INNOVATIONS JOURNALS

Case Report

Exceptional Response in a Patient with mRCC Through Precision-Guided Treatment Involving Immunotherapy Rechallenge with Temsirolimus and Bevacizumab

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ABSTRACT

Comprehensive genomic profiling (CGP) and the subsequent discussions in molecular tumor boards (MTBs) are becoming an integral part of personalized cancer care. The patient with metastatic renal cell carcinoma (mRCC) presented here demonstrated an absence of a favorable response accompanied by adverse events after receiving dual immunotherapy with nivolumab plus ipilimumab in combination with a poly (adenosine diphosphate–ribose) polymerase inhibitor, niraparib. This determination was made based on the initial CGP report and the initial MTB. Following the progression of the disease and the emergence of immune-related adverse events, a second CGP was conducted, and several subsequent MTBs were held. The decision was made to transition the patient's treatment to temsirolimus plus bevacizumab, with the rechallenge of immunotherapy with pembrolizumab. The response evaluation revealed a complete radiographic and molecular response. This case study underscores the mounting significance of precision oncology in the management of mRCC, thereby suggesting that mammalian target of rapamycin inhibitor may augment the efficacy of immunotherapy in select patients based on their genomic findings. A digital poster of this case is included in the supplemental materials.

Keywords: metastatic renal cell carcinoma (mRCC), immunotherapy, temsirolimus, bevacizumab, comprehensive genomic profiling (CGP), molecular tumor board (MTB), targeted therapy, precision oncology

INTRODUCTION

Renal cell carcinoma (RCC) is a type of kidney cancer that generally manifests as a tumor in the proximal convoluted tubule of one kidney.[1] Treatment for this specific form of cancer can vary depending on several factors and may include surgery, radiation therapy, targeted therapy, and immunotherapy.[2] Comprehensive genomic profiling (CGP) has made a significant contribution to the field of cancer care by providing insights into cancer biology, facilitating the detection of multiple biomarkers, identifying actionable alterations, and ultimately improving patient outcomes.[3] This case report describes a patient with metastatic renal cell carcinoma (mRCC) who initially did not respond to dual immunotherapy (nivolumab and ipilimumab) combined with the poly (adenosine diphosphate–ribose) polymerase inhibitor (niraparib) and experienced persistent immune-related adverse events

Table 1. The patient's comprehensive genomic profiles (CGPs).

First CGP Results (FoundationOne CDx)			Second CGP Results (Tempus|xT)		
TMB	1 muts/Mb		TMB	1.6 muts/Mb	
MS	Stable		MS	Stable	
PD-L1	CPS 2%, TPS 2%		PD-L1	Negative	
Gene	**Alteration**	**VAF (%)**	**Gene**	**Alteration**	**VAF (%)**
BAP1	Y241fs*1	14.7	*BAP1*	Y241fs	4.9
TSC2	Splice site 774 + 2T>A	10.0	*TP53*	R249fs	3.3
TP53	R249fs*94	10.7			

CPS: combined positive score; MS: microsatellite stability; PD-L1: programmed death-ligand 1; TMB: tumor mutational burden; TPS: tumor proportion score; VAF, variant allele frequency .

(ir-AEs). Following a series of molecular tumor boards (MTBs), the patient exhibited a positive response to a novel combination of pembrolizumab, temsirolimus, and bevacizumab without notable AEs, achieving a complete radiographic and molecular response with minimal residual disease (MRD)–negative status that remains ongoing at 12 months. To the best of our knowledge, this case study is the first to demonstrate how CGP and MTBs were used to personalize cancer treatment for a patient with mRCC, leading to a successful rechallenge with immunotherapy in combination with angiogenesis and mammalian target of rapamycin (mTOR) inhibitors. The patient consented to publication of this case.

CASE PRESENTATION

A 35-year-old asymptomatic woman with RCC and lung and bone metastases was admitted without prior treatment. The CGP using FoundationOne CDx revealed a tumor mutational burden of 1 mutation per megabase, microsatellite stability, *BAP1* Y241fs1, *TSC2* splice site 774 + 2T>A, and *TP53* R249fs94 alterations, with a PD-L1 combined positive score of 2% and tumor proportion score of 2% by immunohistochemistry (Table 1). Following a comprehensive evaluation of the patient's genetic profile by oncologists and cancer scientists in the MTB, and after discussing treatment options with the patient and obtaining consent for off-label treatment, she received dual immunotherapy (nivolumab 400 mg once monthly, ipilimumab 50 mg every 4–8 weeks) along with a PARPi (niraparib 100 mg/d). The treatment was initiated in March 2023, and by October of the same year, stable disease had been achieved. However, niraparib was discontinued in October 2023 due to dyspeptic symptoms. Following dual immunotherapy, an endoscopy revealed grade 1 gastritis, which led to the discontinuation of immunotherapy. However, the patient's symptoms subsequently worsened. Fifteen days later, an endoscopy was performed, which revealed the presence of grade 3 gastritis, accompanied by symptoms such as nausea, vomiting, and weight loss. Consequently, the therapeutic regimen was discontinued. The patient was initiated on a treatment plan consisting of prednisone (1 mg/kg) and supportive care for a period of 5 months. During this time, new liver lesions were treated with radiofrequency ablation. A subsequent CGP test (Tempus|xT; Tempus Labs) was performed on a lymph node biopsy, revealing the same alterations in the *BAP1* and *TP53* genes as previously identified, but this time no *TSC2* alteration was found. Following national and virtual international MTBs, the decision was made to proceed with rechallenge immunotherapy, switching the agent from nivolumab to pembrolizumab (200 mg every 3 weeks). This switch occurred 1 month after the discontinuation of steroids. The patient had discontinued steroids during the last month of the 5-month supportive care period and had received steroids for approximately 3 months. In light of the potential for undetected *TSC2* alterations due to the heterogeneous nature of the tumor, temsirolimus (an initial dose of 10 mg and a maintenance dose of 15 mg administered intravenously per week) was recommended. Furthermore, bevacizumab (400 mg administered every 3 weeks) was added to the treatment regimen, given that *TP53* alterations might have played a role in elevated vascular endothelial growth factor (VEGF) levels. In March 2024, the treatment was reinitiated. After a period of 2 months, positron emission tomography (PET) and computed tomography (CT) scans revealed the disappearance of the bone and mediastinal lesions, indicating a near-complete response (May 2024). However, the first MRD (Signatera; Natera) result was positive (May 2024). Consequently, the patient underwent continuous treatment, which led to a sustained complete response, as evidenced by the most recent combined PET-CT scan conducted in July 2024 (Fig. 1) and the second MRD test result becoming negative, indicating that the patient's condition remains favorable with no evidence of residual disease (July 2024). Furthermore, a third MRD test performed in September 2024 also yielded a negative result, thereby confirming the maintenance of a complete molecular response (Fig. 2). This outcome indicates a noteworthy response to the treatment, with no evidence of residual disease in the most recent evaluations (MRD, December 2024, and combined PET-CT scan, January 2025) (see Figs. 1 and 2). The patient's clinical history, treatments, and evaluation timeline are meticulously delineated (Fig. 3).

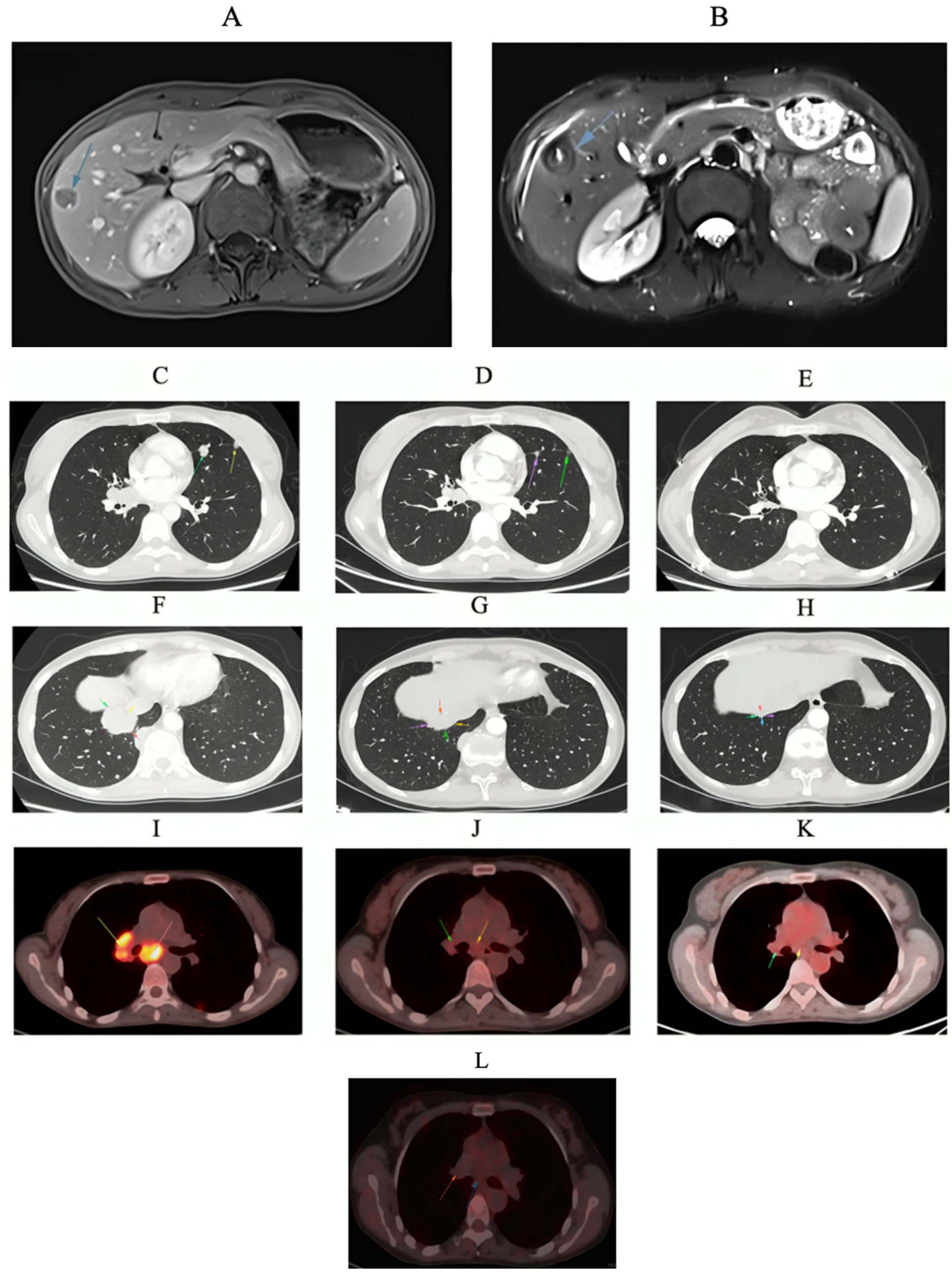

Figure 1. Patient scans showing liver parenchymal lesions (arrows) before (**A**) and after (**B**) treatment course. Thorax CT scans before treatment (**C** and **F**) and after 3 months (**D** and **G**) and 7 months (**E** and **H**) of treatment. PET scans before treatment (**I**) and after 3 months (**J**), 7 months (**K**), and 10 months (**L**) of treatment.

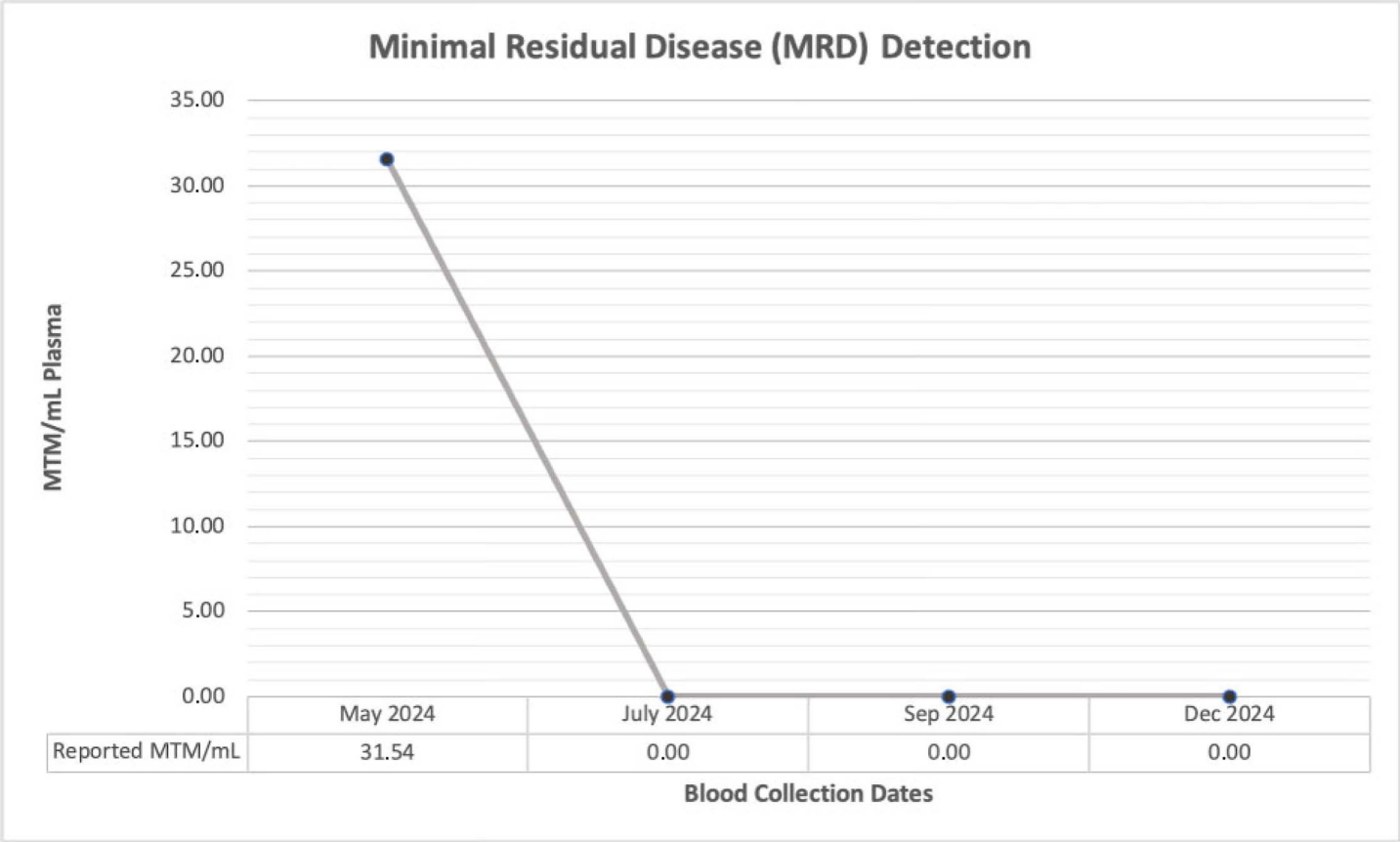

Figure 2. Patient's MRD follow-up.

MRD: minimal residual disease; MTM mean tumor molecules.

DISCUSSION

We present the first case of complete radiologic and molecular response in a patient with mRCC using precision oncology principles, with rechallenge immunotherapy in combination with temsirolimus and bevacizumab after several MTBs. Combination therapies, including antiangiogenic agents, tyrosine kinase inhibitors, and mTOR inhibitors as well as immune checkpoint inhibitors (ICIs), have become the gold standard for mRCC treatment due to their synergistic effects on tumor progression.[4] Despite the encouraging outcomes observed in clinical trials, the response to treatment varies among patient subgroups. Furthermore, the real-world RCC population is heterogeneous, and it is possible that some subgroups will not benefit from these therapies.[5] In the treatment of intermediate- or poor-risk mRCC, dual immunotherapy is regarded as the standard of care.[6] This approach is hypothesized to yield a superior response due to the presence of *BAP1* and other alterations that generate an immunogenic microenvironment.[7,8] On the other hand, *BAP1* mutations have been identified as potential predictive biomarkers for the efficacy of immunotherapy. Patients with *BAP1* mutations have demonstrated a remarkable response to immunotherapy, with significant clinical benefits being observed. Research has indicated that *BAP1*-associated signatures may offer superior predictive value for immunotherapy outcomes in comparison with other treatments, such as VEGFR and mTOR inhibitors.[7] On the other hand, the use of a PARPi has been rationalized by the *BAP1* gene alteration[9] and the objective of enhancing the efficacy of immunotherapy.[10] Studies also show that PARPi and ICI combinations are effective with manageable toxicity in non-RCC cancers.[11] Two considerations provide the rationale for rechallenging this patient with immunotherapy. First, the patient's disease was stabilized during the initial immunotherapy treatment. Second, a *BAP1* alteration was detected in the patient's genomic profile. This alteration is associated with a favorable predictive outcome in patients with RCC treated with immunotherapy.[7] Therefore, we hypothesize that immunotherapy may still be a suitable option. However, we also predicted that there was an alteration in the patient's genomic profile that may reduce the response to immunotherapy. Consequently, we postulate that immunotherapy in combination with other agents may be more beneficial. The process of rechallenging ICIs in the aftermath of severe ir-AEs is a multifaceted and intricate procedure that necessitates a comprehensive, multidisciplinary approach.[12] Despite the risk of ir-AEs, some patients may derive significant clinical benefit from

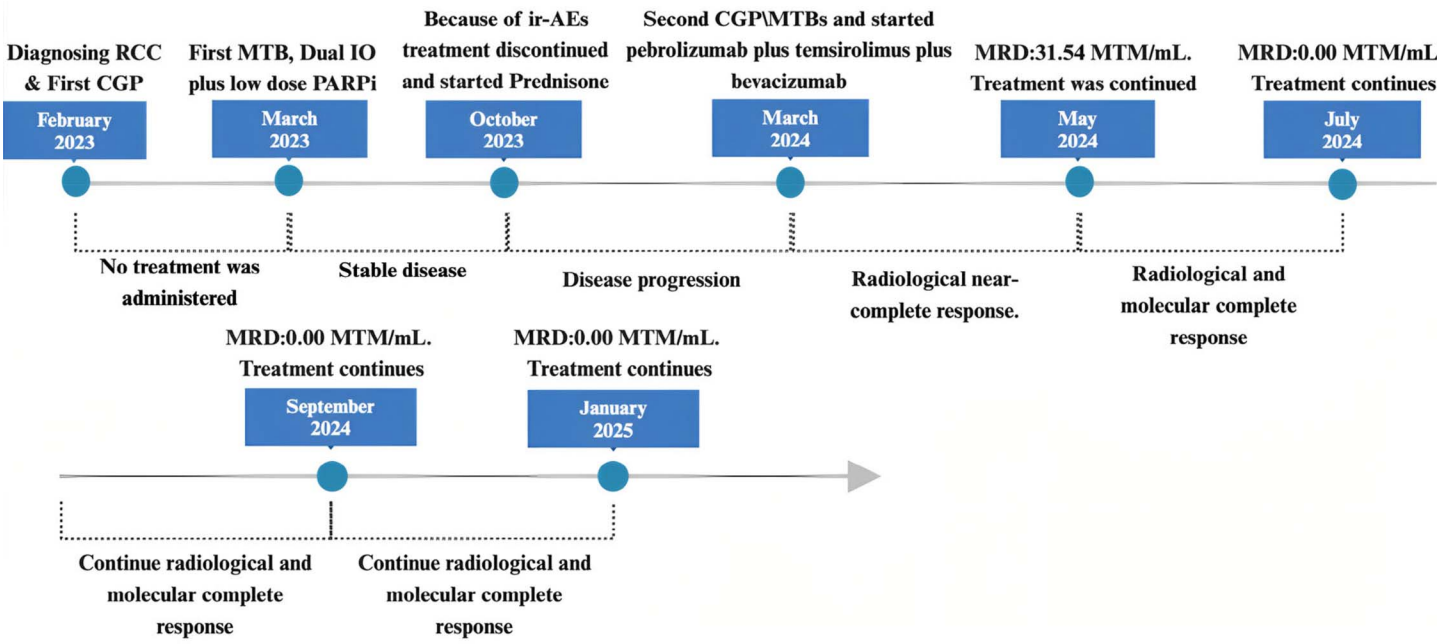

Figure 3. Patient's treatment timeline.

CGP: comprehensive genomic profiling; IO: immuno-oncology therapy; ir-AE: immune-related adverse event; MTB, molecular tumor board; MTM: mean tumor molecules; PARPi: poly (adenosine diphosphate–ribose) polymerase inhibitor; RCC: renal cell carcinoma.

immunotherapy. The decision to rechallenge is usually based on a careful assessment of risks versus potential benefits.[13] In addition, recent advancements in the management of ir-AEs have enhanced the capacity to control these adverse events, thereby rendering rechallenge a feasible option for certain patients.[13] A study by Eldani et al[14] demonstrated that 73% of patients exhibited no recurrence following a rechallenge with ICIs, 13% experienced a recurrence, and 13% developed new ir-AEs. These findings suggest that it may be a safe approach, particularly after ir-AE regression and corticosteroid withdrawal.[14] A case study showed that a metastatic melanoma patient with immune reactions to nivolumab and ipilimumab tolerated pembrolizumab with hydrocortisone pretreatment.[15] Another study reported life-threatening ir-AEs in 0.2%, 0.4%, 2.9%, and 5.9% of patients with renal and colorectal cancers treated with pembrolizumab, nivolumab, ipilimumab, and the combination of ipilimumab and nivolumab, respectively.[16] Furthermore, a preclinical study demonstrated that dual PD-1 and CTLA-4 blockade led to a 77% inhibition of tumor growth in *TSC2* loss cases, which was associated with an increase in tumor-infiltrating $CD8^+$ and $CD4^+$ T cells and a decrease in T regulatory cells, granulocyte-like myeloid derived suppressor cells, and regulatory $CD11b^+$ DCs.[17] In light of these findings, a decision was made to proceed with an immunotherapy rechallenge, operating under the supposition that immunotherapy might still prove to be of benefit.

The PI3K/AKT/mTOR pathway, which plays a role in numerous biological processes, is found to be hyperactivated by *TSC1* and *TSC2* loss-of-function mutations. These mutations, which have been identified in over 40 tumor types, have the potential to serve as a prognostic indicator, suggesting an individual patient's response to mTOR inhibitors.[18] A phase II study demonstrated a low response rate of 7% to everolimus in a pan-cancer cohort of patients with mTOR pathway alterations. Notably, two patients achieved objective responses; one of them had uterine cancer with biallelic TSC2 inactivating mutations.[19] Additionally, a phase II study indicated that alterations in *AKT1*, *TSC1*, and *TSC2* genes and *CTNNB1* mutations may serve as predictors of clinical benefit from temsirolimus treatment. Furthermore, *CTNNB1* alterations have been associated with a prolonged progression-free survival.[20] In contrast, the RECORD-3 trial demonstrated that mutations in *TSC1*, *TSC2*, and *mTOR* did not have a significant effect on progression-free survival in patients with RCC treated with everolimus.[21] A study that received FDA approval demonstrated that temsirolimus enhanced median overall survival and progression-free survival by 49% among 626 patients diagnosed with advanced RCC. However, the study population was not selected based on specific gene alterations, and therefore it did not account for the potential effect on subgroups of patients with particular gene alterations.[22] The use of mTOR inhibitors is a double-edged sword, because they can have both immunosuppressive and immunostimulatory effects.[23] In a case of advanced, poorly differentiated thyroid cancer that progressed after lenvatinib and nivolumab plus ipilimumab with *PTEN* and *TP53* mutations, treatment with temsirolimus in combination with nivolumab plus ipilimumab dual immunotherapy resulted in significant clinical improvement and disease control for approximately 6 months.[24]

Another case study demonstrated an almost complete response to PD-1 blockade in a mesenchymal tumor. The subsequent identification of a *PTEN* mutation indicated a potential resistance to immune checkpoint therapy, suggesting that the mTOR pathway might contribute to immune resistance.[25]

The identification of a *TP53* alteration is another salient issue in this patient. A pan-cancer study demonstrated that mutation of the *TP53* gene serves as a marker for VEGF overexpression, a pivotal protein involved in angiogenesis, the process by which new blood vessels form to supply the tumor with nutrients and oxygen.[26] Furthermore, studies have shown that the administration of VEGF and VEGFR inhibitors leads to a higher response rate among patients with a *TP53* mutation.[27] In renal cell carcinoma, VEGF plays a critical role in tumor growth and metastasis by promoting the formation of new blood vessels that supply the tumor with nutrients and oxygen. Bevacizumab is a monoclonal antibody and effectively inhibits VEGF, depriving the tumor of these essential resources and thereby slowing its growth and spread.[28] In addition, the administration of combination therapy has been demonstrated to induce a transformation of a low immunoreactive tumor into a hot tumor.[29] The combination of bevacizumab and ICIs has been the subject of investigation as a potential treatment for various types of cancer, including RCC.[29] Moreover, a multitude of studies have demonstrated that the combination of bevacizumab and the mTOR inhibitor temsirolimus exhibits antitumor activity and is well tolerated.[30]

This case report is subject to certain limitations, including a relatively small sample size. On the other hand, the alteration in the *TSC2* gene has not yet been characterized in any of the relevant databases. However, given that the c.774 + 1G>T alteration is reported to be pathogenic, it is likely that the c.774 + 2G>T alteration also results in dysfunction of the *TSC2* tumor suppressor gene. Although temsirolimus and bevacizumab enhanced the efficacy of immunotherapy, their individual efficacy in this case remains unclear and requires further study.

CONCLUSION

This case study documented a patient with high-risk mRCC who exhibited an inadequate response to the combination of dual immunotherapy and PARPi initially recommended by the MTB. Subsequent MTBs provided critical insights that led to a reevaluation of the patient's clinical status and genomic profiling. This process resulted in a successful rechallenge with immunotherapy combined with angiogenesis and mTOR inhibitors. Although these agents are approved as monotherapies for mRCC, this represents the first case report of a triplet combination guided by a specific genomic profile, which makes it a significant case study. However, the efficacy of this triple therapy is not yet fully understood, and further research is needed to elucidate the mechanisms by which mTOR inhibitors and immunotherapy work together. The paucity of literature on the personalized treatment of treatment-refractory or treatment-naive patients with mRCC who have refused standard therapy represents a knowledge gap that this case study aims to address. In addition, it may be useful for further refinement of subgroup analyses for personalized treatment approaches in patients with mRCC and specific genetic alterations.

SUPPLEMENTAL MATERIAL

Supplemental materials are available online with the article.

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