

Case Reports

Sunitinib-induced Nephrotic Syndrome in Association with Drug Response in a Patient with Xp11.2 Translocation Renal Cell Carcinoma

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We report the case of a patient with metastatic renal cell carcinoma with Xp11.2 translocation/transcription factor E3 (*TFE3*) gene fusion who had presented with sunitinib-induced nephrotic syndrome in association with favorable and durable treatment response. The nephrotic syndrome was managed successfully by discontinuing sunitinib and symptomatic treatment. The 27-year-old female patient presenting with right upper abdominal pain was diagnosed with Xp11.2 translocation renal cell carcinoma on the right side with multiple pulmonary and hepatic metastases. She underwent radical nephrectomy and took a daily dose of 37.5 mg sunitinib. Partial response to sunitinib was achieved and maintained for 5 months, but when nephrotic syndrome occurred, drug intake was discontinued. The nephrotic syndrome gradually resolved around 2 months after discontinuation of sunitinib and medical management. Our case highlighted the favorable response of a particular non-clear cell type renal cell carcinoma to sunitinib and the specific toxicity associated with the antiangiogenic effect of sunitinib.

Key words: Xp11.2 translocation renal cell carcinoma – sunitinib – transcription factor E3 – nephrotic syndrome

INTRODUCTION

About 1–3% of renal cell carcinomas (RCCs) with Xp11.2 translocation that result in gene fusions involving the transcription factor E3 (*TFE3*) gene have been classified as clear or papillary-type RCCs (1,2). However, the therapeutic efficacy of interferon, interleukin-2 (IL-2) or combination chemotherapy in Xp11.2 translocation RCC is not similar to that in the clear or papillary type. In 2004, the Xp11.2 subtype was introduced as a genetically distinct entity into the World Health Organization classification of renal tumors (3).

Sunitinib is an orally administered, small-molecule, multi-target receptor tyrosine kinase inhibitor, which inhibits receptors including the vascular endothelial growth factor receptor and platelet-derived growth factor receptor. It has been approved by the Food and Drug Administration for the

treatment of RCC (4), but the major clinical efficacy trials of this drug had not been established in Xp11.2 translocation RCC. The common side effects of sunitinib include fatigue, diarrhea, nausea, anorexia, hypertension, a yellow skin discoloration, hand–foot skin reaction and stomatitis (5).

We report a case of translocation RCC in a young woman with widespread metastatic disease. She had shown a durable response to sunitinib treatment, but the treatment had to be discontinued because of sunitinib-related nephrotic syndrome.

CASE REPORT

A 27-year-old woman initially presented with right upper quadrant abdominal pain for 2 weeks. She had a history of smoking half a pack of cigarette a day for 6 months without

any systemic disease. She underwent abdominal computed tomography (CT) in a local hospital, and the CT revealed a huge calcified mass in the right kidney with tumor invasion of the liver. She was suspected of having metastatic RCC. Then, she visited our urology outpatient department for a tumor biopsy and management. Investigations conducted after admission in April 2009 showed a right renal tumor about 10×6.5 cm in size with calcification in the upper pole of the right kidney and extending into the posterior segment of the right hepatic lobe and inferior vena cava. Several confluent soft tissue nodules (ranging in size from 1.5 to 2.0 cm) were observed in the lingular segment of the left upper lobe of the lungs. Lung metastasis was also highly suspected. Analysis of the sono-guided aspiration and biopsy sample suggested a diagnosis of metastatic RCC. At baseline, she was in Memorial Sloan-Kettering Cancer Center intermediate-risk category mainly because of anemia and less than 1 year between diagnosis and the need for systemic treatment. She underwent open right radical nephrectomy and S6 wedge resection of the liver on 22 May 2009, and wedge resection of the left upper and lower lobes of the lung with lymph node dissection on 7 July 2009. Histological analysis showed a renal carcinoma with immunoreactivity patterns of RCC and CD10, psammoma bodies and ossification, and Fuhrman nuclear grade 3 (Fig. 1). Immunostaining for TFE3 showed diffuse nuclear immunoreactivity, confirming the diagnosis of Xp11.2 translocation RCC (Fig. 2). Pathological analysis of the lung nodules confirmed the diagnosis of metastatic RCC.

TREATMENT REVIEW

The patient was initially treated with five cycles of 1000 mg/m^2 gemcitabine on days 1 and 8, and 1000 mg/m^2 capecitabine twice daily on days 1–14 of each 3-week cycle. Post-treatment CT showed disease progression. She was then

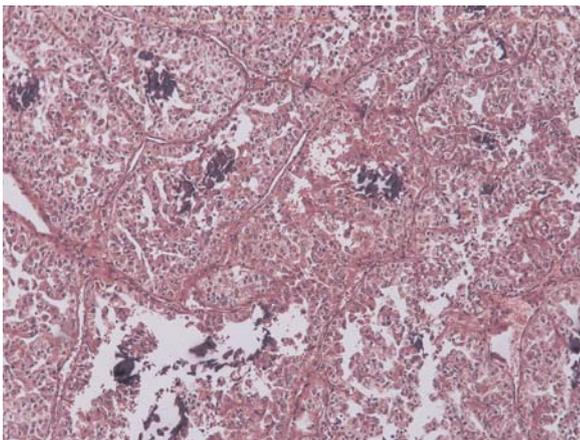


Figure 1. The tumor is composed of polygonal tumor cells with abundant eosinophilic cytoplasm arranged in a nested structure. Focal calcification is observed [hematoxylin and eosin (H&E) stain, original magnification: $\times 100$].

treated with a daily dose of 37.5 mg sunitinib. Three months later, follow-up chest CT revealed residual metastases in the left and right lungs, showing regressive interval change; in comparison with the previous studies. A reduction of more than 50% in the size of measurable lesions was observed to be consistent with a partial response according to the Response Evaluation Criteria in Solid Tumors (Fig. 3).

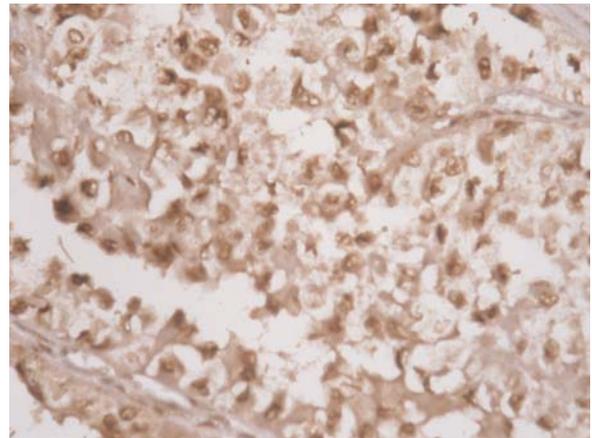


Figure 2. The tumor cells show diffuse nuclear transcription factor E3 (TFE3) staining (TFE3 stain, original magnification: $\times 400$).

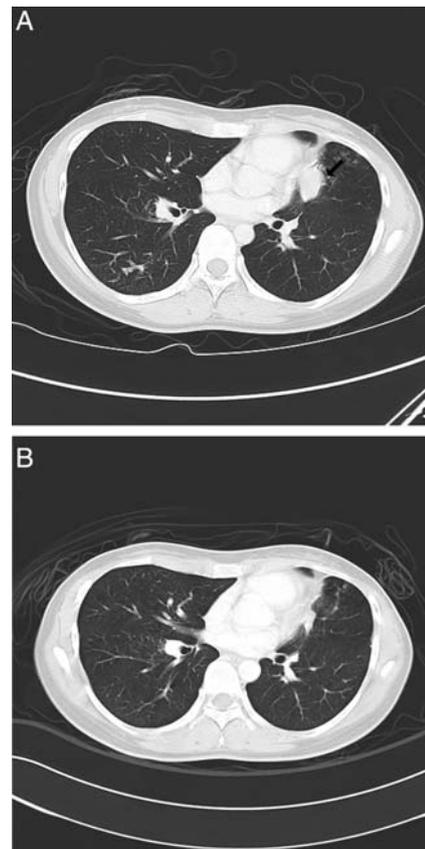


Figure 3. Chest computed tomography (A) before starting treatment with sunitinib and (B) after 12 weeks of treatment with sunitinib.

However, progressive hand–foot skin reaction of grade II was observed after 3 months of therapy. Sunitinib was discontinued for 1 week and then recommenced at a daily dose of 25 mg.

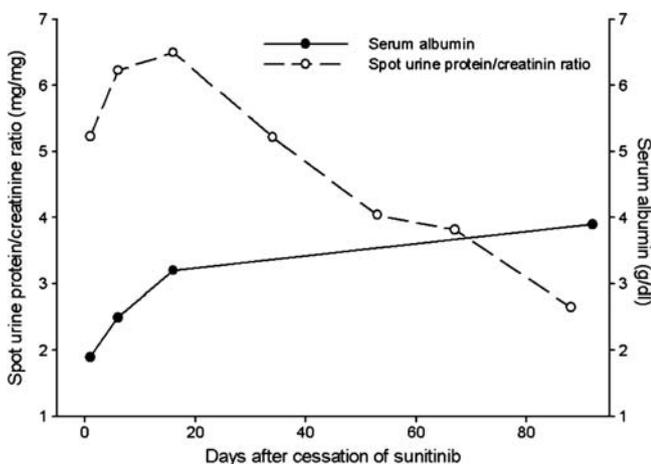
Five months later, the patient complained of progressive edema of both her legs and foamy urine. Her biochemical data were as follows: serum creatinine, 1.8 mg/dl; albumin level, 1.9 g/dl; cholesterol level, 225 mg/dl; C3, 74.2 mg/dl; and C4, 13.8 mg/dl (normal range: C3: 79–152 mg/dl; C4: 16–38 mg/dl). Antinuclear antibodies (ANA), antineutrophil cytoplasmic antibodies (ANCA), and anti-ds-DNA antibody were within the normal range. Immunoglobulin G/A/M of serum was not elevated. Hepatitis B virus, hepatitis C virus and human immunodeficiency virus (HIV) were also all negative. Urinalysis revealed severe proteinuria without hematuria. No non-steroidal anti-inflammatory drugs, antibiotics or herbal supplements were used throughout the course of the sunitinib therapy. Physical examination revealed basal fine crackles in both the lungs and severe edema of the lower legs. Spot urine protein/creatinine was 5.23 (mg/mg). Abdominal sonography showed that the left renal size was normal without hydronephrosis. No evidence of renal vein thrombosis was confirmed by CT with contrast media. Sunitinib was completely discontinued and adequate quantity of diuretics and protein supplements was given. This resulted in a gradual decrease in the serum creatinine levels as well as the daily protein loss. The patient recovered from the nephrotic syndrome through medical management, around 2 months after the discontinuation of sunitinib. The changes in serum albumin and urine protein/creatinine levels are shown in Fig. 4. Now, the patient was prescribed treatment with everolimus (10 mg/day).

DISCUSSION

In children or young adults, RCC associated with Xp11.2 translocation has been reported predominantly. This subtype has been found in one-third of the pediatric RCC patients, and 65% of these patients present with advanced-stage disease (6,7). Clear cell RCCs account for 15% of the renal carcinomas in children, whereas 70% of renal carcinomas in adults and 53% of renal carcinomas in young adults (8,9). However, RCC with Xp11.2 translocation is rare in adults, and the actual figures have not yet been estimated. However, RCCs with the *TFE3* gene fusion were initially reported to have a papillary architecture and were easily confused with the papillary subtype because of prominent eosinophilic cytoplasm, as revealed by hematoxylin and eosin staining, and some morphological overlap such as psammomatous calcification (9). RCC with the *TFE3* gene fusion is usually negative for cytokeratin expression, but it exhibits focal positivity for vimentin and strong reactivity for CD10 and TFE3 (10,11). In our study, nuclear staining for the TFE3 protein was the most sensitive and specific test for detecting RCC with Xp11.2 translocation (Fig. 2). According to studies by Argani et al. (12), nuclear immunoreactivity for the TFE3 protein is a highly sensitive (97.5%) and specific (99.6%) assay for neoplasms with the *TFE3* gene fusion.

Major randomized clinical trials have not been conducted on the response of Xp11.2 translocation RCC to various therapeutic regimens. Meyer et al. (9) reported a variety of therapeutic interventions and observed a rapidly progressive course with a mean survival of 18 months following diagnosis. Recent studies have documented various systemic treatments for this subtype of RCC. These treatments include chemotherapy with gemcitabine plus capecitabine, IL-2 therapy or investigational therapies using PS341 (proteasome inhibitor) and NK92-cell infusion (9). A few studies have reported good or partial response in Xp11.2 translocation RCC patients treated with sunitinib. Numakura et al. reported a 43-year-old woman with Xp11.2 translocation and multiple lung metastases treated with a daily dose of 50 mg sunitinib for two cycles. The CT revealed partial regression of this metastasis, and the therapeutic response has been maintained for more than 3 years (13). In the present case, the patient with Xp11.2 translocation RCC did not respond to gemcitabine plus capecitabine therapy, but responded to treatment with sunitinib.

The Xp11.2 translocation RCCs demonstrate abundant lipid droplets and glycogen ultrastructurally. The structure is similar to the conventional clear cell RCC. However, rare rhomboid granules or crystals are similar to alveolar soft part sarcoma (ASPS) (20). Therefore, Xp11.2 translocation RCCs display the ultrastructural features of both conventional clear cell RCC and ASPS. The presentation of ASPS is notoriously refractory to chemotherapy than to that of conventional clear cell RCC. The underlying biology may be driven by the ASPL (alveolar soft part sarcoma locus)–TFE3 gene fusion shared with ASPS. The ASPL–TFE3 fusion protein



	Day 1	Day 6	Day 16	Day 34	Day 53	Day 67	Day 88
Spot UP	680.2	195.9	299.2	239.6	257.7	342.5	40.0

Figure 4. Nephrotic syndrome assessed by serum albumin concentration and urine protein/creatinine level after discontinuing sunitinib treatment in a 27-year-old woman with metastatic Xp11.2 translocation renal cell carcinoma. Spot UP, spot urinary protein (mg/dl); Day 1, day 1 after cessation of sunitinib.

may transactivate the MET promoter *in vitro* which increases MET mRNA and protein expression. The expression would exhibit decreased growth in response to either a selective inhibitor of the MET tyrosine kinase or RNA interference-mediated knockdown of MET *in vitro*. Therefore, MET tyrosine kinase inhibitor may be a potential novel agent in Xp11.2 translocation RCCs (21).

Renal toxicity related to the vascular endothelial growth factor (VEGF) pathway has been described with the VEGF-depleting antibody or tyrosine kinase inhibitor of VEGF receptor (VEGFR). The pathogenesis of renal toxicity and proteinuria in anti-VEGF therapy likely relates to perturbation of the podocyte–endothelial VEGF axis signaling (15,16). VEGF is constitutively expressed by podocytes, and VEGFRs are present on normal glomerular capillary endothelial cells (17). After inhibition of VEGF signaling by VEGFR antagonist, it reflects the importance of VEGF in normal renal function and results in renal pathology manifested by loss of endothelial fenestrations in glomerular capillaries, proliferation of glomerular endothelial cells (endotheliosis), loss of podocytes and proteinuria in mice (17). Besides, in animal data report, circulating VEGF-A can be neutralized by injection of anti-VEGF-A antibodies, or soluble VEGF-R1. It induced proteinuria, glomerular endothelial cell detachment and suppression of nephrin, an important protein for maintaining the glomerular slit diaphragm. Such findings implicate the role of VEGF in the maintenance of the glomerular filtration barrier that prevents leakage of plasma proteins into urine (18,19). Thus, proteinuria with nephrotic change and impaired renal function could occur in humans treated with anti-VEGF antibody.

Nephrotic syndrome caused by sunitinib is a very rare complication. In our study, severe proteinuria without hematuria, hypoalbuminemia, hypercholesterolemia, generalized edema, low C3/C4 level and normal ANA/ant-ds-DNA/ANCA were found. Hepatitis B virus, hepatitis C virus or HIV was all negativity. CT with contrast media revealed no evidence of renal vein thrombosis. IgA or ANCA-mediated nephritis and immune-mediated glomerulonephritis were unlikely according to clinical presentation and blood analysis. Nephrotic syndrome resolved after cessation of sunitinib without any immunosuppressant treatment. Thus, nephrotic syndrome induced by sunitinib was impressed. To date, sunitinib-related nephrotic syndrome and acute renal failure have only been reported in a single case of RCC (14). In that case report, renal biopsy revealed ischemic acute tubular necrosis with minimal change nephropathy, and the patient had to undergo hemodialysis because of renal failure. In our study, the use of sunitinib could be discontinued because of early detection of renal function impairment and proteinuria, and this aided the patient's recovery without the need for an invasive procedure.

To summarize, we report a case of Xp11.2 translocation RCC that was successfully treated with sunitinib, which had to be discontinued because of the occurrence of sunitinib-related nephrotic syndrome. We recommend regular

monitoring of serum creatinine and urine protein in patients undergoing sunitinib therapy.

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Conflict of interest

None declared.

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