Brain Metastasis in a Patient with a Sarcomatoid Variant RCC with Well-controlled Extracerebral Metastases by Temsirolimus

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Abstract. *Background: The sarcomatoid variant of metastatic renal cell carcinoma (RCC) has often an aggressive course and a poor prognosis, particularly when accompanied with brain metastasis. Case Report: We describe the case of a patient with sarcomatoid variant RCC in whom brain metastasis was observed as a new lesion during treatment with temsirolimus, despite other extracerebral metastatic lesions being well-controlled and progression-free. Results: This discrepancy between the effectiveness of temsirolimus for extracerebral metastases and the simultaneous progression of brain metastases of RCC raises a concern that while vascular endothelial growth factor (VEGF)-targeted therapy may have clinical efficacy, it may also carry a risk for new brain metastases due to weakening of the structure of the blood brain barrier. Conclusion: This case indicates that computed tomography monitoring of the brain should be regularly performed during VEGF-targeted therapy in patients with sarcomatoid variant RCC, even if brain metastases are absent and extracerebral metastatic lesions are well controlled.*

Brain metastases occur in 2% to 17% of patients with metastatic renal cell carcinoma (mRCC) (1). RCC patients with brain metastases typically have a poorer outcome after medical intervention than those with other sites of metastasis, with a reported median overall survival (OS) of 4-5 months after diagnosis and treatment of cerebral lesions (2). The sarcomatoid variant of RCC is a spindle cell phenotype that can be present in any subtype (clear cell, papillary, chromophobe or unclassified). Disease in patients with metastatic sarcomatoid variant RCC usually has an aggressive course and a poor prognosis, with a median OS of 3-10 months (3).

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Case Report

A 66-year-old Japanese man was presented with left abdominal discomfort. He had an Eastern Cooperative Oncology Group performance status (ECOG PS) score of 0 and no relevant history or family history. Physical and laboratory examinations showed no remarkable findings. Contrast-enhanced computed tomography (CT) of the head, chest, abdomen, and pelvis revealed a right pulmonary nodule (2.5×2.7 cm), several smaller left pulmonary nodules, and a bulky enhanced tumor (12.0×11.0 cm), involving the left kidney (Figure 1). The tumor was clinically diagnosed as a left mRCC, cT3a<N0M1 according to the tumor-node-metastasis (TNM) system (6). Open left nephrectomy was performed and histopathological analysis identified a pT3a RCC with clear and spindle cell morphologies (Figures 2 and 3). A growing volume of bilateral lung metastatic nodules and local recurrence from the left psoas muscle, adjacent to the surgical margin were revealed by a postoperative CT scan performed one month after surgery.

Initially, sunitinib (50 mg/day) was administered as a six-week cycle comprising treatment for four weeks, followed by a two-week rest period. The patient received four cycles of sunitinib before apparent tumor progression in pulmonary lesions was revealed by CT scan. Secondary treatment with subcutaneous IFN-α injection [6 million units (MU)] was started three times per week and was continued for two months. During these protocols, the patient showed further progression of pulmonary lesions and locoregional recurrence, and developed fatigue, anemia and pleural effusion, all of grade 3.

At this point, treatment with temsirolimus was started as the third therapy at a dose of 25 mg i.v. per week. After only two weeks of treatment, a CT scan showed a partial response of both the pleuropulmonary and locoregional lesions (Figure 4). The patient's general condition was improving and no significant toxicities were seen after two months of this therapy. Treatment with temsirolimus was continued for five months until a CT scan revealed disease progression with a new metastatic lesion in the brain, despite other metastatic lesions remaining progression-free (Figure 5). The patient died in March 2012, 14 months after the initiation of therapy.

Discussion

For many years, treatment options for RCC have been limited to immunotherapy due to the inherent resistance of these tumors to chemotherapy and radiotherapy. The only drugs approved for RCC in the past 30 years are IFN-α and interleukin-2 (IL-2), but a benefit has only been seen in a small percentage of patients and sometimes with significant toxicity (7). The sarcomatoid component can occur with any histological type of RCC and is associated with a worse prognosis and rapid progression (3). An ECOG trial suggested modest activity of a regimen of gemcitabine/doxorubicin chemotherapy in 39 patients with metastatic sarcomatoid RCC, with an objective response rate of 16%, median PFS of 3.5 months, and median OS of 8.8 months (8).

The molecular features of the cells that comprise of sarcomatoid differentiation have not been extensively characterized. Expression of S-phase kinase-associated protein-2 (Skp2), Ki67, vascular endothelial growth factor (VEGF), KIT, S6 kinase, hypoxia-inducible factor 1 alpha (HIF-1α), carbonic anhydrase IX and glucose transport protein, and *p53* mutations have been studied in this tumor type (7). It has been suggested that both sarcomatoid and clear cell components of RCCs are derived from the same cells. VEGF overexpression in clear cell and non-clear cell tumors suggests that VEGF-targeted therapies may have a role in the management of sarcomatoid RCC (9). The outcome of patients with advanced RCC has improved substantially through the introduction of targeted therapy, such as sorafenib, sunitinib, temsirolimus, bevacizumab (in combination with IFN-α), and everolimus, all of which have shown efficacy in large randomized controlled trials.

Golshayan *et al*. showed clinical activity of VEGF-targeted therapy in patients with mRCC with sarcomatoid features, most notably in cases with a clear cell histology and a low percentage of sarcomatoid elements (10). In our case, the percentage of sarcomatoid elements from nephrectomy specimens was more than 20%. Furthermore, the sarcomatoid elements were located very close to the surgical margin. Therefore, the local recurrence from the left psoas muscle adjacent to the surgical margin may have been derived from sarcomatoid elements in the original tumor. The PFS, following treatment with sunitinib in our case (4.8 months) was similar to cases with ≥20% sarcomatoid elements (4.3 months), compared to those with <20% (6.8 months), as reported in Golshayan *et al*. (10).

Temsirolimus as a single agent was found to significantly prolong median PFS and OS compared with IFN-α monotherapy in patients with mRCC and a poor prognosis, including cases with clear and non-clear cell histology (5). A central pathology review was unavailable and further discrimination of non-clear cell types was not made, but some of these cases were probably sarcomatoid RCC. In a retrospective review of 63 patients with RCC with sarcomatoid features, Molina *et al*. (11) found a PFS of 3 months (95% confidence interval, CI=2-4) and an OS of 10 months (95% CI=8-14). Thirty-four patients received targeted-therapy, including 29, 3 and 2 cases treated with sunitinib, sorafenib, and temsirolimus, respectively. One patient had a partial response to temsirolimus, and a relatively high level of overexpression of mTOR pathway markers was found in immunohistochemical staining of specimens of sarcomatoid-variant clear cell RCC (11).

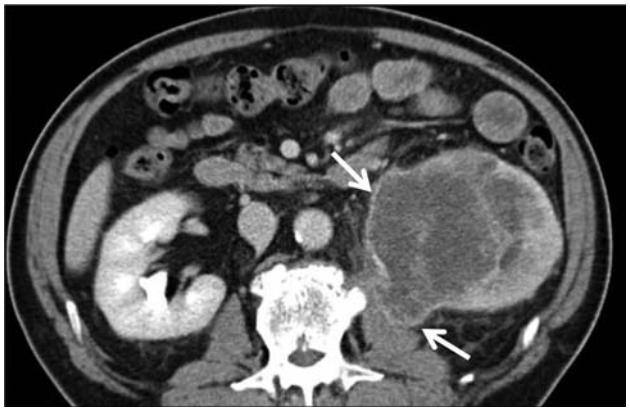

Figure 1. *Pre-treatment computed tomographic scan, showing an enhanced bulky tumor of the left kidney adjacent to the ipsilateral psoas muscle (arrows).*

The European Association of Urology guidelines recommend temsirolimus as first-line treatment for high-risk patients with advanced mRCC, regardless of tumor histology or nephrectomy status, with the goal of increasing OS (12). The findings described above suggest that our case was particularly suitable for temsirolimus treatment due to the histopathological findings of RCC with clear and spindle cell morphologies. Indeed, our patient responded well to temsirolimus in terms of the good control of extracerebral metastases that remained in a progression-free state. However, simultaneous development of brain metastasis occurred and may also have been associated with an effect of temsirolimus.

Temsirolimus reduces expression of HIF-1α and HIF-1β *in vitro*, resulting in reduced expression of VEGF and a potential antiangiogenic effect (13). The microvasculature of the brain parenchyma is lined by a continuous, non-fenestrated endothelium with tight junctions and little pinocytic vesicle activity. This structure, the blood brain barrier (BBB), limits the entrance of circulating macromolecules into the brain parenchyma. The BBB and the lack of a lymphatic system are responsible for maintaining the brain as an immunologically privileged site and for protecting the brain against entrance of most drugs and invasion of microorganisms. However, the BBB does not prevent invasion of the brain parenchyma by circulating

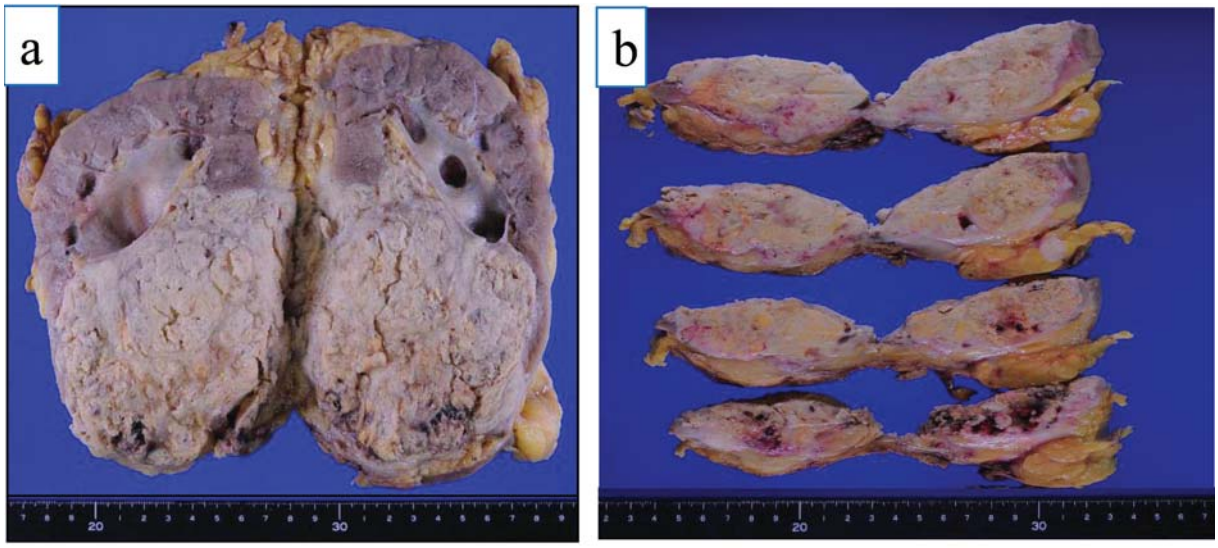

Figure 2. *Gross findings of the resected kidney showed a poorly demarcated tumor from the middle portion to the lower pole (a). The tumor was yellowish-white at the cut surface (b).*

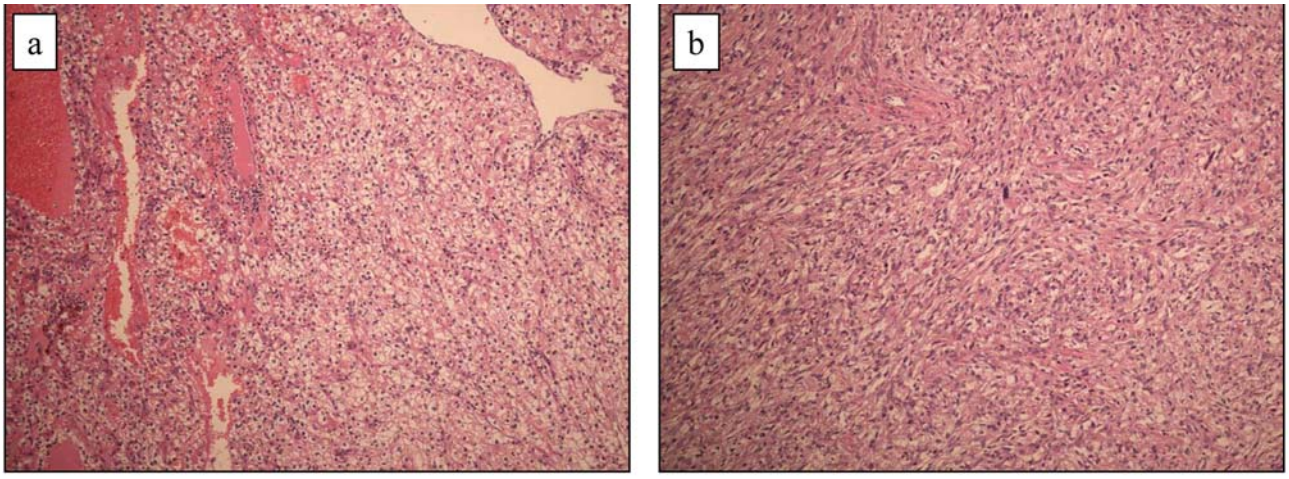

Figure 3. *Microscopic findings (hematoxylin-eosin, reduced from ×100) showed that the tumor cells were composed of clear cells (a) and spindle cells (b).*

metastatic cells. Indeed, metastases in the brain develop in 10% to 40% of all patients with solid tumors (14). The lipophilicity of temsirolimus allows it to cross the BBB, and thus temsirolimus has promising antitumor effects for several types of refractory tumors (15).

These reports suggest a hypothesis for the discrepancy between the effectiveness of temsirolimus for extracerebral metastases and progression of RCC cells into brain metastases during temsirolimus treatment in our case. Thus, temsirolimus may have altered the structure of the BBB to permit the drug and circulating mRCC cells to invade the brain parenchyma. If brain metastases are present in patients with mRCC, the structure of the BBB may already have been breached by circulating metastatic RCC cells. However, the balance between the number of circulating metastatic RCC cells and the dose of temsirolimus might be very important in determining whether temsirolimus increases the risk for onset of brain metastasis in RCC patients with extracerebral metastases.

This proposal requires examination in large prospective studies of patients with sarcomatoid variant mRCC. However, our case raises a significant concern that while VEGF-targeted therapy may have clinical efficacy, there is also the risk of

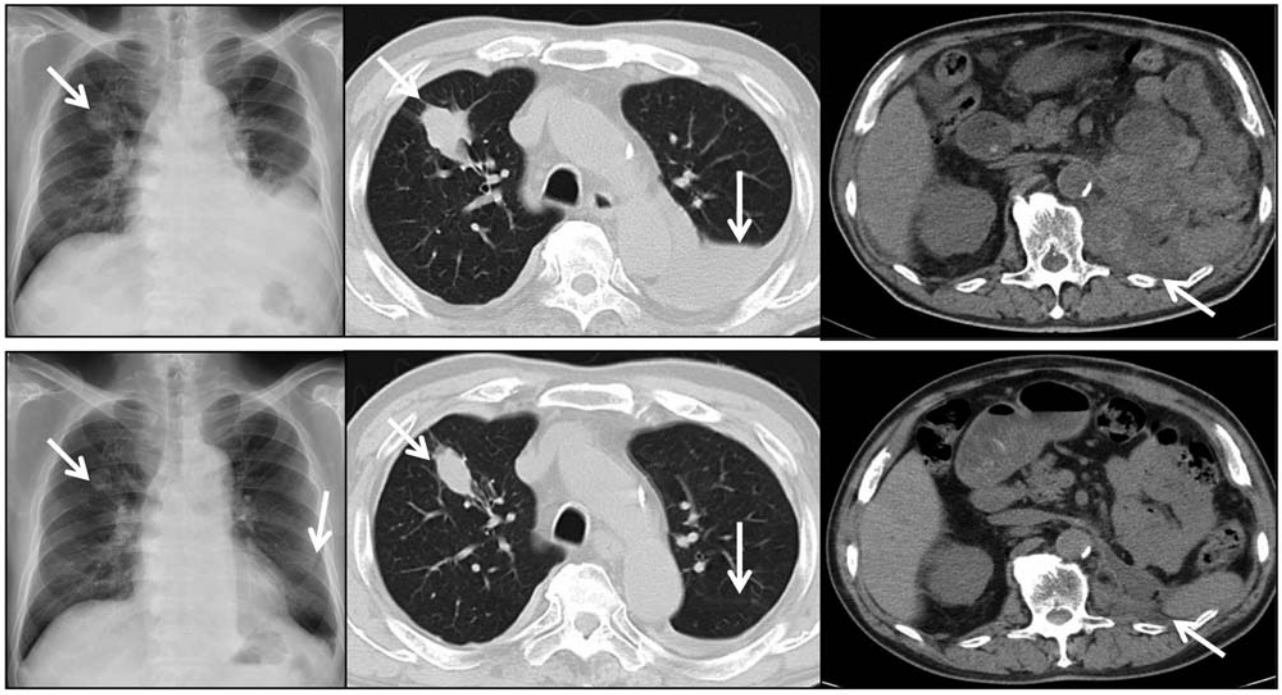

Figure 4. *Chest X-ray and computed tomographic scan showing a partial response of both pleuropulmonary and locoregional lesions (arrows) after only two weeks of temsilorimus treatment. Upper: Pre-treatment, Lower: post-treatment.*

causing new brain metastasis in patients with mRCC, by weakening the structure of the BBB. Therefore, we suggest that CT monitoring of the brain should be performed regularly during VEGF-targeted therapy, even if extracerebral metastatic lesions are well-controlled by the treatment in patients with sarcomatoid variant RCC without brain metastases.

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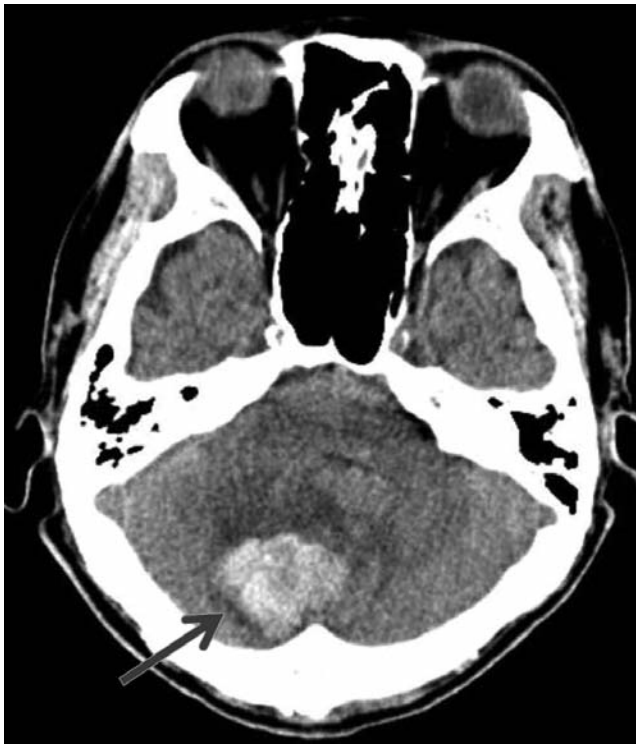

Figure 5. *Computed tomographic scan showing a new brain metastatic lesion (arrows) after five months of temsilorimus treatment.*

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