

Case Report

Renal-Limited Thrombotic Microangiopathy due to Bevacizumab Therapy for Metastatic Colorectal Cancer: A Case Report

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Keywords

Bevacizumab · Nephrotic syndrome · Colorectal cancer · Thrombotic microangiopathy

Abstract

An 88-year-old Japanese man received bevacizumab for colorectal cancer with liver and peritoneal metastasis, during which nephrotic range proteinuria occurred (7.66 g/day). Renal biopsy showed endothelial damage with subendothelial swelling and a double contour of the glomerular basement membrane, which indicated a diagnosis of thrombotic microangiopathy (TMA). After bevacizumab was stopped, proteinuria decreased to 1 g/day. During the clinical course, this patient had no extrarenal manifestations. This case suggests that renal injury

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induced by bevacizumab is characterized by nephrotic range proteinuria and histological TMA, and is a renal-limited condition that differs from systemic TMA related to thrombotic thrombocytopenic purpura.

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Published by S. Karger AG, Basel

Introduction

Bevacizumab is a monoclonal antibody for recombinant human vascular endothelial growth factor (VEGF) [1]. Targeting the VEGF signaling pathway has become an important modality of anticancer therapy and bevacizumab has been approved for the treatment of various types of advanced cancer.

Proteinuria is one of the severe side effects of bevacizumab [2]. The primary cancers for which anti-VEGF therapy has frequently been reported to cause renal injury include renal cell carcinoma along with adenocarcinoma of the ovary, breast, and lung, and renal biopsy shows thrombotic microangiopathy (TMA) in patients with this complication [3]. However, there have been few reports of TMA in patients receiving bevacizumab for metastatic colorectal cancer.

Here we report a patient who developed nephrotic range proteinuria during bevacizumab therapy for metastatic colorectal cancer. Although renal biopsy showed TMA-like changes, the patient did not have any of the clinical features of thrombotic thrombocytopenic purpura (TTP), such as microangiopathic hemolytic anemia (MAHA), thrombocytopenic purpura, fever, neurological abnormalities, and renal dysfunction. This case suggests that BV-related TMA is a renal-limited condition that differs from TTP-related systemic TMA.

Case Report

An 88-year-old Japanese man was initially admitted to our hospital with malaise and anemia when he was aged 85 years. At that time, he was 161.3 cm tall and weighed 61.7 kg, with a blood pressure of 121/56 mm Hg and a temperature of 36.1°C. Laboratory tests showed that he had a hemoglobin of 8.3 g/dL, serum albumin of 3.6 g/dL, and proteinuria of 0.07 g/day (Table 1, Table 2). Colonoscopy revealed cancer of the ascending colon. Contrast-enhanced computed tomography showed a tumor in the ascending colon with direct infiltration of the liver, but metastasis was not detected. The patient underwent laparoscopic-assisted colectomy, D3 lymph node dissection, and partial hepatectomy (S6). The pathological stage of the tumor was III B (T4b N1 M0). Adjuvant chemotherapy was not performed because of the patient's age. At the age of 86 years, liver metastasis was detected by 2-deoxy-2-[F-18] fluoro-D-glucose positron emission tomography (FDG-PET). Treatment was initiated with bevacizumab (7.5 mg/kg every 3 weeks) and capecitabine (1,000 mg/m² twice daily for 14 days of a 21-day cycle). After 14 cycles of bevacizumab, urinary protein increased from 1+ to 3+ and serum albumin decreased from 4.0 to 3.2 g/dL. At the age of 87 years, FDG-PET revealed disappearance of liver metastasis so bevacizumab therapy was stopped. Thereafter, urinary protein decreased to 2+ and serum albumin improved to 4.0 g/dL. At the age of 88 years, FDG-

PET revealed peritoneal metastasis and bevacizumab was restarted. However, severe leg edema and nephrotic range proteinuria soon occurred, leading to the present admission.

On examination, the patient was 161.5 cm tall and weighed 70.3 kg (weight gain of 9 kg), with a blood pressure of 156/98 mm Hg and a temperature of 36.0°C. Laboratory findings were as follows (Table 1): total protein, 5.1 g/dL; albumin, 2.2 g/dL; creatinine, 1.57 mg/dL; proteinuria, 4+ and 7.66 g/day; and selectivity index, 42.6. The total dose of bevacizumab was calculated to be 10,290 mg. Renal biopsy was performed to investigate the cause of his proteinuria.

Renal Biopsy Findings

Light microscopic examination of the renal biopsy specimen revealed global sclerosis in 15 out of 81 glomeruli and segmental sclerosis with adhesions in 15 glomeruli (Fig. 1a). Sub-endothelial swelling was noted with a double contour of the glomerular basement membrane (GBM) and mesangial injury with mesangiolytic (Fig. 1b–d). Tubulointerstitial fibrosis and atrophy occupied 50 % of the renal cortex. Arteriolar hyalinosis was moderate, while interlobular arteriosclerosis was severe. Immunofluorescence demonstrated weak partial positivity for IgM and C3 in the mesangial region (Fig. 2). Electron microscopy revealed endothelial injury with subendothelial edema and a double GBM contour, as well as effacement of the foot processes, but there were no electron-dense deposits (Fig. 3). These findings were consistent with a diagnosis of thrombotic microangiopathy with focal segmental sclerosis.

Clinical Course

After withdrawal of bevacizumab, proteinuria decreased to 1 g/day and serum albumin was elevated to 3.8 g/dL. His leg edema also improved. At the age of 89, computed tomography revealed lung metastasis and panitumab therapy was initiated (6 mg/kg every two weeks). Because peritoneal metastasis was detected by magnetic resonance imaging, treatment with irinotecan was added (150 mg/m² every two weeks), but the patient's general condition deteriorated and he died (Fig. 4). After bevacizumab was stopped, proteinuria remained around 1 g/day. Throughout treatment with bevacizumab, there were no changes of the platelet count, red blood cell count, or renal function, as well as no fever or neurological abnormalities.

Discussion

Bevacizumab therapy is reported to be associated with an increased risk of hypertension and proteinuria. Wu et al. found that the incidence of nephrotic range proteinuria (>3.5 g/day) was 2.2% in patients receiving bevacizumab [2]. Izzedine reported that TMA is the most frequent form of renal injury associated with anti-VEGF therapy [3].

According to a meta-analysis, bevacizumab therapy improves the overall survival, progression-free survival, and overall response rate in patients with colorectal cancer [1], but inhibition of VEGF results in injury to podocytes and endothelial cells. The podocytes interact with glomerular capillary endothelial cells to create the filtration barrier in the renal glomeruli. VEGF is expressed by podocytes, while VEGF receptors are expressed by both glomerular

cells and endothelial cells [4]. In mice, targeted heterozygous deletion of VEGF expression by podocytes caused the glomerular capillary loops to become filled with swollen necrotic endothelial cells, along with loss of podocyte foot processes, resulting in dose-dependent proteinuria [5, 6].

While there have been several case reports about TMA associated with bevacizumab therapy, there have only been a few such reports in patients with metastatic colorectal cancer. Frangie et al. reported a patient with clear cell carcinoma who developed proteinuria and hypertension during bevacizumab therapy, which subsided after cessation of bevacizumab [7]. In addition, Eremia et al. reported 6 patients who developed proteinuria and hypertension related to bevacizumab, with their primary cancers being hepatocellular carcinoma, bronchoalveolar carcinoma, small cell lung cancer, metastatic pancreatic carcinoma, and metastatic ovarian cancer [8]. Moreover, Usui et al. reported 4 patients with TMA induced by bevacizumab, one of whom had colon cancer, but the level of proteinuria was only 2.6 g/day [9].

TMA is pathologically characterized by generalized microvascular occlusion due to platelet thrombi, while its five clinical features are microangiopathic hemolytic anemia (MAHA), thrombocytopenic purpura, fever, neurological abnormalities, and renal dysfunction [10]. Various causes of TMA have been reported, including congenital TTP associated with severe deficiency of plasma ADAMTS13 activity (Upshaw-Schulman syndrome) [11], drug reactions, connective tissue disease, malignancy, transplantation, and pregnancy. Recently, TAFRO syndrome has been reported as a new form of TMA [12]. In TAFRO syndrome, the kidneys show diffuse endocapillary proliferation with mesangiolytic as typical features of TMA, but there is no podocyte injury with foot process fusion and proteinuria is only slight.

In conclusion, we evaluated a patient with colorectal cancer who developed nephrotic syndrome after initiation of bevacizumab therapy. Renal biopsy showed TMA with injury to podocytes and endothelial cells, but there were no extrarenal complications. This case suggests that bevacizumab induces renal-limited TMA, which appears to differ from TTP-related systemic TMA (with its five characteristic clinical features).

Statement of Ethics

The present study adhered to the Declaration of Helsinki, and the patient gave his consent for the case report to be published.

Disclosure Statement

The authors declare no competing financial interests. The authors also declare that they have no conflicts of interest.

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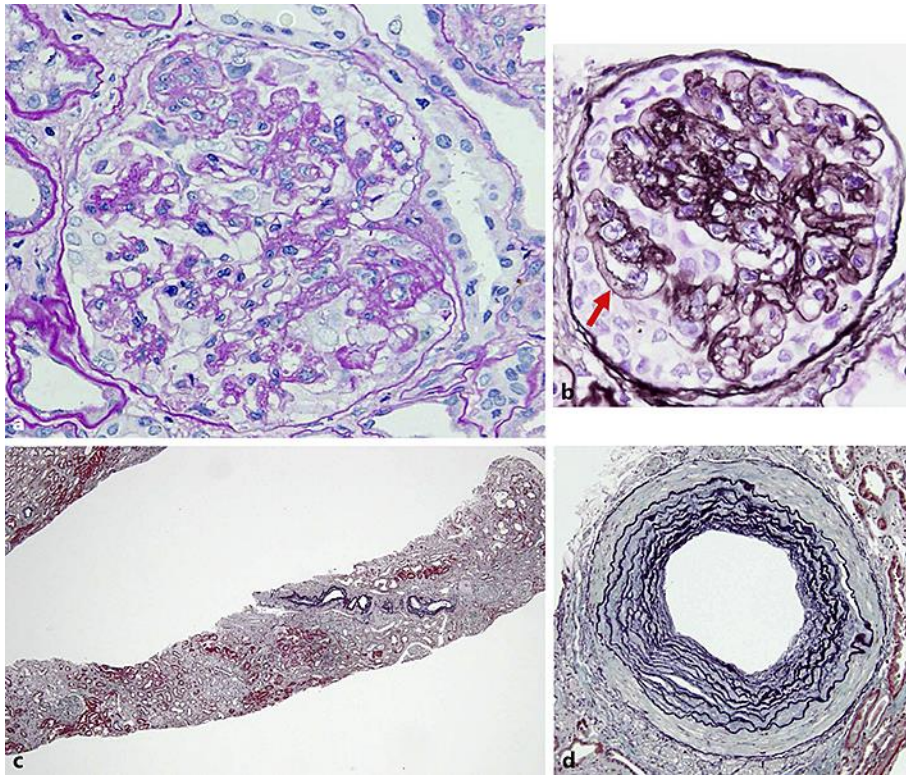


Fig. 1. Light microscopic findings at renal biopsy. **a:** Periodic acid-Schiff (PAS) stain shows segmental sclerosis (arrow) with adhesions. **b, c:** PAS stain shows endothelial cell injury and swelling (arrow). **d:** Periodic acid methenamine-silver stain shows endothelial cell swelling with a double contour of the glomerular basement membrane (arrow).

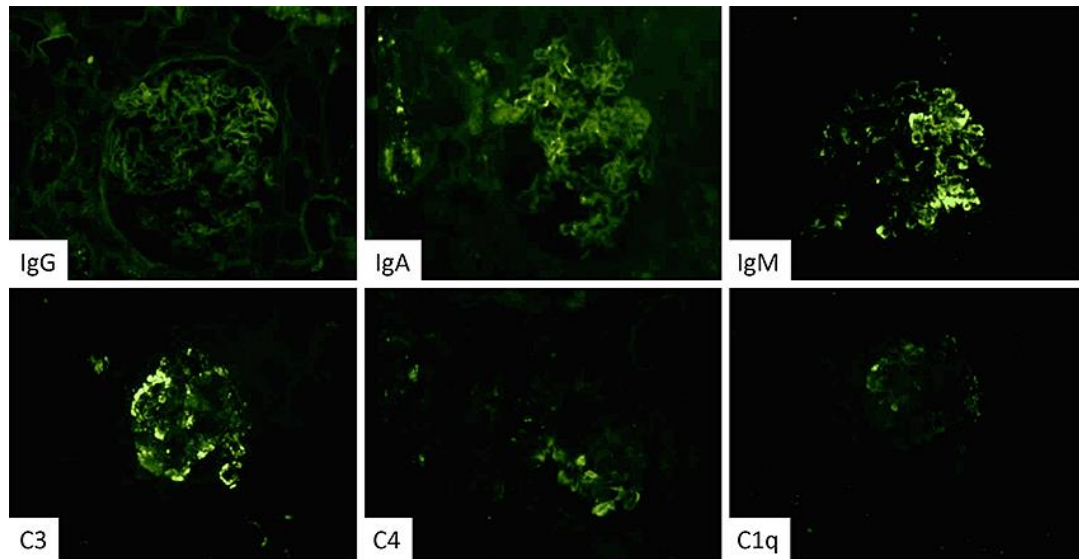


Fig. 2. Immunofluorescence demonstrates weak partial positivity for IgM and C3 in the mesangial region.



Fig. 3. Electron microscopy reveals endothelial injury with subendothelial edema and a double GBM contour, as well as effacement of the foot process, but there are no electron-dense deposits.

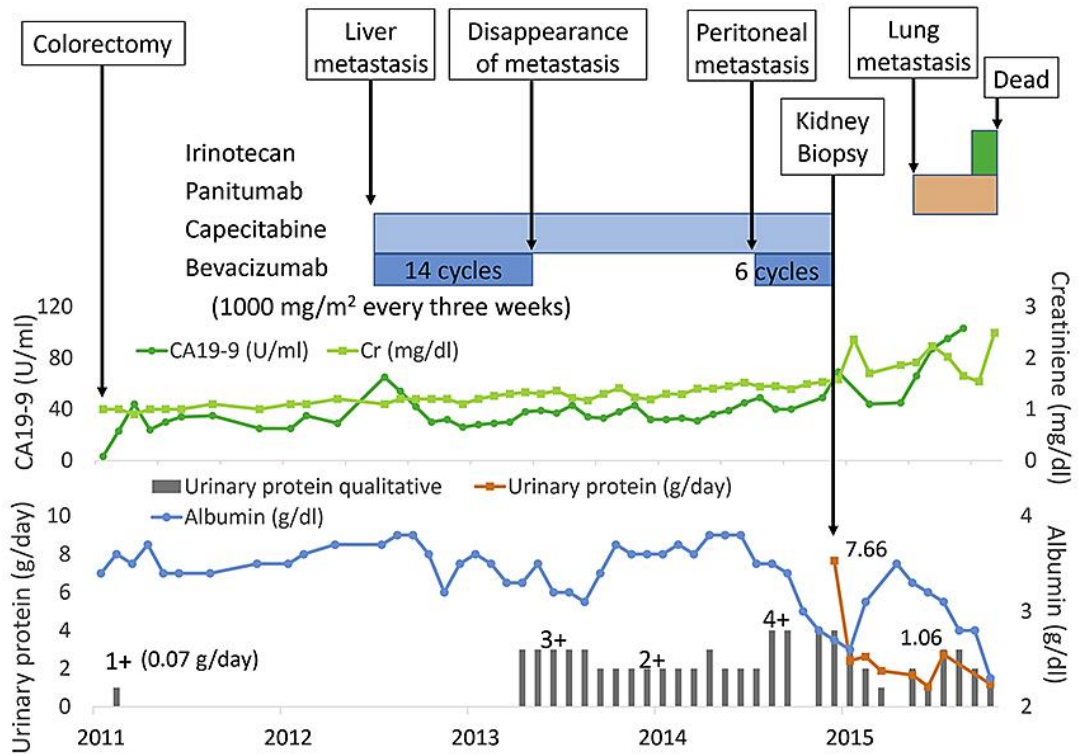


Fig. 4. Clinical course. Bevacizumab: Avastin. Capecitabine: Xeloda.

Table 1. Laboratory findings

			Normal range	
Age	85	87		
Body weight	61.7	70.3		kg
White blood cells	6,700	6,600	3,200–7,900	/ μ L
Hemoglobin	8.3	14.8	11.3–15.0	g/dL
Hematocrit	28.1	42.6	34.0–46.3	%
Platelets	293	121	155–350	$\times 10^3$ / μ L
Total protein	7.6	5.1	6.9–8.4	g/dL
Albumin	3.6	2.2	3.9–5.2	g/dL
Transferrin	ND	177	190–300	mg/dL
AST	16	31	13–33	IU/L
ALT	9	13	117–350	IU/L
LDH	196	272	119–229	IU/L
ALP	228	175	117–350	IU/L
γ -GTP	21	27	9–109	IU/L
Urea nitrogen	25	22	8–21	mg/dL
Creatinine	1.0	1.57	0.46–0.78	mg/dL
eGFR	54.2	32.7	>90	/min/1.73
Uremic acid	5.2	6.4	2.5–7.0	mg/dL
HbA1c	ND	5.9	4.6–6.2	%
Triglyceride	ND	79	30–150	mg/dL
Total Cholesterol	ND	273	122–240	mg/dL
HDL Cholesterol	ND	68	35–70	mg/dL
LDL Cholesterol	ND	171	<140	mg/dL
Na	138	140	139–146	mmol/L
K	4.3	3.9	3.7–4.8	mmol/L
Cl	104	104	101–109	mmol/L
corrected Ca	8.9	9.7	8.7–10.1	mg/dL
P	3.5	3.0	2.8–4.6	mg/dL
Fe	14		80–120	μ g/dL
Unsaturated iron binding capacity	370		173–263	μ g/dL

AST, aspartate aminotransferase; ALT, alanine transaminase; LDH, lactate dehydrogenase; ALP, alkaline phosphatase; GTP, glutamyl transferase; eGFR, estimated glomerular filtration ratio; HDL, high density lipoprotein-cholesterol; LDL, low density lipoprotein-cholesterol; BJP, Bence Jones Protein; NAG, N-acethyl- β -D-glucosaminidase; α 1MG, α 1-microglobuline; β 2MG, β 2-microglobuline; eGFR, corrected Ca, selectivity index are calculated as previously reported [10–12].

Table 2. Laboratory findings (continued)

			Normal range	
Total bilirubin	0.6	1	0.3–1.1	mg/dL
IgG	ND	771	870–1700	mg/dL
IgA	ND	335.4	110–410	mg/dL
IgM	ND	83.2	35–220	mg/dL
ANA	ND	negative	negative	
Cryoglobulin	ND	negative	negative	
CH50	ND	53	30–50	U/ml
C3	ND	107	86–160	mg/dL
C4	ND	33	17–45	mg/dL
CRP	0.9	2.7	0.0–0.3	mg/dL
APTT	32.4	28.7	27.0–40.0	sec
PT	58.8	75.7	>75	%
BNP	ND	1998.5	<18.4	pg/mL
VEGF	ND	154	<38.3	pg/mL
CEA	3.5	7.2	0.8–4.8	µg/mL
CA19-9	32	69	<36	U/mL
anti-p53 antibody	840.00	1400.00	<1.30	U/mL
Urine				
pH	5.5	6.0		
Specific gravity	1.026	1.011		
Red blood cell	1-5	many		/HPF
Proteinuria	0.07	7.66	<0.1	g/day
Transferrin	ND	265		mg/L
IgG	ND	49.2		mg/dL
BJP	ND	negative	negative	
NAG	ND	50.0	0.8–5.0	IU/gCr
α1MG	ND	33.3	1.0–17.8	mg/L
β2MG	ND	10892	14–329	µg/L
Selectivity index	ND	42.62		

AST, aspartate aminotransferase; ALT, alanine transaminase; LDH, lactate dehydrogenase; ALP, alkaline phosphatase; GTP, glutamyl transferase; eGFR, estimated glomerular filtration ratio; HDL, high density lipoprotein-cholesterol; LDL, low density lipoprotein-cholesterol; BJP, Bence Jones Protein; NAG, N-acetyl-β-D-glucosaminidase; α1MG, α1-microglobuline; β2MG, β2-microglobuline; eGFR, corrected Ca, selectivity index are calculated as previously reported [10–12].