

Novel Pathogenic Variant of Fumarate Hydratase in Hereditary Leiomyomatosis and Renal Cell Carcinoma Syndrome (HLRCC): A Case Report

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Keywords:

Hereditary leiomyomatosis and renal cell carcinoma (HLRCC); Fumarate hydratase (FH); Mutation; Brain metastasis; Case report

Abbreviations:

HLRCC: Hereditary leiomyomatosis and renal cell carcinoma; RCC: Renal cell carcinoma; ccRCC: Clear cell RCC; nccRCC: Non-clear cell RCC; PRCC: Papillary renal cell carcinoma; FH: Fumarate hydratase; CT: Computed tomography; MRI: Magnetic resonance imaging; AFP: Alpha fetoprotein; CEA: Carcinoembryonic antigen; CA19-9: Carbohydrate antigen 199; NGS: Next generation sequencing; TKIs: Tyrosine kinase inhibitors; PD-1: Programmed cell death-1; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease; PFS: Progression free survival; DFS: Disease-free survival; OS: Overall survival.

1. Abstract

Background: Hereditary leiomyomatosis and renal cell carcinoma syndrome (HLRCC) is a rare genetic disease, which is caused by the mutation of fumarate hydratase (FH) gene and inherited by autosomal dominance.

Case Description: We reported a 32 years old female patient with HLRCC associated renal cell carcinoma (RCC). The patient was young, had a previous history of early-onset uterine fibroids, and had a family history of RCC. Next generation sequencing (NGS) suggested FH gene mutation, but no skin lesions. Tyrosine kinase inhibitors (TKIs) was given after definite diagnosis, however, the disease progressed rapidly right after second-line treatment of TKIs,

and brain metastasis occurred. Finally, she died of stage IV HLRCC-RCC with liver, bone, adrenal gland, brain, pancreas and retroperitoneal lymph node metastases. The overall survival (OS) was 7.43 months.

Conclusions: We found that c.698G>T (p.Arg233Leu) may be a new germline pathogenic variant of FH gene, confers an increased risk for HLRCC-RCC. We also shared a case of HLRCC-RCC related brain metastasis, which provides clinical experience for the diagnosis and treatment of rare diseases.

2. Introduction

Hereditary Leiomyomatosis and Renal Cell Carcinoma (HLRCC), also known as Reed's Syndrome, is a rare disease. Due to the lack of knowledge about the disease, the incidence rate of this disease has not been counted. A literature review only identified a total of 672 HLRCC cases worldwide from 82 case reports and 15 cohorts (up to November 28th, 2019) [1]. HLRCC is caused by the pathogenicity change of Fumarate Hydrate (FH) gene [2]. Mis-sense mutation is the most common and is inherited by Autosomal Dominant (AD) inheritance [3]. According to previous literature reports, about 80-90% of women with HLRCC have early-onset

multiple uterine leiomyomas, with a median age of 32-35 years [4, 5], which is earlier than the onset age of ordinary fibroids in 40-50 years old [6]; About 75% of patients have cutaneous leiomyoma, and 15-30% of patients with HLRCC have secondary Renal Cell Carcinoma (RCC) [7]. To date, only few publications have described HLRCC associated RCC (HLRCC-RCC).

In 2016, HLRCC-RCC was firstly added to the World Health Organization (WHO) histopathological classification of renal tumors, which is typically type II Papillary Renal Cell Carcinoma (PRCC), and belongs to non-clear cell RCC (nccRCC) [8]. However, due to the small number of patients and the lack of corresponding large-scale randomized controlled clinical trials, only a few numbers of phase II clinical trials showed Sunitinib, Sorafenib, Everolimus and other targeted drugs are effective in the treatment of nccRCC, but their efficacy is poor compared with that of clear cell RCC (ccRCC) [9-11]. The National Comprehensive Cancer Network (NCCN) guidelines for RCC recommend the preferred clinical trial or Sunitinib for the first-line treatment of nccRCC in 2019, with the evidence level is 2A. As there is no consensus and standard on the treatment of HLRCC [12], we can only refer to the treatment of nccRCC. We present the following case in accordance with the CARE reporting checklist.

3. Case Presentation

We present the following case in accordance with the CARE reporting checklist. A 32 years old woman was admitted to our hospital on February 3rd, 2021 with the chief complaint of finding liver mass for more than 3 months. The patient's vital signs were stable at admission: the body temperature was 36.4°C, the pulse was 80 times/minute (regular), the respiration was 18 times/minute (regular), the blood pressure was 124/90mmHg, BMI index was 19.88 and the Eastern Cooperative Oncology Group (ECOG) performance score was 1. In December 2021, the patient developed nausea, vomiting, fatigue, left iliac pain, and the symptoms continued unabated. In January 2021, she has intermittent low fever in the afternoon, about 38 degrees Celsius, and the fever subsided by itself. Laboratory examination results showed AFP, CEA, CA724 and CA199 were within the normal range, CA125 and CA153 were 2643 U/ml and 44 U/ml respectively, which were significantly higher than the normal value. The patient's normal health status is general, denied other systems' diseases. She was diagnosed with C type hepatitis in 2011 and had a history of uterine fibroids surgery in 2019 (the age of onset was less than 30 years old), had a history of drinking and had not quit, unmarried and not pregnant, had a family history of PRCC (patient's uncle) (Supplementary Figure 1).

In October 2020, the patient found multiple occupying lesions in the liver through abdominal ultrasound, but without special treatment. In January 25th, 2021, abdominal and pelvic enhanced CT showed: (1) multiple space occupying lesions in liver parenchyma, considering the possibility of liver metastasis; (2) retroperitoneal

enlarged lymph nodes with high possibility of metastasis; (3) abnormal enhancement shadow of left kidney, unclear boundary with left psoas major muscle and left renal vein, considering neoplastic lesions, adjacent invasion may not be excluded; (4) multiple bone signals in pelvis are uneven, with visible enhancement and possible bone metastasis; (5) the gastric antrum is slightly enhanced, so further gastroscopy is recommended; (6) cystic changes in the left adnexal area (Figure 1). In February 5th, 2021, the patient underwent ultrasound-guided liver mass puncture biopsy, the pathology showed liver metastatic poorly differentiated cancer. Combined with the results of immunophenotype and imaging examination, the possibility of renal origin was high (Supplementary Figure 2). Immunohistochemical staining showed tumor cells: PCK (+), PAX8 (+), PAX2 (+), CAIX (individual+), CK7 (-), CK20 (-), Villin (-), CDX2 (-), Hepatocyte (-), TTF-1 (-), GATA-3 (partial+), CK5/6 (-), P40 (-), CD56 (partial weak +), CD10 (-), INI-1 (+), TFE3 (-). The next generation sequencing (NGS) showed FH gene missense mutation (c.698G>T), and the amino acid change was p.Arg233Leu. Combined with the patient's medical history, signs, imaging and molecular pathology, it was clearly diagnosed as HLRCC-related RCC stage IV with liver, bone and retroperitoneal lymph node metastases.

The patient started tyrosine kinase inhibitors (TKIs) Sunitinib targeted therapy on February 20th, 2021 (6-week cycles of 4 weeks with treatment followed by 2 weeks without treatment), and was treated with Zoledronic acid every month. The curative efficacy was assessed as partial response in May (Figure 2). Since June, the patient felt abdominal distension, dyspepsia, intermittent lower limb and perineal swelling. On July 15th, ultrasound showed peritoneal effusion, so abdominal puncture and drainage were performed. 2000ml white chyloid peritoneal effusion was drained intermittently. During this period, 720000U of Endostar (recombinant human endostatin, an anti-angiogenesis drug) was perfused intraperitoneally, and the ascites became clear after perfusion. At the same time, abdominal and pelvic MRI and pulmonary CT suggested disease progression (Figure 3 A, B). Axitinib combined with programmed cell death-1 (PD-1) mAb was proposed to be treated as second-line therapy, however, considering the patient's severe hypothyroidism and moderate anemia, PD-1 was not suitable for the time being. Therefore, the targeted therapy of Axitinib (5mg po bid) was started on July 29th. The patient developed hypertensive crisis (blood pressure was reached to 190/110mmHg) and two seizures on August 2rd, but there were no obvious abnormalities in emergency cranial CT. After sedation, dehydration, hypotension and antiepileptic treatment, epilepsy did not occur again, further brain MRI suggested that the left frontal parietal lobe has abnormal signal (about 2mm in diameter) (Figure 3 C-F). Combined with the medical history, considering the possibility that the patient's previous seizure was caused by brain metastasis and peritumoral edema. After the blood pressure was controlled, Axitinib was restored to 5mg bid orally on August 6th. The patient had yellow staining

of skin and sclera around August 28th, accompanied by disturbance of consciousness, the test showed that bilirubin increased, and abdominal CT showed intrahepatic bile duct dilatation. After comprehensive evaluation by interventional doctors, interventional drainage of bile was not suitable for the time being. The patient had extensive metastasis of renal cancer with obstructive jaundice,

hepatic encephalopathy, hepatorenal syndrome and disturbance of consciousness, the general condition was very poor, and was in the end-stage of malignant tumor, which had no indication of tumor specialist treatment. At 14:02 on September 4th, 2021, the patient had limb convulsions, and the family refused all rescue measures. At 14:06, the patient was declared clinical death, with an OS of 7.43 months (Figure 4).

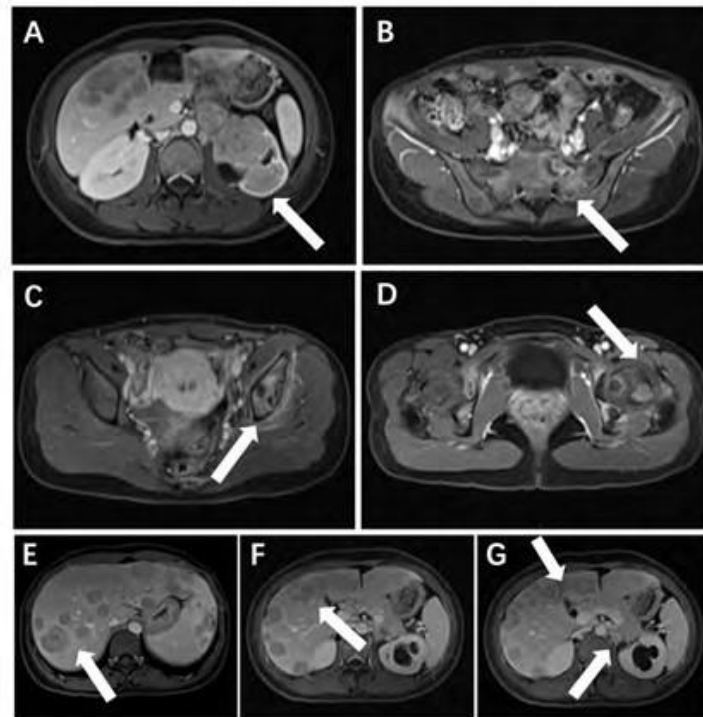


Figure 1: Abdominal and pelvic enhanced CT images at initial diagnosis. (A) The boundary between left renal space occupying lesion, left psoas major muscle and left renal vein is unclear; (B, C, D) Multiple bone signals of pelvis are uneven, with visible enhancement; (E, F) Multiple hepatic parenchymal space occupying lesions; (G) Retroperitoneal enlarged lymph nodes. Tumor site indicated by white arrow.

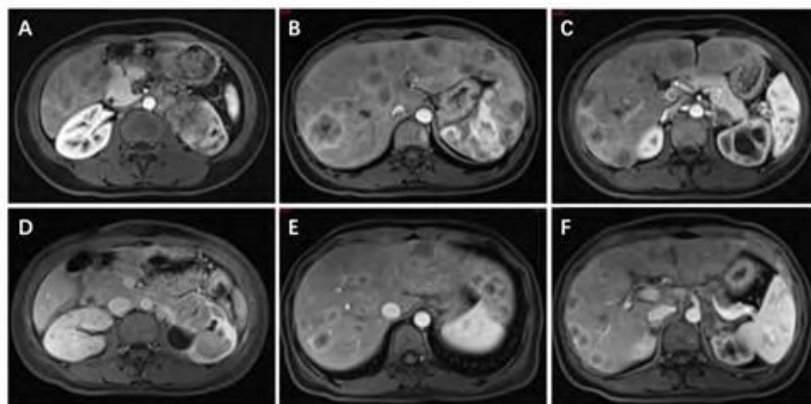


Figure 2: Imaging evaluation after first line treatment. According to RECIST v1.1, the efficacy evaluation after first-line Sunitinib targeted therapy showed partial response (PR). Imaging results in (A,B,C) February, 2021 and (D,E,F) May, 2021.

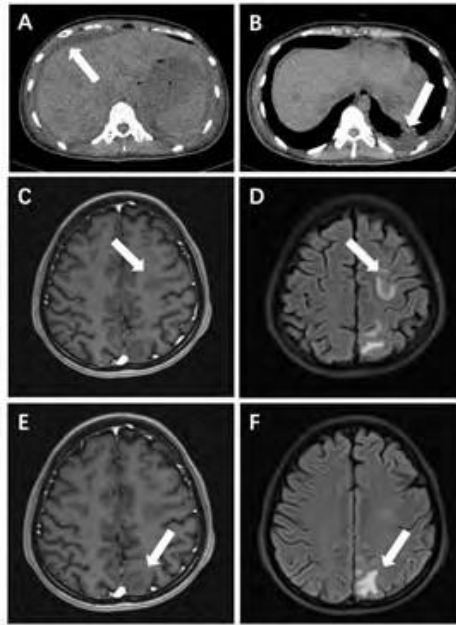


Figure 3: CT and MRI showed disease progression. The patient developed (A) peritoneal effusion; (B) pleural effusion; (C, D) brain metastasis (about 2mm in diameter); (E, F) peritumoral edema.

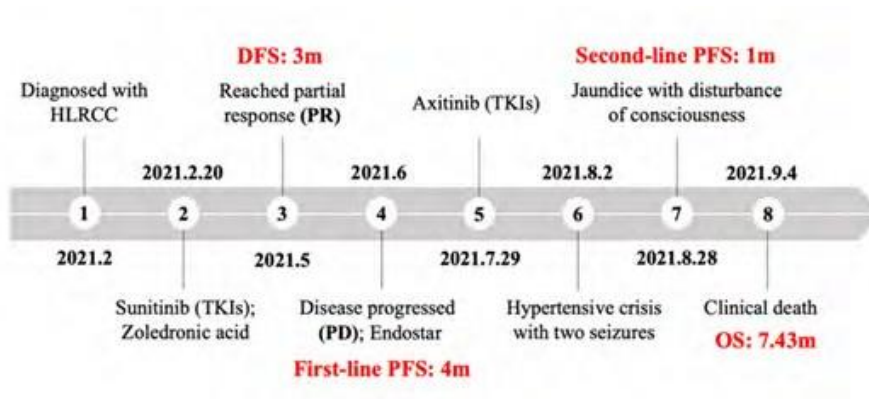
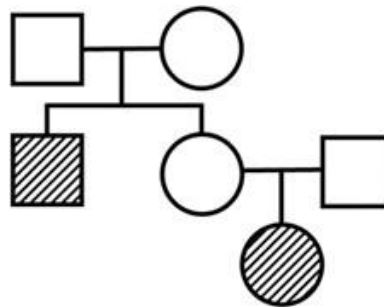
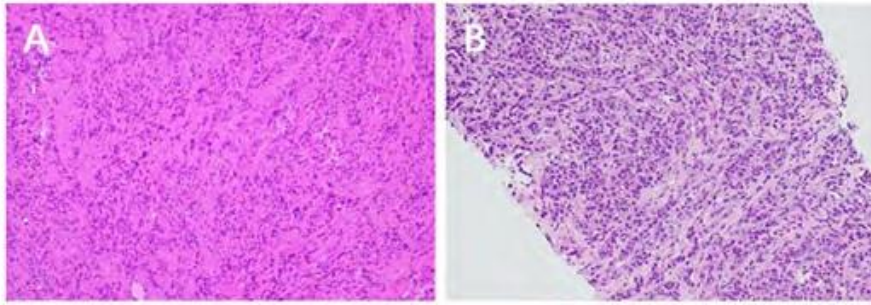


Figure 4: Timeline of the case.



Supplementary Figure 1: Family genetic pedigree.



Supplementary Figure 2: Patient's previous pathological images (40X).

4. Discussion

According to the 2020 International Agency for Research on Cancer (IARC) GLOBOCAN statistics, kidney cancer ranks sixteenth (2.23%) in the new cancer cases worldwide (431288/19.3 million) [13]. HLRCC related RCC is associated with FH gene germline mutation and leiomyomatosis, which is very rare and mostly hereditary [14]. FH gene can encode fumarate hydratase in tricarboxylic acid (TCA) cycle, located on the q-arm of chromosome 1 (chr1q43). The loss of heterozygosity of FH gene can lead to the accumulation of fumarate, and then competitively inhibit prolyl hydroxylase, making hydroxyl inducible factors (HIF)-1A and 2A hydroxylation, resulting in cell pseudohypoxia³.

For the diagnosis of this patient, she had a history of early-onset uterine multiple myoma, found FH gene mutation, and had a family history of PRCC, so it was clearly diagnosed as HLRCC-RCC, however, the skin and mucosa of the patient's limbs, trunk, neck and face were normal in color, without rash, nodule, subcutaneous bleeding, etc., no skin lesions were found. Through NGS detection, we found that the FH gene mutation in this patient was different from the changes of cDNA in previous reports [15, 16], which was c.698G>T and the amino acid change was p.Arg233Leu. Therefore, we speculated that this missense mutation may be a new variant for HLRCC. In addition, the patient had brain metastasis. Based on the Surveillance Epidemiology and End Results (SEER) database, the probability of brain metastasis was 12.1% in 6667 cases of metastatic RCC [17], but there was no literature report on the probability of brain metastasis of HLRCC-RCC. Benjamin Chaucer et al [18] reported a case of HLRCC related encephalitis, which was induced by Nivolumab, a PD-1 blocker, it may be due to FH gene mutation leading to the abnormality of PD-1 metabolism. Our case can be used as a description of brain metastasis caused by FH gene deficiency, but the specific mechanism still

needs to be explored through basic research. At the same time, the patient developed rapidly after second-line Axitinib treatment and did not use PD-1 treatment. The indications of PD-1 in such diseases and the effectiveness and safety of PD-1 need to be verified by clinicians in practice in the future.

Through this case report, there are some implications for the clinical diagnosis and treatment of HLRCC and HLRCC-RCC: (1) for the children who has family history of RCC, early-onset uterine and cutaneous leiomyoma, it is recommended to carry out HLRCC related screening from the age of 8 to achieve early detection and early treatment, such as periodic renal imaging and predictive testing for FH mutation; (2) explore the indications of PD-1 for nccRCC. For our patients, due to the rapid progress of the disease, there was no opportunity to use PD-1 for immunotherapy. Therefore, when meeting such patients, trying to use PD-1 early is also an enlightenment of this case; (3) Cutaneous leiomyoma is only seen in some patients, and so as our patient. Thus, we should ask the patient's medical and family history more comprehensively to avoid missed diagnosis. The process of clinical diagnosis and treatment of rare diseases are worthy of our in-depth research and thinking.

5. Conclusion

We reported a case of HLRCC-RCC with brain metastasis, and found that a new germline mutation of FH gene may increase the risk of the disease, which will bring new ideas and perspectives to the diagnosis and treatment of such rare diseases and also emphasize the importance of further exploring rare diseases and the necessity of early screening rare genetic diseases.

6. Funding

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