A Case Report of Aggressive Fumarate Hydrase-deficient Renal Cell Carcinoma With Loss of HLA Antigens

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Abstract. Background: Fumarate hydrase (FH)-deficient renal cell carcinoma (RCC) is a rare RCC subtype, and FH-deficient RCC may be misdiagnosed as another type of RCC, such as type 2 papillary RCC or collecting duct carcinoma. FH and 2-succinocysteine (2SC) are useful diagnostic markers for FH-deficient RCC and can be measured using immunohistochemistry (IHC). Case Report: A 30-year-old female with 3-month history of fatigue and left-flank mass was diagnosed with a 20×13×10 cm left-side renal mass with massive inferior vena cava (IVC) tumor thrombus that extended into the right atrium. She underwent nephrectomy and IVC thrombectomy, and a pathological diagnosis of type 2 papillary RCC was made. Four months after the surgery, computed tomography scan showed multiple liver metastases not observed immediately after surgery. Systemic treatment with sorafenib was initiated; however, she did not respond and died 3 months after treatment. Subsequent review of hematoxylin and eosin-stained sections indicated morphologic characteristics consistent with FH-deficient RCC, and IHC staining was negative for FH but positive for 2SC, indicating a diagnosis of FH-deficient RCC. Further immunological analyses revealed the loss of HLA-class I, b2 microglobulin, and HLA-DR antigens in cancer cells. In addition, a few CD8-positive cytotoxic T cells and CD163-positive tumor-associated macrophages were noted. Conclusion: An immunosuppressive tumor microenvironment that facilitates cancer immune evasion might be associated with the rapid progression and poor prognosis in our patient. Further investigation of the tumor immune microenvironment in patients with FH-deficient RCC is warranted.

Fumarate hydrase (FH)-deficient renal cell carcinoma (RCC) was formerly described as a subtype of hereditary leiomyomatosis and RCC syndrome–associated RCC in the 2016 World Health Organization (WHO) classification (1). However, in the revised WHO classification published in 2022, FH-deficient RCC was classified as an independent tumor entity defined by negative FH immunohistochemical (IHC) staining, positive 2-succinocysteine (2SC) IHC staining, and/or pathogenic FH mutation in the tumor, regardless of the presence or absence of a clinical or family history of skin or uterine leiomyomas (2). FH-deficient RCC exhibits a variety of histopathological features; thus, it can be misdiagnosed as another RCC subtype, such as type 2 papillary RCC, tubulocystic RCC, or collecting duct carcinoma (3). A previous comprehensive genomic analysis of papillary RCC demonstrated the presence of a CpG island methylation phenotype in a certain proportion of patients diagnosed with type 2 papillary RCC, and these patients harbored an FH mutation. Such patients were shown to have a very poor prognosis (4).

In our previous study, we evaluated the tumor immune microenvironment in a cohort of patients with locally advanced RCC with pT3 and pT4 (5). The cohort included 4 patients who had been diagnosed with papillary RCC. One patient (case no. 28) was FH-negative and 2SC-positive on IHC staining, and this patient’s perioperative clinical course...
was reported previously (6). Here, we report the patient’s subsequent clinical outcomes and findings regarding the tumor immune microenvironment. All procedures were performed in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments. Informed consent was obtained from the patient to be included in the study.

Case Report

The patient was a 30-year-old female who had a 3-month history of fatigue and left-flank mass. Computed tomography (CT) scan revealed a 20×13×10 cm left-side renal mass with massive inferior vena cava (IVC) tumor thrombus that extended into the right atrium (Figure 1A) without visceral findings.
metastases. Multiple small uterine leiomyomas were observed in the CT scan at diagnosis of the renal mass (Figure 1B and C). No family history of skin or uterine leiomyomas was noted. The patient underwent radical nephrectomy and IVC thrombectomy, and the tumor was completely resected. Four months after the surgery, the patient developed abdominal distension and fatigue. CT scan showed multiple liver metastases (Figure 1D) not observed immediately after surgery. Systemic treatment with sorafenib was initiated; however, she did not respond and died 3 months after treatment.

The patient in the present case was initially diagnosed pathologically with type 2 papillary RCC. However, pathological re-review of hematoxylin and eosin–stained sections indicated morphologic characteristics consistent with FH-deficient RCC, and IHC staining was negative for FH and positive for 2SC (Figure 2). Therefore, a diagnosis of FH-deficient RCC was made. In addition, immune cell infiltration was rare in this case. Therefore, additional pathological examinations were performed to evaluate the immune cell infiltration and HLA antigens in more detail using a tissue microarray. IHC analysis of cancer cells from this case revealed the loss of HLA-class I, b2 microglobulin (B2M), and HLA-DR antigens (Figure 3A). Few CD8-positive cytotoxic T lymphocytes (CTLs) and CD163-positive tumor-associated macrophages (TAMs) were observed in this case (Figure 3B). In contrast, high expression of HLA-class I antigen and B2M as well as increased numbers of CTLs and TAMs were observed in analyses of samples from other RCC cases (Figure 3C).

Discussion

The patient in the present case was diagnosed with type 2 papillary RCC in 2010, primarily because FH-deficient RCC had not yet been accurately described and was not classified as an independent entity in the WHO classification at that time. However, careful observation of the clinical findings, including the presence of multiple uterine leiomyomas, the relatively young age of onset, and the rapid metastatic recurrence, might have led to suspicion of FH-deficient RCC.

In the present study, we identified a case of FH-deficient RCC among patients previously diagnosed with type 2 papillary RCC in a cohort of locally advanced RCC with pT3 and pT4. Notably, this case was clinically very aggressive, and pathological analysis revealed an immunologically
Figure 3. Immunohistochemical analysis of immune-related molecules. Immunostaining data were obtained from a previously published study (5).
“cold” tumor. Infiltration of numerous immune cells into the RCC tumor microenvironment is well described, and immunotherapy using an immune checkpoint inhibitor (ICI) has become standard therapy for advanced RCC in recent years. Other studies have reported that almost all cases of primary RCC express HLA-class I antigens (7, 8), whereas loss of HLA-antigens in cancer cells has been observed in several cancers other than RCC and related to immune escape of cancer cells (9). The present case was also negative for HLA-DR, although HLA-DR expression in cancer cells is reportedly observed in approximately 50% of RCC cases and well correlated with lymphocyte infiltration (5). HLA-DR expression in cancer cells is one of several markers that can be used to predict the efficacy of ICI therapy (10, 11). We previously reported a case of metastatic RCC with high HLA-DR expression that showed a complete response to anti–PD-L1 therapy (12). These data highlight the importance of monitoring HLA-class I and II expression in RCC for the prediction of ICI therapy response.

As FH-deficient RCC is a rare subtype of RCC, only a few studies have described the immune microenvironment in FH-deficient RCC. Kiyozawa et al. examined lymphocyte and myeloid cell infiltration in 7 cases of FH-deficient RCC, and they reported an average density of infiltrating CD8-positive T cells and CD33-positive myeloid cells (including immature monocytes and TAMs) of 43 and 7 cells per 5 high-power fields, respectively (13). These numbers were significantly lower than those reported for clear cell RCC. Kiyozawa et al. also observed PD-L1 expression in 2 of the 7 cases. Sun et al. demonstrated that hypermethylation at CpG sites in genes related to the epithelial-mesenchymal transition pathway was potentially highly immunogenic, despite a low mutation burden (14). They also reported that ICI therapy was more effective against FH-deficient RCC than conventional tyrosine kinase inhibitor therapy. Another group recently reported that ICI therapy prolonged overall survival in patients with FH-deficient RCC, although the effect was not statistically significant (p=0.174) (15). In this reference, 17% and 47% of cases exhibited partial response or stable disease, respectively. Thus, ICI therapy is potentially effective for treating FH-deficient RCC; however, no data regarding HLA expression in cancer cells was described. It might be preferable to examine HLA expression before initiating ICI therapy.

In conclusion, IHC analysis for FH and 2SC is useful for the diagnosis of FH-deficient RCC, even in patients previously diagnosed with papillary RCC. An immunosuppressive tumor microenvironment that facilitates cancer immune evasion might be associated with rapid progression and poor prognosis. Further investigation of the tumor immune microenvironment in patients with FH-deficient RCC is warranted to develop an appropriate treatment strategy using ICIs.

Conflicts of Interest
All Authors have no conflicts of interest to declare in relation to this study.

Authors’ Contributions
YM and YK gathered the patient’s data and wrote the article. YK and KK were responsible for pathological diagnosis of this case. TM and TA carried out the immunohistochemistry. KT, SO, SU, and TK discussed the data and helped write the article. All Authors approved the final article.

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