Case Report

Sustained systemic response paralleled with ovarian metastasis progression by sunitinib in metastatic renal cell carcinoma: Is this an anti-angiogenic potentiation of cancer?

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Abstract

Metastatic renal cell cancer is associated with poor prognosis and survival and is resistant to conventional chemotherapy. Therapeutic targeting of molecular pathways for tumor angiogenesis and other specific activation mechanisms offers improved tumor response and prolonged survival. A 48-year-old, female patient presented with large right renal mass with features suggesting of renal cell cancer without metastasis on contrast enhanced computed tomography (CT). Right radical nephrectomy was done. After 9 months of surgery, she got metastasis in lung, liver and ovary. The patient received sunitinib via an expanded access program. After eight 6-week cycles of sunitinib, a reassessment CT scan confirmed an excellent partial response with the almost complete disappearance (90%) of liver and lung metastasis but the adnexal mass had increased in size (>10 times) and the possibility was thought of second malignancy. Excision of the mass performed. Histopathology of the mass depicted metastatic renal cell cancer. There is possibility of a 'site-specific anti-angiogenic potentiation mechanism' of malignancy in relation to sunitinib based upon the preclinical studies, in reference to the index case. Regression of one site with concurrent progression is possible. The exact mechanism of site-specific response, especially organ specific progression by vascular endothelial growth factor inhibitors in metastatic renal cell cancer warrants further study.

Key Words: Anti-angiogenic potentiation, metastatic renal cell carcinoma, ovarian metastasis, site-specific response, sunitinib, tyrosine kinase inhibitor, vascular endothelial growth factor pathway inhibitors

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INTRODUCTION

Metastatic renal cell cancer is associated with poor prognosis and survival and is resistant to conventional chemotherapy. Therapeutic targeting of molecular pathways for tumor angiogenesis and other specific activation mechanisms offers improved tumor response and prolonged survival. The management of metastatic renal cell carcinoma (mRCC) has been revolutionized by the advent of these therapies. The targeted therapies available to treat metastatic kidney cancer include vascular endothelial growth factor (VEGF) inhibitors, bevacizumab, sorafenib, sunitinib, pazopanib and the mTor inhibitors temsirolimus and everolimus. Numerous preclinical studies have demonstrated that VEGF pathway inhibitors suppress primary tumor growth and metastasis. However, it has been recently reported that short-term VEGF and vascular endothelial growth factor receptor inhibition can paradoxically accelerate tumor invasiveness and metastasis in certain models.[1]

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CASE REPORT

The present case is about a 48-year-old, female patient had presented fullness of abdomen, right flank pain and on and off hematuria for last 1 month. Computed tomography (CT) imaging revealed a large localized tumor of the left kidney with features not suggesting of any metastasis [Figure 1a]. Right radical nephrectomy was done and grossly it was a 18 cm × 15 cm × 6 cm tumor replacing upper pole of kidney. Histopathology came out as clear cell RCC with Furhman`s grade III with no capsular invasion and adrenal and hilar vessels were free of tumor. In the routine follow-up at 3 months, she had no complaints and CT scan was unremarkable. After 9 months of surgery, she complained of pain in the right hypochondrium radiating to shoulder. Ultrasonography followed by CT chest and abdomen was performed which delineated multiple liver metastasis, few lung metastasis and small ovarian mass (3 cm × 4 cm) [Figure 1b and c]. Fine-needle aspiration cytology of the liver lesion confirmed it as metastasis from RCC [Figure 1d]. Bone scan of the whole body did not show any evidence suggestive of skeletal metastasis.

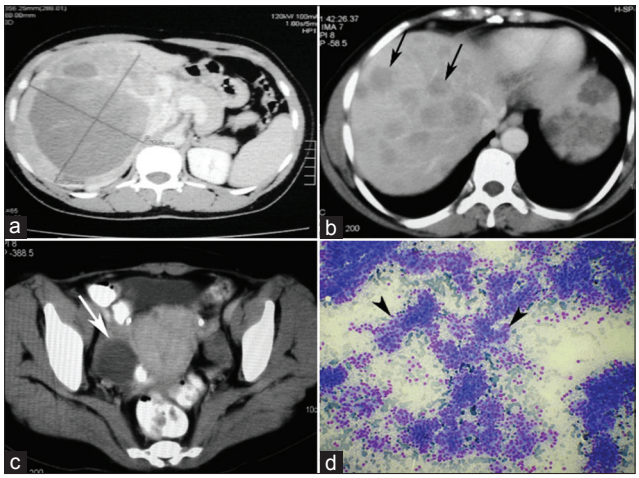

Figure 1: Axial views of computed tomography scan showing large right renal mass abutting and displacing inferior vena cava, (a) multiple liver lesions showing early washout (black arrows) (b) and uterus and right adenexal mass (3 cm × 4 cm) (white arrow). (c) Photograph of fine needle aspiration cytology smear (Giemsa ×200) from liver showing clusters of malignant cells with predominant perivascular arrangements (arrow heads) (d)

The patient received sunitinib via an expanded access program at standard dose of 50 mg orally continued for 28 days followed by 14 days off. She was kept under strict follow-up for complications and objective response of the tyrosine kinase inhibitor (TKI). After two 6-week cycles side-effects experienced by the patient included grade I mucositis, grade I skin changes, grade 2 taste and grade I fatigue. Due to this, the patient was converted to dosage of 37.5 mg orally once daily (for 28 days followed by 14 days off). The patient tolerated this regimen well with no further adverse events. After eight 6-week cycles of sunitinib she complained of lower abdomen discomfort. A reassessment CT scan of the patient's chest, abdomen and pelvis showed an excellent partial response with the almost complete disappearance (90%) of liver and lung metastasis [Figure 2a]. However, the adnexal mass had increased in size (10 cm × 8 cm) and the possibility was thought of second malignancy [Figure 2b]. The decision was taken to remove this adnexal mass and intra-operative the mass was found to be adherent with a part of omentum. Excision of the mass along with omentectomy performed. Histopathology of the mass depicted metastatic RCC with Furman's grade III having micro papillary growth in few areas along with compressed ovarian parenchyma with remnant follicles at periphery. Furthermore, omentum showed metastatic deposits along with vascular emboli [Figure 3a and b]. At 6 months of follow-up after second surgery she had stable disease with no new complaints.

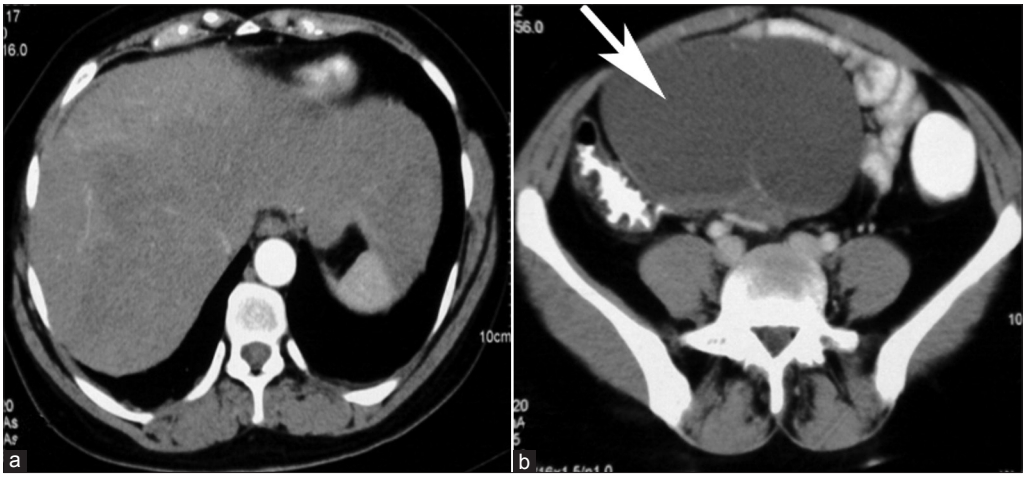

Figure 2: Axial views of computed tomography scan showing significant reduction in liver metastasis (a) and increase in size of ovarian metastasis (10 cm × 8 cm) (white arrow) (b)

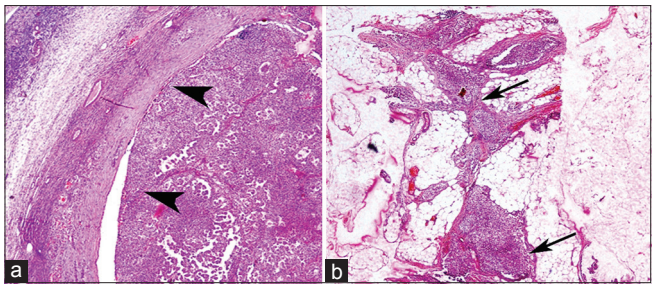

Figure 3: Photograph of histopathological section showing metastatic deposits of renal cell carcinoma (arrow heads) (few areas showing micropapillary pattern) along with compressed ovarian parenchyma with remnant follicles at periphery (a) and omentum showing metastatic deposits (black arrows) along with vascular emboli (b)

DISCUSSION

A review of current treatment options showed that sunitinib's response rate (34-44%) is superior to that of other treatment options, such as IL-2 (15-20%), chemotherapy (5%) and interferon-α (IFN-α) (12%).[2,3] However, it is unclear how a change in tumor size corresponds to overall survival benefit. A randomized, phase III trial demonstrated sunitinib's longer overall survival compared with IFN-α (26.4 vs. 21.8 months; $P = 0.051$) plus improvement in response (47% vs. 12%; $P < 0.001$) and progression-free survival (11 months vs. 5 months; $P < 0.001$) in the first-line treatment of patients with metastatic RCC. The overall survival highlights an improved prognosis in patients with RCC in the era of targeted therapy.[4]

Despite these promising results, 20-30% of mRCC patients show no response to sunitinib and even those that do respond initially will inevitably develop resistance and progress after several months of treatment.[4] Importantly, preclinical studies are revealing mechanisms that allow tumors to exhibit intrinsic or acquired resistance to VEGF-targeted agents. These mechanisms include the stimulation of angiogenesis by alternative pro-angiogenic growth factors, the enhanced recruitment of pericytes or pro-angiogenic myeloid cells or the utilization of alternative tumor vascularization mechanisms such as vascular co-option.[1,5,6] More recent work suggests that pharmacological inhibition of angiogenesis could also accelerate the growth of metastases.[7] Further to this, administration of sunitinib after resection of the primary tumor increased the incidence of metastasis in mice.[8] These data imply that anti-angiogenic agents could accelerate the growth of metastases both in the adjuvant setting and in patients with established metastatic disease.

According to Response Evaluation Criteria in Solid Tumors (RECIST) criteria, an increase of 20% or more of the sum of target lesions, development of a new lesion, or unequivocal progression of non-target lesions constitutes disease progression.[9] However, it seemed unusual that this patient's right ovarian metastasis had progressed while all other lesions had responded to sunitinib. Therefore, after several discussions with the multidisciplinary team and the patient, sunitinib treatment was continued until systemic disease progression. Despite progression of ovarian metastasis, sustained response was achieved with sunitinib in this patient for over a year. As targeted treatments such as sunitinib have a large disease stabilization effect, conventional response criteria might be less helpful than when used to evaluate responses to cytotoxic chemotherapy. Thus, this case demonstrates that clinical judgment continues to play a pivotal role in this new era of targeted therapy. It further emphasizes the need of reclassification of the RECIST criteria especially when dealing with TKIs.

We also noticed a micro-papillary growth pattern in few areas of histopathology of mRCC in the resected ovarian specimen. This emphasizes the difference in the morphogenesis between primary tumor and the metastatic one. It also raises few questions whether the change in the variety of cancer is part of anti-angiogenic potentiation mechanism and whether it could have affected poor treatment response of sunitinib on mRCC at ovarian site. These queries warrant further study of tumor cell biology.

In the present case, sunitinib treatment resulted in a site-specific response; reasons for this remain unclear. In a study by Jafri and Porfiri[10] described a case of a patient treated predominantly with continuous sunitinib who had a good partial response to sunitinib in the lungs, liver, adrenal gland and lymph nodes but dural progression, which they confirmed by magnetic resonance imaging and positron emission tomography as tumor growth in the subarachnoid space at the spinal level of L2-L3. According to them, sunitinib equally distributes throughout body organs, still the differential response is plausible. We propose the possibility of a 'site-specific anti-angiogenic potentiation mechanism' of malignancy in relation to sunitinib based upon the preclinical studies, in reference to the index case. Regression of one site with concurrent progression is possible. In light of these findings, research should now be focused on understanding the aspects of tumor cell biology that determine response and resistance to anti-angiogenic therapies with regard to different organ sites. This report describes, to the best of our knowledge, the second only case of site specific differential response of sunitinib in mRCC apart from the report by Jafri and Porfiri.[10]

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