CASE REPORT

Hereditary leiomyomatosis and renal cell cancer (HLRCC): cutaneous and renal manifestations requiring a multidisciplinary team approach

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SUMMARY

Cutaneous leiomyomas are rare tumours of smooth muscle origin associated with disorders such as hereditary leiomyomatosis and renal cell cancer (HLRCC) syndrome. HLRCC is an autosomal dominant syndrome caused by loss of function mutations in the fumarate hydratase gene. Sufferers of this disorder are predisposed to the development of tumours of the skin and/or uterus, with a further subset of HLRCC families at risk of renal cell carcinoma with papillary features. This syndrome is rare and carries with it a significant rate of mortality. A multidisciplinary approach to care is critical in the management of these patients and their families. The dermatologist can play a central role in this process, coordinating care between specialist medical and allied health teams.

BACKGROUND

The intention of this case report is to educate healthcare professionals and to provide an update on hereditary leiomyomatosis, a rare multisystem disease with dermatological manifestations. An opportunity emerged when the patient presented to the Gold Coast Hospital, Southport, Australia and was confirmed to have this condition. The objective in publication of this case report is to enhance awareness of this disease that may present to any clinician, and offers them treatment and referral options in an effort to improve patient outcomes.

CASE PRESENTATION

An otherwise well, 44-year-old man presented with a 2-week history of intermittent painless haematuria and night sweats associated with a 3-month history of unintentional weight loss. Urological workup was suspicious for right-sided renal carcinoma and the patient underwent a laparoscopic nephrectomy (see figures 1 and 2). Operative histopathology was unusual revealing a primary renal carcinoma with mixed, solid, papillary and tubulocystic architecture and features suspicious for hereditary leiomyomatosis (see figures 3–7). The patient's twin brother had recently passed away from a metastatic kidney tumour (unknown type and we have no further information on his disease).

The patient was referred to genetic counselling services. Testing found a mutation in the fumarate hydratase (FH) gene, confirming the diagnosis of hereditary leiomyomatosis and renal cell

cancer (HLRCC). Further exploration of the family history revealed a son who required renal dialysis from birth and who had recently undergone an unrelated donor kidney transplant. Genetic testing was recommended for other family members, and the patient was referred to dermatology for a baseline review.

At dermatological review, the patient made no report of any present or past skin lesions of concern; however, examination revealed a suspicious lesion at the left angle of the mandible, which was biopsied.

INVESTIGATIONS

Left mandible skin biopsy. Histopathological findings from that biopsy were in keeping with a diagnosis of cutaneous leiomyoma (CL).

Operative histopathology was unusual revealing a primary renal carcinoma with mixed, solid, papillary and tubulocystic architecture and features suspicious for hereditary leiomyomatosis (see figures 8 and 9).

The histopathology was then sent for further expert urological pathology opinion and further immunohistochemical stains. A broad panel of immunohistochemical stains were performed, including FH and S-(2-succino)-cysteine (2SC). The negative FH stain together with the positive 2SC stain strongly supports a diagnosis of HLRCC.

DIFFERENTIAL DIAGNOSIS

Renal cell cancer.

TREATMENT

Laparoscopic right-sided nephrectomy.

Genetic counselling and testing confirming HLRCC.

OUTCOME AND FOLLOW-UP

Ongoing dermatology and urology surveillance.

DISCUSSION

HLRCC is historically linked to 'Reed' syndrome and 'Multiple Cutaneous and Uterine Leiomyomata'.^{1 2} The first reports of the condition emerged in 1973. It was not until 2001 however, that a clear association between cutaneous, uterine and renal cell tumours was established.^{3 4} The estimated prevalence for this condition is approximately 180 families worldwide.⁵ Clinically, the

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Figure 1 CT (coronal section abdomen) showing a 4.7 cm right renal mass indenting the renal pelvis, as well as upper and lower pole calyces, without obstructing the collecting system.

mean age of presentation is 25 years, with between 90% and 100% of mutation carriers reportedly affected by the age of 45.⁵ While patients may develop tumours of the uterus or kidney, the most common clinical manifestation is that of the skin. CLs occur in 76%–100% of all HLRCC sufferers.⁶ CLs can be classified based on smooth muscle of origin and their clinicopathological features into piloleiomyomas, angioleiomyomas and genital leiomyomas. CLs present as multiple, firm, flesh-coloured nodules (10 to 100, size range 0.4–2.5 cm) occurring on the extensor surfaces of the trunk and extremities and as papulonodules or pedunculated lesions on the genitalia. Depending on subtype, pain may be a feature, with 50% of angioleiomyomas and 90% of piloleiomyomas marked by pain and paraesthesia. In contrast, genital leiomyomas are typically painless.⁵ In the case of a single leiomyoma,

Figure 2 CT (transverse section abdomen) showing a 4.7 cm mass within the anterior mid-portion of the right kidney.

Figure 3 Right kidney: H&E stain, $\times 40$, low-power image showing sarcomatoid area (left) and tubulopapillary area (right).

treatment is focused on the excision of the lesion. Multiple lesions are managed with locally destructive methods such as electrocoagulation, cryotherapy and CO₂ laser ablation in combination with oral and topical medications designed to alleviate discomfort, including analgesics and antidepressants. CLs are prone to reoccur within 6–15 years of removal. As such, ongoing review by a dermatologist is recommended.²

As well as skin leiomyomata, a significant percentage of HLRCC-afflicted women will also develop uterine leiomyomata or fibroids (up to 20, size range 1.5–10 cm). Development of these tumours is signalled by irregular menstrual cycle, menorrhagia and pain. These lead to myomectomy or hysterectomy in 68% of HLRCC women on or before the age of 40.⁶ Controversy

Figure 4 Right kidney: H&E stain, $\times 200$, medium-power image showing tubulopapillary area.

Figure 5 Right kidney: H&E stain, $\times 600$, high-power image showing tumour cells with characteristic eosinophilic macronucleoli and perinuclear halo.

exists regarding their potential for malignant transformation.⁶ Following surgical extraction, histopathological analysis for the presence of nuclear features in uterine smooth muscle tumours may aid in early detection of HLRCC, resulting in surveillance for renal carcinoma.⁷

In the kidney, HLRCC sufferers are predisposed to the development of renal tumours, renal cysts and cystic renal tumours. Renal tumours associated with HLRCC are typically a form of type 2 papillary RCC and have an early age of onset (10–44 years).⁵ Cancers that develop in the setting of HLRCC are aggressive and carry a significant risk of metastasis, even at a size of less than 1 cm.⁶ Therefore surveillance, cryo-ablation and radiofrequency ablation are not recommended in the management of HLRCC-associated

Figure 7 Right kidney: H&E stain, $\times 400$, high-power image showing sarcomatoid tumour with pleomorphic rhabdoid cells.

kidney cancers. Fortunately, the rate of penetrance for renal tumours is low, estimated at between 14% and 18%.⁶

Germline mutations in the FH gene that encodes the tricarboxylic acid cycle enzyme, FH, are thought to be responsible for this inherited autosomal dominant syndrome.^{5 8} The mutation ultimately results in the accumulation of intracellular levels of fumarate and 2SC. This mechanism has led to improvements in histopathological detection with 2SC immunohistochemistry.^{9 10} As highlighted in this case and reported in the literature, a key step in establishing the diagnosis has been pathologists' suspicion based on histological features of kidney tumours.¹¹

Genetic testing plays an important role in the management of these patients, and their family, and often serves as the referral point to the multitude of disciplines involved in their care. As

Figure 6 Right kidney: H&E stain, $\times 400$, high-power image showing sarcomatoid tumour with atypical mitosis.

Figure 8 Left angle of mandible: H&E stain, $\times 40$, low-power image showing cutaneous leiomyoma within superficial and mid-dermis.

Figure 9 Left angle of mandible: H&E stain, × 400, high-power image showing bland-spindled smooth muscle cells in a cutaneous leiomyoma.

CLs are typically the first clinical manifestation of this disease, dermatologists can be instrumental in the early detection and referral of sufferers providing them with the best treatment outcomes.

Given the condition involves a number of organs, it is important to emphasise the need for a multidisciplinary team approach for these patients care. The contribution of dermatologists, dermatopathologists, urologists, uropathologists and obstetricians in early detection of patients with possible HLRCC-related stigmata is so appropriate, and timely genetic testing and counseling can be undertaken to reduce morbidity and mortality.

Learning points

- ▶ Educate healthcare professionals and promote awareness
- ▶ Update on hereditary leiomyomatosis
- ▶ The role of histopathology
- ▶ The need for a multidisciplinary approach to healthcare for these individuals

Rare diseases in which there is widespread variation in phenotypic manifestations exemplified by HLRCC display challenges for clinicians regarding impregnable surveillance and screening protocols. Hence, we recommend collaborative decisions in a multidisciplinary team to consider individual circumstances for life-long follow-up. Surveillance and screening should include periodic renal imaging, preferably consisting of yearly renal MRI and predictive testing for a FH mutation, offered from 8 to 10 years of age.¹²

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