Pathological Phenotype of Uterine Leiomyomas from Patients With Hereditary Leiomyomatosis and Renal Cell Cancer (HLRCC) Syndrome

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Background

- HLRCC Syndrome is an autosomal dominant disorder resulting from mutations in the fumarate hydratase gene, which predisposes patients to cutaneous and uterine smooth leiomyomas as well as renal cell carcinoma.
- Renal cell carcinomas in HLRCC have a penetrance of 20%, but tend to be very aggressive. Uterine leiomyomas have a penetrance of over 90% and usually present in young women. Therefore, their recognition may offer an opportunity to identify patients with HLRCC and their families who may in turn be directed to renal cancer surveillance.
- The histological features of HLRCC uterine leiomyomas have recently been described and include: 1) frequent hypercellularity, 2) frequent nuclear atypia, 3) ≤ 3 mitotses/10 HPF, 4) occasional cells with large multinucleated or single nuclei, 5) orangeophilic prominent nucleoli with a surrounding perinucleolar halo. The sensitivity and specificity of these features has not been studied to date.
- We present a comparison of the pathological features of uterine leiomyomas from patients with known HLRCC Syndrome to those of patients with no known history of HLRCC.

Design

- 4 patients with HLRCC Syndrome confirmed by genetic analysis and uterine leiomyomas, and 100 patients under the age of 41 with symptomatic uterine leiomyomas (multiple with at least one ≥3 cm or solitary ≥10 cm) and no personal or family history of HLRCC Syndrome were identified. Tumours were derived from hysterectomy and myomectomy specimens.
- The following tumour pathological features were recorded for both patient groups:
  - Tumour number
  - Tumour size
  - Cellularity
  - Mitotic activity
  - Nuclear enlargement
  - Presence of prominent nucleoli and perinucleolar clearing

Results

- Symptoms recorded for the sporadic group of patients with leiomyomas included: pain, prolapse or pressure, menorrhagia, infertility and endometriosis. Of the patients with HLRCC, two had pelvic pain, one had menorrhagia and one was asymptomatic.
- The clinicopathological features of HLRCC and presumed sporadic leiomyomas are summarized in Table 1.
- Increased cellularity (8%) and focal cells with prominent nucleoli and focal perinucleolar clearing (67%) were commonly found in sporadic uterine leiomyomas.
- The most distinguishing characteristic of HRLCC uterine leiomyomas as compared to sporadic uterine leiomyomas was the presence of diffusely distributed cells (5-10%) with a *combination of both* enlarged (3x) nuclei with irregular contours *and* eosinophilic nucleoli with perinucleolar clearing (Figure 1).
- There was no nuclear atypia in any of the HLRCC uterine leiomyomas.
- The presumed sporadic leiomyomas had 0-4 and all HLRCC leiomyomas had 1 mitosis/10HPF.

Results

Table 1: Clinicopathologic Features of Uterine Leiomyomas of Patients with Known HLRCC Syndrome Compared to Presumed Sporadic Uterine Leiomyomas

Clinicopathologic Feature	Known HLRCC Patients (n=4)	Presumed Sporadic Patients (n=100)
Patient age (years)	Mean 36.7 Range 29-41	Mean 36.4 Range 24-41
Surgical Procedure:		
Hysterectomy	2	50
Myomectomy	2	50
Number of uterine leiomyomas:		
Single	0	17
Multiple	4	83
Size (cm)	Mean 11.0 Range 6.3-16.7	Mean 8.7 Range 3.0-19.2
Cellularity:		
Normal	2	92
Mixed	1	3
Increased	1	5
Mitoses:		
≤ 5 /10 HPF	4	100
> 5/10 HPF	0	0
Nuclear enlargement and irregular contour:		
Present	4	16
Absent	0	84
Prominent nucleoli and perinucleolar clearing:		
None	0	28
Focal	2	67
Diffuse	2	5

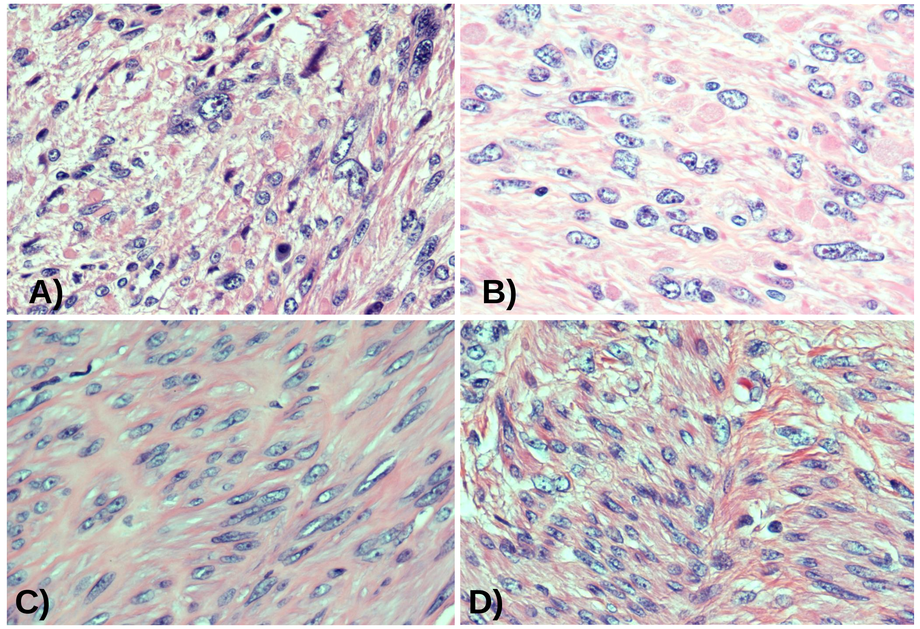

Figure 1: H & E 600 x. A) and B) Histological features of uterine leiomyomas of patients with known HLRCC. HLRCC leiomyomas contain diffusely distributed cells with nuclei 3 times the size of the background nuclei. In addition, the nuclei have irregular contours, prominent eosinophilic nucleoli and perinucleolar clearing .

C) and D) Histological features of presumed sporadic leiomyomas. Focal cells with prominent nucleoli and perinucleolar clearing may be seen, however, they lack the eosinophilic nucleoli of HLRCC leiomyomas.

Conclusions

- The most distinguishing characteristic of HRLCC uterine leiomyomas as compared to sporadic uterine leiomyomas was the presence of diffusely distributed cells (5-10%) with a *combination of both* enlarged (3x) nuclei with irregular contours *and* eosinophilic nucleoli with perinucleolar clearing.
- Recognition of specific morphologic features in uterine leiomyomas may identify patients who can benefit from genetic testing for HLRCC syndrome. If subsequently diagnosed, these patients and their family members can be followed by renal cancer surveillance programs.

References

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