Successful Management of Metastatic Chromophobe Renal Cell Carcinoma with Nivolumab plus Ipilimumab

Aditya Ravindra[1], Laila Dahmoush[2], Rohan Garje[1,3*]

1. Department of Internal Medicine, University of Iowa, Iowa City, IA
2. Department of Pathology, University of Iowa, Iowa City, IA
3. Miami Cancer Institute, Baptist Health South Florida. Miami FL.

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ABSTRACT

Chromophobe renal cell carcinoma (chRCC) is a rare histologic variant that is morphologically and molecularly distinct compared to the more common clear cell renal cell carcinoma (ccRCC). Due to the relatively lower incidence and lack of phase III trials, treatment for metastatic chRCC is often extrapolated from ccRCC. In this case report, we discuss a 58-year-old male with metastatic chRCC who was treated with nivolumab and ipilimumab and achieved a complete response. Though there are no definite predictive biomarkers, tumors that respond to checkpoint inhibitors (CPI) have a high immunogenic gene signature, high PD-L1 expression, MSI instability, or a high tumor mutational burden. Despite a comprehensive genetic profile predicting poor response to CPI, the current patient showed sustained radiologic response over three years. This case challenges the current paradigm of predicted response to CPIs in the setting of chRCC and shows that further biomarker driven research is needed to evaluate the efficacy of these agents in chRCC.

INTRODUCTION

Renal cell carcinoma (RCC) is the eighth most common malignancy in the United States.[1] RCC can be divided into the more common clear cell renal cell carcinoma (ccRCC) and non-clear cell renal cell carcinoma (nccRCC). Chromophobe renal cell carcinoma (chRCC) is the third most common histologic variant of RCC, accounting for 5% of cases.[2] Although computerized tomography (CT) is the preferred imaging modality in diagnosis and staging, histologic and molecular analysis are required to differentiate the histologic variants of RCC. chRCC can be differentiated by its characteristic aneuploidy with the entire loss of chromosomes 1,2,6,10,13, and 17. The high expression of mitochondrial gene mutations and accumulation of abnormal mitochondria suggest that the organelle is important in the pathogenesis of chRCC.[3] ChRCC can also occur in autosomal dominant genetic syndromes such as Birt-Hogg-Dube' and tuberous sclerosis complex.[3]

There is limited evidence regarding the first-line treatment of metastatic chRCC.[2] VEGFR-TKIs (cabozantinib and sunitinib) and mTOR inhibitors (everolimus) have traditionally been utilized in the treatment of nccRCCs due to their proven efficacy in ccRCC.[4] Nivolumab, a PD-L1 inhibitor, has also shown promise in treating ccRCC resistant to VEGFR-TKIs, but there are limited evidence in the current literature addressing their efficacy in the treatment of chRCC.[2,5] We present the case of a patient with cabozantinib-resistant chRCC successfully treated with nivolumab and ipilimumab.

CASE PRESENTATION

The patient is a 58-year-old Caucasian male who initially presented with left flank and lower abdominal wall pain associated with a 30-pound weight loss over one year. Magnetic resonance imaging (MRI) of abdomen showed a large

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* *Corresponding Author:* Rohan Garje, MD
Chief of Genitourinary Medical Oncology, Miami Cancer Institute, Baptist Health South Florida
8900 N. Kendall Drive | Miami, FL 33176 Email Id: rohan.garje@baptisthealth.net

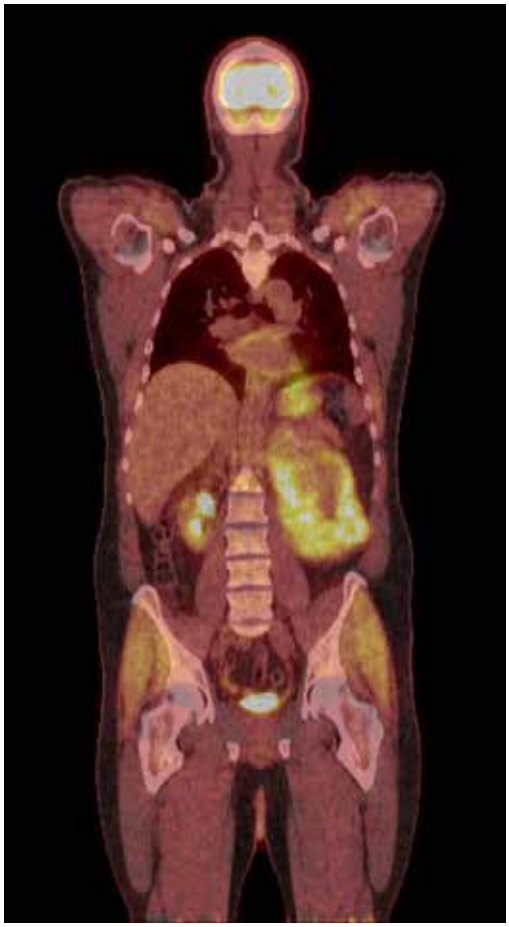

FIGURE 1 | PET-CT at the diagnosis of left-sided chromophobe renal cell carcinoma (April 2018)

left renal mass with invasion of the left renal vein. PET/CT confirmed FDG avid left kidney mass. (**Figure 1**) Biopsy of the mass confirmed chRCC. Subsequently, he underwent left nephrectomy with lymph node dissection and adrenalectomy. Pathology confirmed chRCC with extensive tumor necrosis, lymphovascular invasion, renal sinus and perinephric fat invasion. (**Figure 2A & 2B**) The surgical margins were negative as well as the lymph nodes and adrenal gland were negative for metastatic disease. Reassessment after surgery with CT and bone scan revealed a solitary lytic lesion in the first lumbar vertebrae, and the patient received 30Gy/3fxs stereotactic body radiation to the area.

Subsequent restaging with CT showed disease progression with biopsy-proven liver metastases two months after surgery, and he started first-line systemic therapy with cabozantinib 40 mg daily. Due to the development of severe hand-foot syndrome, the dose of cabozantinib was reduced to 20 mg daily. Despite six months of therapy, the patient continued to have significant disease progression, including new sites of metastases in the lungs. (**Figure 3A & 3B**). At this point in the disease course, therapy was switched to dual checkpoint inhibitor therapy with nivolumab and ipilimumab. Following the fourth cycle of this regimen, reassessment with CT showed partial response with improved liver metastases and resolution of the lung metastases. However, immunotherapy was discontinued after 5 months due to development of an immune-related adverse event (IRAE) in the form of polyneuropathy causing Bell's palsy, dysphagia, and bilateral lower extremity weakness. Brain and spine imaging was negative for metastatic disease or stroke. Cerebrospinal fluid analysis showed an increase in protein levels but was otherwise unremarkable for infection. He was treated with a prolonged tapering dose of high dose prednisone with gradual improvement of symptoms. Despite stopping therapy after 5 months due to IRAEs, he has ongoing complete response in the liver, lung without any evidence of active cancer for over 3 years now (**Figure 4**). Also, he has recovered from the IRAEs.

DISCUSSION

Although localized chRCC can be managed with surgery alone with excellent outcomes, metastatic disease requires the addition of systemic therapy with palliative intent and is generally associated with poor outcomes. The ASPEN phase II randomized control trial of 108 nccRCC patients showed everolimus, when comparable to sunitinib, showed improved overall response rate (33% versus 10% respectively).[4] Within VEGFR-TKIs, cabozantinib has been shown to have improved progression-free survival when compared to sunitinib in randomized controlled trials.[6]

After finding resistance to cabozantinib, we initiated second line therapy with nivolumab plus ipilimumab. In a retrospective analysis of 39 patients with nccRCC treated with nivolumab with or without ipilimumab, only seven patients showed objective response 6 months after therapy initiation.[7] This is in comparison to the phase 3 CheckMate 214 trial that showed objective response rate of 42% in patients with ccRCC treated with nivolumab plus ipilimumab treatment in first line setting. In another review by Bersanelli *et al*, the objective response rates with CPIs as monotherapy or in combination with other TKIs in chRCC ranged anywhere between 0% to 28.5%.[8] The studies evaluating nivolumab plus cabozantinib, atezolizumab plus cabozantinib and pembrolizumab plus lenvatinib showed objective response rates of 0%, 11% and 13.3% respectively.[8] Overall the decreased responses in chRCC when compared to ccRCC can be explained by the unique molecular pathogenesis with lower PD-L1 expression, microsatellite stability, and low tumor mutational burden (TMB) in chRCC.[2] Targeted genomic sequencing with FoundationOne testing which combines DNA and RNA sequencing to identify common genomic alterations and complex nucleic acid fusion events was performed on the patient's tumor specimen. The tumor was also found to be MSI-stable with a TMB of 4 mutations per megabase. PD-L1 immunohistochemical analysis revealed a tumor proportion score of 1%.

Despite the lack of any predictive markers of response to checkpoint inhibitors on the genomic profile, our patient responded well to

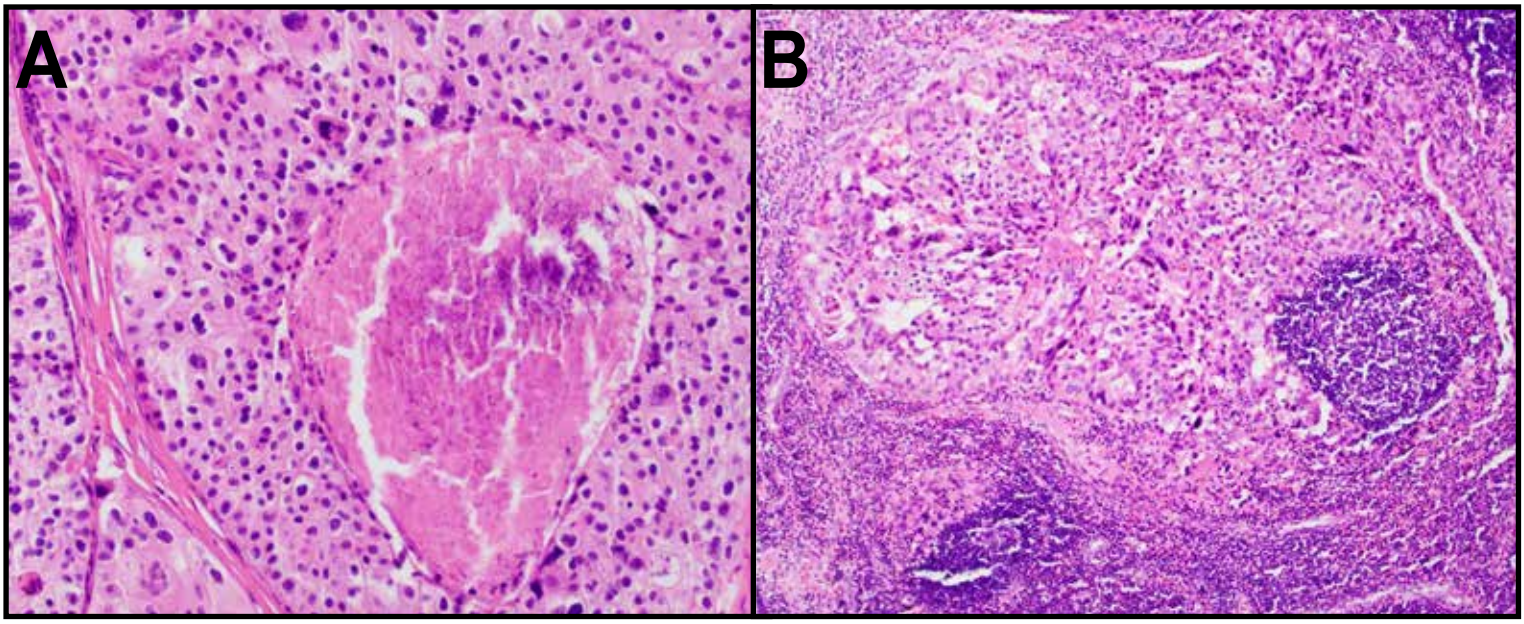

FIGURE 2 | A) Chromophobe renal cell carcinoma, eosinophilic variant with the characteristic eosinophilic tumor cells showing perinuclear halos surrounding irregular raisinoid nuclei. The center of the tumor shows necrosis.
2B) Metastatic chromophobe renal cell carcinoma replacing most of a lymph node.

combination immunotherapy, albeit with serious immune-related adverse events (IRAEs). A couple of retrospective studies in patients with metastatic RCC treated with CPI revealed a correlation between the incidence of IRAEs and improved oncologic outcomes.[9,10] The exact mechanism underlying this association is unclear. One hypothesis is bystander effect of activated cytotoxic T-cells in an organ with low-level inflammation that is potentiated after an IRAE with CPI therapy. In particular, local inflammation caused by IRAEs may activate the immune system and lead to an increased antigen presentation, release of pro-inflammatory cytokines, and recruitment of immune cells to the tumor microenvironment. This could lead to an increased efficacy of the CPI therapy, as the immune system recognizes and responds to the tumor antigens. In a post-mortem study of patients with fulminant myocarditis secondary to CPI, T-cell receptor gene sequencing revealed similar high frequency TCRs in T cells om myocardium and tumor tissue.[11] Another study revealed similar T-cell clones and antigens in the tissue obtained from the site of IRAEs and tumor.[12] Though the onset of IRAE is a potential clinical marker of response to CPI, it is critical to identify those individuals at risk before therapy and understand the underlying mechanism that can aid in enhancing oncologic outcomes

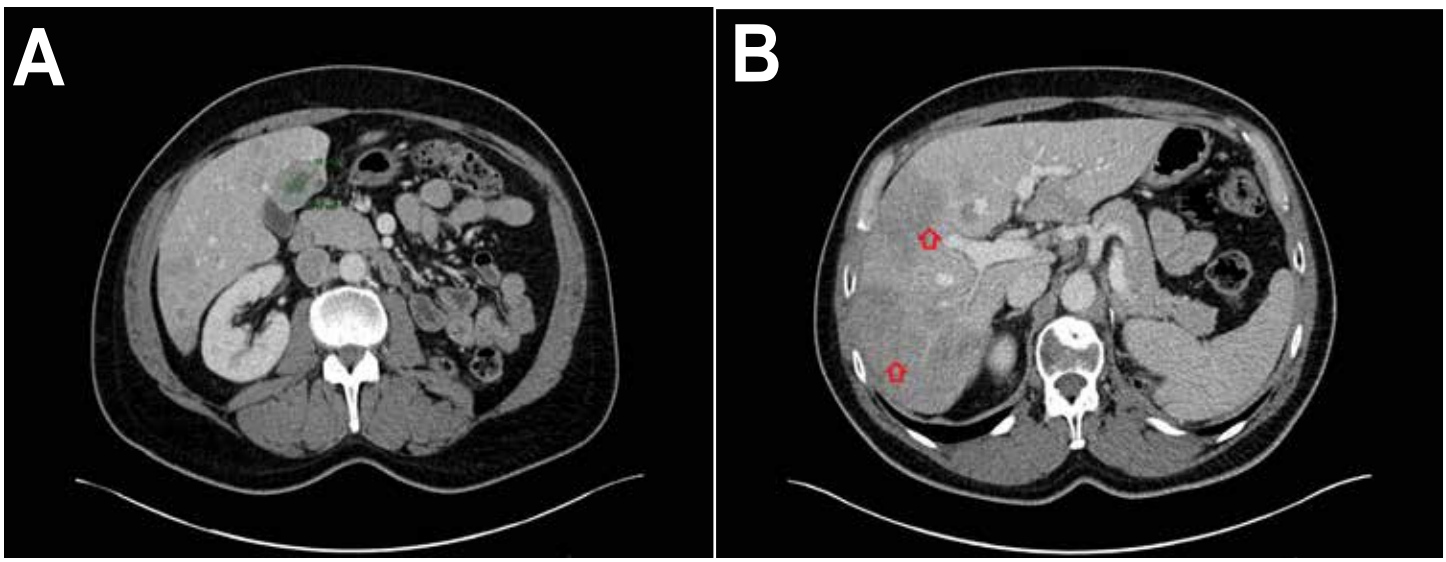

FIGURE 3 | A) A 3.7 cm left liver lobe metastasis after cabozantinib therapy (March 2019).
3B) Multifocal liver hypodensities suggestive of metastases (March 2019)

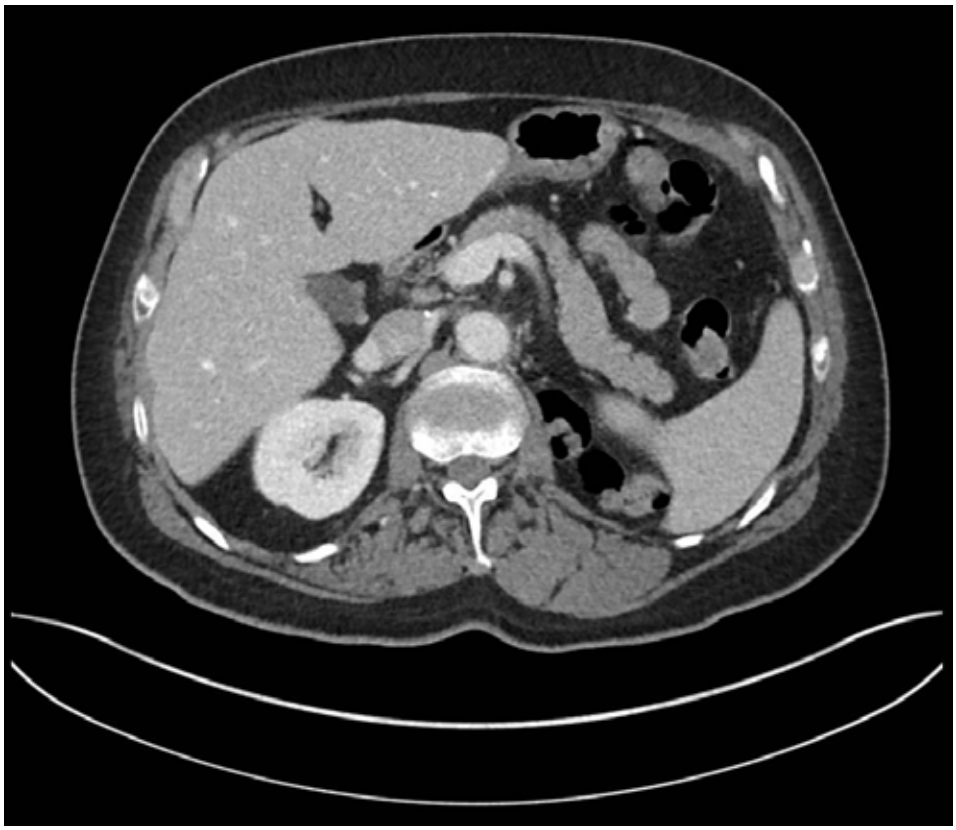

FIGURE 4 | CT scan 3 years after short course therapy with nivolumab and Ipilimumab (October 2022) with complete resolution of liver metastases

while minimizing serious IRAEs.

In summary, while CPIs have shown some promise in the treatment of metastatic chRCC, more biomarker driven research is needed to fully understand their effectiveness in this specific subtype of RCC. Despite having low PD-L1 expression, MSI-stability, and a low TMB, our patient had a durable response with nivolumab and ipilimumab. Additional studies of nivolumab and ipilimumab are needed in a larger cohort of metastatic chRCC, along with further elucidation of mechanisms of IRAEs.

ABBREVIATION

FDG PET: fluorodeoxyglucose (FDG)-positron emission tomography
CTLA-4: cytotoxic T-lymphocyte-associated protein 4
PD-1: programmed cell death protein 1
PD-L1: programmed death ligand 1
mTOR: mammalian target of rapamycin
VEGFR-TKI: vascular endothelial growth factor receptor-tyrosine kinase inhibitors
RCC: renal cell carcinoma
ccRCC: clear cell renal cell carcinoma
nccRCC: non-clear cell renal cell carcinoma
chRCC: chromophobe renal cell carcinoma
CPI: checkpoint inhibitors
MSI: microsatellite instability
TMB: tumor mutational burden

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