Nephrotic syndrome as adverse event induced by ramucirumab: A case report

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Abstract

We report a case of nephrotic syndrome as an adverse event induced by ramucirumab and consider the previous literature. A 76-year-old man diagnosed with sigmoid colon cancer underwent laparoscopic sigmoidectomy. Because of the recurrence of sigmoid colon cancer, FOLFIRI (fluorouracil, leucovorin, and irinotecan) plus ramucirumab was selected as the second-line chemotherapy after the first-line chemotherapy of five cycles of mFOLFOX6 (modified fluorouracil, leucovorin, and oxaliplatin) plus bevacizumab. Thirty-five days after the initial administration of ramucirumab, weight gain and severe edema of both legs were noted, and he was diagnosed with nephrotic syndrome. Since the nephrotic syndrome developed within a short period after the administration, a ramucirumab-induced adverse event was strongly suspected. After starting trichlormethiazide, urinary output markedly increased and the body weight promptly decreased. He was discharged on the 17th day after admission with significant weight loss and recovery from nephrotic syndrome. Nephrotic syndrome may develop immediately after ramucirumab administration even after switching from multiple doses of bevacizumab. Physicians must be aware of clinical signs such as edema and weight gain as well as laboratory data in daily clinical practice.

Introduction

In recent years, vascular endothelial growth factor (VEGF) inhibitors have occupied an important position in the treatment of colorectal cancers. It is well-known that bevacizumab, a human monoclonal antibody that binds to VEGF, can cause renal adverse events such as proteinuria and nephrotic syndrome [1-7]. However, there have been reports of only a few cases of renal adverse events, especially nephrotic syndrome, induced by ramucirumab, a human monoclonal antibody that binds to VEGF receptor-2, and the clinical course is unclear. Here, we report a case of nephrotic syndrome induced by ramucirumab and consider the previous literature.

Case Report

A 76-year-old man was diagnosed with sigmoid colon cancer in our hospital, and laparoscopic sigmoidectomy with D3 lymphadenectomy was performed. Since the final pathological diagnosis was T4b (Si: abdominal wall) N1b (2/9) M0 stage Ⅲc (JSCCR 9th edition)/stage ⅢC (UICC 8th edition), he received capecitabine monotherapy as postoperative adjuvant chemotherapy. After 2 cycles of the chemotherapy, a re-increase of the CEA level was noted. Enhanced computed tomography (CT) and positron emission tomography (PET)-CT revealed multiple lung and bone metastases. Since RAS gene mutation was detected, mFOLFOX6 (modified fluorouracil, leucovorin, and oxaliplatin) plus bevacizumab was selected as the first-line chemotherapy after radiation therapy for bone metastases. Grade 2 (according to CTC-AE) hypertension was observed as an adverse event of bevacizumab, and amlodipine besilate (5 mg/day) was administered. He had mild renal dysfunction (creatinine level of 1.08 mg/dl, estimated glomerular filtration rate (eGFR) of 51.5 ml/min.) before the start of chemotherapy, but progression of renal dysfunction was not noted throughout the entire course of first-line chemotherapy. After 5 cycles of mFOLFOX6 plus bevacizumab had been administered, we changed to FOLFIRI (fluorouracil, leucovorin, and irinotecan) plus ramucirumab as the second-line chemotherapy because of a re-increase in the CEA level and the growth of lung metastases with enhanced CT (PD according to RECIST). Seven days after starting the second-line chemotherapy, mild facial edema was noted; however, the body weight showed no change from the baseline. On day 14, severe edema of both legs was noted and there was a further weight gain of 4.3 kg compared with day 7 (Fig. 1). Spironolactone (25 mg/day) was started, but it was not effective for edema. On day 21, grade 3 neutropenia was seen and granulocyte-colony stimulating factor (G-CSF) was administered. On day 35, neutropenia improved, but grade 2 thrombocytopenia was seen. There had been a further weight gain of 12.4 kg compared with the baseline weight and edema of both legs impaired walking.

No cardiovascular symptoms such as dyspnea on effort was seen and no Cardio-Thoracic Ratio (CTR) expansion was seen on x-rays. He was diagnosed with nephrotic syndrome with a serum albumin level of 3.0 g/dL and urinary protein-to-creatinine ratio (UPCR) of 9.01 g/gCr. Since the nephrotic syndrome developed within a short period after the administration of the second-line chemotherapy and he had been no history like diabetes mellitus and collagen disease causing secondary nephrotic syndrome, a drug-induced adverse event was strongly suspected, especially by ramucirumab. Grade 3 hypertension was observed, and so telmisartan (40 mg/day) was started addition to the previously administered amlodipine besilate. On day 41, he was referred to the nephrology department and hospitalized (Laboratory data on admission is shown at Table1). On the admission day, azosemide (60 mg/day) was started. On day 45 (5^{th} day after admission), spironolactone was discontinued, trichlormethiazide (2 mg/day) was started, and telmisartan was increased (80 mg/day). After starting trichlormethiazide, urinary output markedly increased and the body weight promptly decreased. On day 50 (10^{th} day after admission), his body weight was shown to have reduced by 9.2 kg since hospitalization (only 2.5 kg above the baseline weight) and UPCR markedly recovered (2.04 g/gCr). Gait disorder and severe edema also improved with weight loss. He was discharged on day 57 (17^{th} day after admission) with a body weight 3.2 kg lower than the baseline weight (reduced by 15.9 kg over the course of hospitalization), mild hypoalbuminemia (2.7 g/dL), and normalized UPCR (0.71 g/gCr). Hypertension also improved to the extent that only telmisartan (40 mg/day) was administered. He restarted chemotherapy with FOLFIRI without ramucirumab as an outpatient 3 weeks after the discharge. Despite repeated doses of FOLFIRI, nephrotic syndrome has not been observed even though no maintenance therapy for nephrotic syndrome was done.

Discussion

Molecular targeting drugs play an important role in chemotherapy for advanced and recurrent colorectal cancers, and a search for the presence of RAS gene mutation must be conducted before the selection of such drugs. When RAS gene mutation is detected, epithelial growth factor receptor (EGFR) inhibitors are not recommended, and so the problem arises regarding whether bevacizumab should be continued in second-line chemotherapy after the use of the same drug in first-line chemotherapy. Ramucirumab is a relatively new VEGF inhibitor approved for unresectable advanced and recurrent colorectal cancers in May 2015 in Japan, expanding the options of VEGF inhibitors after second-line chemotherapy in patients with RAS gene mutation. Ramucirumab is often discussed together with bevacizumab in the same series; however, the timing and degree of adverse events may not necessarily match.

Bevacizumab can induce proteinuria as an adverse event, but progression to nephrotic syndrome is relatively rare [5]. Meta-analysis showed that bevacizumab was associated with a 13.3% incidence of all-grade proteinuria and 0.8% incidence of nephrotic syndrome [6]. It has been reported that the incidence of proteinuria and nephrotic syndrome increases in a dose-dependent manner [7], and in the majority of reported cases, these adverse events developed after the repeated administration of bevacizumab [1-4]. Even if proteinuria develops in the early phase of treatment, it is rare for chemotherapy to be discontinued because of it [4].

Meta-analysis also showed that ramucirumab was associated with a 9.4% incidence of all-grade proteinuria and 0.1% incidence of nephrotic syndrome, being lower than those of bevacizumab [8]. Nephrotic syndrome induced by ramucirumab developed in the early phase of treatment in most cases, and in particular, all reported cases of nephrotic syndrome induced by ramucirumab in colorectal cancer chemotherapy were diagnosed after one to two cycles of administration (Table 2) [9-12]. In our case, nephrotic syndrome was diagnosed on day 35 after only one cycle of administration. Even though nephrotic syndrome had already been strongly suspected on day 14 because of severe edema of both legs and a 4.3-kg heavier body weight compared with the baseline, laboratory data on blood and urine failed to reach levels meeting diagnostic criteria. Proteinuria was initially noted on day 21, but it did not

become a warning sign. In recent years, UPCR measurement has been recommended for the early detection of renal dysfunction [13]. However, in our case, clinical symptoms such as edema and weight gain had already been noted on day 14, being before the abnormal laboratory data, which made us anxious that nephrotic syndrome might progress in the future and so discontinue ramucirumab. In our department, body weight measurement is usually conducted on the day of chemotherapy and is simple and useful to determine the risk of renal dysfunction. In addition, bevacizumab had already been administered long term as first-line chemotherapy in most reported cases of ramucirumab-induced nephrotic syndrome [9-12]. This leads to the possibility that the clinical pathways leading to nephrotic syndrome between bevacizumab and ramucirumab differ, and that prior use of bevacizumab is closely associated with nephrotic syndrome after the administration of ramucirumab.

Spontaneous recovery from nephrotic syndrome after the discontinuation of ramucirumab has sometimes been reported [9-11, 14]; however, only a few cases have been reported whereby patients promptly recovered from nephrotic syndrome as a result of active therapeutic intervention [12]. The majority of patients receiving ramucirumab had stage 4 cancer, and so early recovery from adverse events and prompt progression to the next treatment are essential. Trichlormethiazide is a thiazide diuretic that acts on distal tubules. In our case, when trichlormethiazide was added early after the start of azosemide, which is a lupus diuretic, the urine volume increased markedly from the next day and the body weight also started to decrease. Five days after starting trichlormethiazide, severe edema and nephrotic syndrome were improved with an 8.5 kg weight loss. Of course, the action mechanism of trichlormethiazide against nephrotic syndrome is unclear because the exact mechanism of nephrotic syndrome as an adverse event is unknown [9]. However, there is another case in which trichlormethiazide was markedly effective [12], and it may be worthwhile to administer if faced with the current situation that there is no other recommended treatment for nephrotic syndrome as an adverse event caused by ramucirumab.

There are some patients for whom renal biopsy was performed to determine the etiology, and thrombotic microangiopathy (TMA) was considered to be the main pathological finding [9, 14]. In our patient, renal biopsy would have been conducted had the response to drug therapy been poor, but biopsy was not done because early improvement was noted. The accumulation of knowledge from a pathological perspective is also awaited.

In conclusion, nephrotic syndrome may develop immediately after ramucirumab administration even after switching from multiple doses of bevacizumab. Physicians should be aware of clinical signs such as edema and weight gain as well as laboratory data in daily clinical practice.

Declarations

Compliance with Ethical Standards

Conflict of interest: The authors declare that they have no conflict of interest.

Ethics approval: All procedures performed in studied involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Consent to participate: Informed consent was obtained from all individual participants included in the study.

Consent to publish: The participant has consented to the submission of the case report to the journal.

Data availability: All data generated or analyzed during this study are included in this published article.

References

1. Murase H, Iseki H, Ogawa A, et al (2019) A case of nephrotic syndrome due to SOX plus Bmab therapy for liver metastasis of rectal cancer (in Japanese). Gan To Kagaku Ryoho 46:288-290
2. Matsui K, Sato H, Yokoyama Y, et al (2018) Nephrotic syndrome caused by thrombotic microangiopathy during bevacizumab treatment for lung metastases after rectal cancer surgery: a case report. Shimane J. Med. Sci. 35:21-25
3. Kitamra E, Nojima M, Endo S, et al (2015) Complications of hypertension and nephrotic syndrome due to bevacizumab maintenance therapy for recurrent ovarian cancer (in Japanese). Chiba Journal of Obstetrics and Gynecology 9:38-42
4. Ono A, Chiyoda T, Nomura H, et al (2018) A retrospective analysis of the cases who had bevacizumab-related severe adverse events in gynecologic cancer (in Japanese). Tokyo Journal of Obstetrics and Gynecology 67:396-400
5. Hatake K, Doi T, Uetaka H, et al (2016) Bevacizumab safety in Japanese patients with colorectal cancer. Jpn J Clin Oncol 46:234-240
6. Wu S, Kim C, Baer L, et al (2010) Bevacizumab increases risk for severe proteinuria in cancer patients. J Am Soc Nephrol 21:1381-1389
7. Zhu X, Wu S, Dahut W, et al (2007) Risks of proteinuria and hypertension with bevacizumab, an antibody against vascular endothelial growth factor: systemic review and meta-analysis. Am J Kidney Dis 49:186-193
8. Arnold D, Fuchs CS, Tabernero J, et al (2017) 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
9. Fujii T, Kawasoe K, Tonooka A, et al (2019) Nephrotic syndrome associated with ramucirumab therapy: a single-center case series and literature review. Medicine (Baltimore) doi: 10.1097/MD.0000000000016236
10. Yamada R, Okawa T, Matsuo K, et al (2019) Renal-limited thrombotic microangiopathy after switching from bevacizumab to ramucirumab: a case report. BMC Nephrol doi: 10.1186/s12882-018-1194-9.
11. Sakabe R, Shirakawa K, Yosihmura K, et al (2018) Nephrotic syndrome induced by ramucirumab for metastatic rectal cancer (in Japanese). Gan To Kagaku Ryoho 45:1205-1207
12. Shingai T, Fukuzaki T, Okimura S, et al (2019) A case of nephrotic syndrome induced by FOLFIRI plus ramucirumab for metastatic descending colon cancer (in Japanese). Gan To Kagaku Ryoho 46:2155-2157
13. Saito Y, Kitagawa K, Sato J, et al: (2019) Urine protein/creatinine ratio measurement is useful to continue anti-angiogenic agent treatment (in Japanese). Gan To Kagaku Ryoho 46:1741-1745
14. Ozawa M, Hasegawa R, Inoue T, et al (2019) Clinicopathological findings of drug-induced TMA in 2 cases treated with anti-VEGF antibody (in Japanese). Akita Nephrology Dialysis Transplantation 22:97-103

Tables

Table 1:

Laboratory data on admission

Blood test				Urine test	
White blood cell	9100/μL	C-reactive protein	0.21 mg/dL	pH	6.0
Neutrophil	52.4%	IgG	1140 mg/dL	Protein	3+
Lymphocyte	23.0%	IgA	305 mg/dL	Occult blood	2+
Hemoglobin	11.6 g/dL	IgM	89 mg/dL	Gravity	1.025
Hematocrit	35.8%	Complement 3	105 mg/dL	Red blood cell	1-4 /HPF
Platelet	100.000/μL	Complement 4	32 mg/dL	White blood cell	1-4 /HPF
Total protein	5.8 g/dL	CH50	65 IU/mL	Protein	2107 mg/dL
Albumin	3.0 g/dL	HBs Ag	(-)	Creatinine	251 mg/dL
Blood urea nitrogen	31 mg/dL	HCV	(-)	UPCR	8.39 g/gCr
Creatinine	1.55 mg/dL				

HPF: high power field

Table 2:

Nephrotic syndrome after administration of ramucirumab for colorectal cancer (review of literature)

	Age/sex	Cycles of R-mab administration before nephrotic syndrome	Co-administrated anti-cancer drugs	Time from initial administration to diagnosis (days)	Time to recovery from start of treatment	B-mab administration in previous chemotherapy	Cycles of B-mab administration
Our case	76/M	1	FOLFIRI	35	15 days	Yes	5
Yamada et al[9]	75/M	2	FOLFIRI	44	25 days	Yes	23
Sakabe et al[12]	48/F	1	FOLFIRI	28	20 days	Yes	22
Shingai et al[10]	50/F	1	FOLFIRI	14	58 days	Yes	52
Fujii et al[11] (3 cases)	73/F	1	FOLFIRI	22	1 month	Yes	N/A
	50/F	2	FOLFIRI	42	2 months	Yes	N/A
	73/M	1	FOLFIRI	21	7 months	Yes	N/A

R-mab: ramucirumab B-mab: bevacizumab F: female M: male N/A: not applicable

Figures

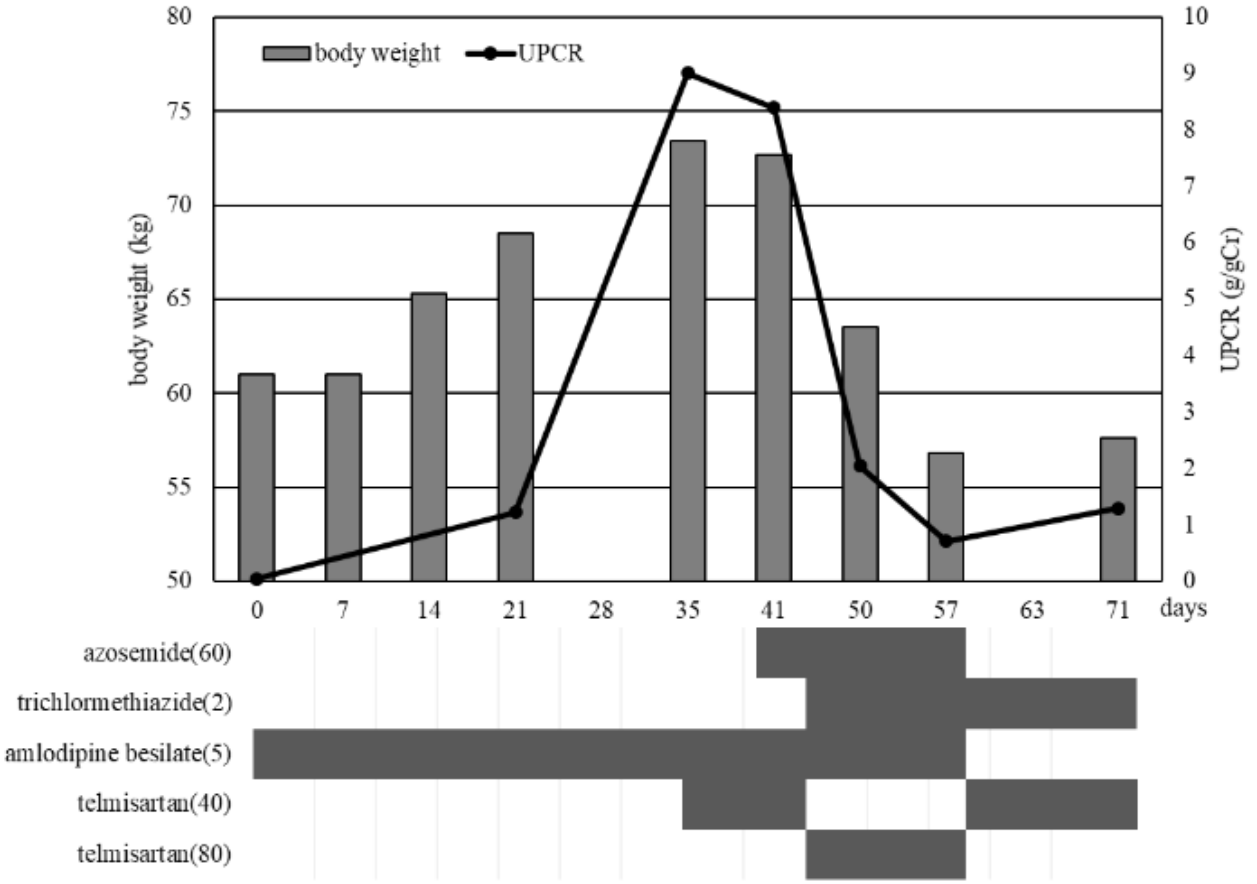

Figure 1

Clinical coarse of our case. Ramucirumab was administered on day 0. The body weight had already increased on day 14; however, an increase in the UPCR level was finally noted on day 35. Both of them were promptly recovered after the administration of trichlormethiazide. The unit of the numerical value in brackets after the drug name is mg.