Case – Remission after repeated palliative RT in metastatic MiT family translocation RCC

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Acknowledgements: The authors would like to acknowledge the contributions of Drs. John Radwan and Sebastien Hotte in the care of this patient.


Published online May 21, 2024

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CASE REPORT

A previously healthy woman in her fourth decade presented with left flank pain and gross hematuria in the late 1990’s. Computed tomographic (CT) imaging revealed a 7x7cm renal mass involving the upper pole of the left kidney and a 3x8cm paraaortic lymph node without other evidence of metastases. She underwent a left nephrectomy and lymphadenectomy. Pathology reported clear cell RCC, Fuhrman grade 3, and the final stage was pT3bN1M0 (stage III). Two years later, her cancer relapsed with nodal masses in the posterior mediastinum, retroperitoneum, and pelvis (Figure 1). Interferon-α was initiated but was discontinued after three months due to disease progression.

She received palliative radiotherapy 20Gy/5 fractions (F) directed towards the recurrent disease, which had filled the entire renal bed/left flank and extended to lower thoracic and lumbar spine. She tolerated radiotherapy well and had excellent radiological response; however, within three

KEY MESSAGES

- Some renal cell carcinomas, such as MiT translocation type, may be radiosensitive.
- Immune mechanisms have been implicated in metastatic RCC patients who are long term survivors.
- Repeated courses of palliative radiation appear to have triggered these in our patient.
months, there was further progression in the left flank, and she again received radiation 20Gy/5F. She received oral AE941 for nearly one year in a clinical trial and then her tumor progressed with bilateral T12 paravertebral masses. As this required retreatment of a previously irradiated area, she received 20Gy/13F to these areas as an oblique pair going through the left flank, spine, and contralateral right sided tumour. Again, she tolerated radiotherapy well and imaging demonstrated partial regression of the left paravertebral mass and stability of a large mediastinal mass.

She received GD-0039 in a phase II trial discontinued after two months due to disease progression. Her chronic cancer pain reached crisis levels, and a pain specialist was consulted and initiated methadone and dexamethasone. Restaging abdominal CT scan reported increase in a left retroperitoneal mass, a large left paraspinal mass measuring 8x6cm at level of T12, and metastases to bone with tumour infiltration into T11, T12 vertebral body and ribs, T11/T12 foramina, encasing the aorta and extending into posterior mediastinum and left psoas muscle. She received two courses of concurrent simplified intensity-modulated arc therapy: 30Gy/10F above the diaphragm and 20Gy/10F below the diaphragm. Her pain improved, and imaging showed regression of masses in both locations.

Eight months later, she presented with pain in the right shoulder and imaging identified a 2x1cm lesion in right paravertebral area near the posterior thoracic inlet. She was treated with 40Gy/16F to the right supraclavicular area (Figure 2a). Two months afterwards, she started treatment on a phase I clinical trial with an agonist monoclonal antibody to the TRAIL receptor 2 (TR2J). After receiving one dose, she developed signs and symptoms of spinal cord compression confirmed by magnetic resonance imaging (MRI) at the T3-5 level. Study therapy was discontinued, and she was treated with radiotherapy to a total dose of 21Gy/11F. Symptoms resolved, and with the sponsor’s permission, treatment with TR2J resumed and continued for 20 months. She developed symptoms of T12 radiculopathy, and MRI confirmed progression of disease with destruction of left side of T12 vertebral body, expansion of proximal left 12th rib, and a new T12 paraspinal soft tissue deposit. Drug therapy was stopped, and she received radiotherapy 30Gy/10F to the lesion on right of T12 vertebrae (Figure 2b) and 20Gy/10F to left rib at the same level.

A decade after diagnosis, MRI spine showed stable disease without any new bone abnormalities, spinal cord, or cauda equina compression. She continues to be followed by her pain specialist on a modest dose of methadone for chronic pain. As of the date of this report, she is considered to be in complete remission without clinical signs or symptoms of recurrence.

A second review of the pathology specimen in 2023 reclassified the renal tumor as a micro-ophthalmia transcription (MiT) family translocation RCC based on positive staining on TFE3 (Figure 3). These tumors are characterized by a Xp11 translocation with TFE3 gene fusions and typically have an aggressive course. MiT family translocation RCC was included into the World Health Organization classification in 2004 and it is a rare entity, accounting for approximately 1% of all RCC.²³
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DISCUSSION
Our patient with metastatic RCC experienced seven episodes of symptomatic disease progression treated with 11 courses of radiation therapy within seven years (including re-irradiation of several areas). She was treated with IFN-α and three other investigational systemic agents, with symptomatic and radiological disease progression on all four. She never received treatment with vascular endothelial growth factor (VEGF) receptor or immune checkpoint inhibitors but appears to have achieved complete remission and continues to live disease-free 25 years after her diagnosis of metastatic disease. It is our clinical impression that she is in remission due to the only treatment that was repeatedly and unequivocally effective for her cancer: external beam radiotherapy. This is remarkable as palliative radiotherapy is not thought to have this potential.

Spontaneous regression of RCC is a well-recognized but uncommon phenomenon reported in approximately 1% of metastatic RCC cases. Therefore, while we cannot rule out the mechanisms of spontaneous regression as contributing to her prolonged disease control, in her case no remissions unrelated to radiation treatment were observed, and her clinical course of repeated progression and response to radiotherapy weigh against this. Although she had documented symptomatic and radiological progression on all systemic agents she received, a delayed long-term response to the effects of systemic therapy represents another possibility. Long-term survivors have been reported in a small number of patients in most clinical trials of drug therapy in metastatic RCC. However, without exception these patients first show objective response to therapy, and this includes IFN-α, the only “standard” systemic agent she received. Given the type, timing, and lack of response to systemic therapies, we consider a contribution of these to her ultimate outcome very unlikely.

The use of conventional radiotherapy for metastatic RCC has been very limited due to preclinical evidence showing the high level of radio-resistance. However, it is recognized that different cell lines of RCC may have differing intrinsic radiosensitivities related to molecular/genetic features or other factors yet unidentified. Rastogi et al. reported that of 963 patients with RCC treated with palliative radiation between 2001 and 2006, 23 (2.4%) patients survived at least 5 years, and 17 (1.8%) patients were free of disease. Local radiotherapy may also be associated with regression of metastatic cancer (abscopal effect) presumed due to immunologically mediated processes. In a meta-analysis of reported cases of abscopal effect, 16% were metastatic RCC, making it the second-most-reported cancer.

It is possible that MiT family translocation RCCs are inherently more radiosensitive. This is the first report of prolonged benefit after radiation treatment response for this uncommon entity. In two previously reported cases of MiT family translocation RCC that achieved remission, patients were treated with combinations of anti-VEGF and immune checkpoint inhibitors without radiation therapy. Our case demonstrates a unique circumstance where repeated doses of localized palliative-dose radiotherapy appear to have facilitated prolonged remission in a patient with metastatic RCC, emphasizing the need for better understanding of RCC biology and predictors of therapeutic response.
REFERENCES


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FIGURE AND TABLES

**Figure 1.** Timeline from 1999–2023 depicting key treatments and events. The figure is an original creation by Aruni Jayatilaka, Dr. Eric Winquist and Dr. Sympascho Young, based on information gathered through chart review.

Key disease progressions:
1. Apr-2000: Mass in posterior mediastinum and retroperitoneum had gotten larger (no measurements)
4. Oct-2002: CT scan shows 60-70% increase in left retroperitoneal mass, less so with posterior mediastinal mass.
5. Large left paraspinal mass 80mm at level of T12
6. Dec-2006: Destructive lesion involving left half of thoracic vertebra reported in T12 (metastatized, prior history of T12).

MRI shows destructive left T12 vertebral body with pedicle involvement, new soft tissue paraspinal deposit on right side of T12.

Radiation treatments
Experimental systemic therapies
Key events
Figure 2. (a) Radiation treatment plan from 2004 for disease recurrence in the right posterior thoracic inlet (40Gy in 16 fractions). (b) Radiation treatment plan from 2006 for destructive disease recurrence involving half of T12 vertebral body (30Gy in 10 fractions).

Figure 3. Xp11 translocation renal cell carcinoma with TFE3 gene fusion. The image demonstrates a mixture of papillary and micropapillary patterns. Stains were performed on the initial (a) H&E stain to better characterize the tumor. Tumor is characterized by a (b) negative CK7 stain, (c) positive AMACR stain, and (d) positive TFE3 stain, in concordance with description of MiT family translocation renal cell carcinoma.