Hereditary leiomyomatosis and renal cell cancer is a genodermatosis with an autosomal dominant inheritance pattern. It is a tumour predisposition syndrome characterized by cutaneous and uterine leiomyomas, and increased susceptibility to develop renal cell carcinoma. There are 200–300 families with hereditary leiomyomatosis and renal cell carcinoma reported worldwide, but the syndrome is believed to be underdiagnosed. Cutaneous leiomyomas are small smooth muscle tumours that tend to grow over time. Larger lesions, in particular, can cause pain or itching. Uterine leiomyomas have a high penetrance in women with hereditary leiomyomatosis and renal cell cancer. They frequently cause symptoms, and surgical intervention is often necessary. Hereditary leiomyomatosis and renal cell cancer-associated renal cell carcinomas have a high potential to metastasize. Patients are diagnosed by genetic testing if a pathogenic mutation is demonstrated in the gene encoding fumarate hydratase. Immunohistochemistry may be a useful diagnostic approach in patients without a detectable pathogenic mutation. Diagnosed patients should be monitored for renal tumours in a lifelong surveillance programme.

**Key words:** hereditary leiomyomatosis; cutaneous leiomyomas; uterine leiomyomas; renal cell carcinoma; cancer surveillance.

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Hereditary leiomyomatosis and renal cell cancer (HLRCC) is a rare genodermatosis with an autosomal dominant inheritance pattern, caused by inherited or de novo mutations in the gene encoding fumarate hydratase (FH) (1). HLRCC is a tumour predisposition syndrome characterized by the propensity to develop single or multiple cutaneous leiomyomas (CLM), uterine leiomyomas (ULM), and renal cell carcinomas (RCC). Blum & Jean (2) linked leiomyomas of the skin with uterine leiomyomas for the first time in 1954. In the literature, the syndrome is referred to as Reed’s syndrome, multiple cutaneous and uterine leiomyomatosis (MCUL), and leiomyomatosis cutis et uteri, amongst other names (3). The eponym Reed’s syndrome dates back to 1973, when Reed and colleagues noticed an accumulation of the condition in 2 families with an autosomal dominant inheritance pattern (4). The syndrome was subsequently renamed HLRCC in 2001, when the condition was linked with an increased susceptibility to certain subtypes of RCC (5).

**EPIDEMIOLOGY**

The exact prevalence of HLRCC is unknown; however, 200–300 families have been reported in the literature (1, 3). Mostly Western-European, Finnish and North-American families have been reported (6–8). Gardie et al. reported 44 families with confirmed HLRCC in France (9). Toro et al. reported 35 HLRCC families in North America (7), where Wei et al. (10) later reported an additional 21 families. Lehtonen et al. (6) reported 7 Finnish families with HLRCC. Reports of Colombian, Japanese, Indian, Chinese and African-American HLRCC families suggest that the syndrome occurs worldwide (10–14). HLRCC is believed to be an underdiagnosed syndrome, and the actual number of HLRCC families is likely to be higher (8).

**PATHOPHYSIOLOGY**

The genetic predisposition to CLM, ULM and RCC is caused by mutations in the FH-gene on chromosome 1q (5). HLRCC is an autosomal dominant disease with sporadic cases reported (8, 15). 

*FH* acts as a tumour suppressor gene in accordance with Knudson’s 2-hit hypothesis (5, 16). Tumour tissue displays biallelic *FH* inactivation where an acquired somatic *FH* mutation can be demonstrated in addition to the inherited germline mutation (17, 18). An excess of 200 unique potential pathogenic FH variants have been reported (19). The gene product is the enzyme fumarate hydratase.
CLINICAL MANIFESTATIONS

HLRCC displays a broad clinical spectrum, as some cases with FH mutations are asymptomatic while others have severe cutaneous, uterine or renal manifestations (9, 21). The penetrance of CLMs has been reported to be higher in men with FH mutations compared with women, as a study reported that CLMs were present in all men by age 35 years, while being present in only 55% of women (6). Predicting the phenotype based on a specific inherited gene variant is not possible (1, 9, 23). Due to recruitment of individuals based on positive findings in studies and publications of HLRCC, the prevalence of clinical manifestations might be overestimated (7, 8, 10).

Cutaneous leiomyomas

CLMs are the most frequent manifestation of disease leading to a diagnosis (8). They are benign, firm, smooth, skin-coloured to erythematous or hyperpigmented papulonodules (3, 8, 30) (Figs 1 and 2). CLMs range in size between 2 and 20 mm in diameter (3, 8). Histologically, CLMs are subdivided into piloleiomyomas, genital leiomyomas and angioleiomyomas. Piloleiomyomas, being the most frequent in relation to HLRCC, emerge from the arrector pili muscles of hair follicles (Fig. 3) (3). Angio-

Fig. 2. Surgical excision of cutaneous leiomyomas on the chest of a 20-year-old patient under current investigation for hereditary leiomyomatosis and renal cell cancer. (A) Cutaneous leiomyomas prior to surgical excision. (B) Keloid formation following surgical excision.
increase in number and size over time, and especially larger lesions tend to be symptomatic (15, 21). Individuals with CLMs have reported a moderate to severe negative impact on their quality of life caused by their skin lesions (8). The potential of cutaneous and uterine leiomyomas to transform into leiomyosarcomas is not well established. Only 6 cases of cutaneous leiomyosarcomas have been reported in FH mutation carriers (7, 10, 23, 33, 34), 2 of which presented with rapid growth of an existing CLM (23). Similarly, uterine leiomyosarcomas have rarely been linked to HLRCC (4–6, 35). Leiomyosarcomas are difficult to distinguish clinically from CLMs, but may be larger, ulcerated, irregularly shaped and increasingly painful (3). Histopathological examination of tumour tissue is required for a firm diagnosis (36). These tumours rarely metastasize (3). Although speculative, looser diagnostic criteria of leiomyosarcomas in the past may have led to uterine and cutaneous leiomyomas being mistaken for leiomyosarcomas (23).

**Uterine manifestations**

Uterine fibroids range in number between 1 and 20, and in diameter between 1 and 10 cm (7, 10). HLRCC-associated ULMs are diagnosed in the 2nd to 5th decade, with a mean age of 30 years (6–8, 10). ULMs occur in 73–100% of HLRCC families and in 76–100% of women with HLRCC (7–10, 15, 21, 23). In 7–14% of cases, ULMs are the only disease manifestation (8, 10). The mean age at diagnosis of ULMs is 28–30 years, ranging from 18 to 53 years (7, 8, 10, 37). In the general public, the prevalence of symptomatic uterine fibroids is 9% (38), and they are diagnosed approximately 10 years later than in women with HLRCC (37). The majority of women with HLRCC-associated ULMs experience gynaecological symptoms, mainly dysmenorrhea, followed by menorrhagia and irregular menses (7, 8, 21, 37). Women with HLRCC often experience gradual worsening of these symptoms prior to diagnosis (8). HLRCC-associated ULMs are associated with female infertility characterized by difficulty achieving conception and occurrence of miscarriages (8). Up to 91% of women with a pathogenic FH mutation undergo surgical intervention, such as hysterectomy or myomectomy, at a mean age of 35–36 years (7, 10, 23), and many undergo surgery before the age of 30 years (7, 10). HLRCC-associated ULMs are associated with various degrees of negative impact on quality of life (8).

**Renal manifestations**

HLRCC-associated RCC display a broad spectrum of architectural growth patterns, including papillary, tubulo-papillary, tubular, solid and cystic elements (10, 23, 39–41). The syndrome mainly predisposes to RCCs of a type 2 papillary morphology (PRCCII), but tumours of collecting duct, clear cell, sarcomatoid and oncocytic origin have also been reported (7, 9, 22, 23, 40). RCCs are predominantly solid and unilateral, but can also be multifocal and bilateral (10, 14, 40, 42). Tumour cells have large nuclei, with prominent inclusion-like eosinophilic nucleoli, surrounded by a perinuclear clear halo of cytoplasm (40, 43). Renal tumours vary in size between 2 and 22 cm in diameter (5, 7, 8). RCCs usually display an aggressive growth pattern, with invasion of nearby tissue, and a high potential to metastasize (14, 23, 44). Symptoms include haematuria, flank pain, lower back pain, palpable mass and symptoms from metastases (3). Patients can debut with RCC as the only clinical manifestations of the syndrome (10, 45). HLRCC-associated RCCs have a poor prognosis, with a 5-year survival of 31%, as reported by Toro et al. (7). Furthermore, Muller et al. reported a median survival of 18 months for metastatic disease (23). RCC is diagnosed in approximately 14–62% of HLRCC families (7, 9, 10), and in 16–24% of individuals with HLRCC (7, 9, 10, 23). However, a Dutch study found that only 6% of patients with HLRCC were diagnosed with RCC (21). The mean age at diagnosis of HLRCC is 39–46 years (range 10–90 years) (6–9, 14, 41, 46, 47), approximately 20–25 years earlier than the diagnosis of sporadic RCC in the general European and American population (48, 49).

**MANAGEMENT**

The need for treatment of CLMs is individual and depends mainly on pain and cosmetic appearance of the lesions. Conservative approaches involve avoiding symptomatic triggers, such as direct contact and changes in temperature (3). Issues of cosmetic appearance might be solved by choice of clothing and use of make-up (3). CLMs can readily be removed by standard excision, electrodesection, CO2 laser ablation or cryotherapy (3, 21). The choice of surgical intervention depends largely on the preferences of the clinician. However, the indication for cosmetic
recently proposed to trigger genetic testing, in cases sug-

59). Pathological screening of ULM morphology was

individuals without features suggestive of HLRCC (57,

58). This is due to somatic biallelic inactivation rather

is a commonly seen phenomenon in sporadic ULMs (57,

58). Random inactivation of FH

testing (50). Routine molecular screening of ULM tissue

A diagnosis of HLRCC is confirmed through genetic

tissue and possibly retroperitoneal lymph node dissec-

(47). If possible, nephron-sparing surgery with partial

nephrectomy is preferred in order to preserve renal

function (47). There is no standard treatment option for

metastatic disease, and very limited treatment data avail-

able (51). Medical treatment options usually interact

with components of the mammalian target of rapamycin

(mTOR) pathway and the HIF pathway, including vascular

endothelial growth factor (VEGF), platelet-derived growth

factor (PDGF) and epidermal growth factor (EGF) (47,

51). The most commonly prescribed drugs targeting these

pathways are bevacizumab, temsirolimus, everolimus,
pazopanib, axitinib, sunitinib, sorafenib and erlotinib

(47, 51). These agents may be used in combination, in

order to achieve the best response (47, 51, 52). Choice of

treatment modality depends largely on patient preferen-
ces and comorbidities (3). Bevacizumab in combination

with erlotinib showed promising results in the treatment

of metastasized HLRCC-associated RCC (51, 52). There

is currently ongoing research of the use of inhibitors of

glycolysis in the treatment of HLRCC-associated RCC,
as the tumour cells are dependent on glycolysis for ATP

production due a TCA cycle defect (47, 53). However,
such therapies have not yet proven effective (54).

DIFFERENTIAL DIAGNOSES

The differential diagnostic considerations depend on the clinical findings. CLMs are rare and their presence should always lead to a suspicion of HLRCC (1, 43, 68). A large number of skin tumours may cause pain (69). The most relevant differential diagnostic considerations to painful CLMs are shown in Table II (3, 30, 69–71). Although the clinical spectrum of CLMs is broad, many of these tumours can readily be eliminated as likely differential

Table I. Proposed diagnostic criteria for hereditary leiomyomatosis and renal cell cancer (HLRCC)

<table>
<thead>
<tr>
<th>Criteria</th>
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<tbody>
<tr>
<td>Definitive criteria</td>
</tr>
<tr>
<td>Detection of pathogenic germline fumarate hydratase-mutation.</td>
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<tr>
<td>Multiple cutaneous leiomyomas with at least 1 histologically confirmed.</td>
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<tr>
<td>Family disposition to HLRCC and at least 1 minor criteria.</td>
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<tr>
<td>Single solitary histologically confirmed cutaneous leiomyoma.</td>
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<tr>
<td>Multiple severely symptomatic uterine leiomyomas onset &lt;40 years.</td>
</tr>
<tr>
<td>Type 2 papillary renal cell carcinoma onset &lt;40 years.</td>
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</tbody>
</table>

Definitive criteria set a firm diagnosis. Major criteria are highly suggestive of HLRCC, and minor criteria should raise suspicion of the syndrome. Having a first-degree family member who meets at least one of the above-mentioned criteria is also suspicious of HLRCC.
Table II. Clinical differential diagnoses of painful cutaneous leiomyomas

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Neoplasia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adipose</td>
<td>Angiolipoma</td>
</tr>
<tr>
<td>Eccrine</td>
<td>Eccrine spiradenoma</td>
</tr>
<tr>
<td>Fibrous</td>
<td>Hidradenoma</td>
</tr>
<tr>
<td>Infiltrative</td>
<td>Cutaneous metastasis</td>
</tr>
<tr>
<td>Muscle</td>
<td>Glomus tumour</td>
</tr>
<tr>
<td>Neural</td>
<td>Granular cell tumour</td>
</tr>
<tr>
<td>Vascular</td>
<td>Blue rubber bleb naevus</td>
</tr>
</tbody>
</table>

In cases of atypical presentation other diagnoses may be considered (3, 30).

diagnoses based on the clinical findings. A biopsy is required for a firm diagnosis (30).

ULMs are frequent in the general population and constitute the most common pelvic tumour in women (72).

The main differential diagnoses in relation to renal tumours are the autosomal dominant renal cancer syndromes: hereditary papillary renal cancer (HPRC), Von Hippel-Lindau syndrome (VHL) and Birt-Hogg-Dube syndrome (BHDS) (73). Predisposition to papillary type 1 RCC is the only manifestation of HPRC (1). VHL is characterized by clear cell RCC and renal cysts (74). Other common findings include central nervous system haemangioblastoma, pancreatic tumours and cysts, and pheochromocytoma among others (74). VHL can be differentiated from HLRCC by the lack of cutaneous and uterine lesions (1). BHDS is associated with lung cysts, that may erupt and cause pneumothorax, and a triage of skin lesions, including fibrofolliculomas, trichodiscomas and acrochordons (skin tags) (75). Distinctive from CLMs, fibrofolliculomas and trichodiscomas are painless, pale, millimetre small lesions, and are mainly located on the face, neck and upper torso (75). The renal tumours seen in BHDS constitute in a wide histological spectrum. Patients most often present with hybrid tumours, a combination of chromophobe RCC and renal oncocytoma, but also chromophobe RCCs, clear cell RCCs or renal oncocytomas are frequently associated with BHDS (75). BHDS is not associated with an increased frequency of ULMs (1).

SURVEILLANCE

There is a lack of consensus regarding a surveillance programme of pathogenic FH-mutation carriers (30). Although suspected, a firm association of cutaneous leiomyosarcomas with HLRCC has not been established (23). We recommend a thorough dermatological examination every second year, starting from the onset of CLMs (Table III). Patients should be instructed to seek medical attention in case of rapid growth in skin lesions. Annual ultrasonic gynaecological examinations starting at the age of 20 years, in FH mutation carriers, is recommended in order to diagnose and monitor asymptomatic ULMs (Table III) (3, 21, 50). Prevention of RCCs is a major focus of the surveillance programme (21). Renal surveillance by annual contrast-enhanced magnetic resonance imaging (MRI) is proposed to start at the age of 10 years by Patel et al. (3), and at the age of 8 years by Schmidt & Linehan (50). Due to numerous reports of HLRCC-associated RCC in individuals younger than 20 years of age (8, 40, 46, 76, 77), the youngest reported at age 10 (30), we propose annual MRI scans starting at age 10 years (Table III). While renal ultrasound has been suggested to play a role in assisting MRI in the surveillance programme (21), Schmidt & Linehan does not recommend this modality for routine screening of HLRCC-associated renal tumours (78). Furthermore, family members of patients with proven HLRCC should undergo early genetic testing in order to be included in the surveillance programme at an early age (1, 78).

PROGNOSIS

The prognosis of HLRCC depends first and foremost on the detection of HLRCC-associated renal cancers. It is imperative to diagnose the syndrome early, and include patients in an aggressive surveillance programme, so that renal tumours are diagnosed and treated in time.

GENETIC COUNSELLING

At-risk family members and offspring of confirmed FH-mutation carriers should undergo genetic testing in order to identify the necessity for inclusion in the surveillance programme. HLRCC patients and at-risk family members should be offered genetic counselling and be provided with information regarding the syndrome (1). FH mutation carriers should ideally receive genetic counselling before starting a family, in order to discuss the following prior to pregnancy: fertility issues, prenatal testing options, and risk-assessments with regards to passing on the pathogenic gene variant to offspring (1).

The authors have no conflicts of interest to declare.

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