Hereditary Leiomyomatosis and Renal Cell Carcinoma: A Case Report

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ABSTRACT:

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Multiple cutaneous leiomyomas, benign smooth muscle tumors, most often occur as part of a disease known as hereditary leiomyomatosis and renal cell carcinoma (HLRCC). HLRCC is a rare autosomal dominant syndrome resulted from a germline heterozygous mutation of *fumarate hydratase* gene on chromosome 1q42.3–q43. It is characterized by multiple cutaneous leiomyomas, renal cell carcinomas, and in women, uterine leiomyomas. The condition was previously known as multiple cutaneous and uterine leiomyomatosis or Reed syndrome. We report a case of 49-year-old male patient who presented with multiple asymptomatic, reddish brown colored, slow-growing papules on his left cheek for over a year. Skin biopsy of the lesion showed the diagnosis of leiomyoma. Direct sequence analysis of the patient's blood sample showed a heterozygous germline missense mutation of *fumarate hydratase* gene which led to the diagnosis of HLRCC.

Key words: Cutaneous leiomyomas, leiomyoma, hereditary leiomyomatosis and renal cell carcinoma, *fumarate hydratase* gene

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Case report

A 49-year-old Thai man visited the Institute of Dermatology with the complaint of progressive multiple reddish brown papules on his left cheek for over a year. The lesions were asymptomatic and slow-growing. The patient had no underlying medical conditions and no current medication. He denied family history of renal cell carcinoma or uterine leiomyoma. None of his family member had similar skin condition as shown in the pedigree diagram (Figure 1).

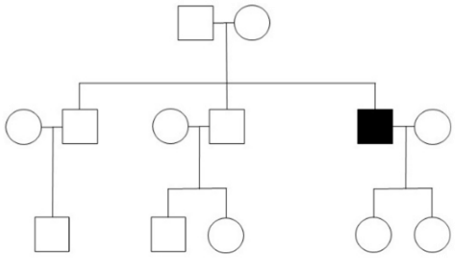

Figure 1 The pedigree diagram of the patient's family

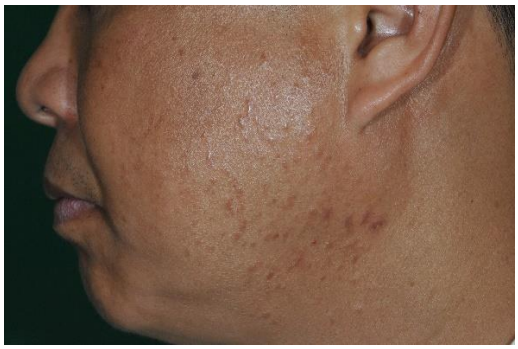

Figure 2 Multiple discrete ill-defined, firm, non-scaly, reddish brown-colored, smooth surface papules on the left cheek

Physical examination revealed multiple discrete ill-defined, firm, non-scaly, reddish brown colored, smooth surface papules on the left cheek (Figure 2). Other systemic examination were unremarkable.

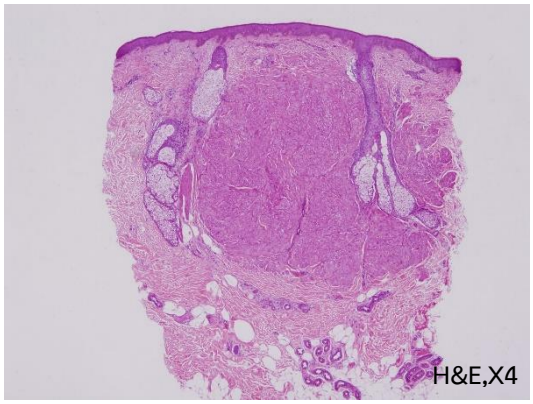

Figure 3 Histopathology displays a well-defined dermal lesion composed of bland-looking spindle cells arranged in interlacing fascicular fashion

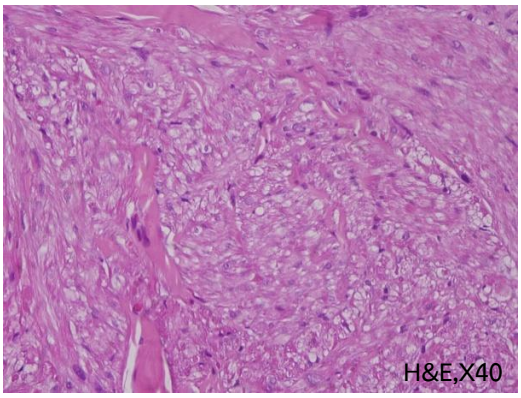

Figure 4 The spindle cells contain elongated, eel-like nuclei and pink cytoplasm

The skin biopsy specimen showed a well-defined dermal lesion composed of bland-

looking, elongated, eel-like nuclei and pink cytoplasm spindle cells arranged in interlacing fascicular fashion. Neither mitosis nor necrosis was present. The histopathology diagnosis was compatible with leiomyoma (Figure 3-4).

Direct sequence analysis of the patient's blood sample was performed with the patient's inform consent. It revealed a heterozygous germline missense mutation c.1189G>A (p.Gly397Arg) occurred at exon 8 of *fumarate hydratase* (*FH*) gene (Figure 5). Previous report suggested that this variant was pathogenic[1]. Based on the patient's clinical, histopathological findings, and genetic testing, the final diagnosis was compatible with hereditary leiomyomatosis and renal cell carcinoma (HLRCC).

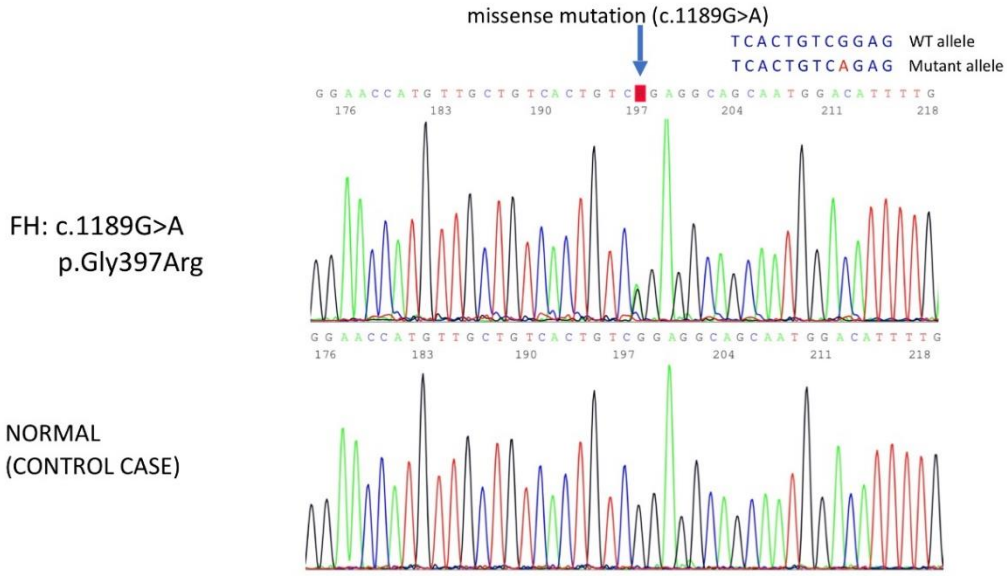

Figure 5 Direct sequence analysis of the *FH* gene showed heterozygous missense mutation c.1189G>A

Discussion

Cutaneous leiomyomas are benign smooth muscle tumor, often presented with multiple rather than solitary lesions[2]. HLRCC is a rare autosomal dominant disease that predisposes affected individuals to multiple cutaneous leiomyomas, renal cell carcinomas, and uterine leiomyomas. The condition was previously known as multiple cutaneous and uterine leiomyomatosis (MCUL) or Reed syndrome. Yet because of the increased risk of renal carcinoma, recently it has been termed as HLRCC[3].

HLRCC is caused by a heterozygous germline mutations in the tumor suppressor gene, *fumarate hydratase* (*FH*) on chromosome 1q42.3–q43. *FH* gene encodes the fumarate

enzyme, which converts fumarate to malate in the Krebs cycle. Several mutations over the *FH* gene that have been identified including missense (58%), frameshift (27%), nonsense (9%), and whole gene deletions (7%)[4,5].

Cutaneous leiomyomas are the most common, specific, and earliest clinical presentation of HLRCC, occurring in about 76-100% of the patients[5]. The lesions usually become apparent between 10 and 50 years old, with the mean age of 25 years old. Cutaneous leiomyomas can be classified into 3 categories based on origin of the smooth muscle and their clinicopathological features, including piloleiomyomas, genital leiomyomas, and angioleiomyomas. Piloleiomyomas are the most common subtype, deriving from arrector pili muscles of the hair follicle. 90% of the patients experienced the symptom of sharp shooting pain. Such symptom can occur spontaneously or can be induced by stress, cold, trauma, pressure. Another leiomyoma subtype is the painless genital leiomyoma, deriving from vulvar and dartos muscle of the genitalia and the smooth muscle of the nipple and areola. Lastly, the angioleiomyomas subtype, deriving from smooth muscles of blood vessels[3]. In HLRCC, any subtype of leiomyomas can be found with varied patterns and distributions, such as segmental or zosteriform, symmetrical, linear, bilateral or disseminated. The common sites of involvement are trunk, face, neck, and extensor surface of extremities. The malignant transformation of cutaneous leiomyomas to cutaneous leiomyosarcomas is rare[3].

Histopathology examination is required for the definite diagnosis of cutaneous leiomyomas. The microscopic examination shows a proliferation of smooth muscle fiber bundles composed of eosinophilic cytoplasm with elongated blunt-ended nuclei (described as cigar- or eel-shaped) distributed within the dermis. Immunohistochemistry reveals positive staining with anti-desmin and anti-a smooth muscle actin[6].

Patients with HLRCC are at risk of developing kidney cancers, with most affected individuals developed solitary or unilateral renal tumors. Only a few cases of bilateral HLRCC renal tumors have been reported. The most common subtype is type 2 papillary renal cell carcinoma (RCC) followed by collecting duct cancer. Other subtypes such as oncocytoma, clear cell carcinoma and Wilms tumor have been described. The tumors are usually asymptomatic but can be presented with hematuria, lumbar pain, flank pain or palpable mass[3,4]. In North American and French cohorts, 14%–18% of HLRCC patients had been reported to develop RCC, showing that penetrance for renal cancer in HLRCC is low[2]. The renal tumors in the setting of HLRCC are usually aggressive and carried a risk of metastasis, regardless of the tumor size[3]. Two-

thirds of *FH* mutation carriers with RCC died of metastatic disease, within 5 years of the diagnosis[7]. Annual renal screening for renal tumors is recommended in individuals with *FH* germline mutation. Magnetic resonance imaging and/or computerized tomography are the modalities of choice[2].

Early onset uterine leiomyomas (fibroids) are a common manifestation, occurring in 90% female diagnosed with HLRCC. It can cause dysmenorrhea, menorrhagia and irregular menstrual cycle. Yet, the risk of developing uterine leiomyosarcoma in HLRCC patients is low and has only been reported in Finnish population. It is a highly aggressive malignant tumor that is usually occur before the 3rd decade of life[2,4-5]. 68% of HLRCC female had myomectomy or hysterectomy on or before the age of 40. Hence, an annual gynecologic screening and early diagnosis of uterine leiomyomas are important as it is associated with the fertility issues[2,8].

The diagnostic criteria for HLRCC is composed of the major criteria of multiple cutaneous leiomyomas presentation, with at least one histologically confirmed. Minor Criteria include: 1) solitary cutaneous leiomyoma and family history of HLRCC, 2) early onset renal tumors of type 2 papillary histology, and 3) in women, multiple early-onset (<40 years of age) symptomatic uterine leiomyoma. Diagnosis is likely when the major criteria or two or more minor criterias are met. The definitive diagnosis of HLRCC is confirmed by the presence of a germline mutation in the *FH* gene[2,3].

To date, in term of the treatment modalities, there is no definitive cure for HLRCC. Symptomatic treatments with cryotherapy, surgery, and laser have been performed. Surgical excision is the standard treatment for solitary leiomyomas. Excision of multiple lesions tends to cause scarring and poor cosmetic results. CO2 laser ablation is one of the therapeutic options in cases with multiple and painful cutaneous leiomyomas, as it facilitates myolysis and provide pain relief[2-4,6]. Other treatment options include cryotherapy, electrocoagulation and electrodesiccation in combination with pain-relieving medications such as nitroglycerine, nifedipine, gabapentin, doxazosin and phenoxybenzamine. Recurrences found in approximately 50% of the cases[2-4,6].

Since cutaneous leiomyomas are typically the first clinical manifestation of HLRCC, the highly aggressive cancer predisposition syndrome, dermatologists plays an important role in detecting and diagnosing the disease. Comprehensive history taking, including the family history, and complete physical examination in patients with multiple cutaneous leiomyomas should be performed. Multidisciplinary team approach is essential for the appropriate management. Screening for

uterine leiomyomas and RCC with genetic counseling can reduce the morbidity and the mortality of the disease[9,10].

Our patient had been treated with CO2 laser ablation without any complication. Some of the lesions were still uncured. Counselling for the risk of RCC development was performed. After the referral to the urologist, KUB ultrasonography demonstrated no abnormalities. The investigation of computerized tomography scan or magnetic resonance imaging to detect small tumors was suggested, however due to the patient's personal and financial issues, no further evaluation was done. The genetic counseling was advised, with suggestion for *FH* gene testing in the first-degree relatives.

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