Fumarate hydratase-deficient renal cell carcinoma arising in acquired cystic kidney disease in a hemodialysis patient: Diagnostic clues from percutaneous renal mass core needle biopsy: A case report

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Abstract. A 76-year-old male patient with a 30-year history of dialysis presented with persistent fever and hematuria. Computed tomography and magnetic resonance imaging suggested a cyst infection associated with acquired cystic kidney disease. Although cyst drainage was planned, ultrasonography incidentally detected a solid mass within the kidney cyst, prompting a switch from drainage to percutaneous biopsy. Histopathological examination revealed fumarate hydratase-deficient renal cell carcinoma, and nephrectomy was performed. Diagnosis of dialysis-associated renal carcinoma relies on imaging techniques. However, it can be difficult to identify malignant tumors in a polycystic kidney using imaging alone, and pathological confirmation by biopsy is often required. The present report highlights the usefulness of performing needle biopsy for suspected masses using the same method that is used by nephrologists for kidney biopsy in cases in which determining the lesion nature from imaging alone is difficult and in hydratase-deficient renal cell carcinoma arising in acquired cystic kidney disease as a dialysis-associated renal carcinoma.

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Abbreviations: 2SC, S-2-succinylated-cystaine; ACKD, acquired cystic kidney disease; ADPKD, autosomal dominant polycystic kidney disease; AMACR, α-methylacyl-CoA racemase; CRP, C-reactive protein; CT, computed tomography; FHdRCC, fumarate hydratase-deficient renal cell carcinoma; MRI, magnetic resonance imaging; RCC, renal cell carcinoma; TKV, total kidney volume

Key words: FHdRCC, ACKD, kidney biopsy, nephrectomy, hemodialysis

Introduction

Fumarate hydratase-deficient renal cell carcinoma (FHdRCC) is a molecularly defined renal cell carcinoma (RCC) according to the WHO classification of urinary and male genital tumors (1). It occurs due to the inactivation of the FH gene. FH deficiency causes the accumulation of fumarate in the mitochondria, which acts as an oncometabolite in the cytoplasm, leading to RCC (2). It is common in males and is a highly aggressive metastatic carcinoma. However, it has rarely been reported as dialysis-associated renal carcinoma.

RCC diagnosis relies on imaging techniques. Computed tomography (CT) or magnetic resonance imaging (MRI) are used to confirm RCC (3). However, it is sometimes difficult for imaging alone to identify renal masses as malignant tumors in cystic kidney diseases such as autosomal dominant polycystic kidney disease (ADPKD) or acquired cystic kidney disease (ACKD). In such cases, pathological confirmation by biopsy is required.

Here, we report a case of FHdRCC that was developed in a patient with ACKD who presented with fever and hematuria. This case indicates that it is important to perform a renal mass biopsy if its radiographic images are equivocal and that it can be performed in the same way as percutaneous kidney biopsies.

Case report

Case presentation. A 76-year-old Japanese male started hemodialysis at the age of 47 years with an unknown etiology. The patient had no personal or family history of malignancy. Intermittent gross hematuria was observed at 75 years of age. Enhanced computed tomography (CT) and cystoscopy

at another hospital showed no malignancy but revealed polycystic kidneys. He was referred to our hospital with persistent fever and an elevated C-reactive protein (CRP)-suspected cyst infection in ADPKD.

The total kidney volume (TKV) was 616 ml (right: 288 ml; left: 328 ml). The cyst distribution differed from that in ADPKD; he was diagnosed with ACKD. He was exhausted and presented with hematuria and associated fever, which seemed to be a symptom of cystic hemorrhage. Therefore, transcatheter embolization of the bilateral renal arteries was performed. Only the left artery could be embolized because of right arterial stenosis (Fig. 1A). Nevertheless, hematuria and fever subsequently ceased. At three-month follow-up, his TKV had decreased to 380 ml (right: 256 ml, left: 94.6 ml), and the left kidney had shrunk.

Four months after embolization (one year after onset of symptoms), he re-presented with persistent elevated CRP, fever (temperature around 37.6˚C), and hematuria over two weeks. The patient was admitted to our department. On admission, the patient height and weight were 165 cm and 57.4 kg, respectively. His vital signs were stable (body temperature, 37.1˚C; blood pressure, 123/64 mmHg; heart rate; 56 bpm). The patient had no abdominal or back pain. The laboratory test findings are listed in Table I. His CRP was elevated to 8.01 mg/dl, whereas other hematological parameters, including hemoglobin (11.0 g/dl) and serum creatinine (5.36 mg/dl, elevated as expected in a dialysis patient), were within the anticipated ranges for a dialysis patient. CT showed a thickened cyst wall in the right kidney (Fig. 1B). MRI demonstrated the same cyst, with decreased diffusion on diffusion-weighted images, slightly high intensity on T1-weighted images, and low intensity on T2-weighted images (Fig. 1C-E). TKV was slightly increased to 426 ml (right: 334 ml, left: 91.5 ml), and the right side became swollen. These findings, together with the CRP elevation, were suggestive of a cystic infection or hemorrhage, and antibiotics were administered.

As there was little improvement in the fever and CRP levels, we attempted cyst drainage on day 8. Examining the cyst using echography incidentally revealed a highly echoic and solid mass (Fig. 1F). The mass was punctured using a biopsy needle gun that is used in percutaneous kidney biopsy, while remaining in the lateral position (Fig. 2A and B). Six white hard core biopsies were obtained without complications (Fig. 2C).

Kidney mass biopsy findings. Light microscopy of the biopsy specimen (Fig. 2D-F) revealed cribriform-pattern invasive RCC. The tumor demonstrated a mixed cellular pattern: some cells had prominent atypical nuclei and clear cytoplasm, while others were small and round, with surrounding eosinophilic macronucleoli and gritty calcification. Immunohistochemistry was performed on formalin-fixed, paraffin-embedded sections using the following primary antibodies: PAX8 (rabbit polyclonal, 1:2,000 dilution; cat. no. 10336-1-AP, Proteintech, distributed by Cosmo Bio, Tokyo, Japan); GATA3 (mouse monoclonal, clone L50-823, 1:1 dilution; cat. no. 418201, Nichirei Biosciences, Tokyo, Japan). It revealed positive nuclear *PAX8* expression and negative *GATA3* expression. These findings suggest an uncommon renal cell carcinoma, such as molecularly defined RCC.

Table I. Laboratory findings on admission.

Laboratory values	Patient result	Reference range
Blood biochemistry		
Total protein, g/dl	7.3	6.6-8.1
Albumin, g/dl	3.6	4.1-5.1
Aspartate aminotransferase, U/l	3	13-30
Alanine aminotransferase, U/l	9	7-13
Lactate dehydrogenase (IFCC), U/l	239	124-222
Alkaline phosphatase (IFCC), U/l	130	38-113
γ-glutamyl transpeptidase, U/l	59	9-32
Total bilirubin, mg/dl	0.4	<1.5
Urea nitrogen, mg/dl	41.0	8.0-20.0
Creatinine, mg/dl	5.36	0.46-0.79
Uric acid, mg/dl	4.0	2.6-7.0
Sodium, mmol/l	142	138-145
Potassium, mmol/l	5.1	3.6-4.8
Chloride, mmol/l	102	101-108
Calcium, mg/dl	9.1	8.8-10.1
Phosphate, mg/dl	4.1	2.7-4.6
C reactive protein, mg/dl	8.01	<0.14
Complete blood count		
White blood cell count, x$10^3/\mu$l	6.6	4.0-11.0
Hemoglobin, g/dl	11.0	12.0-16.0
Hematocrit, %	36.8	35.1-44.4
Platelet count, x$10^3/\mu$l	272	120-450

IFCC, International Federation of Clinical Chemistry and Laboratory Medicine.

Clinical course. The body temperature of the patient remained around 38˚C, and his CRP remained around 8-19 mg/dl. As renal cancer was detected by biopsy, we decided to perform right nephrectomy. On day 20, the patient underwent total right nephrectomy. The patient had no severe post-operative complications and had good pain control. On day 23, he underwent hemodialysis without difficulties and was in a good condition during the night nurse rounds; however, 30 min after a nurse's round, he was found in cardiac arrest. Cardiopulmonary resuscitation was promptly performed; however, the patient remained unresponsive and died. We considered that the patient vomited following postoperative paralytic ileus, which led to asphyxiation.

Nephrectomy findings. Macroscopic findings in the kidneys are shown in Fig. 3A. The tumor lacked a pseudocapsule and exhibited infiltrative growth. Microscopically, the tumor had a papillary, adenoductal, and solid architecture. The tumor cell nuclei were round and highly atypical, and the cytoplasm was clear. Eosinophilic amorphous material was evident in the papillary architecture. Microcalcifications were also observed (Fig. 3B and C). Immunohistochemistry was performed on formalin-fixed, paraffin-embedded sections using the following primary antibodies: alpha-methylacyl-CoA racemase

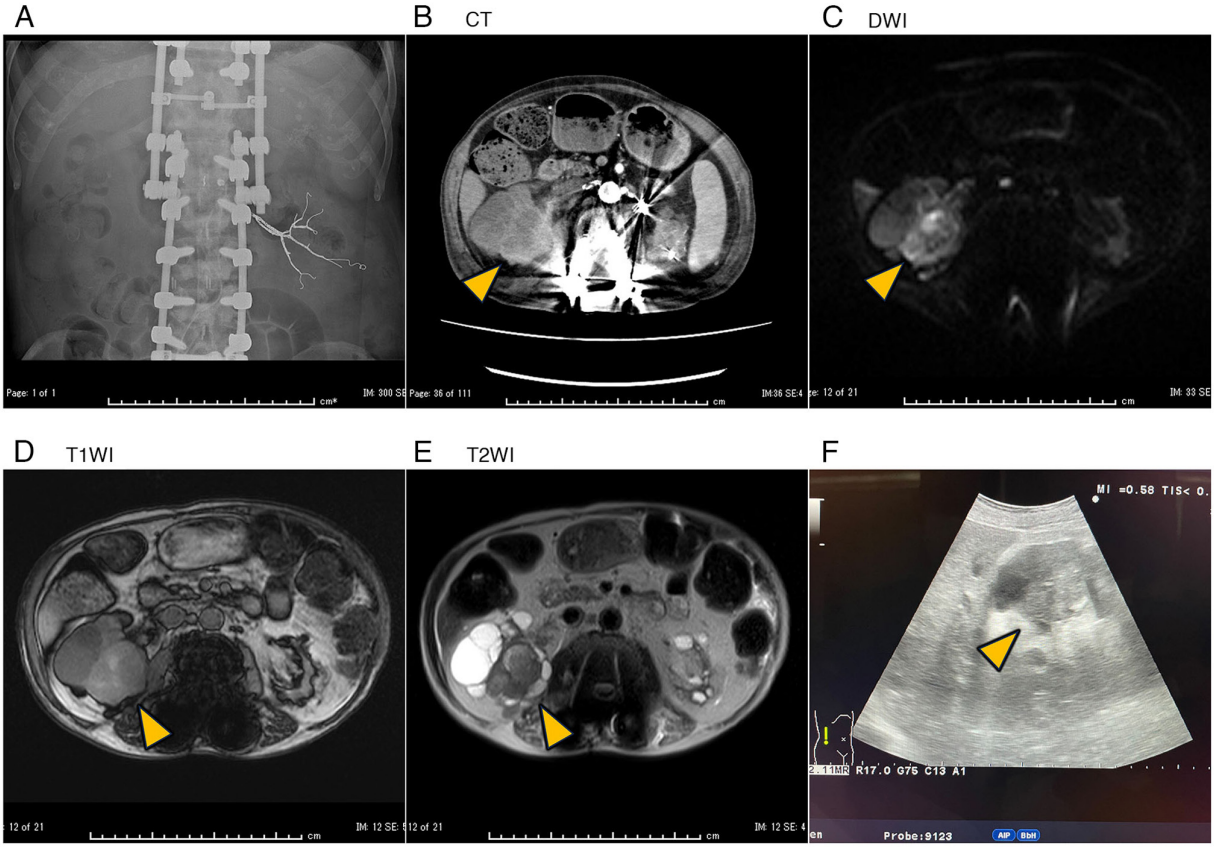

Figure 1. Kidney imaging findings. (A) Abdominal X-ray image after renal transcatheter artery embolization with platinum microcoils. The left kidney only was embolized due to renal artery stenosis in the right kidney. (B) Contrast-enhanced CT image. The cyst wall of the right kidney appears thickened (arrowhead). (C-E) MRI images of the kidney. The cyst was shown with decreased diffusion intensity in (C) DWI, slightly high intensity in (D) T1WI, and low intensity in (E) T2WI (arrowhead). (F) Ultrasound image of the right kidney: A highly echoic mass (~4 cm in diameter) was identified in the cyst (arrowhead). CT, computed tomography; DWI, diffusion-weighted imaging; T1WI, T1-weighted imaging; T2WI, T2-weighted imaging.

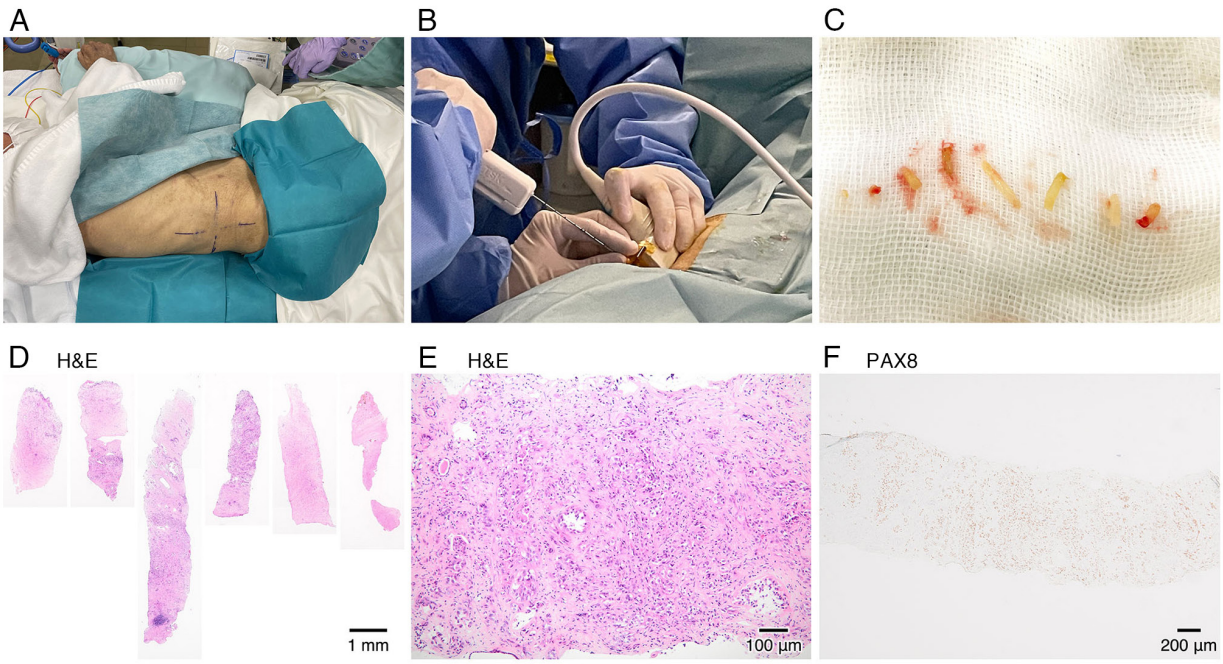

Figure 2. Needle biopsy procedure of the right kidney mass. (A) The patient was laying in left lateral position for the biopsy. (B) The renal mass biopsy was performed under echo-guidance using a biopsy gun, which is usually used in kidney biopsy. (C) Specimen of the renal mass in the cyst. Six cores were collected. (D-F) Light microscopy of the biopsy specimens showed renal cell carcinoma with cribriform invasive growth. (D) Low-magnification image of the whole specimens (H&E staining). Scale bar, 1 mm. (E) The tumor exhibited a mixed cellular pattern: Some cells had prominent atypical nuclei and clear cytoplasm, while others were small and round with surrounding eosinophilic macronucleoli and gritty calcification (H&E staining). Scale bar, 100 μm. (F) Immunohistochemistry showed positive nuclear expression of PAX8. Scale bar, 200 μm. PAX8, paired box 8.

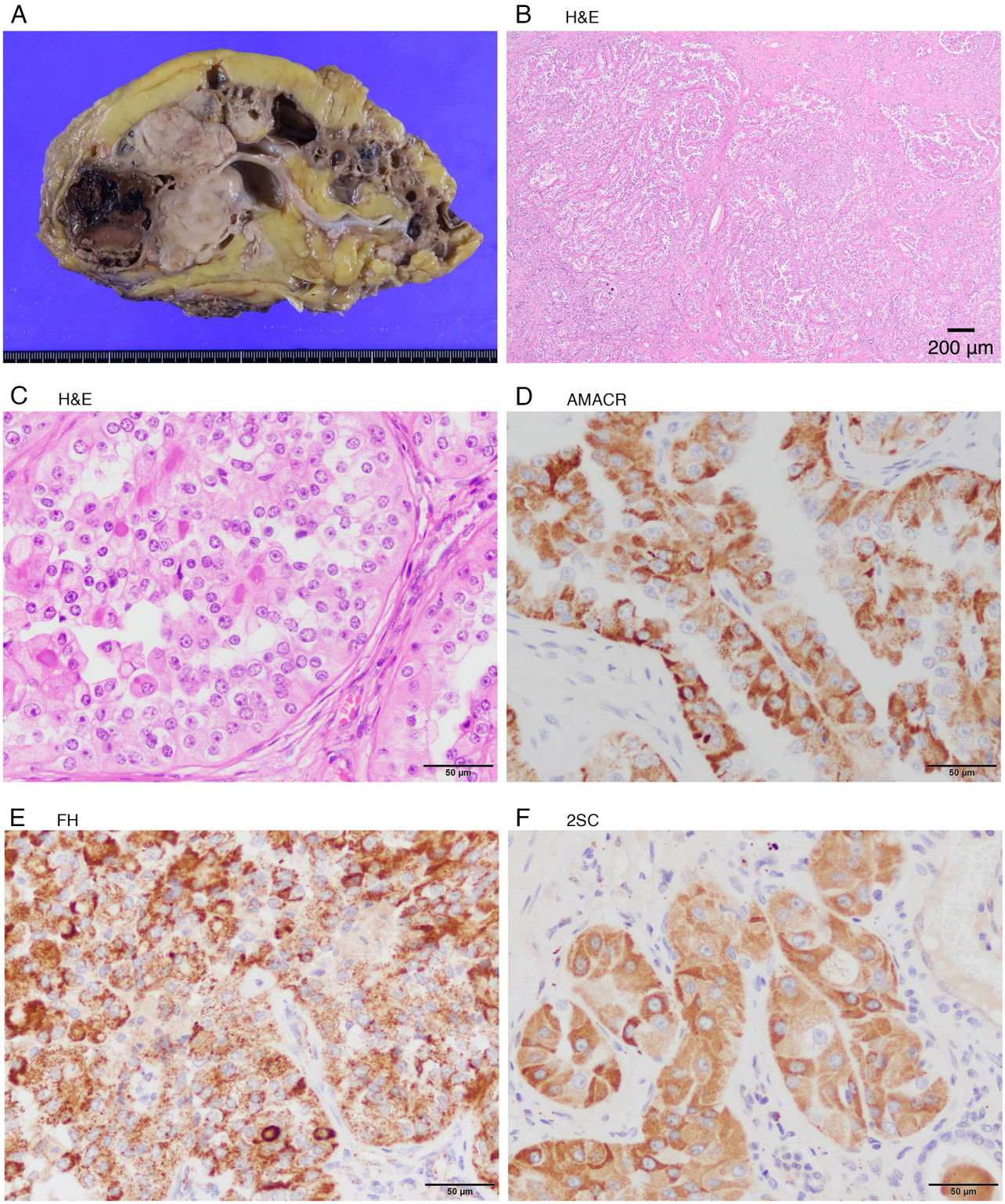

Figure 3. Nephrectomy findings. (A) Macroscopic finding of the kidney. A white, nodular and solid tumor (6.5x5.6x4.5 cm) was present at the upper pole of the kidney. Numerous small to medium-sized cysts with gelatinous contents were observed in the kidney. (B) Low power view of the renal mass (H&E staining). The tumor lacked a pseudo-capsule, grew infiltratively, and exhibited papillary, adenoductal and solid architecture. Scale bar, 200 μm. (C) High power view of the renal mass (H&E staining). The tumor cell nuclei were round and highly atypical, and the cytoplasm was clear. Eosinophilic and amorphous material was evident in the papillary architecture. Some microcalcifications were present. Scale bar, 50 μm. (D) Immunohistochemical staining showing positive expression of AMACR. (E) Immunohistochemical staining showing positive expression of FH. (F) Immunohistochemical staining showing positive expression of 2SC. Scale bar, 50 μm. 2SC, S-2-succinylated-cystaine; AMACR, α-methylacyl-CoA racemase; FH, fumarate hydratase.

(AMACR) (mouse monoclonal, clone 13H4, 1:300 dilution; cat. no. M3616, Dako, Glostrup, Denmark), Fumarate hydratase (FH) (rabbit polyclonal, 1:500 dilution; cat. no. ab95950, Abcam, Cambridge, UK), S-2-succinylcysteine (2SC) (rabbit polyclonal, 1:500 dilution; cat. no. crb20005017d, Discovery Antibodies, UK), TFE3 (mouse monoclonal, clone MRQ-37,

1:50 dilution; cat. no. 354R-16-RUO, Cell Marque, Rocklin, CA, USA), TFEB (mouse monoclonal, clone C-6, 1:100 dilution; cat. no. sc166736, Santa Cruz Biotechnology, Dallas, TX, USA). It was positive for α-methylacyl-CoA racemase (AMACR), FH, and S-2-succinylated-cystaine (2SC) (Fig. 3D-F), and was negative for *TFE3* and *TFEB*. Although FH staining was positive, concurrent 2SC positivity, which accumulates with FH loss, indicates that FH preserves its antigenicity but lacks enzymatic activity. These findings confirmed the diagnosis of FHdRCC (staged pT3NxM0).

Genetic analysis. The WHO Classification states that FHdRCC is important because it should initiate genetic counselling for the patient's family. To determine the *FH* genetic mutation, we obtained approval from the institutional ethics committee and the patient's family for genetic analysis of stored blood samples. Genetic testing for hereditary leiomyomatosis and renal cell cancer (HLRCC) was performed at the Kazusa DNA Research Institute (Chiba, Japan). Comprehensive analysis of the FH gene using targeted next-generation sequencing did not reveal any pathogenic or likely pathogenic variants. The patient was diagnosed with an isolated FHdRCC.

Discussion

We encountered a rare case of FHdRCC arising from acquired cystic kidney disease as dialysis-associated renal carcinoma. This case highlights that imaging alone has limitations in diagnosing malignant tumors arising in an acquired cystic kidney. In addition, the rare carcinoma diagnosis was only achieved after obtaining a biopsy. Therefore, this case was regarded as a valuable model that demonstrates the importance of actively performing biopsies for suspected masses.

FHdRCC is uncommon in dialysis-associated renal carcinomas. In a Japanese multicenter study, ACKD-associated RCC was found to be the most common type, followed by clear-cell RCC, in patients undergoing long-term dialysis (4). FHdRCC has rarely been reported. Doi *et al* (5) reported a 75-year-old male with FHdRCC in the left kidney 7 years before the induction of dialysis; however, this case was not FHdRCC occurring in a patient undergoing dialysis as that observed in our case. ACKD-associated RCC often needs to be differentiated from FHdRCC owing to its histopathological similarities such as abundant granular eosinophilic cytoplasm. However, it differs by the presence of intratumoral oxalate crystals and absence of FH deficiency (6). Our case was diagnosed with FHdRCC based on 2SC positivity. Pollard *et al* (7) reported that FH deficiency causes the overexpression of hypoxia-inducible factors, leading to proliferative renal cyst development. Adam *et al* (8) reported that the loss of FH causes KEAP1 succination and Nrf2 dysregulation independent of hypoxia-inducible factors, leading to renal cysts and tumors. Considering these reports, it is interesting to speculate that FH deficiency may also be associated with ACKD.

Patients undergoing dialysis should undergo regular kidney imaging assessments for RCC surveillance; however, this may sometimes be insufficient for patients with ACKD. The standard diagnosis of RCC is based on the use of imaging techniques. Ultrasonography is recommended for the initial screening, while computed CT and MRI are used to confirm RCC. The Bosniak classification is recommended to categorize cystic renal masses (3). Rahbari-Oskoui and O'Neill (9) also suggested that a complex cyst categorized as Bosniak class III or IV should prompt contrast-enhanced CT or MRI. This classification is useful for evaluating single cystic masses, which is similar to the Bosniac Class IV case that was reported by Doi *et al* (5). However, it is difficult to evaluate masses that emerge in multiple cysts, which were observed in our case. Our case was considered a Bosniak class IIF, which typically indicates a benign or indolent lesion; however, this was not the case.

If imaging was insufficient to diagnose RCC, a biopsy was deemed as necessary. The European Association of Urology guidelines on RCC do not prohibit renal mass biopsy and propose situations for renal biopsy (10). Volpe *et al* (11) reported that among 100 biopsies of renal masses, 84 were malignant, with 93% of the RCCs accurately classified and graded with 100% concordance with surgical specimens. Although the outcome of our case was unfortunate, we consider that the biopsy enabled a definitive diagnosis of the rare aggressive tumor, leading to nephrectomy.

The 2020 Kidney Biopsy guidebook in Japan also supports the safety of renal tumor biopsy in cases of difficult diagnosis and reports a minimal risk of serious hemorrhagic complications or cancer cell dissemination after biopsy (12). Sawa *et al* (13) reported that renal biopsy which was performed for fever of unknown origin revealed an intravascular lymphoma. A perirenal mass biopsy was performed in the sitting position, which led to a diagnosis of extramedullary relapse of acute lymphoblastic leukemia (14). Both patients are still alive without any post-biopsy complications. Additionally, the present case demonstrates that renal tumor biopsies can be performed in the same manner as percutaneous kidney biopsies, even in the lateral position.

The biopsy technique was the same as that of ultrasound-guided biopsy using a biopsy gun, which has already been reported. However, conventional sequencing involves the suspicion of malignancy on imaging before performing a biopsy. In contrast, in our case, the puncture was initially intended for a presumed cyst, but a mass was incidentally discovered during the procedure, essentially reversing the sequence of events.

One limitation of our study is that we cannot exclude the possibility that this diagnosis was achieved, to some extent, by serendipity. A core needle biopsy, not limited to the kidney, may result in an insufficient sample volume (15). In our case, we were able to obtain a sufficient number of cores (six in total); however, if the mass had been smaller, an accurate diagnosis might not have been possible. Moreover, forcing the procedure may increase the risk of bleeding and metastasis. Although obtaining a biopsy cannot be considered as useful in all cases, a biopsy should be obtained whenever feasible.

In conclusion, we reported FHdRCC as a type of dialysis-associated kidney cancer. This case indicates that it is important for patients with ACKD undergoing dialysis to undergo imaging to detect RCC. If the findings are equivocal, a biopsy should be performed to establish a definitive diagnosis and guide appropriate management. Our case highlights the usefulness of needle biopsy using the same method used

by nephrologists for renal biopsy in cases where determining the lesion nature using imaging alone is deemed as difficult.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

YO conceived the study, acquired, analyzed and interpreted the data, and wrote the manuscript. HK contributed to clinical interpretation and differential diagnosis, and critically revised the manuscript. AS provided genetic counseling and interpreted genetic testing as a genetics specialist. KK, SI, YT, KO and YoN performed pathological evaluations, and revised the manuscript as pathologists. KM and YuN performed the nephrectomy, contributed to surgical interpretation and specimen acquisition, and critically revised the manuscript as surgeons. SK, MY, TS, YU and NS contributed to clinical investigation and data acquisition (dialysis parameters, laboratory and imaging data), participated in diagnostic discussions, conducted the literature review and revised the Discussion, and critically revised the manuscript. YO and HK confirm the authenticity of all raw data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

The present study was conducted in accordance with The Declaration of Helsinki and its revisions. According to the Ethical Guidelines for Medical and Health Research involving Human Subjects in Japan, ethical approval is not necessary for case reports.

Patient consent for publication

Informed, voluntary and written consent for publication was obtained from the patient's family.

Competing interests

The authors declare that they have no competing interests.

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