development during embryogenesis (vasculogenesis) and neo-vasculature formation for tissue repair in adult (angiogenesis) [1]. VEGF is also a central mediator of tumor-related angiogenesis, with increased expression, which determines prognosis in some of the solid tumors [2]. In the last decade, VEGF inhibitors have been developed as anti-angiogenic strategies to aid in cancer therapy [3]. As specific agents, VEGF inhibitors include a number of neutralizing anti-VEGF antibodies and those that target the VEGF receptors (VEGFRs), the most common being bevacizumab (Avastin), which was approved by the United States Food and Drug Administration (FDA) in 2004 [1]. When given in combination with chemotherapy or as single-agent administration, bevacizumab has been shown to prolong the survival of patients with colorectal, lung, and breast cancer. Small-molecular-weight VEGFR tyrosine kinase inhibitors used for cancer therapy include sunitinib (Sutent, SU11248), sorafenib (Nexavar, BAY 43–9006), axitinib (Inlyta, AG013736), and pazopanib (Votrient, GW786034), which inhibit multiple receptors, such as VEGFR-1, 2, and 3; platelet-derived growth factor receptor β; FMS-like tyrosine kinase 3 (Flt-3), and c-Kit protein [1].

These selective targeting agents are generally tolerated well with less frequency of life-threatening toxic effects and untargeted organ damage. However, a number of clinical trials and basic experiments with VEGF inhibitors have demonstrated frequent occurrence of dose-related nephrotoxicities, such as hypertension and proteinuria [4,5], where severe hypertension has occasionally lead to discontinuation of the VEGF inhibitor. However, the incidence and severity of proteinuria is less common than that of hypertension, and appeared to be less critical clinically secondary to glomerular abnormalities during treatment with VEGF inhibitors. Though rare, a more serious VEGF inhibitor–associated kidney injury, thrombotic microangiopathy (TMA), is a well-documented complication [6,7]. Characteristically, the manifestation of TMA in the patients with bevacizumab administration appears to be localized in the kidney, with little or no involvement of systemic microvasculature [6]. Several biopsy-proven cases have been reported with bevacizumab and other forms of VEGF inhibitors, which revealed glomerular and/or arterial TMA [6,8–14]. Experimental data have shown that VEGF inhibitors are implicated in glomerular injury [7]. Overall, human clinical trials, biopsy-proven exceptional cases, and animal experiments indicate that VEGF inhibitors are likely to result in glomerular disease during long-term treatment.

Herein, we analyzed the clinicopathologic findings of kidney injury in 5 patients with administration of VEGF inhibitor for cancer therapy, the spectrum of parenchymal features and pathophysiologic mechanisms in cancer patients. A review of the frequency of kidney-related adverse effects in previously reported clinical trials using VEGF inhibitors, documented anecdotal and series of renal biopsy cases, and the role of concomitant nephrotoxic agents are discussed.

2. Materials and methods

2.1. Case series, pathological features, and immunohistochemistry

Five cases treated with VEGF inhibitors and with kidney disease are identified from our renal biopsy files from 2008 to 2010. The kidney biopsies were processed in the renal pathology laboratory at Weill Cornell Medical College, Cornell University, New York, using standard techniques for light microscopy, immunofluorescence, and electron microscopy. Demographic, clinical, laboratory, and follow-up data with pathological findings were obtained from retrospective chart review, summarized in Tables 1–3. Immunohistochemical stain on paraffin-embedded tissue was performed using rabbit polyclonal antibody to hemoglobin (Dako North America Inc, Carpinteria, CA) on 3 cases suspected of having hemoglobin-containing tubular casts, using Bard Max Autostainer (Leica Microsystems, Buffalo Grove, IL).

2.2. Research ethics

This study was approved by the institutional review board of Weill Cornell Medical College, Cornell University, Ithaca, NY, as well as Memorial Sloan-Kettering Cancer Center, New York, NY. Informed consent of patients was not required by the institutional review board because the study was a retrospective review of clinical records and pathological results only.

3. Results

3.1. Clinical and laboratory findings

The clinical, laboratory and treatment information of the 5 patients are shown in Table 1. The age range was 55 to 67 years, and 4 of 5 were women, treated for glioblastoma multiforme, breast, colon and lung cancer, and metastatic tumor of unknown origin. Clinical renal manifestations developed 2 to 15 months after therapy with bevacizumab in 4 cases and sorafenib in 1 case. All patients presented with acute kidney injury. One patient had worsening of pre-existing hypertension (case 5), and 3 with new onset hypertension, all requiring anti-hypertensive medication. Proteinuria and hematuria were observed in 3 cases, none of which were nephrotic and ranged from 0.9 to 2.6 g/24 hours. Case 3 revealed transient hemoglobinuria due to intravascular hemolysis. Renal biopsy was performed in 2 cases because of acute kidney injury (AKI) without urinary findings (cases 2, 5). Regarding hematologic abnormalities, 3 patients were clinically diagnosed with TMA (cases 1–3) according to typical symptoms including AKI, hemolytic anemia, and thrombocytopenia, and 1 patient was suspicious for TMA (case 4). Lastly,

Table 1 Clinical and laboratory findings at renal biopsy, therapy, and prognosis

	Case 1	Case 2	Case 3	Case 4	Case 5
VEGF inhibitor	Sorafenib	Bevacizumab	Bevacizumab	Bevacizumab	Bevacizumab
Dose, duration (mo)	800 mg/day, 2	10 mg/kg, 5	NA/NA	150-450 mg, 10	15 mg/kg, 10
Clinical information					
Age (y)/gender	55/F	59/M	54/F	62/F	67/F
Type/duration of cancer	Metastatic tumor, unknown origin/7 y	Glioblastoma multiforme/6 mo	Breast cancer/NA	Colon cancer/11 y	Non–small cell lung cancer/17 mo
Clinical onset after therapy (mo)	2	5	NA	28 (including drug withdrawal)	15
Peak blood pressure (mmHg)	128/79	157/96	160/66	166/88	160/88
Urinary protein (g/gCr or g/day)	2.4	Undetectable	0.9	2.6	Undetectable
Hematuria	Microscopic	Negative	Microscopic	Microscopic	Negative
SCr baseline/at biopsy (mg/dL)	1/1.6	1.1/4.0	0.9/ESRD	0.9/5.3	1.1/2.1
Hematologic features	HA, TP	HA, SCT, TP	HA, SCT	Anemia, TP	No
Clinically diagnosed TMA	Definite	Definite	Definite	Suspicion	No
Combination therapy					
Prior chemotherapy	Capecitabine, bevacizumab	No	NA	5FU, panitumumab, cetiximab, methotrexate, irinotecan	No
Concomitant chemotherapy	Gemcitabine	Temozolomide	Carboplatin, paclitaxel	Zoledronic acid, cisplatin, methotrexate, irinotecan, 5FU, capecitabine, dacarbazine, streptozocin	Pemetrexed, carboplatin
Treatment					
Cessation of VEGF inhibitor	Yes	Yes	Yes	Yes	Continued 5 doses, then ceased
Administration of glucocorticoid	No	No	Yes	No	Yes
Dialysis	No	Yes	Yes	Yes	No
Prognosis					
Resolution of hypertension	Stable	Recovered	Recovered	Recovered	Persistent
Final blood pressure (mmHg)	108/77	141/77	125/66	111/67	On AHT
Final urinary protein	Undetectable	NA	Undetectable	>30 mg/dL	Undetectable
Final SCr (mg/dL)	1.1	ESRD	0.5	1.5	1.6
Follow-up duration after diagnosis (mo)	33	5	24	5	16

Abbreviations: TMA, thrombotic microangiopathy; M, male; F, female; HT, hypertension; NA, not available; Cr, creatinine; SCr, serum creatinine; ESRD, end-stage renal disease; HA, hemolytic anemia; SCT, schistocytes; TP, thrombocytopenia; ARB, angiotensin II receptor blocker; AHT, anti-hypertensive medication; 5FU, fluorouracil.

case 5 revealed AKI and hypertension treated with angiotensin receptor blocker but no urinary or hematologic abnormalities. No significant serologic findings were identified in 3 patients tested (cases 1, 3, and 4). There was no history of prior exposure of the kidneys to radiation.

3.2. Histopathological findings

The histopathological findings of the 5 cases are summarized in Table 2. A common pathological finding in all cases was diffuse or focal endothelial injury seen in glomeruli and small arterial vessels along with varying degrees of ischemic glomerular changes attributed to endothelial injury. Only 2 samples (cases 1, 2) exhibited typical features of TMA in both glomeruli and arterioles (Figs. 1 and 2), with patients receiving bevacizumab and sorafenib, respectively. In both cases, the glomeruli displayed endothelial swelling, capillary microthrombi and mesangiolysis suggesting active disease lesions (Fig. 1A, B). Intra-luminal thrombi were seen in adjacent arterioles (Fig. 1C). In addition, chronic glomerular changes, such as global collapse, double contour appearance of capillary walls, focal microaneurysms, segmental sclerosis, and focal

Table 2 Renal pathological findings

	Case 1	Case 2	Case 3	Case 4	Case 5
Light microscopy					
Cortical area of total sample (%)	80	100	100	10	80
Total number of glomeruli	32	25	46	4	67
Number of segmental/ global sclerosis	0/2	1/1	0/2	2/0	0/11
Glomerular lesions	Diffuse active and chronic endothelial injury, (thrombi, mesangiolysis, double contour, hyalinosis), moderate	Focal active and diffuse chronic endothelial injury (thrombi, mesangiolysis, double contour, hyalinosis, FSGS lesions), moderate	Diffuse endothelial injury with endothelial swelling and collapse, mild to moderate, mainly ischemic change	Diffuse endothelial injury with segmental double contour, FSGS lesions, mainly ischemic change	Focal and mild endothelial injury with segmental double contour, collapse, mainly ischemic change
Acute tubular injury	Focal, mild	Diffuse, mild	Diffuse, mild to moderate	Diffuse, severe	Diffuse, mild
Tubular atrophy (%)	5-10	30-35	5-10	10-15	15-20
Hemoglobin casts	Scattered	Not seen	Frequent	Occasional	Not seen
Interstitial inflammation	No	Mild	No	No	Active, focal, mild to moderate
Interstitial fibrosis (%)	5-10, mild	20-25, mild	5-10, mild	10-15, moderate	15-20, mild
Arterioles	Thrombi, moderate sclerosis	Thrombus, moderate sclerosis	Thrombus, mild to moderate sclerosis	Moderate sclerosis	Moderate to severe sclerosis
Small-sized arteries	Moderate sclerosis	Mild sclerosis	Mild to moderate sclerosis	Mild sclerosis	Moderate to severe sclerosis
Peritubular capillary margination	No	No	No	Yes, moderate	No
Immunofluorescence					
Glomeruli	IgM 1+, fibrinogen 2+ focal, granular in periphery capillary wall	IgM 2+ to 3+, fibrinogen 2+ focal, granular in periphery capillary wall	IgM 1+ focal, granular in periphery capillary wall	Inadequate materials	IgM 1+ focal, granular in periphery capillary wall
Small-sized arteries, arterioles	C3 1+ granular	IgM 2+ granular, C3 2+ granular	C3 1+ granular	Inadequate materials	C3 1+ granular
Electron microscopy					
Wrinkling of GBM	Regular texture	Marked	Mild to moderate	Not done	Focal, mild
Foot process fusion (%)	Focal fusion	Preserved	Preserved	Preserved	
Endothelial swelling	Yes	Yes	Yes	No	
Loss of endothelial fenestrae (%)	100	100	100	10	
Subendothelial abnormalities	Marked	Marked	Focal	Focal	
Mesangiolysis	Yes	Yes	No	No	
Electron-dense deposit	No	No	No	No	
Overall					
Severity of endothelial injury	Severe	Severe	Moderate	Mild	Mild
Pathological diagnosis	Active and chronic TMA, focal tubular injury	Active and chronic TMA, diffuse tubular injury, glomerular ischemia	Active and chronic TMA, diffuse tubular injury, glomerular ischemia	Diffuse endothelial injury, diffuse tubular injury, glomerular ischemia	Focal segmental endothelial injury, diffuse tubular injury, acute interstitial nephritis, glomerular ischemia

Abbreviations: TMA, thrombotic microangiopathy; FSGS, focal segmental glomerular sclerosis; GBM, glomerular basement membrane.

Table 3 Summary of clinicopathological findings in reported biopsy-proven TMA on VEGF inhibitor

Reference	VEGF inhibitor	Dose, duration	Age (y)/gender	Type/duration of cancer	Prior chemotherapy	Concomitant chemotherapy/ nephrotoxins
15	Bevacizumab	10 mg/kg, 2 doses	70/M	RCC/6 y	Interferon-α	No
16	Bevacizumab	10 mg/kg, 15.5 mo	59/M	RCC/3 mo	No	Interferon-α2b, quinapril
16	Bevacizumab	NA, NA	NA/NA	RCC/NA	NA	Interferon-α2b
17	Bevacizumab	400 to 800mg, 3 mo	59/F	Mammary ductal adenocarcinoma/NA	Yes, unspecified	Pamidronate, paclitaxel
13	Bevacizumab	7.5 mg/kg, 24 doses	59/M	HCC/NA	NA	No
13	Bevacizumab	7.5 mg/kg, 4 doses	74/F	HCC/NA	NA	No
13	Bevacizumab	15 mg/kg, 19 doses	56/M	BAC/NA	Cisplatin, gemcitabine	Pemetrexed
13	Bevacizumab	10 mg/kg, 4 doses	62/M	SCLC/NA	NA	Cisplatin, docetaxel, levofloxacin
13	Bevacizumab	10 mg/kg, 12 doses	61/M	PC/NA	NA	Gemcitabine, erlotinib
13	Bevacizumab	15 mg/kg, 29 doses	59/F	Ovarian cancer/NA	Paclitaxel, topotecan	NA
18	Aflibercept	4 mg/kg, 2 doses	59/F	Ovarian cancer/NA	Gemcitabine	LV5FU2-CPT11
19	Sunitinib	37.5 mg/day on 4/off 2 wk cycle, 6 mo	44/F	Malignant skin hidradenoma/2 y	Paclitaxel, adriamycin	NA
20	Sunitinib	50 mg/day on 4/off 2 wk cycle, 10 mo	66/M	RCC/5 y	Interferon-α	Enalapril
21	Sunitinib	25 to 50 mg/day on 4/off 2 wk cycle, 15 mo	72/M	GIST/3 y	Imatinib	No
22	Sorafenib	NA, 10 d	50/M	RCC/7 mo	Sunitinib	No
Total:	Bevacizumab (10), aflibercept (1), sunitinib (3), sorafenib (1)		44-74 (m 61) 9 M: 5 F	RCC (5), HCC (2), ovarian (2), lung (2), Br CA (1), prostate (1), skin (1), GIST (1)	8/9 (89%) with prior chemo	8/13 (62%) with concomitant chemo

Abbreviations: TMA, thrombotic microangiopathy; NA, not available; RCC, renal cell carcinoma; HCC, hepatocellular carcinoma; BAC, bronchoalveolar carcinoma; SCLC, small cell lung cancer; PC, pancreatic cancer; GIST, gastrointestinal stromal tumor, Br CA, breast cancer; LV5FU2-CPT11, leucovorin + fluorouracil + irinotecan; HT, hypertension; UP, proteinuria; RD, renal dysfunction; TP, thrombocytopenia; HA, hemolytic anemia; SCH, schistocytes; FSGS, focal segmental glomerulosclerosis; MCD, minimal change disease; UP, Urinary protein; D, Renal dysfunction.

hyalinosis, were found in these cases (Fig. 1D, E), indicating mixed, acute and chronic lesions associated with TMA (case 2). In 2 other cases (cases 3, 4), most glomeruli revealed segmental endothelial swelling and/or double contours, but no fresh thrombi or mesangiolysis. In case 3, one suspicious intra-arteriolar thrombosis was found. In case 5, some glomeruli showed partial thickening of peripheral capillary walls or double contours by light and electron microscopy (Supplementary Fig. S1A, B). Moderate to severe vascular sclerosis in arterioles and/or small-sized arteries was found in all 5 samples (Fig. 1F).

On immunofluorescence microscopy (IF), fibrinogen within intravascular thrombi was localized in glomeruli and arterioles of 2 cases with typical TMA (cases 1, 2, Fig. 2A, B), staining with IgM was mainly found in the chronic glomerular lesions in 3 cases (cases 1–3, Fig. 2C). IF was otherwise negative in all cases, thus excluding immune-complex type glomerular lesions, confirmed by electron microscopy in 4 of 5 cases. By electron microscopy, cases 1 and 2 revealed diffuse, marked glomerular endothelial injury such as swelling of cytoplasm, total loss of fenestrae, and mild detachment from basement membrane, with narrowing or occlusion of capillary lumina (Fig. 2D, E). Even the mildest case showed subendothelial widening, segmental loss of fenestrae, and rare new basement membrane formation in some glomerular capillaries by electron microscopy (case 5, Supplementary Fig. S1B). However, the foot processes of glomerular podocytes were generally well-preserved in most cases (cases 2, 3, 5; Fig. 2D, E), with 10% to 15% effacement in case 1, which showed active TMA. Glomerular capillary wall wrinkling was distinct in 3 cases, which reflected ischemic change (cases 2, 3, 5; Fig. 2F).

There was diffuse acute tubular injury with focal necrosis in 4/5 cases (Fig. 3A), and focal in 1. Several pigmented hemoglobin-containing tubular casts were present in 3 cases (cases 1, 3, 4), increased in one patient, with an episode of

Table 3 (*continued*)

Clinical onset after therapy	Clinical features	Hematologic features	Pathological findings	Continuation of therapy	Clinical course		
					HT	UP	RD
Few d	HT, UP, RD, HA	TP, HA	TMA	Cessation	Recovered	Recovered	Recovered
9 mo	HT, UP, RD	TP, anemia	TMA with granular IgA dominant fluorescence	Cessation	Recovered	Recovered	Recovered
7 mo	UP	NA	TMA	NA	NA	NA	NA
3 mo	HT, UP, RD	No	TMA	Cessation	Recovered	Recovered	Recovered
9 mo	HT, UP	TP	TMA	Cessation	Recovered	Recovered	NA
1 mo	UP	No	TMA	Cessation	NA	Recovered	NA
9 mo	HT, UP, RD	No	TMA	Cessation	NA	NA	NA
3 mo	UP, RD	NA	TMA	Cessation	NA	Recovered	Recovered
5 mo	UP, RD	TP, SCH	TMA	Cessation	NA	NA	Stable
9 mo	UP	No	TMA	Continued for 8 mo, then ceased	NA	Unrecovered	Stable
7 d	HT, UP	NA	TMA	Cessation	Recovered	Recovered	Stable
2 wk	HT, UP	No	TMA with granular IgA, IgM fluorescence	Continued	Stable	Recovered	Stable
1 wk	HT, UP, RD	TP, anemia, SCH	TMA with FSGS	Cessation	Recovered	Recovered	Recovered
5 mo	HT,UP, RD	TP	TMA-like lesion with FSGS	Reduction	Recovered	Stable	Stable
10 d	HT, UP, RD	NA	TMA and MCD	Cessation	NA	Stable	Recover
1 week –9 months (mean 4.1 months)	HT-67% (10/15), UP-100%, RD-60% (9/15)			Immediate cessation in 79% (11/14)	7 recovered, 1 stable	8 recovered, 3 stable or progressed	6 recovered, 5 stable

intravascular hemolysis clinically (case 3, Fig. 3B), along with evidence of glomerular endothelial injury, without typical pathological findings of acute TMA. Small patches of acute interstitial nephritis with abundant eosinophils and focal tubulitis were found in case 5, as well as diffuse tubular injury and mild glomerular changes (Fig. 3C).

3.3. Treatment and prognosis

The clinical course after pathological diagnosis of these 5 patients are listed in Table 1. The anti-VEGF treatment in cases 1 to 5 was discontinued, but in case 5, VEGF inhibitor administration was resumed for 5 more doses, after the renal function was restored following cessation of anti-VEGF therapy. Steroid therapy was given to two cases including one with superimposed focal acute interstitial nephritis (case 5). However, 3 cases including one biopsy-proven glomerular TMA case needed dialysis therapy initially (cases 2-4), one of whom progressed to permanent dialysis (case 2). Of 4 patients with hypertension, 3 responded after discontinuation of anti-VEGF therapy (cases 2–4), and 4 of 5 patients with renal dysfunction recovered renal function (cases 1, 3-5; final serum creatinine value 0.5-1.6 mg/dL, duration 5–33 months from the time of biopsy). By contrast, all cases demonstrated recovery from proteinuria and anemia to baseline.

4. Discussion

We report 5 cases treated with VEGF inhibitor, manifesting acute impairment of renal function with hypertension and/or proteinuria clinically. Renal biopsy showed histological evidence of glomerular endothelial injury in all cases. The overall pathological findings are depicted in a diagram (Fig. 4). The spectrum of extent and severity of endothelial injury was variable, from a focal glomerular endothelial injury (case 5) to diffuse and active

form of TMA with intravascular microthrombi and global mesangiolysis (cases 1, 2). Most of the cases also showed secondary ischemic changes in the glomeruli, due to intravascular thrombi or chronic endothelial injury in arterioles or small-sized arteries. Additionally, all biopsies revealed diffuse or focal acute tubular injury with or without evidence of tubular necrosis and hemoglobin casts. Intravascular hemolysis, secondary ischemic change due to endothelial injury, and drug-induced tubular toxicity may all have contributed to this finding.

A number of large clinical trials have addressed the frequency of occurrence of kidney-related adverse events, commonly hypertension and proteinuria, which is generally dose dependent, thus mostly permitting them to continue anti-VEGF therapy. Hypertension occurred at an overall incidence of 8% to 67% with bevacizumab [5]. Other forms of VEGF inhibitors were also linked to a higher frequency of hypertension, such as 9% to 63% with aflibercept, 20% with sunitinib, 17% with sorafenib, and 45% to 58% with axitinib [15–17]. The overall incidence of proteinuria in patients with low-dose bevacizumab (3-7.5 mg/kg) was 21% to 41%, and in those with high-dose bevacizumab (10-15 mg/kg), 18% to 63%, also correlating as a dose dependent phenomenon [5]. Those who underwent occasional renal biopsy showed a variety of pathological findings (see Supplementary Table S1).

In the glomeruli, VEGF is constitutively expressed and secreted by the podocytes to maintain the integrity of structure and function through paracrine and possibly autocrine effects via VEGFRs [7,18,19]. VEGF-R2, a receptor demonstrating angiogenic VEGF signaling, is expressed by glomerular endothelial cells in vivo, establishing a transmembrane communication between glomerular podocytes and endothelial cells via its VEGF–VEGF-R2 signaling [20,21]. It is accepted that the paracrine effects via the crosstalk between glomerular podocytes and endothelial cells have a dominant role in the protection against glomerular injury. This is supported by experimental evidence, where genetically engineered murine studies by Eremina et al showed that the reduction of VEGF expression in glomerular podocytes to 50%, using podocyte-specific deletion of a single VEGF allele, led to glomerular endothelial injury, developing histology resembling those in preeclampsia [22]. An additional suppression of VEGF in glomerular podocytes, to approximately 75% reduction, induced glomerular aneurysmal change with severe mesangiolysis [23]. Glomerular endothelial injury and rarely TMA-like appearance is shown to be triggered by excess placenta-secreted anti-angiogenic factor during pregnancy and pre-eclampsia, such as soluble fms-like tyrosine kinase 1 (sFlt1, or VEGFR1) [24].

A review of literature yielded 31 cases and anecdotal reports of documented renal pathological findings following treatment with a variety of VEGF inhibitors (Supplementary Table S1) [4,6,8–14,25–28]. Features of glomerular and/or arterial TMA have been diagnosed in approximately half of these cases (Table 3) [6,8–14]. Characteristically, VEGF inhibitor–associated TMA was restricted to the kidney, with little or no involvement of the peripheral microvasculature [6] and presented with clinical renal features including hypertension, proteinuria, and progressive deterioration of renal function, with relatively less frequent or no hematologic abnormalities such as severe hemolytic anemia or thrombocytopenia [29]. Since the kidney-associated clinical abnormalities cannot always predict underlying renal lesions, a wider use of renal biopsy may help identify VEGF inhibitor–associated glomerular TMA, even in the absence of typical clinical manifestations of TMA. TMA in this setting may trigger secondary hypertension and ischemic parenchymal damage, contributing to further renal injury. The histological findings of chronic or healing phase of TMA in patients attributed to VEGF inhibitor administration may resemble those of hypertensive nephrosclerosis and ischemic nephropathy; 3 such cases were identified in the reported literature (Supplementary Table S1), showing focal segmental glomerulosclerosis, two of which were associated with healed glomerular TMA [9].

In addition to glomerular TMA, various other glomerular diseases, such as cryoglobulinemic GN, collapsing GN [4], immune-complex mediated proliferative GN [25,27], and crescentic GN [4], as well as interstitial nephritis [26] have been diagnosed in patients receiving VEGF inhibitors (Supplemental Table S1). In the present case series, one showed focal active interstitial inflammation with increased eosinophils (case 5), where there was concomitant administration of pemetrexed and carboplatin. Since cases of interstitial nephritis are reported with both pemetrexed and carboplatin [30,31], the influence of these agents was considered in this case. In cancer patients, it is conceivable that the histological features might be modified by other factors including paraneoplastic or drug-induced effects. The anti-VEGF treatment was discontinued in 12 of 15 patients diagnosed with TMA (Table 3). All 6 patients with hypertension responded to treatment following discontinuation of anti-VEGF therapy. All 9 cases with proteinuria and all 8 with renal dysfunction either recovered or were stable. Anti-VEGF treatment in 2 patients diagnosed with glomerular TMA was continued, and the dose was reduced in 1 patient. By contrast, the anti-VEGF treatment in 6 of 11 patients diagnosed with other glomerular diseases were discontinued. All 5 patients with proteinuria and 2 of 2 patients with renal dysfunction recovered following discontinuation of anti-VEGF therapy. Similarly, 2 cases diagnosed with interstitial nephritis and renal dysfunction recovered, 1 despite continuation of and 1 with discontinuation of the VEGF inhibitor, respectively. Most of the VEGF inhibitor–associated renal lesions (16 of 20 patients, 80%) improved their clinical renal abnormalities after discontinuation of VEGF inhibitor therapy. These reported cases with diverse glomerular lesions also revealed significant urinary abnormalities (Supplemental Table S1). However, 2 cases in our series (cases 2, 5) had no urinary abnormality.

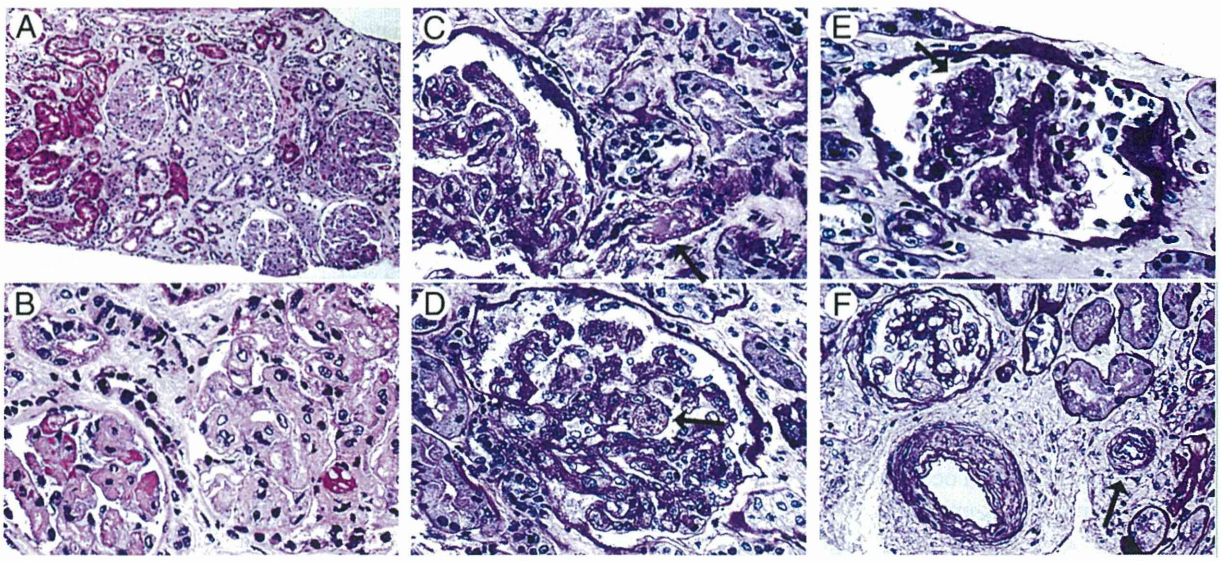

Fig. 1 Light microscopy of typical endothelial injury and active TMA in glomeruli and vessels. Diffuse glomerular findings of microthrombi with segmental double contours and mesangiolysis (A, low power field, case 1; B, high power field, case 2), and arteriolar thrombotic occlusion (arrow) is occasionally seen (C, case 2). Focal microaneurysm in the periphery capillary wall (arrow) (D) or segmental sclerosis (arrow) accompanied with occasional hyperplasia of epithelial cells (E; case 2). Several glomeruli showed global ischemic collapse in most cases with chronic changes (D, case 5). Moderate medial hyperplasia and marked fibrous intimal thickening of arterioles (arrow) and small-sized arteries (F; case 5). A and B, hematoxylin and eosin; C and F, periodic acid–Schiff. Original magnification: A, ×40; B to E, ×400; F, ×200.

To understand the range of pathological findings of kidney diseases in patients treated with VEGF inhibitor, we examined the role of other cancer therapies administered prior to or concomitant with anti-VEGF agents. A review of present case series (Table 1) and previously reported patients with TMA (Table 3, Supplementary Table S1) shows prior or combined administration of a number of chemotherapeutic agents. The development of TMA is well known in association with certain agents such as mitomycin C as well as gemcitabine [32], cisplatin, and interferon-α [33]. In

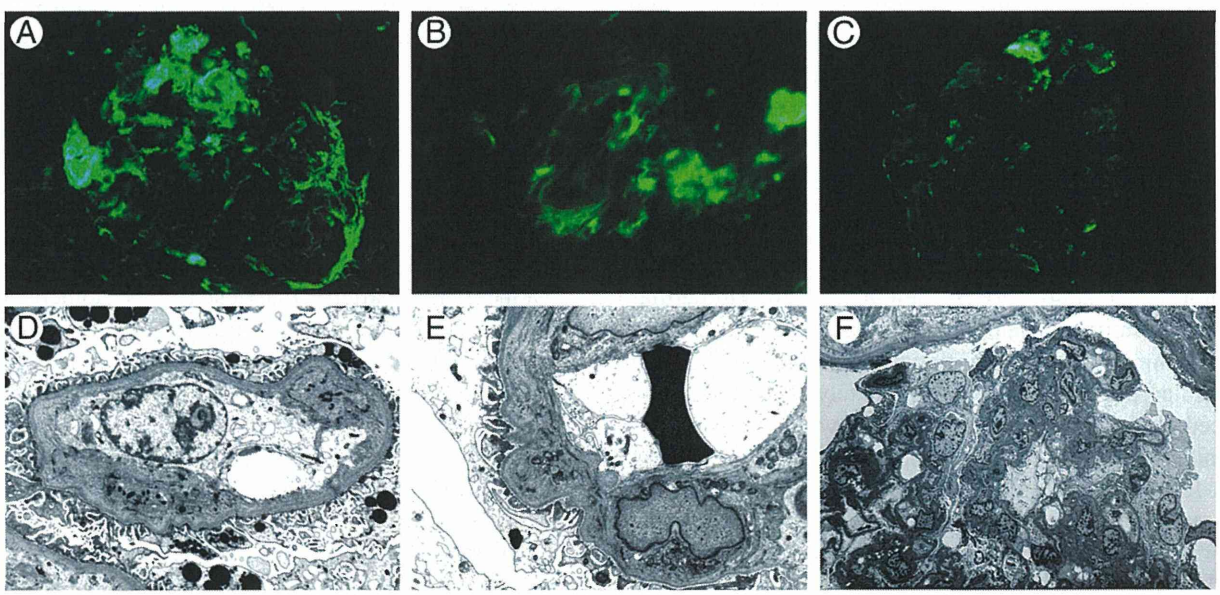

Fig. 2 Immunofluorescence (IF) and electron microscopic (EM) findings in glomeruli and arterial vessels. IF with fibrinogen was localized within glomerular microthrombi in the case of TMA (A, case 2). Fibrinogen by IF was found in arterioles (B, case 1). Immunostaining for IgM was noted in some glomeruli (C, case 2). EM of case with TMA showed glomerular endothelial injury, such as swelling, mild detachment of basement membrane, total loss of fenestrae, subendothelial edema, and cellular interposition, with narrowing or occlusion of the capillary lumina (D, case 1; E, case 2). The foot processes of glomerular visceral epithelial cells were preserved. The glomerular capillary walls often revealed diffuse wrinkling due to ischemic collapse in most cases (F, case 3). Original magnification: A and C, ×200; B, ×400; D and E, ×6000; F, ×1800.

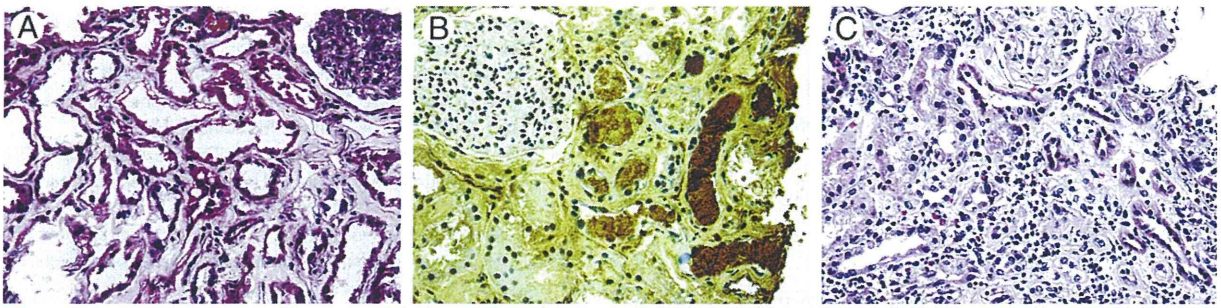

Fig. 3 Light microscopic findings of tubulo-interstitial injury. All samples revealed that mild to severe tubular epithelial degenerative changes—loss of brush border, cytoplasmic vacuolization and focal sloughing of cells—were seen (A, case 3). Acute tubular injury along with intratubular hemosiderin casts were noted in case 3. B, confirmed by immunohistochemistry for hemoglobin. In case 5, small foci of abundant mixed inflammatory infiltrates, such as lymphocytes, monocytes, granulocytes, eosinophils, were observed in the interstitium with focal tubulitis. C, Hematoxylin and eosin. Original magnification: A-C, ×200.

fact, present case 1 with typical TMA, who received a combination of sorafenib and gemcitabine, revealed a severe and active form of TMA in the renal histology, raising the possibility of a synergistic action. Additionally, the influence of prior or concomitant chemotherapies, such as gemcitabine (3 cases [6,11]), cisplatin (2 cases [6]), and interferon-α (4 cases [9,10,13]) should be considered as having a possible role in the development of TMA in previously reported patients. Overall, 89% of biopsy-proven TMA cases received prior chemotherapy, and 62% of them were treated with concomitant chemotherapy (Table 3). So, although adverse effects with VEGF inhibitors are known to have dose dependency, they could be modified or enhanced by other concomitant or prior chemotherapy, which may determine the spectrum and severity of endothelial injury.

In summary, we report clinicopathological data from 5 new cases with kidney disease associated with VEGF inhibitor administration, manifesting endothelial damage including TMA and subsequent ischemic injury. However, apart from VEGF inhibitor, participation of other factors such as intravascular hemolysis, secondary hypertension, ischemic tissue damage due to VEGF inhibitor administration, prior or concomitant chemotherapy, or rarely other medication effects are considered. While glomerular endothelial injury was the most common pathological finding in VEGF inhibitor–associated kidney injury, the spectrum of extent and severity of damage varied, probably

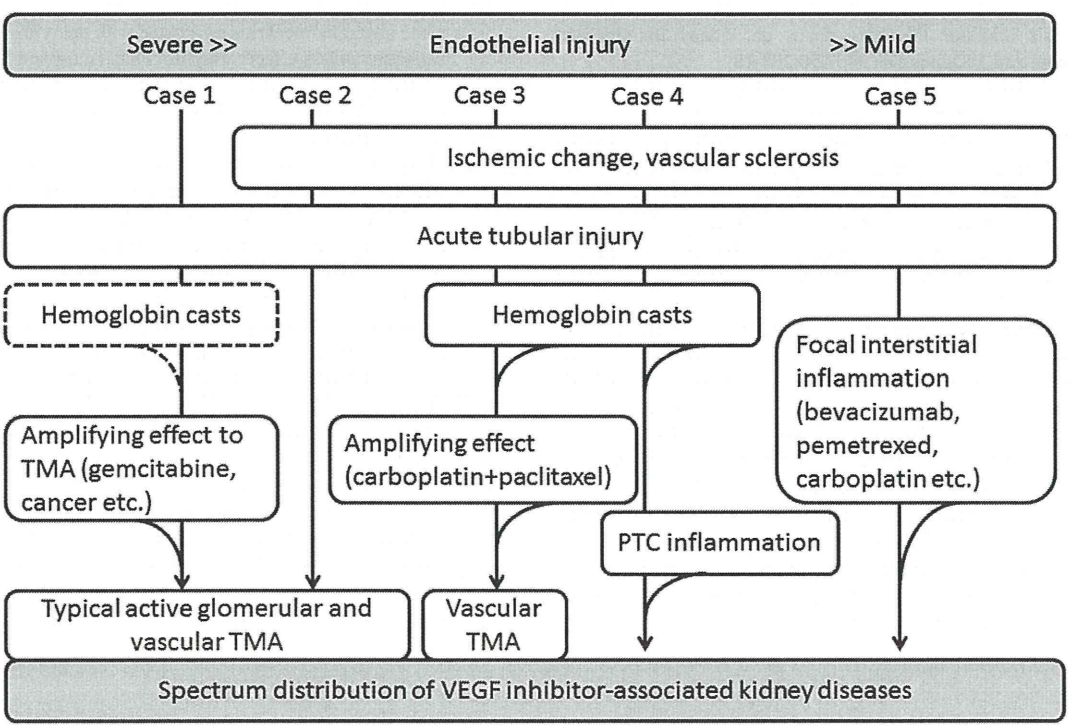

Fig. 4 Spectrum of renal pathological findings in present cases. Abbreviation: PTC; peritubular capillary.

related to host factors and possible effects of other chemotherapeutic agents in patients with VEGF inhibitor treatment. A detailed examination of renal biopsy findings is suggested to identify the varied disease processes for appropriate therapy and management.

Supplementary data

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● 臨 床

女性と高血圧

*1 新潟大学 腎・膠原病内科　**1 同 教授
*2 長岡中央綜合病院 内科 医長
河野 恵美子*1*2　成田 一衛**1

要 旨

女性における高血圧は，妊娠や閉経に関連する高血圧，二次性高血圧が挙げられる．妊娠高血圧症候群（PIH）では，診察時血圧に加え家庭血圧も参考に診断する．降圧薬ではレニン・アンジオテンシン（RA）系阻害薬を避けるべきである．更年期高血圧は，エストロゲンが深く関与するとされ，加えて PIH の既往の有無も関連があるとされる．二次性高血圧の頻度は少ないが，若年に多い大動脈炎症候群による腎血管性高血圧や内分泌疾患に関連したものが挙げられる．

はじめに

男性，女性という分類で高血圧を考えると，女性における高血圧は大きく分けて，① 妊娠に関連した高血圧，② 閉経に関連した高血圧，③ 男性と同様に起りうる一次性および二次性の高血圧，がある．そして，これらの高血圧はその要因によって考慮すべき診断や治療方針が異なる．本稿では，最近発表された『高血圧治療ガイドライン 2014』(JSH2014)[1] の内容を踏まえつつ，性別による高血圧の疫学，女性特有の高血圧について述べる．

キーワード：性差，妊娠，更年期，エストロゲン，二次性高血圧