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Review

Hereditary multiple cutaneous leiomyomatosis

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Identity

Alias

Multiple cutaneous and uterine leiomyomatosis (MCUL)

Hereditary leiomyomatosis and renal cell cancer (HLRCC)

Note

Multiple cutaneous leiomyomatosis (MCUL) is characterized by multiple leiomyomas of the skin and uterus. When associated with renal cell cancer, this syndrome is referred to as hereditary leiomyomatosis and renal cell cancer (HLRCC).

Inheritance

Autosomal dominant with incomplete penetrance and variable expressivity.

Clinics

Phenotype and clinics

Hereditary multiple cutaneous leiomyomatosis is a tumor predisposition syndrome characterized by multiple cutaneous and uterine leiomyomas and an increased risk of developing renal cancer.

The penetrance of leiomyoma of the skin is very high. They tend to develop in the second to fourth decade of life as multiple grouped skin colored to brown-red papules. These benign skin lesions are typically painful in response to touch or cold. Leiomyomas gradually increase in size and number and the extent of skin lesions is variable, even within one family. Some patients suffer from extensive disease, with multiple leiomyomas covering large areas of the body, whereas others only have a few inconspicuous papules.

Interestingly, multiple cutaneous leiomyomas do not exclusively manifest in a diffuse and symmetric fashion. Rather frequently, a segmental manifestation pattern of these tumors can be observed, most likely reflecting mosaicism.

Uterine leiomyomas occur in more than 90% of females with MCUL/HLRCC. These patients may have a medical history of menorrhagia and pelvic pressure or pain, frequently requiring a hysterectomy before the age of 30 years.

Neoplastic risk

A small percentage (1-17%) of families with MCUL also cluster renal cell cancer. The age of onset varies from 16 to 90 years. Type II papillary RCC is the predominant type of kidney malignancy in HLRCC. These tumors tend to be very aggressive. Metastases are seen in more than 50% of affected individuals, even in those with relatively small primary tumors. Furthermore, sporadic cases of collecting duct carcinoma, oncocytoma, clear cell carcinoma, and Wilms tumor have been described.

A minority of female patients with MCUL/HLRCC are apparently predisposed to the development of highly aggressive uterine leiomyosarcoma.

A broad range of other benign and malignant tumors has also been observed in MCUL/HLRCC families. These mostly anecdotal reports include breast, prostate, and bladder cancer, testis leydig cell tumors, ovarian and kidney cysts, cerebral cavernomas, and adrenal gland adenomas. However, the majority of the aforementioned tumors encountered in these families most probably are not directly associated with either MCUL or HLRCC.

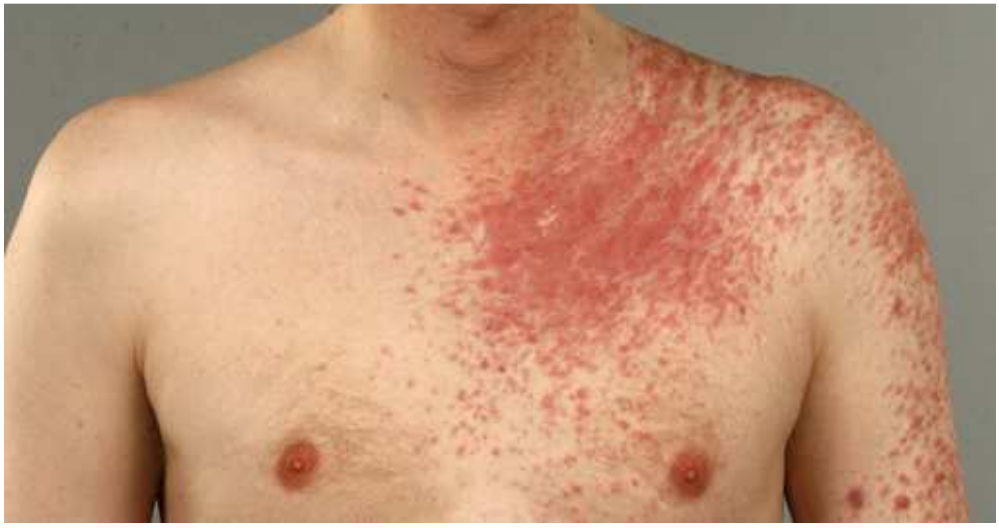

Figure 1. Segementally distributed cutaneous leiomyomas on the left shoulder and chest.

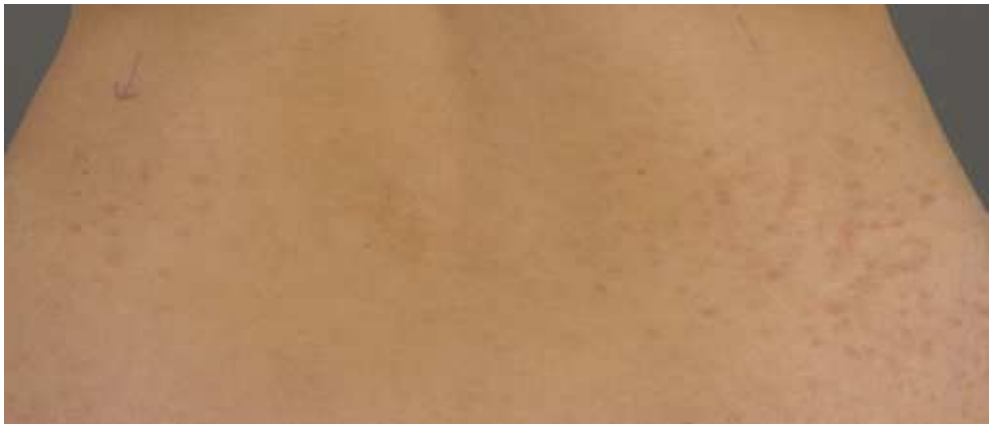

Figure 2. Diffuse and symmetrically distributed cutaneous leiomyomas on the back.

Treatment

While solitary cutaneous leiomyomas can be easily treated by surgical excision, multiple leiomyomas covering large surfaces of the body are difficult to manage. Several different treatment modalities have been described for symptomatic pain relief or tumor destruction in cutaneous leiomyomatosis, including pharmacological agents such as nifedipine, gabapentin, doxazosin, phenoxybenzamine, hyoscine, hydrobromide, and nitroglycerine or invasive therapeutic strategies comprising extensive surgical excision, CO_2 laser ablation and cryotherapy, all with variable success.

For symptomatic uterine leiomyomas different surgical approaches can be considered, including myomectomy, hysterectomy or abdominal uterus extirpation. Prior to recommending a specific therapy the patient's individual concerns should always be respected though, in particular the specific symptoms and their effect on quality of life and the possible request to preserve fecundancy.

Prognosis

Genetic counseling of patients and their relatives should be self-evident. Once the diagnosis of hereditary multiple cutaneous leiomyomatosis is made, affected individuals must be considered at risk for the occurrence of other tumors. Referral of all female patients to a gynecologist for annual evaluation is warranted.

There are no specific screening guidelines for HLRCC, most likely due to the rareness of the disease. We suggest that annual abdominal computational tomography could serve as screening procedure for both the detection of kidney tumors and uterine changes. Magnetic resonance imaging and ultrasound could serve as alternative techniques if contrast-enhanced computational tomography cannot be performed.

Genes involved and proteins

FH (Fumarate hydratase)

Location

1q42.1

DNA/RNA

Description: The FH gene spans 22 kb and consists of 10 exons.

Protein

Note: FH is an enzyme of the Krebs cycle, which catalyzes the conversion of fumarate to malate.

Mutations

Note: To date, approximately 75 different mutations distributed throughout the FH gene have been reported in hereditary multiple cutaneous leiomyomatosis. These sequence deviations include missense, nonsense, frameshift, and splice-site mutations as well as whole gene and exonic deletions and, together, demonstrate the molecular heterogeneity associated with disorder caused by FH mutations.

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