CASE REPORT

Hereditary leiomyomatosis and renal cell cancer syndrome: a family affair

Jiasian Teh,¹ Ned Kinnear,¹ Hannah Douglass-Molloy,² Derek Barry Hennessey¹

¹Austin Hospital, Heidelberg, Victoria, Australia

²Royal Adelaide Hospital, Adelaide, South Australia, Australia

Correspondence to

Dr Ned Kinnear, ned.kinnear@gmail.com

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SUMMARY

A 49-year-old woman with cutaneous and uterine leiomyomas, flank pain and a family history of hereditary leiomyomatosis and renal cell cancer (HLRCC) syndrome sought genetic testing. She was found to harbour a fumarate hydratase (FH) genetic mutation and a previously undetected renal tumour. The patient underwent radical nephrectomy, and remains well at follow-up. HLRCC syndrome is a rare autosomal dominant disease, with patients at increased risk for cutaneous leiomyomas, early-onset uterine leiomyomas and aggressive renal carcinoma. Although the syndrome may manifest life-threatening complications, outcomes may be improved by preventative family screening and surveillance, compelling early diagnosis.

BACKGROUND

Hereditary leiomyomatosis and renal cell cancer (HLRCC) syndrome is an uncommon autosomal dominant condition driven by germ line mutation of the gene coding for fumarate hydratase (FH), a citric acid cycle enzyme. Classically, affected patients develop multiple cutaneous leiomyomas, uterine leiomyomas in female patients and aggressive renal cancer. However, most carriers do not develop all manifestations. This patient's diagnosis led to further testing within the family. The case illustrates the need to consider hereditary causes and syndromal presentations of malignancy.

CASE PRESENTATION

A 49-year-old woman sought genetic counselling subsequent to the identification of germ line FH gene mutation in her brother. Her medical history included depression and multiple cutaneous and uterine leiomyomas, requiring hysterectomy at age 31. She had no regular medications, and was a current smoker with a six pack-year history. The patient had two siblings and three children. Of these, one brother had cutaneous leiomyomas and a known FH mutation diagnosed at age 50, but none of the patient's progeny nor her other sibling displayed characteristics of the phenotype or had undergone genetic testing. Additionally, the patient's mother and maternal cousin had cutaneous leiomyomas and renal cell carcinoma (RCC), being fatal in the latter. The age of diagnosis and histopathology of these two renal cancers was not known.

In our patient, genetic testing confirmed germ line FH gene mutation on exon 10, with deletion of bases thymine and cytosine at nucleotide locations 1475–1476, leading to amino acid histidine

being transcribed at location 492 instead of leucine. Nucleotide numbering was according to the cytosolic FH sequence, with the A of the ATG initiator codon as nucleotide position 1. Amino acid positions were numbered from the translation of the cytosolic FH nucleotide sequence.

After being informed of this adverse genetic result, the patient reported several months of right flank pain with no associated haematuria, weight loss or systemic symptoms. On examination, the patient had multiple cutaneous leiomyomas on her left posterior shoulder and right anterior thigh. Abdominal examination revealed a Pfannenstiel incision scar subsequent to hysterectomy, and was otherwise normal.

INVESTIGATIONS

Urine microscopy was negative for blood, infective markers or bacteria. Routine blood tests were all within normal limits, including estimated glomerular filtration rate of 88 mL/min/1.73 m². Renal tract ultrasound did not reveal any abnormality. However, MRI of the abdomen demonstrated a single renal tumour. This 37 mm cystic mass was located in the upper pole of the right kidney, with multiple enhancing thickened internal septa consistent with a Bosniak III lesion (figure 1). To assist in surgical planning, a contrast CT scan of the chest, abdomen and pelvis with arterial and venous phases was performed 2 weeks later, and confirmed the presence of this solitary tumour. On this modality, it appeared 55 mm in maximum dimension, solid and heterogeneously enhancing (figure 2). There was no evidence of lymphadenopathy, metastatic disease or abnormality of the contralateral kidney. The patient and her investigations were discussed at our institution's uro-oncology multidisciplinary meeting. The consensus was the dimensions were poorly comparable across different imaging modalities, with both scans concerning for malignancy.

DIFFERENTIAL DIAGNOSIS

HLRCC-associated renal cancer was deemed most likely. The differential included benign renal tumour, metastatic renal mass and renal malignancy unrelated to HLRCC syndrome. Upper tract transitional cell carcinoma (TCC) was also considered given the tumour's proximity to the collecting system.

TREATMENT

The patient underwent right laparoscopic radical nephrectomy and adrenalectomy. Histopathology

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Figure 1 Contrast MRI scan of the abdomen and pelvis. T2-weighted images, coronal and axial slices. A 3.7 cm mass is seen in the upper pole of the right kidney. It appears cystic with multiple thick enhancing internal septations.

Figure 2 Contrast CT scan of the abdomen and pelvis, coronal and axial slices. A 5.5 cm heterogeneously enhancing solid mass is seen in the upper pole of the right kidney. There is no evidence of abnormality of the contralateral kidney, lymphadenopathy or metastasis.

demonstrated a unifocal solid renal tumour, 50 mm in greatest dimension. The tumour involved the associated renal vein with extension into renal sinus and hilar adipose tissue, while the renal capsule and adrenal gland were spared. Microscopically, the tumour showed a predominantly tubulocystic growth pattern with focal solid components. In areas, cells displayed large tumour cell nuclei, with prominent, inclusion-like, brightly eosinophilic macronucleoli, often with perinuclear haloing. Lymphovascular invasion was present. Surgical margins were equivocal. Ureteric and arterial margins were clear of tumour, but malignant cells were seen to abut crushed tissue at the renal vein surgical clip margin.

This infiltrative growth and cytomorphology were characteristic of HLRCC-associated RCC (figure 3). No further immunohistochemical stains were available to differentiate between a hereditary and sporadic RCC. However, given the morphology, history of cutaneous and uterine leiomyomatosis and known FH gene mutation, the diagnosis of HLRCC-associated RCC was favoured.

OUTCOME AND FOLLOW-UP

Postoperatively, the patient recovered uneventfully and was discharged after 3 days. Her case was subsequently discussed at our institution's weekly multidisciplinary meeting, with involvement of allied health and nursing staff, and specialists from pathology, radiology, urology, medical oncology and radiation oncology.

Given the high risk of recurrence at the surgical margin and of de novo contralateral tumour, the consensus plan was for surveillance with blood testing and contrast CT scan of the abdomen at 3 and 12 months postoperatively, in addition to routine wound care. In addition, the patient's brother for whom FH gene status was unknown and her three children were all referred for genetic counselling. From this, a multigenerational pedigree was constructed (figure 4). Initial surveillance CT scanning was performed and was normal for all relatives in whom FH gene mutation was detected. This included her elder brother, who underwent first abdominal imaging at age 50.

One month postoperatively, the patient's operative wounds were well healed, but she reported of intermittent mild pleuritic lower left anterior thoracic pain. Examination of the chest did not reveal any palpable tenderness, mass, skin changes or abnormal vital signs. Blood testing including full blood count, serum electrolytes, D-dimer and troponin T were normal, as were electrocardiogram and whole body bone scan. The patient's pain was assessed as likely musculoskeletal in origin, and she was referred to a physiotherapist. Three months postoperatively, the patient's pain had improved. Contrast CT scan of the abdomen at this time revealed only expected postoperative changes. This imaging also included the lower four ribs bilaterally, which were unremarkable.

The patient remains at high risk of recurrence and metachronous RCC. She will receive ongoing imaging surveillance. This

Figure 3 Histopathological tumour preparations with H&E. Low-power view (left; 40× magnification) demonstrates the tubulocystic architecture predominant in this case. High-power view (right; 400× magnification) reveals large tumour cell nuclei, with prominent, inclusion-like, brightly eosinophilic macronucleoli, characteristic of HLRCC-associated RCC. HLRCC, hereditary leiomyomatosis and renal cell cancer; RCC, renal cell carcinoma.

Figure 4 Multigenerational pedigree. Descendants of second degree relatives who do not harbour fumarate hydratase (FH) gene mutation are not shown. Black arrow: the index patient, presented here. Circle: female. Square: male. Red: FH gene mutation present. Green: FH gene mutation not present. Grey: FH status unknown. Diagonal strikethrough: deceased. *: hereditary leiomyomatosis and renal cell cancer syndrome (HLRCC)-associated renal cell cancer (RCC) present.

will consist of either contrast CT scan or MRI of the abdomen and pelvis annually.

DISCUSSION

At least 4% of renal cancers are hereditary. HLRCC syndrome is rare, with cases clustering in families. Less than 200 affected kindreds have been described worldwide, with the largest study to date comprising 41 families.¹ This autosomal dominant condition is characterised by increased risk of cutaneous leiomyomas, early-onset multiple uterine leiomyomas and aggressive RCC. Allowing for the limitations of small studies, estimated risk for each feature among affected individuals is 76%, nearly 100% and 15%, respectively.² Presence of renal cancer determines prognosis. When present in patients, half will present with metastasis and three-quarters will succumb to their disease.²

The syndrome's aetiology was established in 2001 by Launonen *et al*,³ who studied two Finnish kindreds in whom

components of this triad were commonplace, and identified the location of the aberrant FH gene on chromosome 1. This gene normally codes for FH, which catalyses conversion of fumarate to malate in the mitochondrial citric acid cycle. FH-deficient cells accumulate fumarate, which has oncogenic properties.

Patients typically present either due to one or more of the triad's manifestations, or following a positive genetic result in a relative. Definitive diagnosis is made by detection of a FH gene mutation. However, patients with features of the syndrome but without positive genetic testing may reach diagnosis by histological assessment of tumours.¹

Cutaneous leiomyomas are fleshy red or pink coloured papules <20 mm in diameter. They have a segmental distribution and present between the second and fourth decades of life. They may be intermittently painful, typically on provocation by cold or trauma. Biopsy confirmation should prompt genetic testing for HLRCC. In female patients, uterine leiomyomas are

almost universal, multiple, often symptomatic and occur early, before age 40.²

HLRCC-associated renal cancer is a distinct entity recognised by the WHO and the International Society of Urological Pathology. Tumours are usually solitary, aggressive, diagnosed in the fourth or fifth decade and more common in female carriers. Lesions often have a prominent papillary architecture which mimics type 2 papillary RCC. However, other architectural patterns have been described, including tubular, tubulocystic, solid and mixed. Cells are large, with abundant eosinophilic cytoplasm, and display characteristic nuclear features, generally are not found in other renal tumours, which may be only focal within a tumour. These include large nuclei, with prominent, inclusion-like, brightly eosinophilic macronucleoli.^{1 2}

Diagnosis remains challenging, and additional genetic or immunohistochemistry studies are often needed. While there are no accepted diagnostic criteria, diagnosis in this patient was guided by the principles suggested by Smit *et al.*⁴ In this patient, the tumour was predominantly tubulocystic with only focal solid components. This is in keeping with Smith *et al.*'s⁵ recent retrospective study of 29 patients with tubulocystic RCCs, which found that most had FH gene mutations.

Management of HLRCC includes genetic counselling for potential testing, treatment of symptomatic leiomyomas, and surveillance and treatment for renal cell cancer.

Genetic counselling is important as testing carries important ethical and personal considerations for the patient. It offers certainty about the diagnosis, a rationale for renal cancer surveillance and allows for genetic investigation of relatives. Conversely, some may wish to avoid testing. Most patients with FH gene mutations will never develop renal cancer, but will suffer inconvenience, expense and anxiety.²

Symptomatic cutaneous and uterine leiomyomas may be considered for excision, which may require plastic reconstructive techniques for large resections and hysterectomy, respectively.

HLRCC-associated renal cancers are aggressive and in the absence of metastasis require excision. As synchronous or metachronous tumours may require multiple resections, preservation of renal parenchyma is vital. Therefore, partial nephrectomy is preferred. For some tumours, as with this case, their size or location may make nephron-sparing surgery inappropriate, and radical nephrectomy will be necessary.²

For non-metastatic disease, surgery is usually curative and no other therapy is required. Neither radiotherapy nor hormonal therapy has been shown to reduce risk of relapse. Large unresectable renal tumours may respond to neoadjuvant targeted therapy, although results are mixed and large studies are lacking.⁶

Currently, there is no standard therapy for metastatic HLRCC-associated renal cancer, and management follows the same principles as for non-hereditary metastatic RCC.² Cytoreductive nephrectomy has been shown to improve outcomes in appropriately selected patients, as the primary tumour is poorly responsive to systemic therapies and also may seed further metastases.^{2 6} Patients with a single distant metastasis may also be offered metastatectomy. Systemic adjuvant therapies lack strong evidence, although these are being examined currently by several ongoing clinical trials. Cytokine-based immunotherapy, consisting of interleukin-2 or interferon- α , has shown modest effects in shrinking metastases.⁶ Targeted therapies appear more effective, and unlike other systemic therapies, have also been shown to impact the primary tumour. The best understood pathogenic molecular mechanisms in RCC are the mechanistic target of rapamycin (mTOR) and von Hippel-Lindau (VHL) tumour suppressor/hypoxia inducible factor (HIF) pathways,

with the latter including HIF targets such as vascular endothelial growth factor.² Subsequently, several targeted therapies have been approved by the US Food and Drug Administration. Sunitinib and everolimus, working against the VHL/HIF and mTOR pathways, respectively, are among the most promising.⁶

Surveillance for renal cancer requires a high-resolution low-radiation modality at intervals short enough to capture malignancy before metastasis. Renal tract ultrasound has low sensitivity for detecting solid renal tumours, which are often isoechoic, as in this patient. Surveillance recommendations in the literature vary, with the most support existing for annual abdominal MRI scanning.²

Patient's perspective

"After my brother was diagnosed with the syndrome, I thought I should get tested. I didn't expect to have the genetic mutation or kidney cancer. It was a real shock. The operation went well except for chest pain afterwards, which lasted a few weeks. I was really worried the cancer had spread, but thankfully the scans were clear. I'm glad I didn't wait longer to get tested, and that now my children can get screened too."

Learning points

- Hereditary leiomyomatosis and renal cell cancer (HLRCC) syndrome is a recognised rare familial cause of renal cancer and leiomyomas of the skin and uterus.
- Uterine leiomyomas which are multiple, occur early or coexist with cutaneous leiomyomas should raise suspicion for possible HLRCC syndrome.
- Renal cancer development determines prognosis and occurs in 15% of patients.
- Diagnosis allows for genetic testing and renal cancer surveillance for the patient and their family.

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