

Case Report

Successful treatment with sorafenib for sunitinib-refractory metastatic papillary renal cell carcinoma: Potential impact of Raf overexpression on predicting the efficacy of sorafenib

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Abbreviations & Acronyms

ccRCC = clear cell RCC
CT = computed tomography
pRCC = papillary RCC
RCC = renal cell carcinoma
TKI = tyrosine kinase inhibitor

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Introduction: The prognosis of type 2 papillary renal cell carcinoma is often poor. We herein report a case of papillary renal cell carcinoma with liver metastasis that was successfully treated with sorafenib as a second-line therapy.

Case presentation: An 82-year-old man who had undergone radical nephrectomy 5 years previously experienced biopsy-proven liver metastasis. He received sunitinib as a first-line treatment; the dose was initially 12.5 mg/day and was escalated to 25 mg/day, but it was discontinued due to several adverse events. We then switched to sorafenib as a second-line treatment, which resulted in a partial response (51% reduction in tumor size); the patient showed no recurrence 5 months after the initiation of sorafenib treatment. An immunohistochemical analysis revealed the overexpression of Raf in both the primary and metastatic tumors.

Conclusion: As sorafenib blocks Raf signaling, the expression of Raf may serve as a useful predictor of the efficacy of sorafenib.

Key words: papillary renal cell carcinoma, Raf, second-line therapy, sorafenib.

Keynote message

Examining Raf expression may be a clue to predict sorafenib efficacy.

Introduction

With the recent development of molecular-targeted therapy, the strategies for managing metastatic RCC have been dramatically changing. While several drugs have been introduced over the past few years, the ideal sequence has not been established, especially in cases with non-ccRCC.¹ Sunitinib and pazopanib are widely used as a first-line therapy. We herein report a case of sunitinib-refractory papillary type 2 RCC with liver metastasis successfully treated with sorafenib.

Case presentation

An 82-year-old man was referred to our department for further assessment of a left renal mass. He had no remarkable family history. Based on the clinical diagnosis of RCC, laparoscopic radical nephrectomy was performed. A histopathological examination revealed a pT2 type 2 pRCC. Five years after the surgery, follow-up CT scans revealed findings suggestive of solitary liver metastasis. A fine-needle biopsy of the liver lesion showed metastatic pRCC (Memorial Sloan-Kettering Cancer Center risk: intermediate [anemia] and the International Metastatic Renal Cell Carcinoma Database Consortium risk: intermediate [anemia]) (Fig. 1).

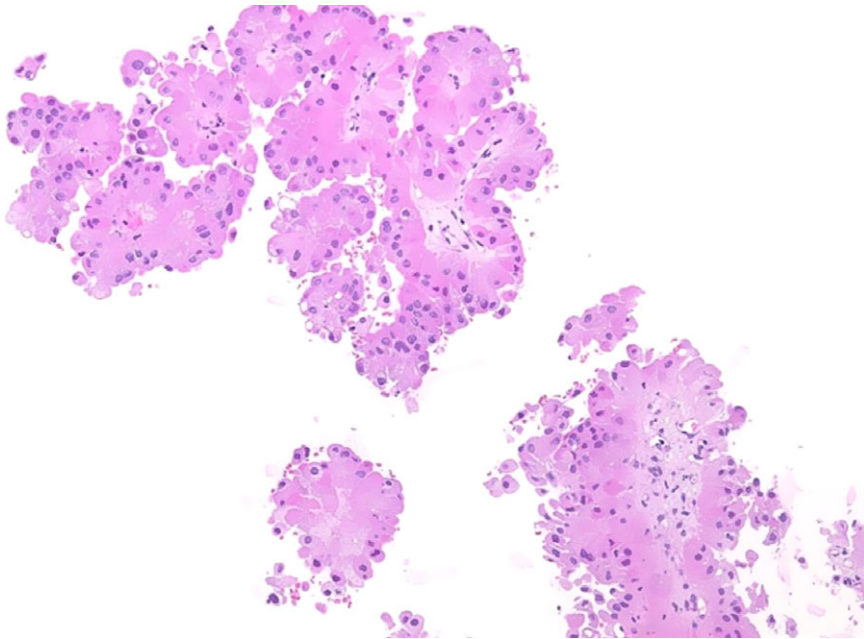


Fig. 1 HE stain of liver metastatic lesion.

He had no remarkable laboratory tests except for anemia and a slight lactate dehydrogenase elevation (white blood cell $3520/\mu\text{L}$; red blood cell $228 \times 10^4/\mu\text{L}$; hemoglobin 8.2 g/dL; platelet $41.6 \times 10^4/\mu\text{L}$; albumin 3.7 g/dL; aspartate transaminase 41 U/L; alanine aminotransferase 30 U/L; lactate dehydrogenase 218 U/L; alkaline phosphatase 168 U/L; creatinine 0.78 mg/dL; blood urea nitrogen 14 mg/dL; estimated glomerular filtration rate 72.9 mL/min/1.73 m²; sodium 139 mEq/L; potassium 4.6 mEq/L; calcium 9.4 mg/dL; corrected serum calcium 9.7 mg/dL). Two weeks after, he was started on sunitinib (12.5 mg/day); the dosage was increased to 25 mg/day (2 weeks of treatment followed up by a 1 week drug holiday). Two months after sunitinib treatment, CT showed no decrease in the size of the liver metastasis. The treatment with sunitinib was discontinued due to loss of appetite (grade 3), anemia (grade 4), diarrhea (grade 1), and renal dysfunction (grade 1). CT after discontinuing sunitinib treatment showed an increase in the tumor volume, and he was started with sorafenib (400 mg/day) as a second-line treatment. Three months after the introduction of sorafenib, his

liver metastasis had reduced in size by about 51%, and he showed no recurrence 5 months after starting sorafenib treatment (Fig. 2).

We also performed immunohistochemistry for determining Raf (ab137085; Abcam, Cambridge, MA, USA) expression in the current case as well as 76 cases of renal tumors in a tissue microarray (KD808; US Biomax, Nashville, MD, USA). The detailed protocol for immunostaining and its scoring are described in our previous study.² Both primary and metastatic tumors in the present case showed higher levels of the Raf expression compared with the other renal tumors included in the tissue microarray (Fig. 3, Table 1).

Discussion

pRCC accounts for 10–15% of all RCC, and type 2 tumor generally shows a worse prognosis than ccRCC or type 1 pRCC.³ The ideal treatment sequence for non-ccRCC, including pRCC, has not been established. For stage 4 non-ccRCC, the recommended grade of sorafenib or sunitinib treatment is

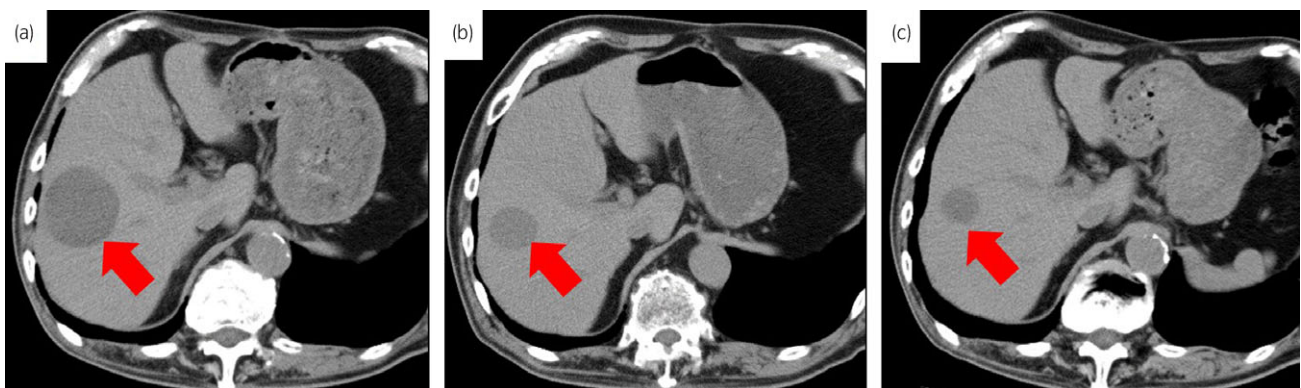


Fig. 2 CT of metastatic lesion (arrow) before (a), 1 month after (b), and 3 months after (c) sorafenib treatment.

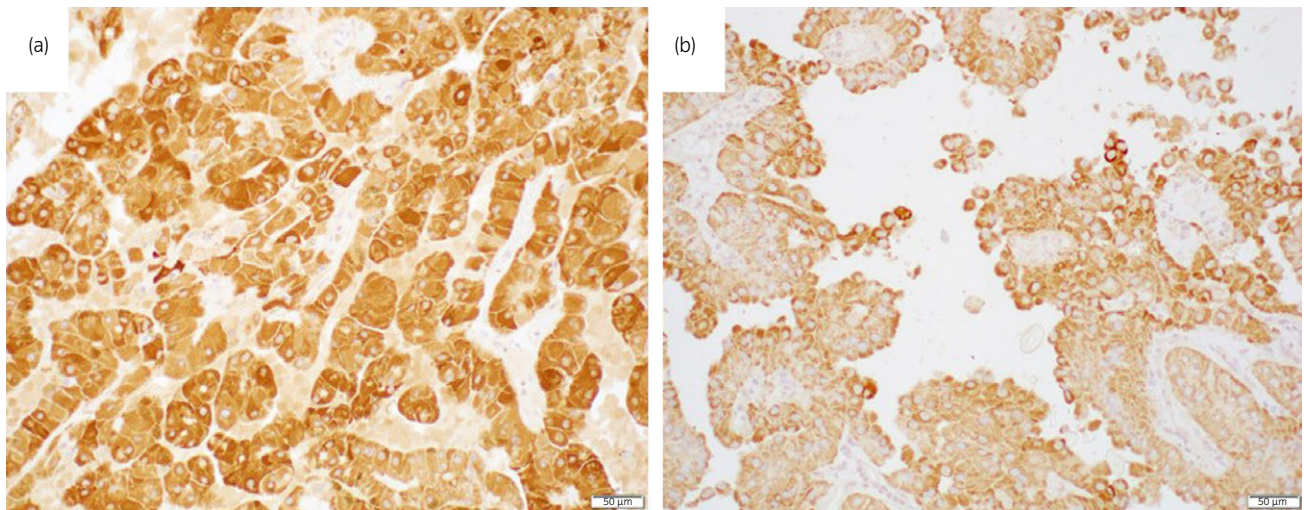


Fig. 3 Immunohistochemistry of Raf expression in primary (a) and liver metastatic (b) lesions.

Table 1 Raf expression in renal tumors

Histological type	Number	Negative	1+	2+	3+
ccRCC	59	39 (66.1%)	17 (28.9%)	3 (5.1%)	0 (0.0%)
Urothelial carcinoma	8	6 (75.0%)	2 (25.0%)	0 (0.0%)	0 (0.0%)
pRCC	3	1 (33.3%)	2 (66.7%)	0 (0.0%)	0 (0.0%)
Chromophobe RCC	1	1 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Squamous cell carcinoma	1	1 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Sarcomatoid carcinoma	4	3 (75.0%)	1 (25.0%)	0 (0.0%)	0 (0.0%)
Metastatic RCC in the lymph node	4	4 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Present case (primary tumor)					x
Present case (liver metastasis)					x

category 2A, and the efficacy is lower than that in ccRCC.⁴ TKIs, such as sunitinib and pazopanib, are typically used as a first-line therapy in patients with RCC. However, the efficacy of these TKIs for type 2 pRCC is often limited. In the present case, a favorable outcome was observed in a patient treated with sorafenib; thus, we examined the factors that might aid in decision-making regarding the administration of sorafenib.

The present patient received sunitinib as a first-line treatment for his pRCC. Consequently, he declined to continue sunitinib treatment due to several adverse effects. The SWITCH trial showed that sorafenib–sunitinib treatment resulted in a better prognosis than sunitinib–sorafenib treatment, and the present case appears to be a rare entity showing the efficacy of sorafenib after sunitinib treatment.^{5,6} Sorafenib is a multikinase inhibitor that blocks Raf, vascular endothelial growth factor receptor, and platelet-derived growth factor.⁷ The IC₅₀ of sorafenib is 245 nmol/L, and sunitinib does not block b-Raf.⁵ Also, a recent study showed the efficacy of sorafenib with minimal adverse events even in RCC patients aged 75 years or older.⁸ In contrast to sunitinib, sorafenib inhibits Raf. The present case showed higher Raf expression in both primary tumor and liver metastatic lesion

than in renal tumor tissues from 76 cases included in the tissue microarray. Sorafenib was thus effective in the present case, possibly due to high Raf expression. In cases of pRCC, the examination of the Raf expression might provide a clue as to whether sorafenib should be administered. On the other hand, there was a discrepancy in the Raf expression between controlled pRCC and our case. We suspected that the Raf expression may vary according to the individual tumor characteristics rather than the pathological type. Thus, the examination of the Raf expression can be useful for deciding whether to administer sorafenib. He was able to continue sorafenib treatment despite being over 80 years of age. This supports the previous findings showing that sorafenib is well-tolerated in elderly patients.⁴

Our patient showed a high Raf expression and a favorable response to sorafenib. Based on these results, the assessment of Raf expression may be indicative of the efficacy of sorafenib treatment. In summary, we present a case of sunitinib-refractory pRCC with liver metastasis successfully treated with sorafenib. Although no previous studies have shown the association between the expression of Raf and the efficacy of sorafenib, the expression of Raf may serve as a useful predictor of the efficacy of sorafenib.

Conflict of interest

The authors declare no conflict of interest.

References

- 1 Pal SK, Signorovitch JE, Li N *et al.* Patterns of care among patients receiving sequential targeted therapies for advanced renal cell carcinoma: A retrospective chart review in the USA. *Int. J. Urol.* 2017; **24**: 272–8.
- 2 Ohtaka M, Kawahara T, Ishiguro Y *et al.* Expression of receptor activator of nuclear factor kappa B ligand in bladder cancer. *Int. J. Urol.* 2018; **25**: 901–2.
- 3 Connor Wells J, Donskov F, Fraccon AP *et al.* Characterizing the outcomes of metastatic papillary renal cell carcinoma. *Cancer Med.* 2017; **6**: 902–9.
- 4 Lee JL, Ahn JH, Lim HY *et al.* Multicenter phase II study of sunitinib in patients with non-clear cell renal cell carcinoma. *Ann. Oncol.* 2012; **23**: 2108–14.
- 5 Adnane L, Trail PA, Taylor I, Wilhelm SM. Sorafenib (BAY 43-9006, Nexavar), a dual-action inhibitor that targets RAF/MEK/ERK pathway in tumor cells and tyrosine kinases VEGFR/PDGFR in tumor vasculature. *Methods Enzymol.* 2006; **407**: 597–612.
- 6 Wen T, Xiao H, Luo C, Huang L, Xiong M. Efficacy of sequential therapies with sorafenib-sunitinib versus sunitinib-sorafenib in metastatic renal cell carcinoma: A systematic review and meta-analysis. *Oncotarget* 2017; **8**: 20441–51.
- 7 Hutson TE, Escudier B, Esteban E *et al.* Randomized phase III trial of temsirolimus versus sorafenib as second-line therapy after sunitinib in patients with metastatic renal cell carcinoma. *J. Clin. Oncol.* 2014; **32**: 760–7.
- 8 Tatsugami K, Oya M, Kabu K, Akaza H. Evaluation of efficacy and safety of sorafenib in kidney cancer patients aged 75 years and older: a propensity score-matched analysis. *Br. J. Cancer* 2018; **119**: 241–7.