

Successful treatment of erythropoietin-producing advanced renal cell carcinoma after targeted therapy using sunitinib: Case report and review of the literature

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Abstract. In general, only $\leq 5\%$ of patients with renal cell carcinoma (RCC) develop paraneoplastic erythropoietin (EPO) overproduction-induced polycythemia. However, a number of reports on EPO-producing RCC are available. The present study aimed to report the first case of a patient demonstrating a therapeutic effect on EPO-producing advanced RCC, subsequent to targeted pre-surgical sunitinib therapy, with a review of the literature. The patient involved was a 62-year-old male who presented with a malformation of the left scrotum. Examination revealed a tumor of 73 mm in diameter along with lymph node metastasis. The histological examination indicated a clear cell RCC containing viable cells as well as hemorrhage and necrosis. EPO in cancer cells was confirmed by immunohistochemistry. Subsequently, a case of EPO-producing RCC with polycythemia was diagnosed. The EPO-producing RCC was successfully treated following targeted presurgical therapy with sunitinib.

Introduction

Renal cell carcinoma (RCC) is a relatively common tumor, accounting for $\sim 3\%$ of the adult malignancies (1). In Japan, a previous nationwide study investigating RCC revealed 7,405 patients (5,063 males, 2,342 females) with a positive diagnosis in 2002 (2).

In general, only $\leq 5\%$ of RCC patients develop paraneoplastic erythropoietin (EPO) overproduction-induced polycythemia (2). However, several studies are available on

EPO-producing RCC. In the present study, the first case of a patient exhibiting a therapeutic effect on EPO-producing advanced RCC subsequent to targeted pre-surgical sunitinib therapy is reported, with a review of the literature.

Case report

A 62-year-old male individual identified a malformation of the left scrotum. On physical examination, a left unilateral varicocele was diagnosed, and redness of the face was observed. Abdominal ultrasonography and computer tomography (CT) scans detected a tumor of 73 mm in diameter at the upper pole of the left kidney and tumor embolism in the renal vein and the inferior vena cava (Fig. 1). Furthermore, lymph node metastasis was detected in the left hilus renalis. A thoracic CT scan demonstrated several nodules in the lung, while the laboratory analysis showed red blood cell (RBC) count, $682 \times 10^6/\text{mm}^3$; hemoglobin (Hb), 21.3 g/dl and hematocrit (Ht) 61.6%. The patient's serum EPO level was 35.8 mU/ml (normal range, 8-36 mU/ml). Written consent was obtained from the patient prior to inclusion in this case study.

The percutaneous biopsy of the left renal tumor was performed in an outpatient setting under ultrasonographic guidance for the histological diagnosis. Subsequent to microscopic examination, the histology of the renal tumor showed clear cell RCC (Fig. 2), which was classified as clinical stage T3bN1M1, according to TNM classification. The patient was classified to be at intermediate risk, according to the Memorial Sloan-Kettering Cancer Center (MSKCC) criteria. The patient first received phlebotomy 3 times/week for polycythemia and then sunitinib (50 mg/day) was administered for 4 weeks at 6-week intervals as pre-surgical therapy. However, as grade 3 liver dysfunction emerged after 12 days of the first treatment cycle, sunitinib administration was transiently terminated and reinitiated at 37.5 mg/day upon improvement. Although grade 1 dysgeusia was observed as a further adverse event during the treatment, sunitinib administration was well-tolerated with no grade 4 treatment-related adverse events. Moreover, white blood cell (WBC) and platelet counts were normal. During sunitinib treatment, hemoglobin and hematocrit counts remained within the normal ranges (11-13 g/dl and 33-46%, respectively).

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Abbreviations: CT, computer tomography; EPO, erythropoietin; MRI, magnetic resonance imaging; RCC, renal cell carcinoma

Key words: erythropoietin, renal cell carcinoma, sunitinib, polycythemia

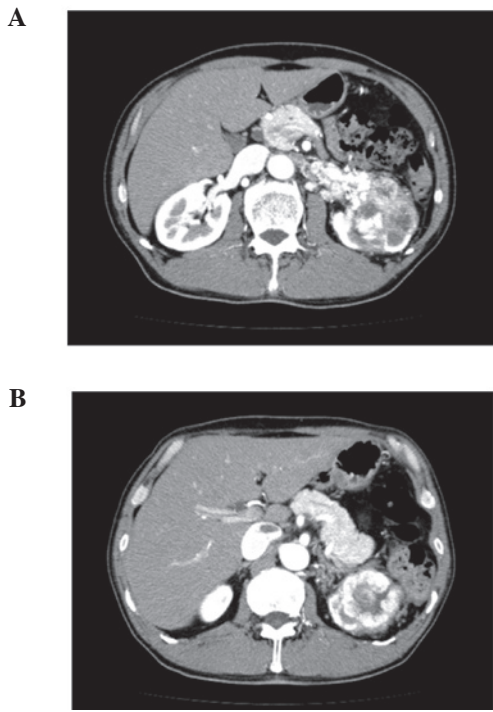


Figure 1. CT scan at diagnosis. Abdominal CT revealed (A) a 73-mm diameter heterogeneously enhanced mass at the upper pole of the left kidney with (B) embolism in the renal vein and inferior vena cava.

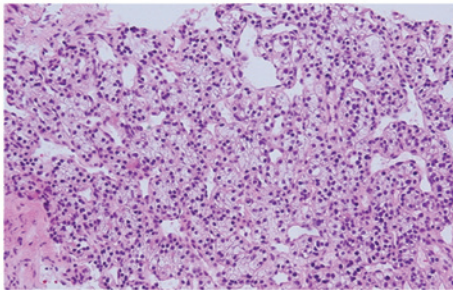


Figure 2. Microscopic appearance of the tumor biopsy specimen showed a clear cell renal cell carcinoma, which proliferated in an alveolar pattern.

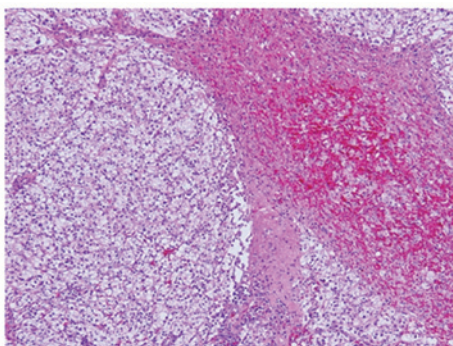


Figure 3. Microscopic appearance of tissue slides from the renal tumor is shown. Histological examination of the tumor showed clear cell renal cell carcinoma. Although most of the tumor had viable cells, hemorrhage and necrosis were present. (H&E; magnification, x100).

After 3 cycles of treatment, 20.4% regression of the tumor was observed on CT based on the response evaluation criteria

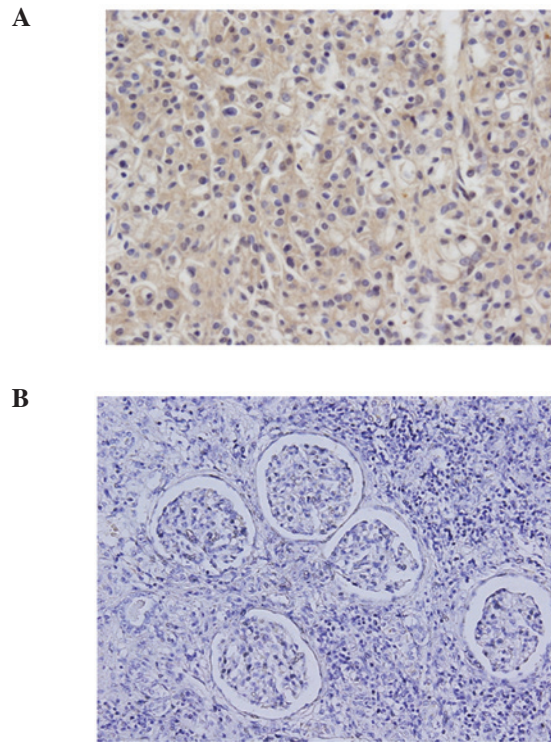


Figure 4. (A) Immunohistochemical staining with erythropoietin (EPO) showed that the cytoplasm of tumor cells was diffuse-positive. (B) Normal kidney tissues were diffuse-negative.

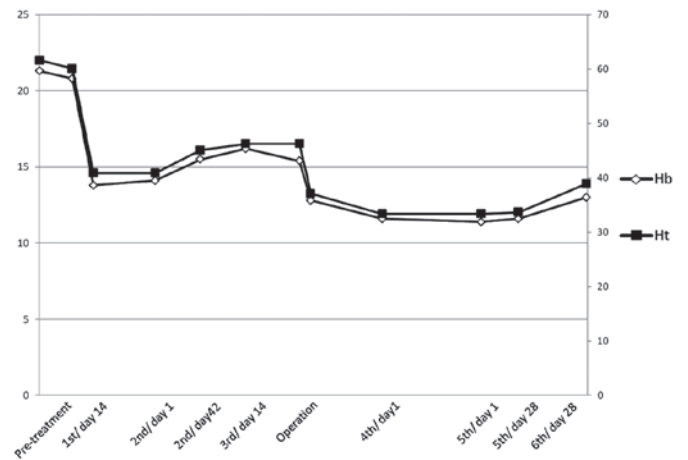


Figure 5. Pre- and post-treatment serum hemoglobin (Hb) and hematocrit (Ht) levels are shown.

in solid tumors (RECIST), while the intravenous tumor embolism had decreased in size. A radical nephrectomy and lymph node resection were performed through an abdominal approach 2 weeks subsequent to the cessation of sunitinib. At the time of the nephrectomy, adherence surrounding the left hilus renalis and the distention of the left renal vein, as well as the gonadal vessels, were observed. Although a left renal vein tumor embolism was detected, no embolism was detected in the inferior vena cava. The surgery lasted for 5 h 32 min, with an estimated blood loss of 2,040 ml. During the perioperative period, part of the wound was dissociated, without additional complications.

Table I. Patient characteristics (n=17).

Characteristics	Value
Median age, years (range)	57 (44-83)
Gender, n	
Males	14
Females	3
Median RBC, 10 ⁴ /μl (range)	709 (570-791)
Median Hb, g/dl (range)	19.2 (17.2-23.2)
Median Ht, % (range)	59.25 (52.1-70)
Nephrectomy, n	17
Other therapy, n	9
IFNα	5
UFT	2
Embolization, n	1
Sunitinib, n	1
Histological type, n	
Clear cell type	14
Unknown	3
Stage, n	
I	2
II	2
III	4
IV	7
Unknown	2

RBC, red blood cell; Hb, hemoglobin; Ht, hematocrit; IFNα, interferon α; UFT, tegafur-uracil.

The histological examination of the tumor showed a clear cell RCC, which had proliferated in an alveolar pattern (Fig. 3). Although most of the tumor contained viable cells, hemorrhage and necrosis were detected. The capsular invasion of the tumor was not observed, rather viable RCC cells were detected in the left renal vein and the gonadal vessels. Furthermore, the lymph node of the hilus renalis contained viable RCC cells. Immunohistochemistry demonstrated EPO in cancer cells, but not in normal kidney tissues (Fig. 4). From the abovementioned result, this was diagnosed as a case of EPO-producing RCC with polycythemia. Subsequent to nephrectomy, sunitinib was re-administered at 37.5 mg per day. The metastatic lesion of the lung was stable at 6 months after surgery, while the hemoglobin and hematocrit were maintained within normal ranges (Fig. 5).

Discussion

EPO, a glycoprotein produced mainly by the kidney, controls erythropoiesis (3). Increased EPO production results in secondary erythrocytosis, which has been reported in a variety of tumors including RCC (4), hepatocellular carcinoma (5) and cerebellar hemangioblastoma (6). Additionally, EPO-producing renal cyst, metanephric adenoma, renal hemangioma and polycythemia-induced hydronephrosis have been thoroughly described (7). In general, only ≤5% of patients with RCC develop paraneoplastic EPO overproduction-induced polycythemia, while approximately 35% develop significant anemia (4,7,8). The glycoprotein hormone EPO is an essential viability and growth factor for the erythrocytic progenitors. The oxygen-dependent regulation of the EPO gene expression is postulated to be controlled by a

Table II. Study characteristics.

Patient number	Study (Refs.)	Year	Age (years)/gender	RBC (10 ⁴ /μl)	Hb (g/dl)	Ht (%)	Treatment	Stage
1	Fujii <i>et al</i> (18)	1976	66/M	650	20.5	63.4	RN	NS
2	Hokayama <i>et al</i> (18)	1976	64/M	NS	21.3	NS	RN	IV
3	Shiga <i>et al</i> (18)	1981	44/M	682	21.5	65.0	RN	IV
4	Ishihara <i>et al</i> (18)	1988	56/F	682	18	54.3	RN	NS
5	Ishibashi <i>et al</i> (18)	1990	58/M	631	17.2	52.1	RN, IFNα, UFT	IV
6	Kanamaru <i>et al</i> (18)	1992	51/M	762	18.4	59.2	RN	III
7	Furukawa <i>et al</i> (18)	1992	83/M	737	17.9	60.5	RN, UFT	IV
8	Yomogi <i>et al</i> (24)	1994	56/M	712	23.2	70.0	RN	III
9	Teishima <i>et al</i> (25)	1996	52/M	660	19.4	59.2	RN, IFNα	IV
10	Yoshida <i>et al</i> (16)	1997	59/F	709	17.9	55.5	RN	II
11	Sato <i>et al</i> (26)	1998	56/F	714	19	59.3	RN	III
12	Noguchi <i>et al</i> (17)	1999	57/M	789	20.4	65.0	RN	I
13	Morita <i>et al</i> (27)	2001	52/M	791	19.4	61.3	RN, IFNα	IV
14	Okuyama <i>et al</i> (18)	2002	46/M	775	18.9	58.5	RN, IFNα	III
15	Rad <i>et al</i> (19)	2008	76/M	NS	NS	55.0	RN, IFNα	I
16	Hirose <i>et al</i> (28)	2011	80/M	570	18.7	55.2	Embolization, RN	II
17	Present case	2012	62/M	682	21.3	61.6	Sunitinib, RN	IV

M, male; F, female; RBC, red blood cell; NS, not significant; Hb, hemoglobin; Ht, hematocrit; RN, radical nephrectomy; IFNα, interferon α; UFT, tegafur-uracil.

hypoxia-inducible transcription factor-1 α (HIF-1 α). HIF-1 α interacts with the Von Hippel-Lindau (VHL) protein and is degraded by ubiquitin-mediated proteolysis in the presence of oxygen. Accumulation occurs under hypoxia due to the inhibition of its proteolytic degradation through the ubiquitin proteasome pathway, while promoting EPO gene transcription. Furthermore, VHL gene product (pVHL) loss has also been detected in 45-80% of clear cell RCC cases (9-11). RCC continuously activates the HIF pathway, while promoting EPO gene transcription (12).

Recent studies have reported that the receptor tyrosine kinase inhibitors of the vascular endothelial growth factor (VEGF) receptor family, such as sunitinib and sorafenib, induce EPO upregulation (13-15). However, in the present study, the administration of sunitinib was successful in inhibiting tumor progression, as well as controlling polycythemia. The present case was most likely controlled by damaging cancer cells and decreasing EPO production to inhibit angiogenesis by not signaling the HIF-VEGF or HIF-EPO pathways. Hokayama *et al* (18) suggested various criteria for erythropoietin-producing tumors: i) coexistence of the tumor and polycythemia, ii) polycythemia consumption following tumor resection, iii) increasing activation of serum or urinary EPO, iv) EPO activation from tumor extracts, v) no additional evidence of the cause of erythrocytosis or -poiesis, including mRNA in the immunohistochemistry as additional evidence.

In the present study, the immunohistochemical staining of tumor tissue also revealed EPO production in tumor cells subsequent to pre-surgical sunitinib therapy. The mechanism of EPO elevation in RCC has been shown to be due to the fact that the tumor is self-producing, as well as to EPO overproduction in normal renal tissue resulting in local hypoxia arising from the tumor. However, in the present study, immunohistochemical staining of normal renal tissue was detected. To the best of our knowledge, 17 patients (14 males and 3 females; median age, 57 years; range, 44-83), including the present case, have been reported thus far with EPO-producing RCC (16-19) (Tables I and II). Most of these patients are male, with the most common histological cell type being RCC (14 cases). Due to the limited number of reports available the prognosis has been insufficient, although in their studies, Sufrin *et al* (20) and Ljungherg *et al* (21) demonstrated that 63 (36/57) and 33% (55/167) of RCC cases showed elevated serum EPO, respectively, whereas a few cases showed polycythemia (20,21). Several studies have delineated that ~8% renal tumors show polycythemia, while ~1.2% of the cases show serum EPO elevation. Michael *et al* (22) reported that the immunohistological expression of EPO in RCC is adversely associated with poor prognosis (22). Furthermore, Westenfelder and Baranowski (4), as well as Westenfelder *et al* (23) showed that EPO is likely to stimulate malignant tumor cells (4,23).

At present, there are few studies available using targeted therapy for EPO-producing advanced RCC. This is the first report to demonstrate a successful treatment of EPO-producing advanced RCC subsequent to targeted presurgical sunitinib therapy. Although the mechanism and the effect of the multi-targeted tyrosine kinase inhibitor on EPO-producing RCC remain to be determined, the present case suggests that sunitinib is likely to inhibit tumor progression, as well as control

polycythemia. Consequently, additional cases are necessary to confirm these results.

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