Exacerbation of diabetic nephropathy mimicking thrombotic microangiopathy during sunitinib treatment for metastatic renal cell carcinoma

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Abstract Sunitinib is an orally administered inhibitor of tyrosine kinase targeting vascular endothelial growth factor receptors (VEGFRs) and has become essential for treating metastatic renal cell carcinoma. Recently, several cases have been reported which showed proteinuria and kidney dysfunction during anti-VEGF therapy. Although previous reports indicated that this side effect is reversible, it is not well understood. We report here the case of a 52-year-old man who presented with hypertension, nephrotic syndrome, and renal dysfunction during sunitinib treatment. Sunitinib was discontinued, but renal function recovery was limited. A renal biopsy was performed because sunitinib was again

required and pathological examination was needed. The renal biopsy showed exacerbation of diabetic nephropathy. After medical treatment, the patient's blood pressure was controlled and serum creatinine level decreased. We considered that the patient could tolerate sunitinib at a minimum effective dose, 25 mg/day. Previous reports suggest that all anti-VEGF drugs may share a common risk for developing renal adverse events, such as thrombotic microangiopathy. Sunitinib should not be restarted if thrombotic microangiopathy is observed. The present case suggests that renal biopsy would be recommended when treatment options and prognosis might be influenced by the actual histological diagnosis.

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Case presentation

Dr. Oya (urologist, conference chairperson)

Good evening, ladies and gentlemen, welcome to the conference. Today we would like to review a metastatic renal cell carcinoma (mRCC) case who was treated with sunitinib. In this case, renal dysfunction and proteinuria appeared in particular after several cycles of treatment and persisted as a problem until discontinuation of sunitinib. First, we will have a presentation of the patient, and then discuss the clinical assessment, treatment, and specific pathology.

Dr. Mizuno (urologist)

The patient is a 49-year-old Japanese man with a history of type 2 diabetes mellitus for 4 years, who underwent left

Fig. 1 Histology of the resected kidney specimen showing clear cells of RCC (H&E, $\times 400$)

radical nephrectomy for RCC in August 2007. Pathologic examination demonstrated a Fuhrman grade 3 clear cell renal carcinoma with sarcomatoid component (pT3b). In May 2008, computed tomography (CT) showed enlargement of the para-aortic nodes. His condition was eventually diagnosed as stage IV mRCC.

Dr. Mikami (pathologist)

The nephrectomy specimen was fixed in buffered formalin and was pathologically evaluated. A mass measuring 7 cm in greatest dimension was located in the lower pole of the kidney. The tumor showed infiltrating borders and invaded the perinephric tissues and renal vein. The ureter and renal artery were free of tumor at their surgical margins. Histologically, the mass was composed of clear cells arranged in an alveolar pattern with a prominent network of small thin-walled vessels and spindle-shaped cells with slightly eosinophilic cytoplasm (Fig. 1). Regional lymph nodes were unaffected by neoplastic cells. Final diagnosis was Fuhrman grade 3 clear cell RCC clear cell type with sarcomatoid changes. Tumor stage was pT3bN0M0 according to the American Joint Committee on Cancer.

Dr. Oya

The pathological examination results indicated locally advanced cancer and the patient had a higher risk of recurrence. Was any adjuvant therapy given?

Dr. Mizuno

The patient received adjuvant interferon-alpha treatment for 6 months. At that time adjuvant interferon was given to patients with locally advanced RCC at our institution. We

no longer induce adjuvant interferon therapy at present, because no adjuvant trial was capable of showing improved survival of non-metastatic RCC patients while exposing patients to unnecessary toxicity [1].

Dr. Oya

The patient developed metastatic cancer and we recommended additional treatment. The most commonly used treatments for mRCC are various forms of targeted therapies. Oral multitargeted tyrosine kinase inhibitors (TKIs) have dramatically improved the clinical outcome of patients with advanced RCC, and these agents have become the standard first-line treatment [2]. Other traditional but less-often used treatments include immunotherapy. Several investigational therapies, including vaccine therapy, are also available.

Dr. Mizuno

The patient was categorized into the favorable group by applying the Memorial Sloan-Kettering Cancer Center (MSKCC) risk stratification. This risk criteria, first published in 1999 and revised in 2002, classifies patients with metastatic RCC as favorable, intermediate, and poor risk according to five pretreatment features [3, 4]. For the treatment of metastatic RCC, sorafenib treatment was initiated, but it was discontinued because of severe adverse events (AEs), including grade 3 liver toxicities. In August 2008, sunitinib was started at a dose of 50 mg/day for a 4-week-on, 2-week-off schedule. At baseline, his weight was 65 kg, serum creatinine was 1.40 mg/dL, and urinalyses were normal.

Dr. Oya

Both sporadic and inherited clear cell RCC are strongly associated with mutations in the von Hippel-Lindau (VHL) tumor suppressor gene [5]. The VHL gene is located on chromosome 3 and has a key role in the hypoxia inducible pathway, inducing hypoxia inducible factor (HIF) ubiquitylation in the presence of oxygen. HIF is a transcriptional complex that mediates the response to a hypoxic environment, resulting in the transcription of genes such as vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) [6]. Vascular endothelial growth factor receptors (VEGFRs) and platelet-derived growth factor receptors (PDGFRs) play an essential role in tumor angiogenesis and growth [7]. In RCC, the VHL/HIF/VEGF pathway is dysregulated and thus represents as a reasonable therapeutic target [8]. Sunitinib and sorafenib, which were administered to this patient, are multitargeted TKIs. Both are small-molecule anti-angiogenic drugs. TKIs have a unique mechanism of action and exhibit a distinct pattern of novel toxicities. Aya,

could you describe patient compliance with the drug and AEs during the treatment?

Aya Inoue (pharmacist)

Sunitinib (sunitinib malate; SU11248; SUTENT[®]; Pfizer) is an orally administered inhibitor of multiple tyrosine kinases, including VEGFRs, PDGFRs, as well as FLT3 and KIT. It affects cancer by inhibiting cell growth, proliferation, cell survival, and angiogenesis [9]. Sunitinib has been approved for the treatment of unresectable or metastatic RCC and is administered at a dose of 50 mg/day for a 4-week-on, 2-week-off schedule. Before starting sunitinib treatment, the patient was informed of not only the drug's effects, but also the AEs. In this patient, compliance with sunitinib was good.

Kazumi Kiyono (nurse)

Most common AEs frequently seen in patients assigned to sunitinib were hypertension, proteinuria, hand-foot syndrome, rash, thrombocytopenia, hypothyroidism, diarrhea, and left ventricular dysfunction [10, 11]. The patient developed grade 2 hypertension and hypothyroidism, but they were successfully treated with amlodipine besylate and levothyroxine sodium.

Dr. Oya

At this point sunitinib treatment was well tolerated by the patient and AEs were successfully managed by the outpatient clinic staff. Dr. Mizuno, please go ahead.

Dr. Mizuno

The patient had stable disease (SD) after nine cycles of sunitinib treatment; however, his serum creatinine increased up to 2.2 mg/dL. Sunitinib was discontinued and his serum creatinine decreased to 1.9 mg/dL. However, as a result of the cessation of sunitinib, his disease became progressive. He was restarted on sunitinib at a minimum effective dose, namely 25 mg/day. In November 2009, he noticed weight gain in the last week of a 4-week-on schedule. He presented with edema, proteinuria, and 3+ occult blood on urine dipstick testing. His blood pressure (BP) increased to 170/100 mmHg with a serum creatinine of 3.30 mg/dL. In November 2010, his serum creatinine increased again, and he was referred to the nephrology department.

Dr. Oya

Dr. Jinzaki, would you explain the radiological evaluation of the efficacy of sunitinib in this patient?

Dr. Jinzaki (radiologist)

Radiological evaluations were conducted at baseline and after every two cycles. The efficacy of sunitinib was evaluated with response evaluation criteria in solid tumors (RECIST) guidelines [12]. The first radiological follow-up showed SD. However, the biological response to TKIs is not completely or correctly assessed by size-based radiological criteria such as RECIST, which were designed to evaluate tumor burden reductions following cytotoxic chemotherapy. In many patients, although a metastatic lesion did not shrink after TKI treatment, a decrease in tumor density (measured in Hounsfield units) on contrast-enhanced CT was observed. As a matter of fact, new morphological criteria for the evaluation of the efficacy of targeted therapies have been developed. For example, the Choi criteria, which define treatment response as a 10 % decrease in size or a 15 % decrease in tumor density on contrast-enhanced CT, have demonstrated a role in the early prediction of RCC patients who will benefit from sunitinib treatment [13].

Dr. Oya

The patient was closely monitored during sunitinib treatment and although sunitinib showed clinical benefit (Fig. 2), we had to discontinue the treatment because of progression of kidney dysfunction. The use of drugs targeting the VEGF pathway has been associated with renal toxicity in some patients. We would like to evaluate this kidney dysfunction from the nephrologist's point of view. Dr. Wakino, what would be a putative cause of this kidney dysfunction?

Dr. Wakino (nephrologist)

At presentation to our department, his medication included 25 mg/day of sunitinib, 2.5 mg/day of amlodipine besylate, and 100 µg/day of levothyroxine sodium. He had gained 6 kg over the last 2 weeks. His pulse was 68/min, and BP was 176/100 mmHg. On physical examination, he showed peripheral pitting edema. Examination of the chest and abdomen was normal. Laboratory findings included leukocyte count $4.5 \times 10^3/\text{IL}$ (neutrophils 65.5 %, lymphocytes 22.0 %, eosinophils 5.6 %, basophils 0.2 %, monocytes 6.7 %), hemoglobin 7.6 g/dL, platelet count $286 \times 10^3/\text{IL}$, sodium 142 mEq/L, potassium 4.1 mEq/L, blood urea nitrogen 32 mg/dL, serum creatinine 3.62 mg/dL, eGFR 13.1 mL/min/1.73 m², total cholesterol 389 mg/dL, total protein 5.6 g/dL, serum albumin 3.0 g/dL, fasting glucose 154 mg/dL, and HbA1c 5.8 %. Urinalysis was 1+ for occult blood, 4+ for glucose, and 4+ for proteinuria by dipstick. The 24-h urine protein excretion was 14.2 g. Urine sediment and chemistry showed red blood cells 3–5/

Fig. 2 Efficacy of sunitinib treatment assessed by CT scan. CT images obtained before (a) and after (b) 4 cycles of sunitinib treatment. The efficacy of sunitinib for metastatic lymph nodes (arrows) was SD, which was evaluated with RECIST criteria

Fig. 3 Light microscopy of structural changes in normal kidney of the nephrectomy specimen. **a** Nodular diabetic glomerulosclerosis (arrow). **b** Normal glomerulus (PAS stain, $\times 400$)

high power field (HPF), white blood cells <2 /HPF, negative for granular casts, fatty casts 10–19/WF, poikilocytes positive, $\beta 2$ -microglobulin 78,708 $\mu\text{g/day}$, *N*-acetyl- β -D-glucosaminidase/creatinine 15.3. The proteinuria selectivity index was 0.42. Renal ultrasound showed normal

kidney. Nephrectomy specimen was reevaluated. Most of the glomeruli were normal (Fig. 3b); however, in some glomeruli, periodic acid–Schiff (PAS) positive nodular deposits appeared in the mesangial space, which suggested nodular diabetic glomerulosclerosis (Fig. 3a). Since

diabetic nephropathy was suspected in the nephrectomy specimen, we consider the putative cause of this nephrotic syndrome to be diabetic nephropathy or sunitinib-induced kidney dysfunction. Sunitinib was discontinued, and the patient was hospitalized to control BP, blood glucose, and anemia. After 2 weeks of treatment, his serum creatinine and 24-h urine protein excretion decreased. A renal biopsy was performed because sunitinib was required to restart.

Dr. Karasawa (nephrologist)

Recent studies have shown that antiangiogenic treatments blocking the VEGF pathway are associated with development of hypertension, proteinuria, and thrombotic microangiopathy (TMA) [14, 15]. Proteinuria after inhibition of the VEGF signaling axis might reflect severe glomerular damage. The filtration barrier in the glomeruli of the kidney cortex has three layers: the fenestrated endothelium, the glomerular basement membrane, and the podocytes with the slit diaphragm. Recent studies demonstrated that VEGF is constitutively expressed by podocytes, and inhibition of the VEGF pathway resulted in the loss of endothelial fenestrations in glomerular capillaries, proliferation of glomerular endothelial cells, loss of podocytes, and proteinuria [15]. In some cases treated with bevacizumab and sunitinib, renal biopsies revealed glomerular TMA, predominantly endotheliosis and membrano-proliferative changes [16, 17].

Dr. Oya

Renal TMA is a severe complication that should prompt discussing the cessation of sunitinib in the vast majority of cases. In this patient, was TMA diagnosed pathologically?

Dr. Hashiguchi (pathologist)

The renal biopsy contained 29 glomeruli, and four of them were globally sclerotic (Fig. 4). In most glomeruli widespread mesangial expansion was observed (Fig. 4a), which suggested diffuse and nodular diabetic glomerulosclerosis. In some of these glomeruli, there were foam cells occupying the lumen of the glomerular capillaries and occasionally hyaline deposits (Fig. 4b). Electron microscopy showed thickening of basement membranes and mesangial sclerosis (Fig. 5). TMA was not confirmed.

Dr. Wakino

The kidney biopsy suggested diffuse and nodular diabetic glomerulosclerosis; however, TMA was not confirmed. Therefore, we considered that the nephrotic syndrome is related to progression of diabetic nephropathy rather than sunitinib-induced TMA. Acarbose and candesartan were started to control the blood glucose level and to slow the progression of diabetic nephropathy. After the initiation of these treatments, the patient's BP was controlled at

Fig. 4 Renal biopsy findings. **a** Diffuse and nodular glomerulosclerosis which was compatible with diabetic glomerulosclerosis. **b** In some glomeruli, areas of mesangiolysis with foam cells (arrow) were present (PAS stain, $\times 400$)

Fig. 5 Electron microscopy of the renal biopsy. Electron dense deposits (*arrow*) in subendothelial space of glomerular basement membrane were present

140/90 mmHg, and serum creatinine level decreased to 2.16. We considered that the patient could tolerate sunitinib at a minimum effective dose, 25 mg/day.

Dr. Mizuno

Three months after re-administration of sunitinib at 25 mg/day, a repeat CT scan showed SD. During this treatment period, renal function remained stable. Thus, sunitinib therapy was continued under careful observation. However, in September 2011, sunitinib was terminated because of disease progression.

Dr. Oya

The patient could tolerate sunitinib treatment but the tumor eventually became resistant to sunitinib.

Dr. Mizuno

In October 2011, his renal function rapidly deteriorated. In November 2011, the patient developed hypercalcemia with a serum calcium concentration of 16 mg/dL. He was treated with saline therapy and zoledronic acid; however, because of his impaired renal function, the saline infusion was stopped. Finally, hypercalcemia was treated by dialysis. In December 2011, the patient died of RCC progression. An autopsy was refused by his family.

Dr. Oya

Patients with advanced RCC often experience hypercalcemia. This is thought to occur because the tumors secrete a protein that mimics parathyroid hormone, which encourages calcium release from the bone. Severe hypercalcemia is often correlated with cancer that has metastasized, breaking down the bone's matrix and releasing calcium into the blood. What are the roles of dialysis in the treatment of severe malignancy-associated hypercalcemia in patients with end-stage renal disease (ESRD)?

Dr. Hayashi (nephrologist/dialysis doctor)

In patients with ESRD, saline therapy can easily lead to fluid overload and requires careful monitoring. Dialysis is a very effective mode of therapy for malignancy-associated hypercalcemia in patients in whom hydration cannot be safely administered and is also considered a treatment of last resort. The dialysis fluid should be maintained with a low level of calcium to remove excess calcium from the blood circulation. Because large quantities of phosphate are lost during dialysis and phosphate loss aggravates hypercalcemia, serum inorganic phosphate should be measured after each dialysis session, and the patient should be treated with oral or intravenous inorganic phosphate during the next fluid exchange.

Final clinical course

1. Locally advanced RCC, clear cell type, adjuvant treatment with interferon.
2. Metastatic RCC treated with VEGFR-TKIs.
3. Proteinuria and kidney dysfunction during sunitinib treatment.
4. Renal biopsy revealed exacerbation of diabetic nephropathy.
5. By controlling BP, VEGFR-TKI treatment was restarted.

Dr. Oya

Owing to the advent of targeted agents, the prognosis of mRCC patients has improved. However, we have encountered several situations making it challenging to control AEs. TKI has on-target AEs including hypertension and proteinuria. Assessment by biopsies is necessary in deciding the continuation of the drug. Here I would like to emphasize that with the increasing treatment options for mRCC we have today, discussions with specialists including urologists,

nephrologists, pharmacists, nurses, and pathologists are inevitable. Thank you for attending the conference.

What we learned from this case conference

1. During anti-VEGF treatment we need to consider renal AEs, including proteinuria and TMA.
2. When we encounter renal AEs during sunitinib treatment, referral to a nephrologist is recommended for additional evaluation.
3. Sunitinib should not be restarted if TMA is observed. Therefore, immediate renal biopsy should be recommended because treatment options and prognosis might be influenced by the actual histological diagnosis.
4. During sunitinib treatment, strict BP and glycemic control are warranted for preventing the development and progression of diabetic nephropathy.

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