by endothelial cells, podocytes, and basement membrane components. VEGF, which is expressed by podocytes both during development and in adults, activates VEGFR-2 on glomerular capillary endothelial cells. The interaction of VEGF produced by podocytes with VEGFR2 on glomerular endothelial cells is critical to the normal function and repair of the system. Clinically, renal adverse effects following anti-VEGF therapies may present as hypertension, asymptomatic proteinuria, and rarely nephrotic syndrome or acute renal failure. The underlying pathologic changes are not always clear. In the few cases where renal biopsies have been performed, pathologic findings have shown proliferative glomerulopathies, thrombotic

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microangiopathy (TMA),[18] and, rarely, interstitial nephritis.[2] In preclinical murine models, heterozygous deletion of VEGF in podocytes led to loss of endothelial cell fenestration, loss of podocytes, mesangiolysis, and proteinuria,[11,26] suggesting that VEGF has a critical protective role in the pathogenesis of microangiopathic process.[9]

Moreover, injection of anti-VEGF antibodies in wildtype mice or targeted deletion of VEGF-A in the podocytes in adult mice resulted in a ''pre-eclampsia-like syndrome'' with endotheliosis, TMA, and decreased expression of nephrin[9,11,27] similar to what has been observed in severe forms of pre-eclampsia.[13,31] We report here what is to our knowledge the largest series of patients with a similar syndrome occurring during anti-VEGF therapy.

MATERIALS AND METHODS

Patients

This is a prospective single-center study concerning an observational cohort of patients. We analyzed patients who were referred for hypertension, proteinuria, and/or renal failure, following VEGF-targeted therapy and who underwent kidney biopsy showing at least 6 glomeruli available for optical microscopy. All patients gave informed consent for the anonymous use of their personal health data. Each patient medical record was thoroughly reviewed with the collection of clinical, biological, and pathologic data at onset, at diagnosis, and at last follow-up. This study was approved by the local ethics committee and was in accordance with the Helsinki declaration of 1975.

The clinical and laboratory studies were assessed at the time of renal biopsy, and follow-up data were available for all patients (Table 1). Each patient was followed over time for the development of specific endpoints, including progression to severe renal failure and death. The following definitions were used:

Hypertension: blood pressure over 140/90 mm Hg at different occasions or already treated with antihypertensive agents; proteinuria with a cutoff value of $\geq$0.5 g/d; glomerular filtration rate (GFR) was estimated with the simplified modification of diet in renal disease (MDRD) formula[22]; stage III to V chronic kidney disease: chronic renal failure with GFR $<$60 mL/min

TABLE 1. Clinical Characteristics of Anti-VEGF-Associated Kidney Diseases

	Anti-VEGF-Associated Kidney Diseases		
Parameter	**TMA (n = 73)**	**MCN/cFSG-Like (n = 21)**	**P**
Characteristic			
Age (yr), mean ± SD	60.08 ± 11.90	59.03 ± 12.11	0.698
Female (%)	71.2	18.5	0.0001
White (%)	94.5	92.6	0.309
Prior nephrectomy	20.5	55.5	0.0006
Past medical history			NS
Hypertension	11	4	
Proteinuria	negative	negative	
aMDRD CrCl $<$60 mL/min/1.73 m^2	1	1	
Diabetes	2	0	
Obesity	4	0	
Anti-VEGF agent			
Bevacizumab	61	1	
VEGF-Trap	5	0	
Sunitinib		13	
Sorafenib	1	5	
Other TKIs	2	2	
Renal parameters (mean ± SD)			
Onset of renal disease (mo) median (range)	3 (0.25–26)	2(0.25–30)	0.155
Hypertension (%)	83.5	48.1	
SBP (mm Hg)	154.89 ± 24.46	143.14 ± 22.83	0.03
DBP (mm Hg)	90.90 ± 16.06	82.77 ± 11.62	0.003
SCr (mg/dL)	1.08 ± 0.54	1.26 ± 0.74	0.196
aMDRD CrCl (mL/min/1.73 m^2)	71.33 ± 28.62	68.88 ± 28.75	0.620
Proteinuria (g/d)	2.58 ± 2.64	3.15 ± 3.86	0.544
Proteinuria $\leq$1 g/d (%)	31.5	29.6	
Serum albumin (g/L)	36.16 ± 5.56	33.88 ± 7.17	0.096
Glomeruli, n	18.53 ± 8.92	15.70 ± 6.26	0.149
Superimposed NAS/FSGS lesions	2.38 ± 2.66	3 ± 3	0.324
Outcome			
Follow up (mo), mean ± SD	14.67 ± 13.14	13.07 ± 13.84	
Alive (%)	53.42	25.9	0.011

Abbreviations: aMDRD = abbreviated modification of diet in renal disease; DBP = diastolic blood pressure; NAS/FSGS, nephroangiosclerosis and its related FSG lesions; SBP = systolic blood pressure; SCr = serum creatinine.

per 1.73 m^2, and biological TMA: association of anemia, thrombocytopenia, low haptoglobin, presence of schizocytes, and elevated lactate dehydrogenase.

We focused mainly on these factors: hypertension present or not at onset, at diagnosis, and at last follow-up. Blood pressure was regularly recorded with the antihypertensive treatment details; this variable was used only as dichotomous: present or absent. Daily proteinuria at diagnosis and at last follow-up with classification according to K-DOQI: <0.30 g/d; 0.30–0.99 g/d; 1.00–2.99 g/d; and ≥3 g/d; this variable was used either as continuous or dichotomous: <1 g/d or ≥1 g/d.

Histology

All biopsy specimens had a part for light microscopy (fixed and prepared using standard techniques) and a part for immunofluorescence-labeling studies (IgG, IgM, IgA, Kappa and Lambda Ig light chains, fibrin, C3 and C1q anti-sera tests on frozen biopsies). Renal light microscopy specimens and immunofluorescence results were systematically reviewed by a senior pathologist without access to the patients' files. Immunohistochemical stains on paraffin-embedded sections were performed to further characterize the glomerular lesions. The primary antibodies used were against Ki-67 (clone MIB-1; Dako), mouse monoclonal antibody against b-dystroglycan (1:50 dilution, clone 43DAG1/8D5; NovoCastra), mouse monoclonal antibody against synaptopodin (1:10 dilution, clone G1D4; Progen Biotechnik), rabbit anti-human podocin (20 mg/mL dilution, clone PODO 11-A, Alpha Diagnostics), anti-VEGF (Santa Cruz Biotechnology), and polyclonal antiserum against WT-1 (C19; Santa Cruz Biotechnology). Biopsy specimens were subjected to immunostaining for synaptopodin and Ki-67, as previously described.[3] Transmission electron microscopy was performed as previously described.[17]

Statistical Analyses

A 2-sided chi-square test was used to compare all qualitative variables. Mann-Whitney rank testing was applied for all comparisons of quantitative variables. The results are expressed as mean values unless stated otherwise. A p value < 0.05 was considered statistically significant.

RESULTS

Clinicopathologic Characteristics

One hundred patients (58 women) were included in the study. Median age was 59.8 years (range, 20–85 yr). The racial distribution was 94 white, 4 black, and 2 Asian patients. The most common cancers included renal cell carcinoma (27 patients), ovarian (16 patients), breast (14 patients), and lung (10 patients) adenocarcinoma, respectively. Other affected organs/cancers were the prostate, rectum, cecum, colon, urethra, endometrium, Fallopian tube, cervix, GIST, adrenal, esophagus, liver, thyroid, melanoma, leiomyosarcoma, glioblastoma, and dendrocytoma. The used adjuvant anti-VEGF treatments included bevacizumab (64 patients), VEGF-Trap (7 patients), and different TKIs (29 patients).

Renal involvement occurred 6.87 ± 7.18 months after the beginning of treatment, characterized by proteinuria (100%, with proteinuria ≤1 g/d in 31%), hypertension (74%), microscopic hematuria (70%), and/or renal failure defined by a creatinine clearance rate below 60 mL/min per 1.73 m^2 (40%). Mean proteinuria, systolic and diastolic blood pressure, serum creatinine, and aMDRD creatinine clearance were 2.74 g/d, 151.72 and 88.71 mm Hg, 1.13 mg/dL, and 70.67 mL/min per 1.73 m^2, respectively. All hypertensive patients required antihypertensive treatment.

Kidney biopsies identified 2 distinct types of renal damage associated with VEGF-targeted therapies: renal TMA in 73 patients and variable glomerulopathies, mainly minimal change disease and/or collapsing-like focal segmental glomerulosclerosis (MCN/cFSGS), in 21 patients (Figure 1). Other glomerular diagnoses included membranous nephropathy (2 cases), IgA nephropathy (2 cases), antineutrophil cytoplasmic antibodies (ANCA)-negative pauci-immune crescentic glomerulonephritis (1 case), and diabetic nephropathy (1 case).

Patients with TMA were predominantly women, compared to patients with glomerulopathies (71.2% vs 18.5%, respectively; $p = 0.0001$), treated with VEGF ligands (65 vs 5), expressed renal disease later (mean onset of renal disease, 6.98 vs 4.83 mo) in a frequent and pronounced hypertension form (see Table 1) despite a lower incidence of prior nephrectomy ($p = 0.0006$). No statistically significant points were found among blood pressure, creatinine serum levels, or creatinine clearance. Half of TMA under anti-VEGF were exclusively renal localized. Pathologic TMA features were intraglomerular exclusively.

Thirty-one percent of TMA patients had proteinuria up to 1 g/24 h (Table 2). Significant differentiating points between 2 groups of patients according to proteinuria levels (patients with proteinuria <1 g/24 h vs those with proteinuria >1 g/24 h) were female sex ($p < 0.009$) and subsequent FSGS-associated lesions ($p < 0.0001$) (see Table 2). No statistically significant differences were found for renal or hematologic parameters (blood pressure, creatinine serum levels, creatinine clearance, hemoglobin levels, platelet and schistocyte counts, haptoglobin levels, or lactate dehydrogenase levels). Furthermore, renal histologic parameters were not significantly different either for percentage of thrombosed capillaries, mesangiolysis, or double contours, suggesting that low-level proteinuria under anti-VEGF treatment might reflect renal TMA and should not be neglected.

The relative abundance of VEGF was reduced in podocytes from patients with MCN/FSGS when compared with normal control kidney tissue, and was undetectable in TMA (pictures not shown) as previously reported.[17] Expression patterns of Wnt-1, KI-67, and synaptopodin were analyzed in all glomeruli of MCN/cFSGS and TMA biopsies related to anti-VEGF therapy and were compared to normal kidney tissue (Figure 2). Wnt-1 expression was significantly reduced in MCN/cFSGS relative to control human kidneys and TMA consisting of a lack of detection in some areas and preservation in others (Figure 2A). The relative abundance of KI-67 was greatly increased in MCN/cFSGS-like lesions, whereas it was not detected in TMA or in control human kidneys (Figure 2B). On the other hand, synaptopodin abundance was clearly reduced in FSGS, as compared with TMA and control human kidneys (Figure 2C). Transmission electron microscopy analysis in glomeruli of patients with bevacizumab-induced TMA and in control kidneys showed major alterations in TMA glomeruli, including duplication of glomerular basement membrane, loss of fenestrations, detachment of endothelial cells from original basement membrane, interposition of cells, and marked effacement of visceral epithelial cell foot processes in some areas. Some podocytes exhibited cytoplasm vacuolization, as well as endoplasmic reticulum enlargement and mitochondrial swelling, suggesting an underlying apoptotic process (data not shown).[17]

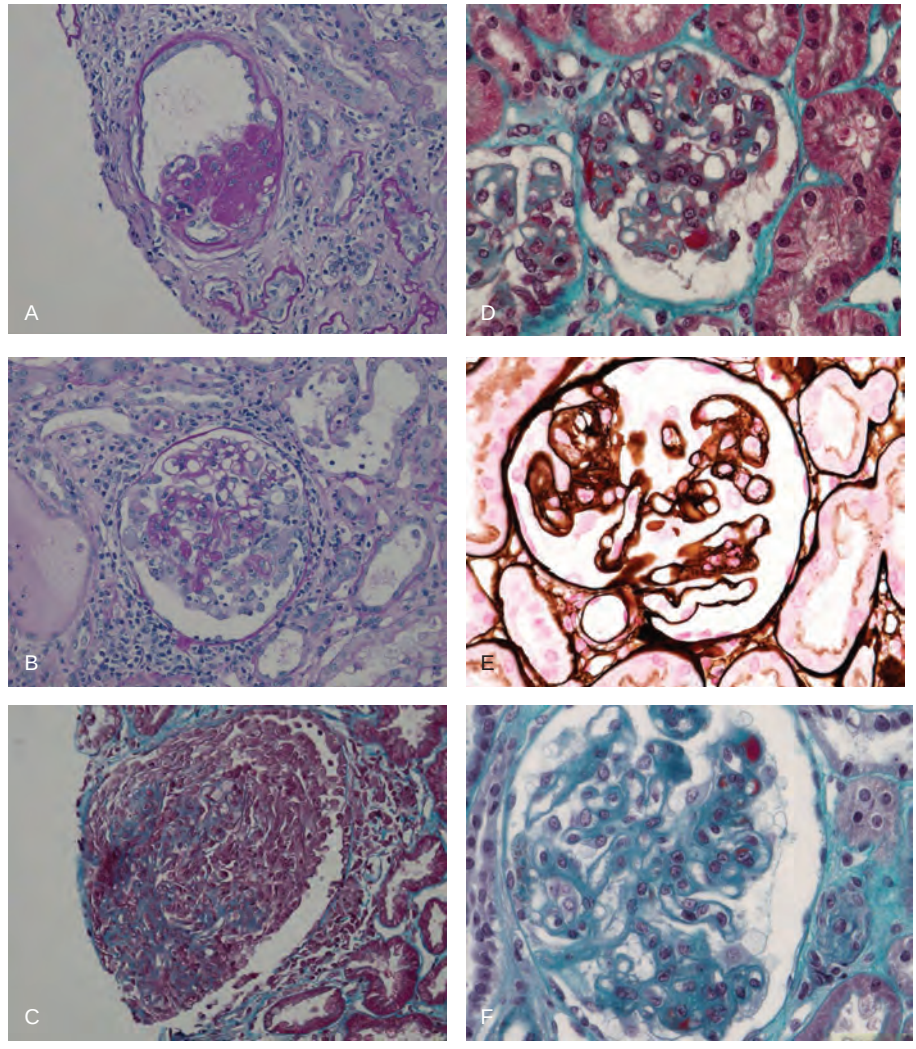

FIGURE 1. Collapsing glomerulopathy (CG) and thrombotic microangiopathy (TMA) lesions in renal biopsies from patients with anti-VEGF agents. CG: there is a collapse of the capillary tuft (A) with overlying swollen and hyperplastic epithelial cells (B) (HES, original magnification × 200) often having a pseudocrescent-like appearance (C) (Masson trichrome, × 200). TMA: luminal thrombosis within the glomerular capillary (D) (Masson trichrome, × 200). The capillary basement membranes were thickened with double-contoured appearance of the capillary wall, best appreciated with methenamine silver stain (E) (× 200) associated with mesangiolysis (F) (Masson trichrome, × 200).

Clinical Outcome

The median follow-up was 12 months (range, 1–80 mo). All patients requested antihypertensive drugs (average, 3 molecules; range, 1–8). Baseline antihypertensive treatment included RAS blocker/thiazide combination, calcium channel blocker, and nebivolol. In all patients, proteinuria and blood pressure decreased and renal function improved only following antihypertensive therapy associated with definitive interruption of the anti-VEGF drug. None required dialysis. Fifty-four patients died during the study due to cancer progression. Four patients required maintenance of an anti-VEGF treatment despite renal TMA: one patient who experienced TMA under VEGF-Trap was switched to bevacizumab and displayed an absence of proteinuria and stable renal function 2 years later without TMA recurrence. Two patients with TMA related to bevacizumab continued this therapy in association with antihypertensive drugs for 8 months despite persistent proteinuria and the occurrence of systemic manifestations (such as hemolysis, thrombocytopenia, schistocytosis), but renal function remained stable. For the fourth patient, the reintroduction of bevacizumab resulted in a more severe recurrence of TMA (hematologic and renal signs).

DISCUSSION

To our knowledge, the current study is the largest series of patients with biopsy-proven kidney damage during anti-VEGF therapy. Anti-VEGF agents induced glomerular diseases such as endothelial damage like intraglomerular TMA or podocytopathies like MCN/cFSGS. Glomerular TMA occurs preferentially under VEGF-ligand, while podocytopathies are more often secondary to TKIs, although one may encounter a few cases of TMA with TKIs and conversely cases of podocytopathies with VEGF ligands.

TABLE 2. Proteinuria level-based comparison in TMA-related to anti-VEGF treatment

	Thrombotic Microangiopathy Related to Anti VEGF Therapy		
	Proteinuria <1 g/d (n = 23)	**Proteinuria >1 g/d (n = 50)**	**Univariate analysis (p)**
Characteristics			
Age (yr) median (range)	58 (42–74)	61 (32–73)	0.998
Female (%)	96.26	41.09	0.001
Caucasian (%)	96.26	95	0.28
Prior use of medication known to induced TMA	11%	18%	
Anti-VEGF agent			
VEGF Ligand (BVZ/VEGF Trap)	21 (21/0)	44 (39/5)	
TKIs	2	6	
Onset of TMA, median (range)	6 (1–24)	5.5 (0.25–26)	0.298
Biological disorders (mean ± SD)			
Hemoglobin (g/dL)	12.26 ± 2.27	11.57 ± 2.39	0.245
Platelets (/mm^3)	186696 ± 95566	178940 ± 91072.2	0.740
Positive schizocytes (%)	21.73	26	0.04
Lacticodeshydrogenase (U/L)	583.82 ± 200.68	616.20 ± 316.66	0.654
Haptoglobin (g/L)	1.33 ± 0.69	1.29 ± 1.09	0.895
Renal parameters (mean ± SD)			
SBP (mmHg)	154.65 ± 20.50	155 ± 26,2834	0.955
DBP (mmHg)	92.17 ± 11.16	90.32 ± 17.95	0.650
SCr (mg/dL)	1.01 ± 0.40	1.12 ± 0.59	0.416
aMDRD CrCl (ml/min/1.73m^2)	68.41 ± 24.68	72.68 ± 30.40	0.557
Proteinuria (g/24 h)	0.63 ± 0.29	3.48 ± 2.76	<0.00001
Serum Albumin (g/L)	38.09 ± 4.59	35.27 ± 5.78	0.062
Microscopic hematuria (%)	69.5	76	0.08
Kidney biopsy			
Glomeruli, median (range)	14 (11–28)	16 (7–50)	0.867
Glomerular thrombi (%)	23.5	25.5	0.335
Mesangiolysis (%)	50	52	0.329
Double contour (%)	55.5	53.9	0.467

Abbreviations: DBP = diastolic blood pressure; FSGS = focal segmental glomerulosclerosis; SBP = systolic blood pressure; SCr = serum creatinine; TKIs = tyrosine kinase inhibitors; TMA = thrombotic microangiopathy; VEGF = vascular endothelial growth factor.

How do the anti-VEGF agents contribute to podocyte injury, and are they necessarily related to TMA lesions? In other words, is it a single TMA lesion with occasional podocytopathy as a consequent damage secondary to vascular occlusion? There are certain morphologic features that are useful in differentiating these lesions.

MCN/cFSGS occurring in the setting of anti-VEGF agents shares immunohistologic features with idiopathic and HIV-associated nephropathy (HIVAN) such as loss of certain podocytes differentiation markers, especially in glomeruli with collapsing glomerulopathy (CG) lesions and proliferation of glomerular epithelial cells as indicated by KI-67 staining (see Figure 2B). Staining for synaptopodin was also absent in the podocytes of collapsed glomeruli (see Figure 2C) and noncollapsed glomeruli in our MCN/cFSGS patients, as previously described in relatively inactive[28] or treated HIV-associated nephropathy.[30] Conversely, in ''reactive'' lesions of CG such as those associated with vascular occlusion,[1] glomerular staining for WT-1 was preserved, and loss of synaptopodin was not global as is typical in idiopathic CG and HIVAN,[1] but rather limited to collapsed segments.[25] Furthermore, we show for the first time that MCN/FSGS lesions are associated with a high abundance of c-mip. In contrast, in TMA, c-mip is not detected.[17] The finding that the TKI sorafenib induces impressive cytoskeleton changes in cultured podocytes[17] suggests that this class of therapy has direct effects on podocytes, which are under investigation.[17]

Taken together, these findings suggest 2 distinct pathophysiologic mechanisms of glomerular damages associated with antiangiogenic drugs. However, how VEGF inhibition can lead to both pathologies remains unclear.

Decreased VEGF availability within the glomerulus may have detrimental effects on kidney function, as the glomerular filtration barrier might be particularly susceptible to toxicity from VEGF inhibitors.[10] Vigneau et al[29] found that, as in preeclampsia, synaptopodin and nephrin expression levels were decreased in kidney biopsy specimens from patients using anti-VEGF agents. The authors noted that podocin expression was also reduced, irrespective of the presence or absence of proteinuria, confirming that deregulation of slit diaphragm proteins is a direct effect of anti-VEGF drugs and not a consequence of the proteinuria.[29]

TMA has been described from case reports of patients treated with bevacizumab,[9,12,24] VEGF-Trap,[15] and sunitinib[5,19,21] and in 1 cohort study.[29] In our experience, TMA related to VEGF/VEGFr inhibitors was mostly localized to

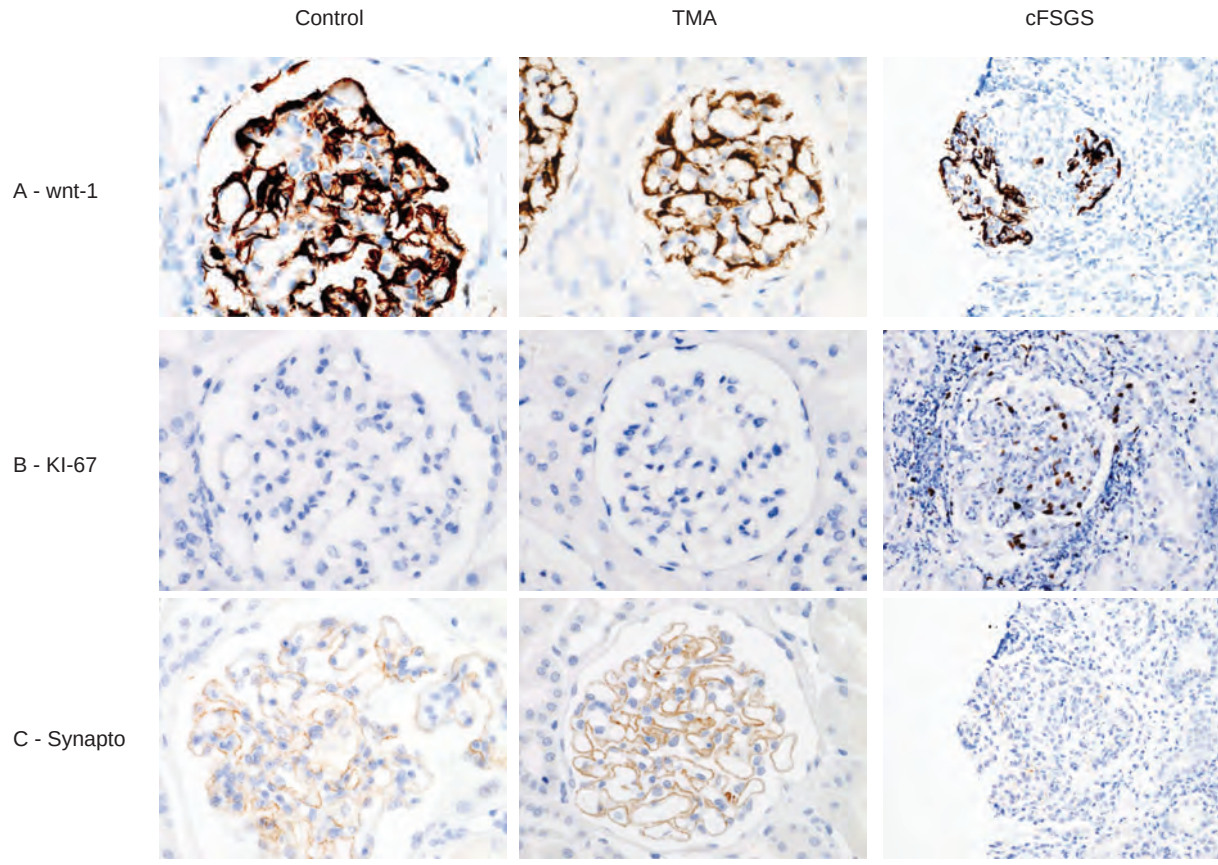

FIGURE 2. Graphic overview of the staining patterns in both kidney biopsies. The relative abundance of Wnt-1 was reduced in podocytes from patients with MCN/cFSGS when compared to control kidney tissues and TMA (A). MCN/cFSGS glomeruli displayed a high abundance of KI-67, whereas KI-67 was absent in TMA glomeruli (B). Staining for synaptopodin showed a positive podocyte-like staining pattern in TMA-proven glomeruli and was absent or significantly weaker in MCN/cFSGS (C). Abbreviation: Synapto = synaptopodin.

the kidney, intraglomerular exclusively, and only half of our patients experienced biological disorders such as thrombocytopenia or schistocytosis.[17] Renal function remained preserved with blood pressure control and anti-VEGF drug withdrawn. These findings help to differentiate TMA related to VEGF/VEGFr inhibitors from other iatrogenic TMA. Indeed, TMA induced by gemcitabine and/or mitomycin is more aggressive with greater hematologic abnormalities, both glomerular and arteriolar renal localization, and a worse renal survival despite gemcitabine discontinuation.[16] There are only a few reports of renal outcome in renal TMA cases related to anti-VEGF agents. In 1 case of sunitinib-induced renal TMA, blood pressure and renal function remained stable and proteinuria became undetectable under irbesartan over 3 months while sunitinib was continued.[5] Another patient who developed TMA under bevacizumab had a favorable response after stopping bevacizumab (normalized blood pressure, disappearance of hemolysis, return of renal function to previous baseline level). Sunitinib introduced 2 months later was stopped after 3 weeks of treatment as a result of the recurrence of severe TMA. Once again, the response of this second episode was favorable in the days after stoppage of sunitinib, although 10 courses of plasma exchange were initially needed.[12] In 1 study, proteinuria decreased and renal function improved only following the definitive interruption of the anti-VEGF drug.[29] In our experience, drug continuation or reintroduction resulted in a more severe recurrence of TMA in 3 out of 4 patients, requiring maintenance of anti-VEGF agents despite renal TMA. It therefore seems more reasonable to stop the culprit drug in the case of TMA.

Collapsing glomerulopathy (CG) describes a pattern of glomerular injury, the main feature of which is severe injury to podocytes with loss of markers of differentiation, proliferation of podocytes, and/or parietal epithelial cells filling the Bowman space, and global or segmental collapse of the capillary tuft.[1,3,7,20] Multiple etiologies of CG have been described, including certain viral infections (most notably HIV but also parvovirus B19 and hepatitis C), drugs, gene mutations, systemic lupus erythematosus, and vascular occlusion, in addition to idiopathic forms.[1,6,14] We found that MCN/cFSGS-like lesions, a less reported podocytopathy lesion, was more frequently in TKIs-treated (20/21) nephrectomized (55.5% vs 20.5%) male (18.5% vs 71.2%) patients. Several pathophysiologic mechanisms have been put forward for the occurrence of MCN/FSGS-like lesions in patients undergoing TKI therapy.[17] The high incidence of RCC in our cohort suggests a possible role for the adaptive hyperfiltration response to nephrectomy. However, despite the fact that our patients with MCN/FSGS were older compared with the TMA group, and had previously received interferon-α, proteinuria was still absent at least 1 year after nephrectomy and developed rapidly only after the initiation of anti-VEGF therapy, ruling out a potential close

link between unilateral nephrectomy and proteinuria, although we cannot exclude the possibility that the former may promote TKI-induced podocyte injury. Furthermore, patients did not receive any bisphosphonate, which is known to be toxic to podocytes.[17] In this setting, the close relationship between the onset of proteinuria and initiation of treatment, and marked podocytosis argues more for drug toxicity, and history of nephrectomy may be a sensitizing factor.

In conclusion, anti-VEGF agents may induce endothelial damage (TMA) and podocytopathies (MCN/FSGS). At the current time, approaches to toxicity management and treatment modifications are largely empirical. Therapeutic or observational studies are needed to identify baseline risk factors and early signs of serious adverse events, and to collect data on safety if antiangiogenesis agents are resumed after recovery from adverse events.

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