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Nephrotic Syndrome Caused by Thrombotic Microangiopathy During Bevacizumab Treatment for Lung Metastases After Rectal Cancer Surgery: A Case Report

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Background: Bevacizumab is a vascular endothelial growth factor (VEGF) inhibitor that may cause hypertension and glomerular injury, although few patients develop nephrotic syndrome. *Case Report*: A 71-year-old man underwent Miles' resection of rectal cancer. Subsequent lung metastasis was treated using FOLFOX (levofolinate, fluorouracil, oxaliplatin) and bevacizumab. Proteinuria was observed after 9 months and leg edema was observed after 17 months. Renal biopsy revealed typical findings for thrombotic microangiopathy. Bevacizumab discontinuation was followed by a rapid decrease in proteinuria with disappearance after 6 months. *Conclusion*: Bevacizumab treatment may need to be stopped or withdrawn if the patient develops proteinuria, renal disorders, and/or hypertension.

Key words: bevacizumab, VEGF inhibitor, thrombotic microangiopathy, nephrotic syndrome

INTRODUCTION

Bevacizumab is an antitumor drug that inhibits vascular endothelial growth factor (VEGF). In Japan, bevacizumab was approved in 2007 and is used to treat unresectable progressive/recurrent colorectal cancer, non-small cell lung cancer, and other cancers. It has been reported that VEGF inhibitors injure the glomerular vascular endothelial cells and podocytes, which can lead to hypertension, proteinuria, renal disorders, thrombotic microangiopathy (TMA), and/or glomerulonephritis [1]. However, few patients develop nephrotic syndrome. We recently encountered a patient who developed nephrotic syndrome during FOLFOX (levofolinate, fluorouracil, and oxaliplatin) and bevacizumab treatment for lung metastasis after rectal cancer surgery, and renal biopsy confirmed a diagnosis of TMA.

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Case report

Patient: A 71-year-old man.

Chief complaint: Leg edema.

History of present illness: The patient underwent total colonoscopy, which revealed stage IIIa rectal cancer in February 2014. Miles' resection was performed in March of the same year, as well as postoperative adjuvant chemotherapy. The initial treatment involved capecitabine starting in May, although it was changed to TS-1 in September based on the emergence of liver injury. Pulmonary metastases were subsequently detected, and treatment was started in November 2015 using FOLFOX (levofolinate: 200 mg/m^2, fluorouracil: 400 mg/m^2, and oxaliplatin: 85 mg/m^2) and bevacizumab (5 mg/kg). Proteinuria was observed in August 2016 and leg edema was observed in April 2017. Nephrotic syndrome was suspected based on the magnitude of the proteinuria (urinary protein: 5.4 g/gCr) and hypoproteinemia (total protein: 5.0 g/dL, serum albumin: 3.0 g/dL).

Past medical history: None.

Social history: The patient had smoked 20 cigarettes/day until 12 years ago and occasionally drank alcohol.

Physical findings: The patient had a height of 167.0 cm, a weight of 71.3 kg, a body mass index of 25.6 kg/m^2, a body temperature of 36.4℃, a blood pressure of 147/74 mmHg, and a normal pulse rate (77/min).

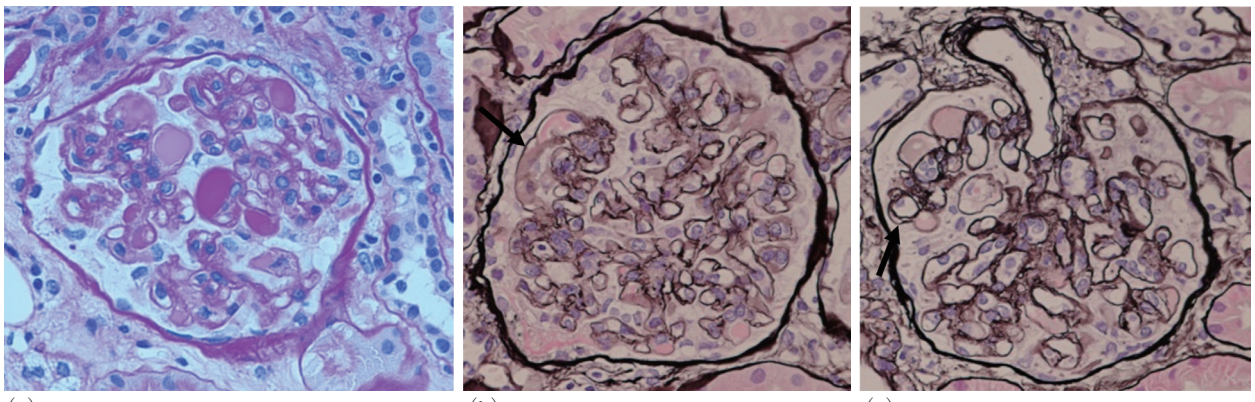
Laboratory data: Urine testing revealed a high degree of proteinuria and the urine sediment contained a fat column and oval fat bodies. Hematuria was not observed. Blood testing revealed hypoproteinemia, although he did not have progressively worsening renal function, lipid metabolism, thrombocytopenia, or anemia.

Image findings: Abdominal ultrasonography revealed a cyst in the lower right pole of the kidney, which was also detected during computed tomography. No other abnormalities were detected, there was no evidence of locally recurrent rectal cancer, and the lung metastases remained contracted.

Renal biopsy: The renal tissue contained a 7:3 ratio of cortex:medulla tissue, with 56 glomeruli including 5 glomeruli that had global sclerosis. Crescent or adhesive findings were not observed. Microscopy revealed exudative lesions in the lumen of the capillary tufts, the subendothelium, and the mesangial region of almost all glomeruli (Fig. 1a).

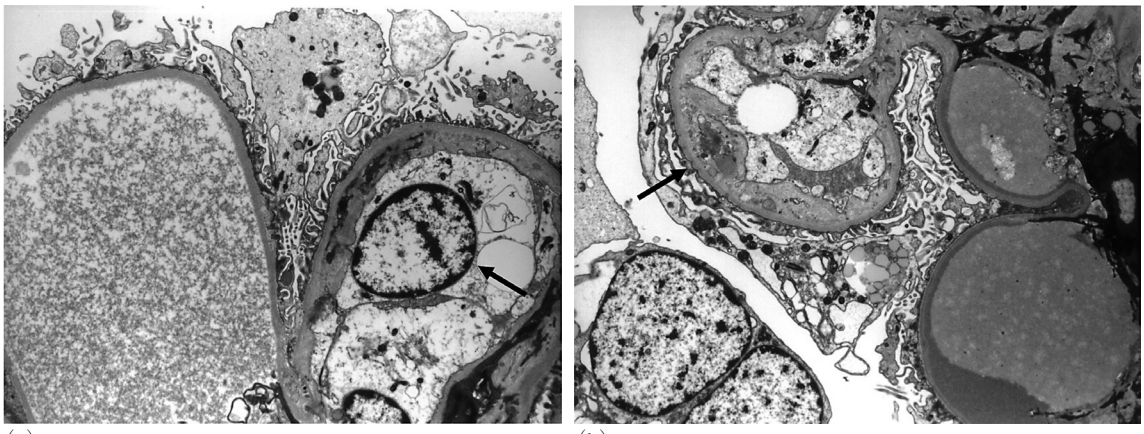
Table. Labolatory findings

Urinalysis		**Blood chemistry**		**Serology**	
Glucose	-	TP	5.0 g/dL	IgG	346 mg/dL
Protein	4+	Alb	3.0 g/dL	IgA	92 mg/dL
Occult blood	2+	T-bil	0.8 mg/dL	IgM	40 mg/dL
RBC	1-4/HPF	AST	27 IU/L	CH50	44.2 U/mL
WBC	1-4/HPF	ALT	22 IU/L	C3	110 mg/dL
Fatty casts	1+	LDH	259 IU/L	C4	25 mg/dL
Oval fat body	1+	T-Cho	206 mg/dL	ANA	(-)
Protein/Cr	5.4 g/gCr	HDL-C	42 mg/dL		
		LDL-C	129 mg/dL	**Coagulation**	
Protein excretion	3.5 g/day	TG	109 mg/dL	PT	0.95
		BUN	26.0 mg/dL	APTT	29.1 sec
Blood cell count		Cr	0.76 mg/dL		
WBC	6,300 /μL	Na	146 mEq/L		
RBC	377×10^4 /μL	K	4.0 mEq/L		
Hb	11.6 /dL	Cl	112mEq/L		
Ht	35 %	Glu	98 mg/dL		
Plt	15.5×10^4 /μL	HbA1c	5.3 %		
		CRP	0.4 mg/dL		



(a) (b) (c)

Fig. 1. Renal biopsy, Microscopy findings
(a) Exudative lesions were observed in the lumen of the capillary tufts, the subendothelium, and the mesangial region (PAS staining). (b) Mesangiolysis was observed (arrow) (PAM staining). (c) Thickening and duplication of the capillary tufts were observed (arrow) (PAM staining).



(a) (b)

Fig. 2. Renal biopsy, Electron microscopy findings
(a) Endothelial cells were swelling (arrow). (b) Edematous enlargement of the subendothelial cavity (arrow), and exudative lesions with electron-dense deposits were observed in the lumen of the capillary tufts.

Mesangiolysis was observed in some glomeruli (Fig. 1b), and thickening and duplication of the capillary tufts were also observed (Fig. 1c). Immunostaining revealed IgM in the mesangial region. Electron microscopy revealed endothelial cell swelling (Fig. 2a), edematous enlargement of the subendothelial cavity, and exudative lesions with electron-dense deposits in the lumen of the capillary tufts (Fig. 2b).

Clinical course: In renal biopsy tissues, typical findings of TMA due to glomerular vascular endothelial injury were observed. There were no other new drugs, and infections or autoimmune diseases that can injure the glomerular vascular endothelial cells were not observed, we diagnosed TMA caused by the bevacizumab treatment. After consulting with the surgeon, we discontinued treatment using FOLFOX and bevacizumab and started treatment using UFT/UZEL (tegafur, fluorouracil, and levofolinate). The proteinuria rapidly resolved after discontinuation of the bevacizumab treatment and disappeared after 6 months. The serum protein levels also gradually increased. At 13 months after the change in chemotherapy, the lung metastases remained contracted and the patient had not experienced recurrence of nephrotic syndrome.

DISCUSSION

We encountered a case of nephrotic syndrome during FOLFOX and bevacizumab treatment for lung metastases after rectal cancer surgery, and renal biopsy confirmed a diagnosis of TMA. The proteinuria rapidly resolved after discontinuation of the bevacizumab, and the original disease does not appear to have progressed during the subsequent treatment.

Bevacizumab is a humanized monoclonal antibody that targets VEGF and is used to treat progressive colorectal cancer, non-small cell cancer, breast cancer, ovarian cancer, cervical cancer, and other cancers. The side effects of bevacizumab are bleeding and retarded wound healing, gastrointestinal perforation, bone marrow suppression, infectious diseases, injury to glomerular vascular endothelial cells, hypertension, proteinuria, renal disorders, TMA, and glomerulonephritis [1]. There are also case reports describing acute renal injury because of interstitial nephritis that was caused by bevacizumab [2, 3]. Furthermore, bevacizumab causes proteinuria in 13.3-61.7% of cases and hypertension in 16.8-36.0% of cases [4-6], with greater risks at higher doses, although grade 3-4 proteinuria is relatively rare 1.0-2.2% of cases [5, 6]. The risk of bevacizumab-related proteinuria is also high among patients with renal cell carcinoma [7]. The renal injury typically manifests after 6.87±7.18 months of anti-VEGF therapy [8], while glomerular injury typically manifests after 2-15 months of bevacizumab treatment [9].

Among renal disorders, TMA is relatively common after treatment using VEGF inhibitors, especially bevacizumab [8, 10], with TMA typically manifesting after 5.75±3.6 months (2-12 months)

of anti-VEGF treatment [10]. There are also case reports of deaths caused by TMA and end-stage kidney disease, which were attributed to bevacizumab [11, 12]. In this context, anti-VEGF-related TMA is confined to the kidney, which may be related to the possibility that podocyte production of VEGF is necessary for maintenance of the adjacent glomerular endothelium [13]. Interestingly, bevacizumab-related TMA may cause IgA deposition in the subendothelium of glomerular capillaries [9, 13-16], although we did not detect any IgA deposition or elevated serum IgA levels.

Proteinuria often improves within 2-9.5 months after discontinuation of bevacizumab [17]. In rare cases, proteinuria and renal disorders may be prolonged or progress, although this is thought to be associated with preexisting nephropathy, severe hypertension, and proteinuria [18]. There are also reports that bevacizumab treatment could be continued without affecting kidney function by providing antihypertensive therapy with renin-angiotensin system inhibitors, even after the appearance of proteinuria [1, 8]. Nevertheless, one patient died because of malignant tumor progression after discontinuation of bevacizumab treatment [13]. Thus, it is important to balance the decision to stop, withdraw, or continue bevacizumab treatment based on the tumor's status, as more severe TMA can be caused by restarting bevacizumab treatment after its withdrawal [8].

Our patient did not have renal cell carcinoma with a high risk of proteinuria, although a nephrotic level of proteinuria was observed after 9 months of treatment using bevacizumab (5 mg/kg). In addition, almost all of the glomeruli had evidence of TMA, although our findings indicated that the rectal cancer and lung metastases were stable. Thus, as continued bevacizumab treatment worsens renal injury, we discontinued that treatment, which led to rapid resolution of the proteinuria and disappearance after 6 months.

CONCLUSION

During bevacizumab treatment, careful attention should be paid to proteinuria, renal disorders, and/or hypertension. If these complications are observed, the decision to stop, withdraw, or continue bevacizumab treatment should be based on the state of the malignant tumor.

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Research involving human participants and/or animals: In this article, studies of human and animal participants are not included.

Informed consent: Informed consent for the treatment and the renal biopsy was obtained from the patient.

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