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Case Report

Impaired growth and development after sunitinib treatment in a child with locally progressive kidney cancer

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Abstract: Objective: To determine the safety and efficiency of sunitinib for renal cancer treatment in a pediatric patient. Methods: A 12-year-old girl with locally progressive renal cancer was hospitalized on June 27, 2011 because of continuous pain in the lower back and abdomen since 2 days and fever since 1 day after sustaining a trauma. Computed tomography revealed a massive, mixed-density lesion (60 × 70 × 70 mm) in the middle and lower parts of the right kidney and a round, mixed-density, retroperitoneal nodule (10 × 16 mm). Right renal cancer with retroperitoneal lymph node metastasis was considered. The patient underwent radical nephrectomy and regional lymph node dissection, and postoperative treatment with sunitinib (25 mg/day) for 4 weeks followed by a 2-week drug-free interval. Eight such 6-week courses were performed, starting from August 1, 2011. Result: The latest follow-up examination was conducted in October 2014. After the first sunitinib course, the patient developed decrustation in the palms and soles. This symptom did not occur after the second course. Skin rash occurred mostly on the back and neck during the third course, and resolved spontaneously during the drug-free interval. It did not recur during subsequent courses. Fatigue, weakness, and intolerance to cold occurred since the first course. The results of routine blood, liver-function, kidney-function, and thyroid-function tests after each course were normal. Conclusion: Sunitinib was safe and effective for renal cancer treatment in our patient, and caused few adverse reactions. However, the drug might impair growth and development in children.

Keywords: Sunitinib, children, renal cancer, growth and development

Introduction

Sunitinib can effectively treat locally progressive renal cancer in adults, but its effects in pediatric patients are still unknown. Here, we report the case of a child with locally progressive renal cancer treated with sunitinib. By recording the results of routine blood, liver-function, kidney-function, and thyroid-function tests, and measuring the height, weight, and growth hormone levels for 3 years after surgery to remove the tumor, we determined that sunitinib was safe and effective for the treatment of renal cancer in children, and caused few adverse reactions. However, evaluation of the Tanner score and bone age indicated that sunitinib might have impaired growth and development in our patient, even though the thyroid and growth hormone levels were normal.

Case report

A girl born through a spontaneous delivery on July 8, 1999, underwent B-scan ultrasonography on June 27, 2011 because of continuous abdominal pain since 2 days and fever since 1 day after sustaining blunt abdominal trauma. The ultrasound examination revealed a substantial lesion in the middle and lower parts of the right kidney. Hamartoma was not excluded. Routine blood examinations yielded the following results: white blood cells, 14.46 × 10^9/L; neutrophils, 84.1%; red blood cells, 4.52 × 10^{12}/L; hemoglobin, 131 g/L; and platelets,

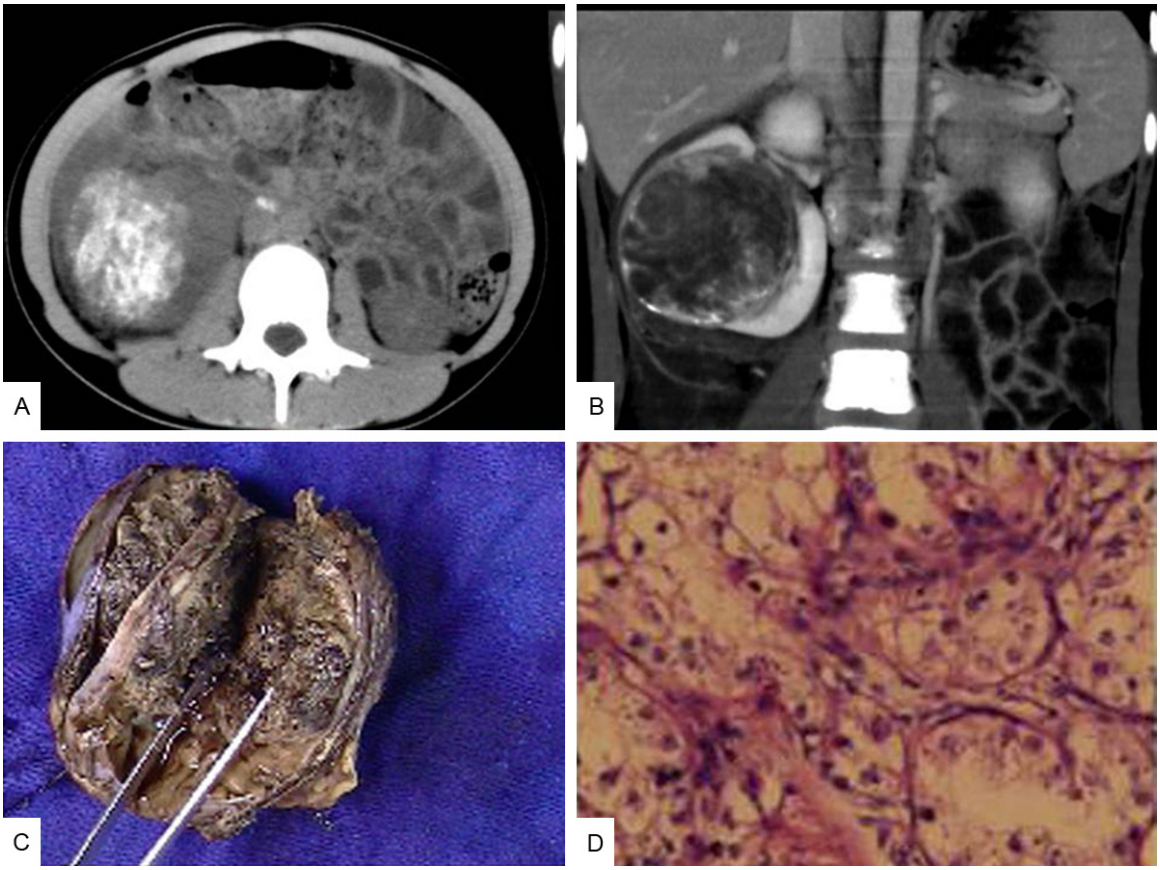

Figure 1. Computed tomography (CT) scans and postoperative pathological examination show that this is a case of locally progressive kidney cancer. A and B show a massive mixed-density lesion measuring 60 × 70 × 70 mm^3 in the middle and lower parts of the right kidney and a round mixed-density nodule measuring 10 × 16 mm^3 in the retroperitoneal area, indicating metastasis of right renal cancer to the retroperitoneal lymph nodes. C shows a mass of 60 × 60 mm that has broken through the renal capsule. D shows clear cell carcinoma classified as nuclear grade II.

253 × 10^9/L. The patient was referred to the urinary surgery department of our hospital, and underwent plain and enhanced computed tomography (CT) after admission. The CT examination revealed a massive, mixed-density lesion measuring 60 × 70 × 70 mm in the middle and lower parts of the right kidney. The CT value was approximately 36-120 HU. Most of the mass was calcified. There was no fat density. The mass did not show any obvious enhancement. The margins of the perirenal fat of the right kidney were not clearly defined. There was a liquid-based low density surrounding the kidney. In addition, there was a round, mixed-density nodule measuring 10 × 16 mm in the retroperitoneal area. A patchy calcified shadow was observed inside the nodule. The non-calcified area of the nodule showed obvious enhancement on CT. A diagnosis of right renal cancer with metastasis to the retroperitoneal lymph nodes was considered (**Figure 1A** and **1B**). After anti-inflammatory and analgesic treatment for 1 week, the fever resolved, the pain improved, and the blood counts returned to normal. At 11 days after admission to our hospital, the patient underwent radical nephrectomy and regional lymph node dissection. Marked enlargement of the right kidney was observed during the operation. The mass was located in the lower part of the kidney and had broken through the renal capsule. There was an enlarged lymph node in the renal hilus. Upon incising the right kidney open, we observed a mass of 60 × 60 mm that had broken through the renal capsule. On cross-sectional examination, the mass was dark red and soft in texture. The postoperative pathological examination suggested a diagnosis of nuclear grade II clear cell carcinoma with cystic degeneration, a large area of necrosis and calcifica-

Table 1. Height, weight, and hormone levels during 3 years of follow-up

Months after medication	0	6	12	18	24	30	36
Height (cm)	152	152.3	152.5	152.5	152.7	152.8	152.8
Weight (kg)	33.5	33.6	33.9	34.1	34.3	34.6	35.1
Growth hormone level (μg/L)	/	4.35	4.03	3.75	3.96	/	/

tion, and lymphatic metastasis to the renal hilus (**Figure 1C** and **1D**). The pathological stage was T1N1M0. The Mayo clinic scale score after radical nephrectomy was 6. The patient's family opted for treatment with a targeted drug after the operation. Therefore, after obtaining approval from the ethics committee of our hospital, we administered sunitinib (Sutent, 25 mg/tablet, manufactured by Pfizer) at a dose of 25 mg/day for 4 weeks followed by an interval of 2 weeks; a total of 8 such 6-week courses were performed starting from August 1, 2011. After the first 4 weeks, the patient developed decrustation on her palms and the soles of her feet, which resolved during the subsequent drug-free interval. This symptom did not occur after the second course. A skin rash consisting of papules with a diameter of approximately 0.5 cm occurred mostly on the back and neck after the third course, but resolved spontaneously during the drug-free interval. The rash did not recur during the subsequent courses. The patient felt fatigue, weakness, and intolerance to cold since the first course. The results of routine blood, liver-function, kidney-function, and thyroid-function tests after each course were normal. No recurrent or metastatic tumor was observed on plain and enhanced CT scans obtained at 6, 12, 24, and 36 months after the operation. The patient had normal height and growth before the operation. We conducted additional laboratory tests and posteroanterior X-ray examinations after starting sunitinib treatment to study the safety and efficiency of this drug in the treatment of renal cancer in children. We found that sunitinib was safe and effective in our pediatric patient, and caused few adverse reactions. However, we observed that sunitinib might have affected the growth and development of our patient.

Materials and methods

Laboratory examination

The follow-up examinations showed that the patient had a slower increase in height and weight, with an increase of only 0.8 cm in height and 1.6 kg in weight during 3 years. Her height was markedly less than the mid-parental height, with a difference of 7.2 cm. The growth hormone level was determined from 6 months after the administration of the medication, once every 3 months for 4 consecutive times. The level was within the normal range (0.55-4.74 μg/L) at all times (**Table 1**).

Posteroanterior X-ray examination

We tested the patient's bone age at the left wrist when she was 15 years old. The height of her mother and father were also recorded. We reviewed articles to determine the standard height range of Chinese teenagers based on the bone age [1].

Tanner scoring system

We graded the sexual maturity of our patient by using the Tanner scoring system.

Results

Laboratory examinations

The follow-up examinations showed that the patient had a slower increase in height and weight, with an increase of only 0.8 cm in height and 1.6 kg in weight during 3 years. Her height was markedly less than the mid-parental height, with a difference of 7.2 cm. The growth hormone level was determined from 6 months after the administration of the medication, once every 3 months for four consecutive times. The level was within the normal range (0.55-4.74 μg/L) at all times (**Table 1**).

Posteroanterior X-ray examination

A posteroanterior X-ray of the left wrist showed that the patient's bone age was inconsistent with her chronological age. Her height was lower than the standard height range based on bone age for Chinese teenagers [1] (**Table 2**).

Tanner scoring system

In our patient, menarche occurred on January 15, 2013. The secondary sexual characteris-

Table 2. Evaluation of bone age of the patient

Height of father (cm)	171
Height of mother (cm)	162
Mid-parental height (cm)	(171 + 162 - 13)/2 = 160
Bone age	15 years
Standard height range of 15-year-old Chinese girls based on bone age (cm)	154.83-165.47

tics at this time included slightly elevated and enlarged, spore-shaped breasts, with palpable gland mass, and slightly enlarged areolas. A small amount of light pubic hair was visible around the labia majora. The sexual maturity of the patient was classified as stage II, according to the Tanner scoring system [2].

Discussion

The incidence of clear cell renal cell carcinoma in children is low, and these tumors account for less than 7% of all malignant renal tumors in children and approximately 2% of all renal tumors. Renal tumors often go unrecognized during the physical examination of children. Therefore, it is common for children with renal tumors to present with symptoms such as hematuresis, stomachache, and abdominal mass. In the case of some children, medical attention is sought because of severe abdominal pain and acute abdomen caused by trauma or spontaneous ulceration, as in the case of our patient. She was admitted to our hospital with acute abdomen because of tumor rupture after trauma and subsequent infection. In children with renal cancers, local calcification is commonly observed on CT scans, and appears by highly dense on plain scans and shows no marked enhancement on contrast-enhanced scans. This can lead to the misdiagnosis of renal cancers as a benign lesion such as nephrotuberculosis or hamartoma in children. Thus, children are more likely to develop locally progressive renal cancer or even metastatic renal cancer than are adults, who generally seek medical attention earlier.

Among adults, approximately 50% of patients with locally progressive renal cancer develop metastasis. It is very important that those with a high risk of metastasis receive adjuvant therapy [3]. Although renal cancer rarely occurs in children, it is prone to cause locally progressive lesions or even metastases. Therefore, it is necessary that children with renal cancer receive adjuvant therapy after surgery. However, renal tumors are not sensitive to chemotherapy and radiotherapy. Large doses of interleukin-12 and alpha-interferon have been used as postoperative adjuvant therapy for progressive renal cancer, with effective rates of less than 15% [4, 5]. Sunitinib is a targeted drug that inhibits multiple kinases. It exerts anti-tumor effects through multiple targets. This new drug was successfully developed based on the knowledge of the molecular biological mechanisms underlying tumorigenesis. The main effect of sunitinib is the inhibition of tumor cell growth and angiopoiesis instead of cytotoxicity, so it has fewer toxic and side effects, and is well tolerated. The application of sunitinib has been limited to the treatment of advanced renal cancers in adults. No study has reported the use of this targeted drug for the treatment of renal cancer in children. However, targeted drugs have been used for the treatment of other solid tumors in children. Dubois et al. used sunitinib powder for the treatment of refractory solid tumors in 12 patients (9 patients with glioma, 1 with ependymoma, 1 with mesothelioma, and 1 with an undefined tumor) [6]. Of these patients, 5 were male, and 7 were female; the average age was 13 years (range, 4-21 years). Sunitinib was administered at a dose of 15 mg/m^2. The observation period was one course, which consisted of administering the medication for 28 consecutive days followed by withdrawal for 14 days. A total of 6 patients developed leucopenia; 5 developed fatigue; 4 developed neutropenia; 4 developed hypertension; and 3 patients suffered dose-limiting toxicity reactions, such as dizziness, back pain, hand-foot syndrome, and intratumoral hemorrhage [6]. In another study [7], sunitinib powder was used for the treatment of refractory solid tumors in 23 patients with an average age of 13.9 years (range, 3.9-20.6 years). The drug was used at doses of 15 mg/m^2 or 20 mg/m^2 for 28 consecutive days, followed by withdrawal for 14 days. Stable plasma

concentrations were observed on day 7. Common adverse reactions were neutropenia, thrombocytopenia, transaminase elevation, fatigue, weakness, and gastrointestinal tract reaction [7]. Janeway et al. used sunitinib for the treatment of progressive imatinib-resistant gastrointestinal stromal tumors in 7 children [8]. The average age of the children was 15 years (range, 10-17 years). They received doses of 25, 37.5, or 50 mg/day based on their age, weight, and tumor response. The drug was administered for 28 consecutive days, followed by withdrawal for 14 days. The dosage was reduced if grade 3 or 4 toxicity occurred. If the toxic reactions decreased to grade 2, the initial dose was resumed. Follow-up was conducted for 18-23 months (average, 22 months). One patient improved (relief of lung metastases); five patients had an average disease progression-free period of 15 months; and one patient showed disease progression. Two patients developed grade 3 toxicity, and in 2 patients, the dosage was reduced due to gastrointestinal reaction, fatigue, and weakness [8]. The above studies suggest that sunitinib is suitable for use in children with locally progressive or metastatic renal cancer, and the incidence and severity of adverse reactions are similar to those observed in adults. Sunitinib treatment is safe if the dosage is appropriately adjusted. However, thus far, there is no report on the impact of sunitinib on growth and development. The patient in our study was followed up for 3 years. After the exclusion of thyroid inhibition, growth hormone deficiency, and genetic disease, we concluded that sunitinib affected growth and development in our patient. Specifically, it inhibited height increase and the development of secondary sexual characteristics. During the treatment, the patient's height increased by only 0.8 cm, and her weight increased by only 1.6 kg. Her secondary sex characteristics were categorized as stage 2 according to the Tanner classification, which is the early stage of growth and development. However, she was actually in the middle-to-late stage of growth and development. Furthermore, we found that the growth hormone level reached a plateau during treatment, and the rapid increase and decrease in growth hormone levels observed in other normal children during development and growth were not detected in our patient. Further investigation is required to determine whether the effect of sunitinib on growth and development is mediated via the inhibition of growth hormone secretion. The possibility that sunitinib inhibited nutrient vessels or growth hormone receptors necessary for organ development has not been ruled out. This can lead to growth and development disorder in children. Further experiments are needed to prove this hypothesis. In conclusion, the findings in the present case suggest that sunitinib impairs growth and development in children; however, this must be confirmed in a larger study.

Disclosure of conflict of interest

None.

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