CASE REPORT

Isolated brain metastasis from a small renal mass

Christopher J D Wallis,^{1,2} Michelle R Downes,³ Georg Bjarnason,⁴ Raj Satkunasivam¹¹Division of Urology, Department of Surgery, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada²University of Toronto, Toronto, Ontario, Canada³Department of Anatomic Pathology, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada⁴Division of Medical Oncology, Department of Medicine, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada**Correspondence to**
Dr Christopher JD Wallis,
wallis.cjd@gmail.com

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SUMMARY

The identification of small renal masses is increasing. Active surveillance is a guideline-approved management strategy for select patients with small renal masses. Metastases during the observation of small renal masses are uncommon, and no cases of brain metastasis have been reported. We report the case of a 73-year-old man who presented with tonic-clonic seizures as the result of a brain metastasis from a small renal mass (3.5 cm in maximal dimension). Treatment with whole brain radiotherapy was undertaken successfully. The patient will undergo surveillance with consideration for systemic therapy at the time of progression.

BACKGROUND

The identification of small renal masses (SRMs), enhancing renal lesions <4 cm in maximal dimension,¹ has increased following the widespread adoption of abdominal cross-sectional imaging. Management options for these patients include active surveillance (AS), partial nephrectomy and ablative treatments.¹ AS is endorsed by the American Urological Association² and European Association of Urology³ guidelines on the management of renal cell carcinoma, particularly for elderly or comorbid patients, due to potential risks or diminishment in quality of life due to intervention.

Metastasis during surveillance of SRMs is very uncommon (<2%).⁴ Further, we are not aware of any cases of brain metastases among these patients.

CASE PRESENTATION

A 73-year-old man presented to our hospital in February 2016 after he was found by his wife to be initially non-responsive and subsequently developed tonic-clonic movements. The patient's seizure activity, which lasted 30 min, abated following treatment with lorazepam and phenytoin by first responders. He was intubated for airway protection and transferred to our hospital for management. Owing to sedation and intubation, neurological examination was unreliable.

The patient's medical history included bradycardia, diagnosed in 2001 and managed with a pacemaker; atrial fibrillation, diagnosed in 2007 and treated with warfarin; neurological episodes not previously diagnosed, first noted in 2001 and manifest with intermittent episodes of unresponsiveness which resolved following the initiation of warfarin therapy for atrial fibrillation (favoured to be transient ischaemic attacks by a consultant neurologist); early onset dementia, noted in the past year with donepezil recently initiated; gout, treated with allopurinol; a history of significant alcohol intake which ceased 4 years ago; and a lifelong smoking

history (>50 pack years). There was no antecedent history of headache or neurological symptoms prior to the onset of seizure.

INVESTIGATIONS

A non-contrast CT imaging identified a 7 mm peripheral ring-enhancing lesion with crescentic increased attenuation and adjacent oedema in the frontal lobe (figure 1A). There was no evidence of midline shift, mass effect or herniation. CT angiography demonstrated non-stenosing plaque and calcification of the carotid bifurcation without evidence of filling defect to suggest acute clot. There was posterior, frontal and parietal flow reduction in the distribution of the middle cerebral artery territory in keeping with a postictal state.

DIFFERENTIAL DIAGNOSIS

Given the enhancing frontal lobe lesion, the differential diagnosis primarily included infectious or metastatic neoplastic aetiologies and he was started empirically on antibiotic therapy.

Figure 1 CT images: (A) non-contrast axial CT of the head demonstrating brain metastasis with surrounding oedema; (B) venous phase coronal CT of the abdomen demonstrating an enhancing left lower pole renal mass.

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Figure 2 Pathological images of brain metastasis: (A) H&E sections of biopsied brain metastasis showing a low power ($\times 2$) interface with brain parenchyma (a) and high power ($\times 10$) image of clear cell renal cell carcinoma (b); (B) PAX-8 immunostain ($\times 10$) showing characteristic nuclear staining typical of renal cell carcinoma.

Further CT imaging of the abdomen showed a 3.5×3.4 cm enhancing left lower pole renal mass and a non-specific right adrenal nodule (1.8 cm) without evidence of disease in the regional lymph nodes (CT of the abdomen, figure 1B). There was no evidence of hepatic disease. Subphrenic fluid was noted in keeping with volume overload presumed to be as a result of resuscitation following seizure activity and low cardiac output. All cultures were negative. After stabilisation, he underwent an excisional brain biopsy, which demonstrated metastatic clear cell carcinoma with prominent vasculature. The cells had small central nuclei and barely visible nucleoli on $\times 10$ magnification (figure 2A). Immunohistochemistry confirmed that the carcinoma was PAX-8 positive in keeping with a clear cell renal cell carcinoma (figure 2B). No sarcomatoid or rhabdoid features were identified.

Further staging investigations, including a CT of the chest and bone scan, showed no evidence of metastatic disease in the thorax or axial skeleton. Communication with the patient's general physician indicated a history of simple renal cysts, and a lesion in the left kidney measuring $3.0 \times 3.0 \times 2.5$ cm on ultrasonographic imaging 4 years previously.

TREATMENT

Following stabilisation, this man was treated with cavity radiation (25 Gy in five fractions, and a boundary of 20 Gy in five fractions). Cyto-reductive surgery was not felt to be appropriate.

OUTCOME AND FOLLOW-UP

He will undergo surveillance following his radiotherapy with a consideration for subsequent systemic targeted therapy. Thus, this man presents with tonic-clonic seizures as the result of an isolated brain metastasis from a SRM.

DISCUSSION

Given this patient's competing risks of mortality from his significant comorbidities, he would be the prototypical candidate for AS of his SRM.

AS for a SRM is still evolving and, as a medical intervention, is in its nascence. The largest prospective study was published in 2011.⁵ Jewett *et al* identified two patients (1.1% of the study cohort) who developed metastasis during observation. A recent systematic review identified 18 patients (of 880; 2%) who

developed metastasis during surveillance.⁶ To the best of our knowledge, the present paper represents the first report of a brain metastasis associated with a SRM managed conservatively and suitable for AS.

While advanced patient age, larger initial tumour size and increased tumour growth have been identified in patients with disease progression on surveillance,⁶ there are no accepted criteria for intervention among patients on AS and prognostic factors are poorly understood. Central tumour location has been proposed as an adverse feature which may preclude a surveillance strategy, though this has not been demonstrated in prospective studies. Further complicating this issue, Jewett *et al*⁵ demonstrated that benign and malignant lesions had similar growth rates.

In addition to developing during surveillance, metastases may be present at diagnosis for patients with SRMs⁷ or may develop following surgical treatment of the primary tumour.^{8–9} Brain metastases are uncommon even among patients who develop metastasis following primary treatment and are almost exclusively seen among patients with locally advanced disease.^{8–9} However, based on the observation that brain metastases are typically symptomatic on presentation, guidelines recommend brain imaging only based on indication.³ Therefore, the incidence of brain metastasis may be underappreciated in patients with renal cell carcinoma as, even in patients with metastatic disease, brain imaging is rarely performed.¹⁰

The role of renal mass biopsy prior to initiation of surveillance in patients such as this remains controversial.¹¹ While uncommon ($\sim 5\%$), the identification of high-risk histological features, such as a sarcomatoid component or intratumoural necrosis, may warrant active treatment due to a more aggressive phenotype.^{12–13}

While the majority (95%) of patients with brain metastasis from renal cell carcinoma have other sites of metastatic disease,¹⁴ patients may experience brain metastasis in the absence of extracranial disease. In this case, there was minimal growth of his primary renal lesion over 4 years and no evidence of progressive intra-abdominal or intrathoracic disease prior to his neurological event.

This case highlights the potential for SRMs to cause significant morbidity. AS fundamentally entails a philosophical and societal acceptance of metastatic risk, and while this range has been quantified (1–5%) and deemed reasonable for low-risk prostate

cancer, the risk and acceptable target for SRMs is unknown. AS remains an important treatment option; it may reduce overtreatment and surgical morbidity while achieving acceptable cancer-specific survival. However, this case highlights our rudimentary understanding of the biology of kidney cancer and limitations of its management in the absence of prognostic markers for risk assessment. The optimal protocol for AS, including selection of appropriate candidates, risk stratification by tumour biology and propensity for metastasis, and the optimal frequency of follow-up and imaging remains to be elucidated.

Learning points

- ▶ While small renal masses have a low metastatic potential, there remains a finite risk of metastasis.
- ▶ Metastasis of kidney cancer may occur in the absence of locoregional progression.
- ▶ The adoption of active surveillance strategies for cancer entails a philosophical and societal acceptance of the trade-off between avoidance of overtreatment with the potential for disease progression.

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Contributors All authors contributed to the literature review. CJDW drafted the report which all authors critically revised. All authors approved the final manuscript for submission.

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