Case Report

Relationship between miR-155 expression and clear cell papillary renal cell carcinoma in the dialyzed kidney

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Abbreviations & Acronyms
AMACR = α-methylacyl-CoA racemase
CA = carbonic anhydrase
CCPRCC = clear cell papillary renal cell carcinoma
CCRCC = clear cell renal cell carcinoma
CK7 = cytokeratin 7
ESRD = end-stage renal disease
mTOR = mammalian target of rapamycin
PRCC = papillary renal cell carcinoma
TSCs = tuberous sclerosis proteins
miRNAs = microRNAs

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Introduction: Clear cell papillary renal cell carcinoma often develops in the context of the dialyzed kidney (end-stage renal disease). However, the relationship between clear cell papillary renal cell carcinoma and microRNA expression in patients with end-stage renal disease remains unclear.
Case presentation: A left renal tumor measuring 22 mm was detected and a radical nephrectomy was performed on a 50-year-old man who had received hemodialysis for the past 6 years. A pathological diagnosis of pT1aNxMx, clear cell papillary renal cell carcinoma was made. We studied the expression of miR-155 in this case and compared it to the expression in nondialysis kidney tissue. The expression level of miR-155 was upregulated in tumor tissue compared with expression levels in the renal cortex for the present case. The expression level of miR-155 in the renal cortex was lower in the present case than in nondialysis kidney tissues.
Conclusion: We demonstrated upregulation of miR-155 in a case of clear cell papillary renal cell carcinoma arising from end-stage renal disease.

Key words: clear cell papillary renal cell carcinoma, ESRD, microRNA, miR-155, mTOR pathway.

Keynote message

CCPRCC often develops in the context of ESRD. The relationship between CCPRCC and miRNA expression in the patients with ESRD remains unclear. We demonstrated upregulation of miR-155 in a case of CCPRCC arising from ESRD.

Introduction

CCPRCC is a histological subtype of renal cell carcinoma,[1,2] which exhibits similar morphological characteristics to CCRCC and PRCC. Prognosis of CCPRCC is reported to be better than CCRCC or PRCC.[2–4] CCPRCC often develops in the context of ESRD. miRNAs are small noncoding RNA molecules which play a crucial role in the regulation of gene expression during carcinogenesis.[5–7] A previous study indicated that the development of CCPRCC in normal kidneys involves miRNA. However, there have been no reports characterizing the relationship between miRNA and CCPRCC in the context of ESRD. In the present study, we identified miR-155 – which has been reported to be associated with ESRD – as a potential regulator of CCPRCC.

Case presentation

We present the case of a 50-year-old man who had been on dialysis for 6 years due to chronic kidney disease caused by glomerulonephritis. Abdominal enhanced computed tomography revealed a 22 mm left renal tumor, and a laparoscopic left renal nephrectomy was performed (Fig. 1a).

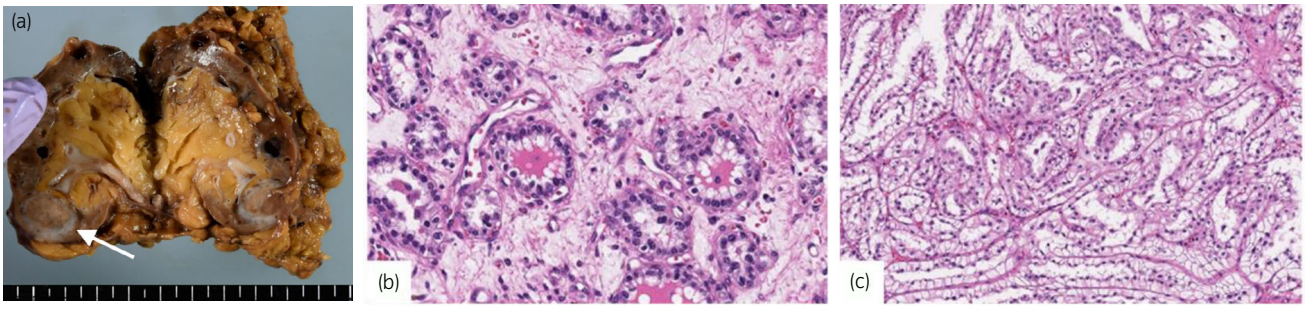

Fig. 1 (a) 22 × 15 mm solid tumor with clear borders in the lower pole of the kidney. (b) Tubular structure is predominant in the prominent region of fibrous stroma (HE, ×200). (c) Cylindrical and papillary structure is the constituent (HE, ×200).

Histopathology revealed clear cells with a tubular, cylindrical, and papillary shape (Fig. 1b,c).

Immunohistochemistry revealed the tumor cells to be diffusely positive for CK7, negative for CD10 and AMACR, and immunoreactive with CA IX in a cup-like distribution (Fig. 2).

Following these findings, a pathological diagnosis of pT1aNxMx, CCPRCC, G2, Fuhrman grade 2, INFa, v0, ly0 was made. The tissue of the renal cortex exhibited a thyroid-like appearance and renal arteriosclerosis, consistent with the histology of ESRD.

We studied the expression of miR-155 in the present case and compared it to that in nondialysis kidney tissue. Total RNA was extracted from frozen specimens of the tumor and renal cortex of the present case using a mirVanaTM miRNA isolation kit. Total RNA was also extracted from the frozen normal renal cortex samples of 96 patients with renal cell carcinoma who did not undergo dialysis. We generated cDNA from the RNA extracted from tumor and renal cortex samples using a TaqMan®microRNA RT kit (Thermo Fisher Scientific, Inc., Waltham, MA, USA). Relative quantitative analysis of miR-155 was carried out using a TaqMan miRNA Assay (Applied Biosystems, Foster City, CA, USA). We found miR-155 expression to be 2.4 times higher in tumor samples than in renal cortex samples of the present case (Fig. 3a). miR-155 expression in the renal cortex was 0.04 times lower in patients with ESRD compared with normal patients (Fig. 3b).

mTOR is a highly conserved serine/threonine kinase that regulates cell growth and metabolism. It has been reported that miR-155 targets TSCs TSC1/TSC2 in the mTOR pathway in CCRCC.[8]

To compare CCPRCC in our patient and CCRCC for regulation of the mTOR pathway by miR-155, we investigated the expression of immunohistochemistry in mTOR pathway. As reported previously, we confirmed a decreased expression of TSC2 and increased expression of mTOR, S6, and 4EBP1 in CCRCC. Moreover, we confirmed the same expression pattern of CCPRCC in our patient (Fig. 4).

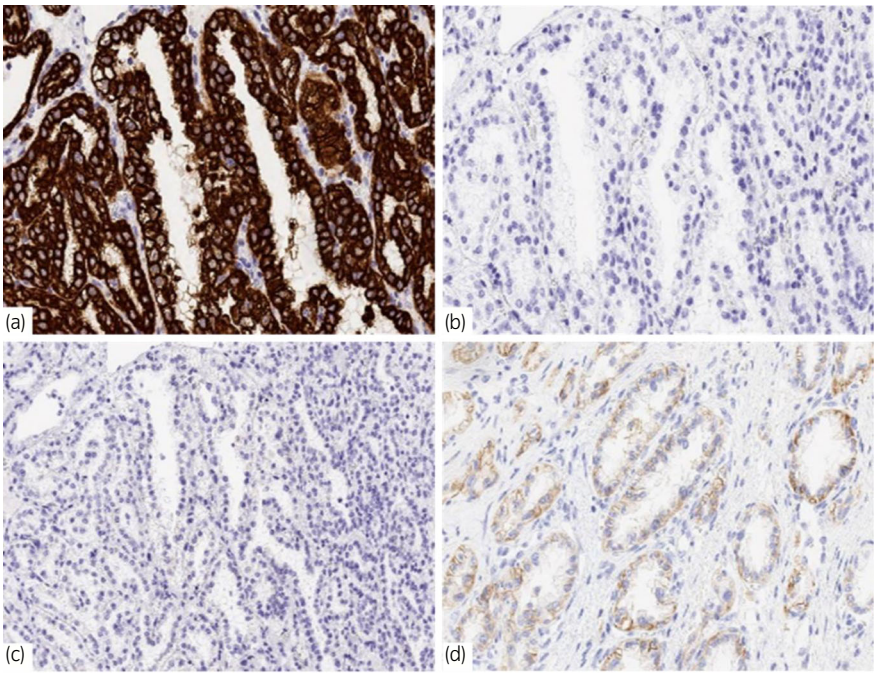

Fig. 2 Representative photomicrographs of this case. CK7 staining shows strong positivity (a, ×200), CD10 (b, ×200) and AMACR (c, ×200) stainings show a negative, and CA IX shows positive with cup-shaped pattern (d, ×200) in this case.

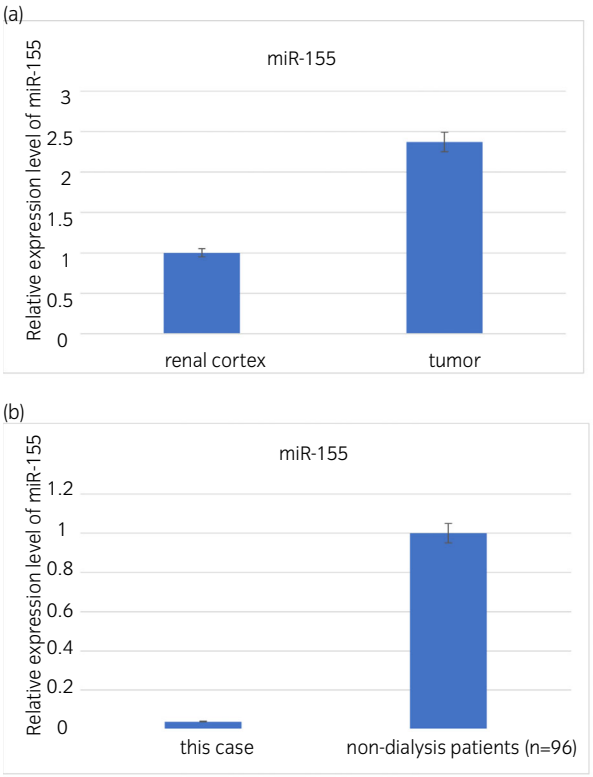

Fig. 3 (a) Relative expression level of miR-155 in the renal cortex and tumor. (b) Relative expression level of miR-155 in the renal cortex of this case and nondialysis patients.

In addition, we investigated the quantitative analysis in our patient using a Mantra™ Quantitative Pathology Workstation with inForm® image analysis software (ParkinElmer, Life Science, Waltham, MA, USA). The positive staining rates of TSC1/TSC2 in the carcinoma were lower than in the renal cortex. Conversely, the positive staining rates of mTOR and 4EBP1 in the carcinoma were higher than in the renal cortex (Fig. 5).

Discussion

Previous studies have indicated that miRNA expression levels are usually lower in patients with ESRD.[9] The association between miR-155 and CCPRCC in patients with nondialysis kidney disease has been reported.[5] However, this relationship has not yet been elucidated in patients with ESRD; hence we focused on miR-155 expression in patients with CCPRCC arising from ESRD. The increased expression level of miR-155 in this case suggested that miR-155 is associated with CCPRCC associated with ESRD. miR-155 has been reported to target TSC1/TSC2.

TSC1/TSC2 expression decreased and mTOR and 4EBP1 expression increased in this case, and no difference was observed in the staining between tumor tissue of the present case and the CCRCC case.

This suggests that the same pathway was involved in this case as in CCRCC.

However, we could not identify a direct relationship between miR-155 and the mTOR pathway in this ESRD case.

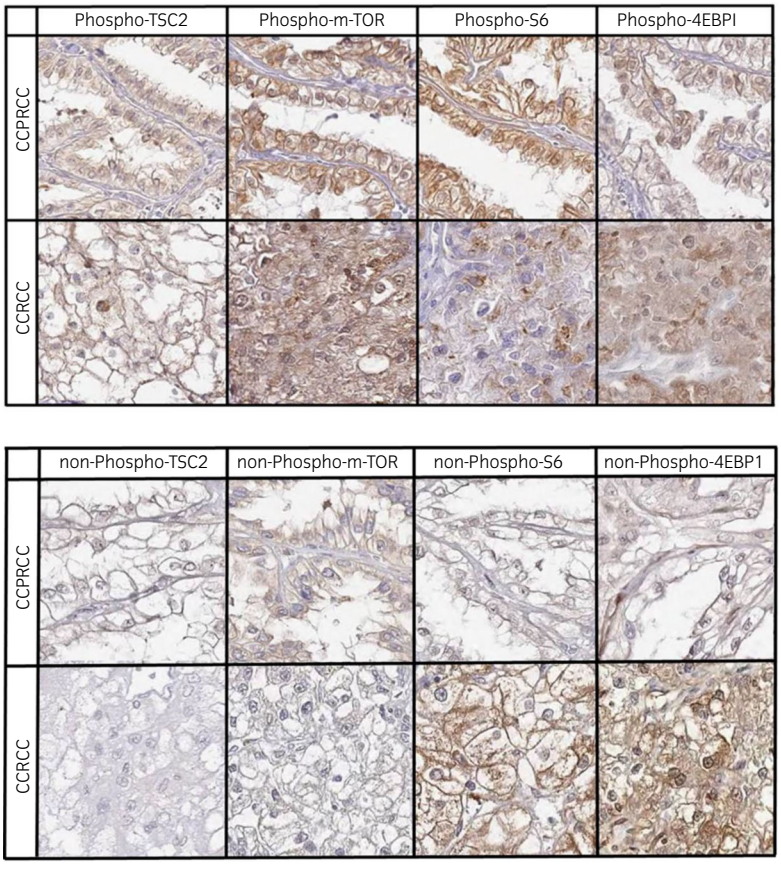

Fig. 4 The staining properties of both phosphorylated and nonphosphorylated antibodies for each protein were evaluated in the tumor tissues of CCPRCC and CCRCC. We confirmed same expression pattern in CCPRCC and CCRCC. TSC1 (anti-TSC1 antibody, sc-377386, Santa Cruz Biotechnology), TSC2 (phosphorylated antibody: anti-TSC2 antibody, ab32554, Abcam/ nonphosphorylated antibody: Tuberin/TSC2 antibody, #3612, Cell Signaling Technology), mTOR [phosphorylated antibody: anti-phospho-mTOR (Ser2448), #2976, Cell Signaling Technology/nonphosphorylated antibody: mTOR (7C10) Rabbit mAb, #2983, Cell Signaling Technology], and 4EBP1 [phosphorylated antibody: anti-phospho-4EBP1 (Thr37/46), #2855, Cell Signaling Technology/nonphosphorylated antibody: non-phospho-4EBP1 (Thr46) (87D12) Rabbit mAb, #4923, Cell Signaling Technology].

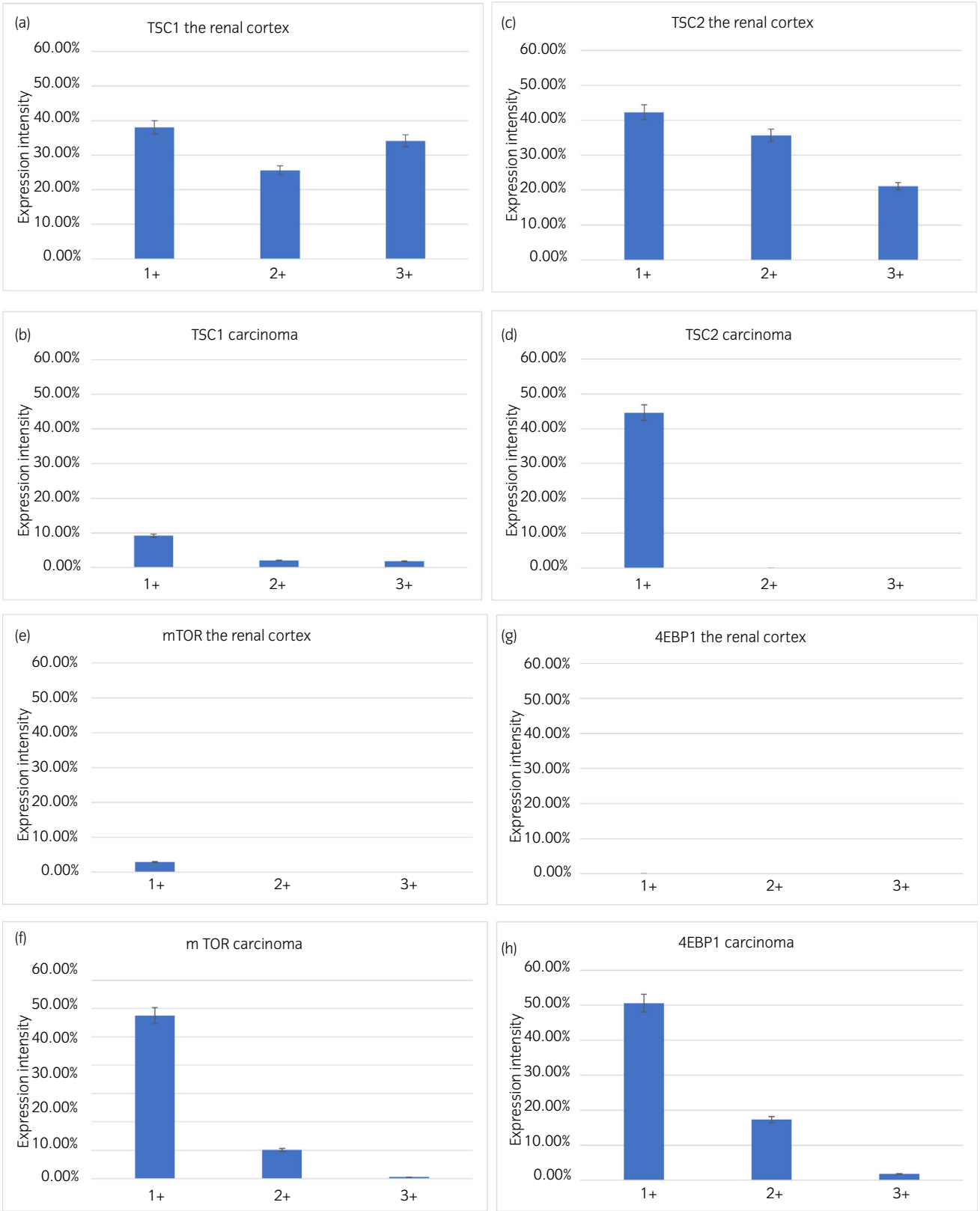

Fig. 5 In the TSC1/TSC2, the positive staining rates in the renal cortex were 98% and 99% (a, c), respectively, and the positive staining rates in the carcinoma were 14% and 44% (b, d), respectively. In the mTOR and 4EBP1, the positive staining rates in the renal cortex were 2.9% and 1.0% (e, g), respectively, and the positive staining rates in the carcinoma were 69% and 70% (f, h), respectively. For quantification of immunohistochemistry, the staining intensity was set at 0 to +3, the area of staining at each intensity was calculated, expressed as a percentage of the total, and taken as the H-score. H-scores (%) and *P* values of the renal cortex *vs* carcinoma were as follows: TSC1, 98% *vs* 13%, $P = 0.313$; TSC2, 99% *vs* 44%, $P = 0.317$; mTOR, 3% *vs* 68%, $P = 0.317$; 4EBP1, 0.07% *vs* 70%, $P = 0.317$.

We plan to conduct a larger study, including more CCPRCC cases, in order to more comprehensively examine the relationship between miR-155 and the mTOR pathway in patients with ESRD.

Conclusion

We describe a case of CCPRCC arising from ESRD and demonstrate the relationship between this tumor type and the upregulation of miR-155. Our results indicate that miR-155 is upregulated in patients with CCPRCC arising from ESRD, and that this occurs in a similar manner to its upregulation in CCRCC via the TSC1/TSC2 target. However, further investigation with larger patient numbers is required to properly elucidate the pathways involved.

Conflict of interest

The authors declare no conflict of interest.

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