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### Significance of Clinical-Pathologic Correlation in a Case of HLRCC

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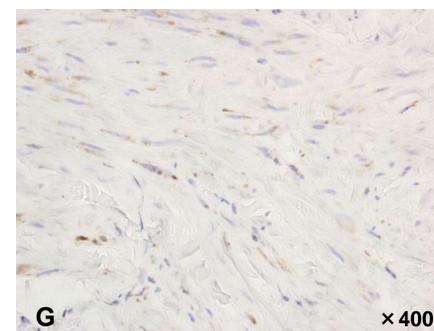
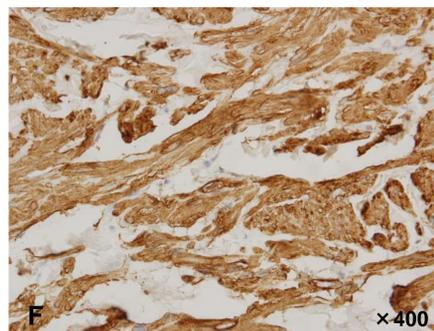
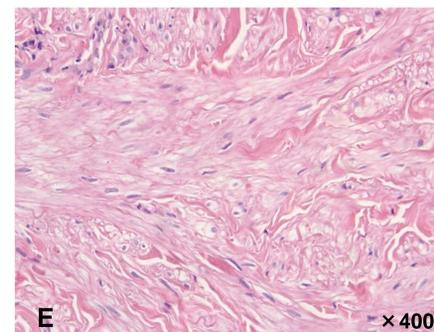
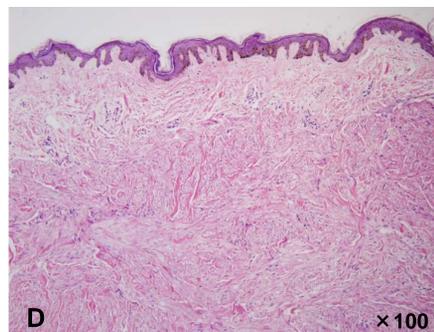
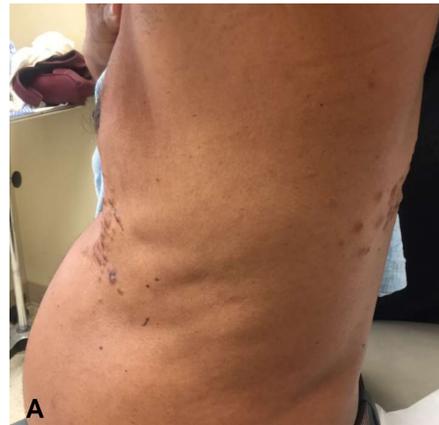
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## BACKGROUND

Hereditary leiomyomatosis and renal cell carcinoma syndrome (HLRCC) is a rare genetic disease, characterized by cutaneous leiomyomata, uterine leiomyomata and renal tumor. This syndrome is inherited in an autosomal dominant manner and caused by mutations in the *fumarate hydratase* (*FH*) gene (1). This genetic alteration predisposes these patients to more aggressive renal tumor compared to other hereditary renal tumors. Hence, it is of great importance to suspect this syndrome upon identification of multiple cutaneous leiomyomata. Here, we present a case report of such rare syndrome, underscoring the significance of clinical-pathologic correlation in identifying patients at high risk of aggressive renal tumor.

## CLINICAL PRESENTATION

- A 54 years old Bengali male presented with multiple painful large firm skin-colored to brown skin lesions over left lower chest/ upper abdomen and back in a T6 dermatomal distribution (Figure A-C).
- He has had such lesions for 26 years, with increase in size and number as well as worsening of pain over time.
- Patient did seek medical help due to progressive severe pain.
- A 4-mm punch biopsy of skin lesion on left chest was performed and the histopathological examination revealed a proliferation of smooth muscle in the reticular dermis, consistent with leiomyoma (Figure D-E).
- The positive immunohistochemical staining for smooth muscle antigen (SMA) supported the diagnosis (Figure F).
- The FH expression detected on immunohistochemical studies, which was neither supportive nor against the diagnosis of HLRCC (Figure G).
- Since this patient has the major criterion for HLRCC, histopathologically confirmed multiple cutaneous leiomyomata, he most likely has this syndrome.
- Mutation analysis, genetic counseling and, more importantly, the evaluation of kidneys for possible malignancy are hindered due to the lack of insurance coverage for genetic testing.



## DISCUSSION

HLRCC, also known as Reed's syndrome, is a rare familial syndrome characterized by multiple, often symptomatic, cutaneous and uterine leiomyomata as well as kidney tumors. It is caused by germline mutations in *FH* gene, which encodes a critical component of citric acid (Krebs) cycle. Lack of FH protein results in a metabolic shift from oxidative phosphorylation to aerobic glycolysis and, consequently, upregulation of genes that promote renal oncogenesis (2). Such alterations also result in the accumulation of 2-succinocysteine (2SC) protein which can be detected by immunohistochemistry and has high sensitivity and specificity for *FH*-deficient tumors. However, FH staining does not show a robust association with *FH* gene mutation, as evidence by FH immunopositivity in our case (3). The characteristic morphologic feature in HLRCC-associated RCC and uterine leiomyomas is large eosinophilic nucleoli surrounded by perinucleolar halos. However, no helpful morphologic clue has been suggested for cutaneous leiomyomas with *FH* gene mutations, emphasizing that the presence of multiple cutaneous leiomyomas should raise the possibility of HLRCC and, hence, prompt the screening for identifying such patients. Given that renal tumors with *FH* mutations are more aggressive compared to other hereditary renal tumors, it is of great importance to suspect this syndrome upon identification of multiple cutaneous leiomyomata.

## REFERENCES

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## Financial Disclosure

NOTHING TO DISCLOSE