CASE REPORT

Rapid development and recurrence of translocation renal cell carcinoma

Ned Kinnear,¹ Sam Wreghitt,¹ Derek Barry Hennessey,^{1,2} Peter Liodakis^{1,3}

¹Department of Urology, Austin Health, Heidelberg, Victoria, Australia

²Department of Urology, Craigavon Area Hospital, Portadown, UK

³Department of Surgery, University of Melbourne, Heidelberg, Victoria, Australia

Correspondence to
Dr Ned Kinnear,
ned.kinnear@gmail.com

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SUMMARY

Translocation renal cell carcinoma (RCC) is a rare aggressive malignancy in adults. A 40-year-old man presented with painless macroscopic haematuria. Initial investigations of renal ultrasound, CT scan, urine culture and urine cytology were normal. On rigid cystoscopy and pyelo-ureteroscopy, bleeding was seen from a normal-appearing right renal upper pole. An arteriovenous malformation was suspected, and laser cauterisation was performed. Left renal biopsy was performed due to proteinuria and suggested IgA nephropathy. The patient represented with haematuria and repeat imaging only 17 months after first presentation displayed a 9.8 cm right renal tumour with renal vein thrombus. An upper tract urothelial cancer was suspected, and the patient underwent right nephroureterectomy. Histopathology revealed translocation RCC, completely excised. Ten months postoperatively, metastasis was seen on surveillance imaging and subsequently confirmed on biopsy. The patient was referred for systemic therapy and remains alive 19 months postprocedure.

BACKGROUND

Translocation renal cell carcinomas (RCCs) are common in children and young adults but unusual in later adulthood. Translocation involving either chromosomal cytogenetic bands Xp11 or 6p21 results in overexpression of microphthalmia transcription factor (MiTF) proteins transcription factor E3 (TFE3) or transcription factor EB (TFEB), which can be detected by immunohistochemistry. Exposure to cytotoxic chemotherapy is the only known risk factor. Affected adults commonly present with stage III or IV disease. Surgery remains the mainstay of treatment. Prognosis depends on the presence of metastasis at presentation but is generally grave. While swift progression postdiagnosis is well known, rapid growth of the primary tumour, as seen in this case, appears not to have been previously reported.

CASE PRESENTATION

A 40-year-old male presented to his community medical service with new onset painless macroscopic haematuria. He denied trauma or other symptoms. His only medical history consisted of thalassaemia trait, and he was taking no medications. He had no personal nor family history of urological malignancy, urolithiasis, renal disease, autoimmune or connective tissue disorder and denied childhood renal infections. The patient reported smoking five

cigarettes per day for 3 years, ceasing 20 years prior to presentation.

On examination, the patient appeared well. Vital signs were unremarkable. His abdomen was soft, non-tender, and no renal nor other masses were palpable. Genital examination was normal. On urine microscopy, numbers of leucocytes, erythrocytes and squamous cells were all within normal limits, and no bacteria grew following culture. Proteinuria was observed and persisted on subsequent testing, measuring ≤ 0.6 g/day. No malignant cells were seen on urine cytology.

Blood laboratory results were normal in all regards, with haemoglobin of 131 g/L, white cell count of 4.2×10^9 /L, platelet count of 201×10^9 /L, estimated glomerular filtration rate of >90 mL/min/1.73 m² and prostate specific antigen of 0.32 ng/L. C-reactive protein was <0.3 mg/L, international normalised ratio was 1.0 and activated partial thromboplastin time was 29 s. On further testing, latent tuberculosis testing via the QuantiFERON TB Gold assay was negative. Antinuclear antibody and both classical antineutrophil and perinuclear antineutrophil cytoplasmic antibody immunoserology were also negative, and complement testing of C3 and C4 was within normal ranges.

Renal tract ultrasound revealed normal upper tracts and bladder wall, a 21 mL prostate and post-void residual urine of 43 mL.

Contrast CT intravenous pyelogram (IVP) displayed a cortical 5 mm Bosniak 1 right midpole renal cyst and a separate 1.5 mm right renal midpole intrarenal calculus. The kidneys and remaining urinary tract otherwise appeared normal. All other abdominal viscera and the visualised lung bases were unremarkable, and there was no lymphadenopathy.

Rigid cystoscopy was performed. The urethra and prostate were normal. A moderate volume of blood clots was found in the bladder and evacuated. Haematuria was visualised from the right ureteric orifice, and no other bladder abnormalities were seen. On right retrograde pyelogram (RGP), a filling defect was visualised in a right upper pole calyx. After no abnormality was seen on right rigid ureteroscopy, on right flexible pyeloscopy, slow bleeding was seen at the same upper pole calyx from a renal papilla, which had otherwise normal appearance. This was laser cauterised, and a 4.8Fr double J ureteric stent was placed. The patient's haematuria settled, and his ureteric stent was removed via flexible cystoscopy 1 week postoperatively.

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Given the proteinuria, following consultation with a renal physician, a biopsy was performed of the inferior pole of the left kidney. There was focal weak positive staining for IgA. Other stains were negative, and the biopsy histology was otherwise unremarkable, with normal architecture and no hypercellularity, atrophy, inflammation, fibrosis nor neoplasia.

The patient continued to have intermittent painless macroscopic haematuria. Seventeen months after initial presentation, he presented to our institution's emergency department in clot-related acute urinary retention. He denied weight loss or systemic symptoms.

On examination, the patient was well but uncomfortable. Abdominal palpation revealed a distended tender bladder, and no other masses. Vital signs were within normal limits. A three-way 22Fr urethral in-dwelling catheter (IDC) was inserted, and multiple small clots were removed via manual bladder washout, following which continuous bladder irrigation was commenced.

INVESTIGATIONS

On blood laboratory testing, haemoglobin had fallen to 113 g/L. Leucocyte and platelet counts, electrolytes and coagulation testing were again normal. Urine microscopy exhibited 200×10^6 /L leucocytes, 300×10^6 /L erythrocytes and scanty mixed growth on culture.

CT IVP was performed, displaying a new heterogeneous 98 mm mass replacing much of the right kidney, from upper to lower pole. The mass demonstrated peripheral enhancement with central non-enhancing portions consistent with necrosis. Two right renal veins were seen without evidence of venous tumour extension. Tumour thrombus was seen to obstruct the lower pole and extend into the proximal ureter. The left kidney was normal. Other abdominal viscera were normal; there was no lymphadenopathy, and visualised lung bases were clear (figure 1).

DIFFERENTIAL DIAGNOSIS

Given only scant supporting evidence for IgA glomerulonephritis, the working diagnosis prior to the patient's representation had been of a small arterio-venous malformation. Following the CT IVP, the leading differentials were renal urothelial malignancy followed by clear cell RCC. Other diagnoses considered included other types of RCC such as

Figure 1 Initial and subsequent contrast CT intravenous pyelogram scans of the abdomen and pelvis during delayed phase, coronal views. (Left) Imaging at first presentation, revealing essential normal kidneys bilaterally. (Right) Repeat imaging seventeen months later. A new heterogeneous mass is seen replacing the mid and upper zones of the right kidney, measuring 98 mm in maximal dimension. The periphery enhances while the central non-enhancing regions are in keeping with necrosis. The contralateral kidney and other abdominal viscera are normal. There is no evidence of lymphadenopathy nor metastasis.

Figure 2 Gross anatomical pathology of right nephroureterectomy specimen. The right kidney is seen bisected coronally, flanked by the right ureter on the left of image and peri-nephric adipose tissue to the right. The tumour, measuring 112×67 mm within the 131×91 mm kidney, extends throughout the upper and lower poles and into the renal pelvis. The remaining parenchyma appears distorted by the bulging tumour. The renal pelvis and proximal ureter are occupied by clot, which is seen to plug the lower pole calyces.

papillary, chromophobe or collecting duct. Benign renal tumour such as oncocytoma was deemed unlikely, as were non-nephrogenic entities such as lymphoma or metastasis from a distant organ.

TREATMENT

The patient was admitted to hospital, and the following day underwent rigid cystoscopy. A large volume of clot was evacuated from the bladder, and bleeding was again seen from the right ureteric orifice. On right rigid ureteroscopy, copious clot was seen to fill the right proximal ureter, not amenable to biopsy or laser cautery. Right RGP was performed, on which the renal pelvis failed to fill with contrast due to ureteric clot.

The patient's haemoglobin continued to fall that day, reaching 102 g/L 24 hours postadmission, so that evening after CT scan of the chest had shown no evidence of metastasis, he underwent laparoscopic right nephroureterectomy, including resection of a formal bladder cuff. Lymph node resection was not performed. The patient's IDC had been removed at the start of the procedure to permit endo-urological instrumentation, and a new three-way 22Fr IDC was inserted at the procedure's conclusion. The patient recovered well and was discharged 2 days postoperatively. CT cystogram conducted 7 days postoperatively found no evidence of bladder leakage, and the patient's IDC was removed.

Histopathology revealed a 112 mm tumour extending from the right renal upper and lower poles into the renal pelvis and proximal ureter. Associated thrombus was seen to plug the renal lower pole and the proximal ureter (figure 2). The tumour invaded the proximal renal vein. Microscopically, the tumour was composed of solid and papillary configurations of pleomorphic large cells with clear to eosinophilic cytoplasm and high grade nuclei. Necrosis was present, mainly in centrally located cells. Perinephric fat invasion was not present, and all margins including bladder cuff were clear of tumour. Immunohistochemistry stain for transcription factor E3 (TFE3) was strongly positive, while negative for carbonic anhydrase, MelanA, AE1 and cytokeratin AE1/AE3 (figure 3), in keeping with grade T3a translocation RCC.

Figure 3 Immunohistochemistry stains of tumour. (Top left) Tumour cells show strong nuclear staining for TFE3. (Top right) Staining for carbonic anhydrase IX is negative. (Bottom left) Staining for MelanA is negative. (Bottom right) Staining for AE1/3 is negative.

OUTCOME AND FOLLOW-UP

Starting 1 month postoperatively, the patient underwent surveillance contrast CT scanning of the chest, abdomen and pelvis (CAP) every 3 months. These were unremarkable, until a CT CAP performed 10 months postoperatively exhibited two suspicious new lung nodules ≤ 7 mm in maximal dimension, and a new 20 mm left hilar lymph node. The patient subsequently reported a recent period of productive cough and exertional dyspnoea, so the decision was made to repeat the imaging in 2 months. This CT CAP, now 12 months postoperatively, revealed four lung nodules, with enlargement of the existing lesions now to ≤ 12 mm. The hilar node remained 20 mm. There was also a new 8 mm lesion in the L2 vertebral body, concerning for metastasis (figure 4).

Endo-bronchial ultrasound guided needle biopsy of the left hilar lymph node revealed atypical cells of varying size and shape, with large nuclei, prominent eosinophilic nucleoli and delicate eosinophilic cytoplasm, positively staining for TFE3 on IHC, consistent with translocation RCC metastasis.

The patient was commenced on sunitinib 50 mg daily, given for 2 weeks on, 1 week off, which he tolerated well. Follow-up CT CAP after 4 months of therapy, 16 months postoperatively, revealed a partial response, with the metastases' diameter decreasing by on average 60%, and none increasing in size. At time of writing, 19 months postoperatively, the patient remains on sunitinib and asymptomatic, with no haematuria, pain, weight loss or respiratory symptoms. He is expected to complete 12 months of sunitinib therapy. His follow-up will consist of CT CAP for every 3 months until 2 years postrecurrence, 6 monthly until 5 years, and then lifelong annual CT CAP thereafter.

DISCUSSION

Translocation RCC is an aggressive acquired renal tumour that occurs due to chromosomal translocations. The most common translocation involves the *TFE3* gene on the 11th cytogenetic band of the petite 'p' arm of chromosome X. At least five specific gene fusion partners are known to result in Xp11 translocation tumour, most frequent being the *PRCC* gene on chromosome 1q21 and the *ASPL* gene on chromosome 17q25. Xp11 translocation results in overexpression of several fusion proteins with contain the C-terminal portion of TFE3 protein, a member of the MiTF protein family.¹

Less commonly, translocations involve the *TFEB* gene, due to rearrangement of chromosome 6p21 and the *Alpha* gene on chromosome 11q12, resulting in t(6;11)(p21;q12) translocation. Rearrangements of the *TFE3* or *TFEB* loci constitute two of the four members of the MiTF family. RCC due to Xp11 and t(6;11) translocation were first described in 1988 and 2001, respectively.² In 2004, the WHO defined translocation RCC as a separate tumour type, with the International Society of Urologic Pathology Vancouver Classification of Renal Neoplasia following suit in 2013.

The oncogenic mechanism of the identified genetic translocations is not known. It is speculated that alteration of MiTF genes may impede cell cycle regulation.

Translocation RCC is a common type of renal malignancy among children and young adults. However, it is uncommon outside this population, representing 1%–5% of primary renal malignancies in adults.¹ Translocation RCC appears to have a female preponderance.^{1,3} However, the only known risk factor is exposure to cytotoxic chemotherapy, especially DNA topoisomerase II inhibitors or alkylating agents.^{1,4}

As with any renal tumour, translocation RCC may present with haematuria, flank pain, flank mass, metastatic symptoms or be detected incidentally on imaging.¹ At presentation, most patients

Figure 4 Surveillance contrast CT scan of the chest, abdomen and pelvis twelve months post right nephroureterectomy. (Left; thorax, axial view, soft tissue settings) In the chest, a 20 mm left hilar lymph node is seen. (Middle; thorax, axial view, lung settings) A 12 mm nodule is apparent in the upper lobe of the left lung anterior to a branching vessel, enlarged from 7 mm 2 months prior. (Right; abdomen and pelvis, coronal view, bone settings) Within the L2 vertebral body, a new 8 mm faintly sclerotic lesion is appreciated, with central hypodensity.

will have stage III or IV disease and 18%–50% will have metastases.^{1,3}

Diagnosis relies on careful morphological assessment and then specialised testing of the resected tumour. The morphological spectrum of translocation RCC is broad and has overlap with many common RCC types.^{1,4} Grossly Xp11 translocation tumour may be solid, tan to grey in colour and often contain necrosis or haemorrhage, as seen in this case, while t(6;11) translocation tumour varies from cystic to solid and may be tan or mahogany in colour. Microscopically, Xp11 translocation RCC displays large, often polygonal, epithelioid cells with discrete borders. Cells have abundant clear to granular eosinophilic cytoplasm and may be arranged in nests or branching papillary structures. Nuclei are generally high grade and enlarged, with variable nuclear membrane irregularity and prominent nucleoli. Translocation RCC due to t(6;11) typically has a biphasic pattern of cell morphology, with the majority of tumour comprised of similar cells to Xp11 tumour, supplemented by a minor population of small eosinophilic cells.⁴ Other authors, however, have described a monomorphic pattern of large polygonal cells.¹ These t(6;11) tumour cells may be arranged in rosette-like, tubular or papillary architecture and display small round hyperchromatic nuclei with occasional small nucleoli. Mitoses are rare, and TFE3 immunohistochemistry staining may be heterogenous.¹

While there is some disagreement in the literature regarding selection of specialised testing for translocation RCC, positive staining of TFE3 or TFE3 protein on immunohistochemistry is generally accepted as diagnostic.^{4,5} False positive and negative rates for translocation RCC with this modality have been reported as 6.7% and 4.3%, respectively.⁵ Fluorescence in situ hybridisation assay may be more sensitive and specific⁴ but is less widely used. Testing via cytogenetic analysis and RNA PCR are also reported but less common again.¹

Correct diagnosis of translocation RCC is important, as established treatment protocols for clear cell or other types of RCC may not apply, given the unique molecular pathways.⁴ However, no published algorithms exist for this uncommon neoplastic entity, with treatment being guided by contemporary management of clear cell RCC and literature reviews. As for other RCC subtypes, surgical resection remains the mainstay of treatment for non-metastatic translocation RCC.⁵ While radical nephrectomy is thought to offer greatest cancer-free survival rates, partial nephrectomy has been successfully performed in a series of four patients with 3 years' follow-up.³ In metastasis-free patients, postoperative adjuvant therapies have been used but appear not to improve outcomes. For those with stage III or IV disease, options include metastatectomy for solitary recurrences, and systemic therapies consisting of immunotherapies interleukin-2 or interferon-alpha, antagonists of vascular endothelial growth factor (VEGF) such as tyrosine kinase inhibitors and bevacizumab, the mammalian target of rapamycin antagonist temsirolimus, chemotherapy or radiotherapy.^{5,6} However, unlike clear RCC, no prospective or large studies exist for any of these modalities in translocation RCC. Adjuvant therapy use varies widely between centres. Approximately half the patients with advanced stage translocation RCC receive such treatment, mainly immunotherapy and anti-VEGF therapies, with weak evidence of superiority in the latter.^{5,6} However, response rates remain low.⁵

Prognosis relies on patient age, translocation type and presence of metastasis on presentation. In children, translocation RCC appears to have a more favourable course than clear cell RCC. However, in adults this relationship reverses. Previously thought similarly indolent in the older demographic, translocation RCC

is now known to behave aggressively, and recur quickly and also commonly, doing so in up to 60% of patients. This appears particularly true of Xp11 translocation RCC, with the less common t(6;11) translocation RCC reported to behave with less hostility and only rarely metastasise.⁴ Unsurprisingly, metastasis at presentation has been associated with poorer outcomes. Ellis *et al*'s systematic review identified 53 patients with translocation RCC of known follow-up duration, of whom eight presented with metastasis. The metastatic and non-metastatic groups had median follow-up of 20 and 54 months, respectively, with corresponding cancer-free survival of 13% and 62%.⁶

These patients should be followed up as for high-risk RCC. Commencing 3–6 months postoperatively, this should consist of chest and abdominal CT or MRI at least every 6 months for 3 years, then annually until 5 years postoperatively, with accompanying history, physical examination and blood testing.

This patient's diagnosis was delayed by the false reassurance of his initial benign thorough workup, in combination with the patient failing to represent despite recurrent haematuria until some 17 months later. In the scenario of macroscopic haematuria with non-diagnostic investigations, clinicians should both encourage patients to represent if the haematuria recurs and reinvestigate.

While translocation tumour is known to often behave aggressively, to the best of the authors' knowledge, rapid growth of the primary tumour has not previously been described. In this patient, the tumour grew from unobservable to 112 mm in 17 months. Acknowledging that growth was likely exponential, this represents a mean growth rate of >6.5 mm per month.

Patient's perspective

'The problem started with blood in my urine. I underwent scans and scopes which all appeared normal. A kidney biopsy showed IgA nephropathy, but I was told it didn't require active treatment. The doctors thought I might instead have misformed blood vessels. The blood in my urine reoccurred on and off, but the bleeding always resolved before I could attend the emergency department. When I had a repeat CT scan I was surprised, as I believe everyone was, that I now had a large kidney mass. I underwent surgery and cannot fault anyone for the treatment I received'.

Learning points

- ▶ Translocation renal cell carcinoma is common in children and young adults but infrequent in later adulthood.
- ▶ Tumours display translocation of genetic material on chromosomes X or 6.
- ▶ This renal malignancy behaves aggressively, with most patient presenting with stage III or IV disease, and up to half with metastasis.
- ▶ Treatment centres on surgical resection, with little evidence for systemic therapies.
- ▶ Patients should be encouraged to represent for reinvestigation if their macroscopic haematuria recurs.

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