Annals of Clinical Case Reports

Case Report
Published: 16 Aug, 2023

Case of Hereditary Leiomyomatosis and Renal Cell Cancer without Cutaneous Leiomyomas Harboring a Heterozygous Germline Mutation in the Fumarate Hydratase Gene

Abe J[1], Hashimoto K[1], Shindo T[1], Nakayama S[1], Ogasawara T[1], Kyoda Y[1], Kobayashi K[1], Tanaka T[1], Takada K[2], Sakurai A[3] and Masumori N[1]*

[1]Department of Urology, Sapporo Medical University School of Medicine, Japan

[2]Department of Medical Oncology, Sapporo Medical University School of Medicine, Japan

[3]Departments of Medical Genetics and Genomics, Sapporo Medical University School of Medicine, Japan

Abstract

A 30-year-old woman was referred to our hospital with a 1-month history of intermittent gross hematuria and low back pain. Dynamic contrast enhanced computed tomography can revealed a hypovascular tumor of 8 cm in diameter in the left kidney. She was diagnosed with renal cell carcinoma T3aN0M0 and underwent a left radical nephrectomy. Histopathological analysis showed papillary type 2 renal cell carcinoma and the tumor cells lacked immunohistochemical expression of fumarate hydratase. This suggests fumarate hydratase deficient renal cell carcinoma. Next-generation sequencing of tumor revealed two *FH* variants. In the one (NM_000143; c.1144A>G) of two, germline *FH* gene variant was confirmed by sequencing DNA extracted from the patient's blood. She was diagnosed with hereditary leiomyomatosis and renal cell cancer. She had uterine fibrosis but no cutaneous leiomyomas. And she had no family history of renal cell carcinoma or these symptoms. Cutaneous leiomyoma is observed in 70% to 100% among patients with hereditary leiomyomatosis and renal cell cancer. While conventional diagnostic criteria require the presence of this symptom, genetic analysis enables us to diagnose hereditary leiomyomatosis and renal cell cancer. We report the case that the patient with an early onset of papillary type 2 renal cell carcinoma was diagnosed with HLRCC-associated renal cell carcinoma by identifying potentially actionable germline *FH* variant.

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Correspondence:
Kohei Hashimoto, Department of Urology, Sapporo Medical University School of Medicine, S16, W1, Chuo-ku, Sapporo, Hokkaido, 060-8543, Japan, Tel: +81-11-611-2111(Ext: 3472); Fax: +81-11-612-2709

Received Date: *31 Jul 2023*
Accepted Date: *11 Aug 2023*
Published Date: *16 Aug 2023*

Citation:
Abe J, Hashimoto K, Shindo T, Nakayama S, Ogasawara T, Kyoda Y, et al. Case of Hereditary Leiomyomatosis and Renal Cell Cancer without Cutaneous Leiomyomas Harboring a Heterozygous Germline Mutation in the Fumarate Hydratase Gene. Ann Clin Case Rep. 2023; 8: 2456.
***ISSN: 2474-1655**.*

Introduction

Hereditary Leiomyomatosis and Renal Cell Cancer (HLRCC) is an autosomal dominant disorder caused by heterozygous germline mutations in the Fumarate Hydratase (FH) gene. FH is a Tricarboxylic Acid (TCA) cycle enzyme that catalyzes the conversion of fumarate into malate [1]. Potential pathogenic mechanism is that intracellular accumulation of succinate and fumarate caused by loss of function mutations in FH inhibit Hypoxia Inducible Factor (HIF) and activate oncogenic pathway [2-4]. Recent genome studies have shown that pathogenic FH variants are observed in 0.1% to 0.3% [5,6]. HLRCC are characterized with symptoms of cutaneous leiomyoma, uterine fibrosis and renal cell carcinoma [7]. Approximately 6% to 20% of carriers with FH variants develop RCC [8]. HLRCC-associated RCC was classified as a separate tumor entity in the 2016 WHO classification [9]. The fifth edition of the WHO classification of urogenital tumors, published in 2022, revised diagnostic criteria of renal cell carcinoma. It highlights the importance of a diagnosis that involves not only morphology but also immunohistochemistry and relevant molecular tests [10]. Conventionally, HLRCC has been diagnosed based on the fact that patients have cutaneous leiomyoma as a major criterion, and have symptomatic uterine fibrosis before age 40, papillary type 2 Renal Cell Carcinoma (RCC) before age 40 and a first-degree familial history of these symptoms as minor criteria [1]. However, penetrance of these manifestations is not always completed. Here, we report the case in which a patient with a heterozygous germline mutation in the fumarate hydratase gene had papillary type 2 RCC and was later diagnosed with HLRCC without cutaneous leiomyomas.

Case Presentation

A 30-year-old woman who had no past history and no family history presented gross hematuria and lumber backache. The dynamic contrast enhanced Computed Tomography (CT) scan showed a left renal mass of 8 cm in diameter, heterogeneously enhanced in the late phase, which indicated

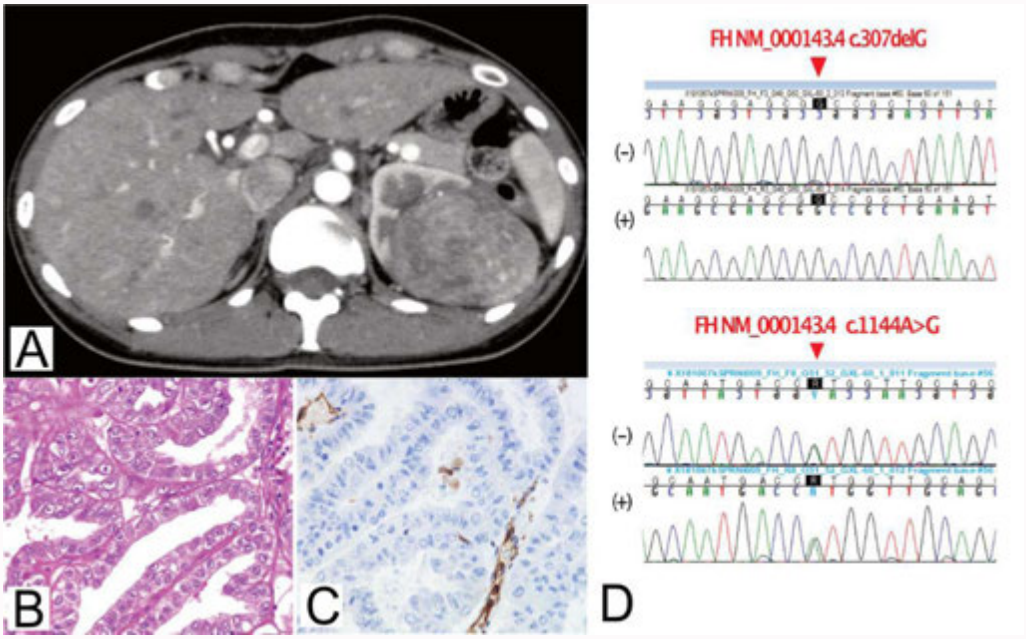

Figure 1A) Computed tomography image showed the left renal tumor which was not enhanced in the early phase.
1B) Hematoxylin Esosin staining showed papillary structure with eosinophilic cytoplasm and a halo around the nucleus. magnification x200
1C) Immunohistochemical staining showed tumor cells were negative for FH. FH: Fumarate Hydratase. magnification x200.
1D) Direct DNA sequencing of exon 8 revealed that two heterozygous variants were found in tumor.

non-clear cell carcinoma (Figure 1A). There was no evidence of metastasis. She was diagnosed with RCC of T3N0M0 and underwent a left radical nephrectomy.

Pathological findings showed that capsulized tumor was mixed with solid and fragile tissue with hemorrhage and necrosis and localized within renal parenchyma (pT2apN0M0). Tumor cells with eosinophilic cytoplasm, nuclear pseudostratification and high prominent nucleoli had extensive papillary growth (Figure 1B). Histological appearance corresponded to papillary type 2 RCC. In addition, immunohistochemical staining showed that FH was negative (Figure 1C). Next-generation sequencing of tumor with FoundationOne® CDx revealed two likely pathogenic variants in the *FH* gene (NM_000143; c.1144A>G, NM_000143; c.307delG) (Figure 1D). In the one (NM_000143; c.1144A>G) of two, germline *FH* gene variant was confirmed by sequencing DNA extracted from the patient's blood. She was diagnosed with HLRCC. Gynecological and dermatological examination revealed uterine fibrosis but had no cutaneous leiomyomas. After genetic counseling, we recommended her family to take germline investigation. She has had no recurrence of HLRCC-associated RCC for two-year follow-up period and will have annual examination of gynecology and dermatology.

Discussion

Here, we presented a case that the challenges associated with the diagnosis of HLRCC in a patient with papillary type 2 RCC who had no family history or cutaneous manifestations. Most of HLRCC-associated RCC are in advanced stage at the time of diagnosis [11]. Their aggressive biological feature confers adverse prognosis for the patient [12]. The average age at diagnosis of HLRCC is known to be young [13]. Wu et al. reported 18 (9.4%) of 190 patients with renal tumor younger than 45 years old had pathogenic germline variant including FH variant [14]. On the process of the WHO classification revision, while papillary RCC type 1 can be regarded as the papillary RCC, papillary RCC type 2 is abolished [10]. It is because papillary RCC type 2 has a heterogeneous molecular background, which can include FH deficiency as well as gene fusions involving *TFE3* or *TFEB*. Approximately 5% of patients with papillary RCC have a CpG island methylator phenotype, which is associated with poor survival rates [15]. Half of these patients also have a mutation in the *FH* gene [15]. In Japan, it is also known that approximately 5% of patients with non-clear cell renal carcinoma have pathogenic variants, such as FH or BAP1. These careers were diagnosed with RCC 15.8 years earlier than those who don't have [16]. That is why physician awareness and understanding of HLRCC is very important for conducting an appropriate management.

Diagnosis based on clinical manifestations, even major criteria, may be with a risk of delayed diagnosis due to incomplete penetration. In some cases, as in the present case, the major criteria are not met [17]. Uterine fibrosis and cutaneous leiomyoma have been reported to be observed in 70% to 80% and 70% to 100% among patients with HLRCC, respectively [7,18,19]. However, uterine fibrosis is more common in women and cutaneous leiomyoma is low in young patients (about 30%) [7,8]. That makes it more complicated to diagnose HLRCC. Therefore, accurate diagnosis by genomic testing is necessary.

In the present case, FH immunohistochemical staining was negative. This indicated loss of function in FH due to its gene alteration. The comprehensive next-generation sequencing analyses revealed two genetic alterations in the *FH* gene. FH variants were evaluated in an online database (Leiden Open Variation Database (LOVD) system) [19]. The FH database includes 107 variants of which 93 are thoughted to be pathogenic and 14 may be non-functional intron variants [18]. It was reported that the most common types of mutations at the protein level are missense in 57%, frameshifts and nonsense in 27%, with the remainder composed of deletions, insertions and duplications [19]. In the present case, the database

revealed the one (NM_000143; c.1144A>G) of two variants was a germline missense mutation in *FH* gene. This missense mutation was located in exon 8 lesion. This germline variant was confirmed by sequencing DNA analysis. Smith DL et al. showed clinical and genetic data from 33 families with suspected of HLRCC on a nationwide level in the Netherlands [8]. Four of the 11 pathogenic FH germline mutations identified were novel mutations, including this missense mutation (NM_000143; c.1144A>G). Of the two family members with this mutation, two had cutaneous leiomyoma and one had uterine fibrosis, but did not develop RCC. Our patient is the first case of HLRCC-associated RCC harboring this missense mutation.

We proposed an approach to the clinical diagnosis and indications for FH mutation analysis. Although we have not been able to confirm the FH mutation in the family, there were no significant findings in the family history. Given that an identified mutation was reported in another HLRCC case, it suggests that this mutation is likely to be *de novo*. Thus, it is very important for urologists to consider possibility of HLRCC-associated RCC for young patients, even having no family history or other clinical manifestations, with papillary RCC. We believe that our findings will be useful in clinical practice.

Conclusion

It is important for young patients with RCC to consider hereditary diseases. If the pathologically FH immunochemical staining of the tumor is negative, it is crucial to investigate the patient's family history and consider dermatological or gynecological screening. Considering the risk of poor prognosis in renal cancer, it is essential to be aware of the importance of a definitive diagnosis, including genetic testing. Cases like this present one, which lack cutaneous leiomyoma, may also occur. After diagnosing HLRCC, it is recommended for family members to undergo genetic testing.

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