The Rare Disease Interdepartmental Science Case Competition (RISCC) is a McGill-based and student-run interdisciplinary case competition. In its first year of operation, RISCC has provided undergraduate students with the opportunity to understand the pathophysiology and socioeconomic challenges associated with a rare disease. In teams of 5 to 7 members, students generate potential research and treatment solutions before delivering an oral presentation for evaluation by faculty members.

MSURJ is proud to collaborate with RISCC by publishing the following abstract from the 2019-2020 RISCC winning team.

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Clinical Manifestations of Hereditary Leiomyomatosis and Renal Cell Carcinoma: a Case Report

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Abstract

Introduction: Hereditary leiomyomatosis and renal cell carcinoma (HLRCC) is a rare genetic disorder etiologically stemming from mutations in the FH gene. This disorder has been reported in 300 families worldwide. We were presented with the following case as part of the Rare Disease Interdepartmental Science Case Competition (RISCC) in order to successfully diagnose the patient and examine the pathophysiology, socioeconomics, and treatment strategy of this disorder.

Case Presentation: A 27-year-old woman presented to the emergency room with a two-week history of hematuria. Her medical history included a single benign skin lesion. She did not report a family history of cancer but stated that her mother underwent a hysterectomy for unknown reasons.

Clinical Investigations: An abdominal ultrasound revealed an isoechoic nodular formation on the right kidney, and CT scans confirmed the presence of a 7-cm renal tumour and extensive leiomyomas in the patient's uterus. Genetic testing revealed a mutation in the fumarate hydratase (FH) gene, leading to the diagnosis of hereditary leiomyomatosis and renal cell carcinoma.

Pathophysiology: HLRCC is a condition caused by an autosomal dominant germline mutation in the FH gene, characterized by skin lesions, uterine leiomyomas, and aggressive renal cell carcinoma. FH acts as a tumour suppressor gene and encodes the fumarase protein. HLRCC arises from a variety of missense mutations in the FH gene that prevent the formation of a full fumarase tetramer. The disease is likely related to the dosage of the gene, rather than the site of mutation. Consequently, there is no known genotype/phenotype correlation. Fumarate inhibits HIF-α hydroxylases, so loss of the FH gene causes fumarate accumulation within cells and prevents the degradation of HIF-α. This induces a state of pseudohypoxia and leads to upregulation of genes involved in cell growth and tumorigenesis. Fumarate accumulation also modulates the Keap1-Nrf2 pathway by inducing activation of Nrf2 and allows for the protection of cancer cells from oxidative and electrophilic stressors. Furthermore, deficiency of fumarase prevents oxidative phosphorylation, thus promoting aerobic glycolysis, the most common method of metabolism used by cancer cells.

Socioeconomics: The risk of infertility and developing an aggressive cancer makes it essential to have frequent and thorough screening procedures early in life for children with a family history of HLRCC. Medical costs, infertility risk, and frequent hospital visits breed anxiety and stress for patients and family members. Fortunately, organizations like HLRCC Family Alliance exist to provide accessible information and represent a welcoming support community.

Treatment Strategy: To treat the patient's renal tumour, we suggest a radical nephrectomy with wide margins due to the aggressive nature of renal cell carcinoma. Additional imaging should be performed to identify and excise any metastatic tumours. The patient should also consult a gynecologist regarding her extensive uterine leiomyomas and will likely undergo a hysterectomy or myomectomy. A full dermatological exam should be performed to locate additional cutaneous leiomyomas. We also strongly suggest that family members undergo genetic testing. Lastly, we recommend the patient connect with support groups such as HLRCC Family Alliance to receive continued social support following her diagnosis and throughout her life.

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