Complete Remission of Liver and Bone Metastases After Nivolumab Treatment in a Patient with Renal Cell Carcinoma: The Potential Implication of MLH1 Mutations

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Abstract
We report a case of complete remission of liver metastasis and near complete remission of bone metastases with nivolumab treatment in a mRCC patient, and discuss the potential implication of MLH1 mutations in this extraordinary response.

Keywords: Complete remission; Mismatch repair deficiency; Immunotherapy; Checkpoint inhibitor; Metastatic renal cell carcinoma; Programmed death 1; Programmed death ligand 1; OPDIVO® (nivolumab); MLH1 mutation

Introduction
The incidence of renal cell carcinoma (RCC) is rising with approximately 63,990 new cases and 14,400 deaths estimated for 2017 [1]. About 25% to 30% of these patients will present with metastatic disease, and an additional 20% to 40% who initially presented with localized disease will progress at some point following diagnosis [2]. Metastatic RCC (mRCC) portends a poor prognosis, with 5-year survival rates of 12% [1]. Hepatic involvement in mRCC has been reported in up to 41% of patients, with a median survival of 7.4 to 27 months without metastasectomy [2,3]. As with other solid cancers metastatic to the liver, once RCC involves the liver it is thought to be the rate-limiting step for survival.

The advent of therapies targeting molecular pathways involved in tumor growth and regulation has come in the wake of increased understanding of tumor biology, leading to a paradigm shift in the treatment of mRCC. In a large randomized study the immunotherapy drug nivolumab (Opdivo®), an anti-PD-1 monoclonal antibody, was shown to be a safe and effective therapy in previously treated mRCC patients [4]. In 2015, the FDA approved nivolumab for patients with advanced RCC following treatment with anti-angiogenic therapy based on improved overall survival compared with the standard of care. Despite these progresses, complete response (CR) is a rare event [5].

We report a case of complete remission of liver metastasis and near complete remission of bone metastases with nivolumab treatment in a mRCC patient, and discuss the potential implication of MLH1 mutations in this extraordinary response.

Case Presentation
A 61-year-old man with mRCC initially presented with metastases to the brain, liver, lung, muscle, and bone. He was initially treated with GammaKnife therapy for his brain metastasis. Subsequently, he was treated with pazopanib (Votrient)* for two months before switching to second-line therapy nivolumab due to poor tolerance and disease progression. After ten doses of nivolumab, a positron emission tomography (PET) scan showed interval resolution of the hypermetabolic activity associated with the T11 vertebral and right liver lobe metastases, along with morphologically stable appearance of the left renal malignancy compared with his baseline PET (Figure 1). Significant decreases in size and activity of the left cervical/supraclavicular

Figure 1: Positron Emission Tomography (PET) scan findings at baseline and after therapy. (A) Hypermetabolic activity associated with a T11 vertebral metastasis (arrow a), right lobe of the liver (arrow b), and primary left renal malignancy. (B) Complete disappearance of the bone (arrow c) and liver lesions (arrow d).
adenopathy and interval decrease in activity associated with a right 5th rib metastasis was also noted. In June 2016, he underwent left nephrectomy, with pathology revealing Fuhrman grade 3 clear cell and papillary RCC. Para-aortic lymph node excision showed mRCC, clear cell type, with extensive necrosis. Pathologic staging was pT1b, pN1, pM1. Genomic analysis of this patient's tumor using circulating cell-free DNA isolated from his blood was performed. Three genomic alterations were detected: MET M1268T; JAK2 V617F; MLH1 R389W.

Discussion

While therapeutic options for patients with mRCC have improved over the last decade, mRCC with liver metastases remains a therapeutic challenge [6]. Biomarkers helping to determine which patients will benefit from these therapies are greatly needed.

Microsatellites are short, repetitive sequences of DNA found throughout the genome [7]. A deficiency in the cell's ability to repair errors in the DNA sequence that occur during cell division leads to changes in microsatellite repeats, causing microsatellite instability [7-9]. The DNA mismatch repair (MMR) system is a biological pathway essential for maintenance of genomic stability and reduction of microsatellite instability [7]. The primary specificity of MMR is recognition and removal of the base-base mismatches, along with insertion-deletion mismatches, generated during DNA replication and recombination [7,8,10]. MMR deficiency due to genetic alteration has been associated with carcinogenesis and progression in RCC [10]. In particular, hMLH1, located on chromosome 3p, appears to be inactivated more frequently in comparison to other MMR genes [8,10]. MLH1 R389W, found in our patient, is a missense mutation (C.1165 c>t R389W hMLH1) that has been previously reported in hereditary nonpolyposis colon cancer (HNPPC) [11].

A recent study showed MMR-deficient colorectal tumors, along with others, are highly responsive to checkpoint blockade with the anti-PD-1 therapy, pembrolizumab [12]. One straightforward explanation for the heightened activity of anti-PD-1 therapies in MMR-deficient tumors is the increased probability of a strong neo-antigen driven T-cell response [13]. Given their ability to generate neo-antigens, MMR-deficient cancers may be uniquely susceptible to immune checkpoint inhibitor therapy [13]. In addition, MMR deficiency is associated with the activation of various signal transduction pathways, which lead to a heightened inflammatory tumor microenvironment mediated by altered cytokine and chemokine expression, promoting immune responses [12,13]. MMR deficiency leads to cellular stress, which may promote T- or NK-cell accumulation, or tumor recognition [13]. Finally, nivolumab was found to reverse T-cell exhaustion in the tumor microenvironment, adding to the possible mechanisms of anti-PD-L1-mediated immune response [6]. Patients experiencing an exceptional response may help determine the genetic context that results in the strongest response to molecularly targeted (i.e. anti-PD-L1) cancer therapies.

We report here an "exceptional responder" with complete remission of liver metastasis and near complete resolution of bone metastases after nivolumab treatment for mRCC. After a comprehensive genomic analysis of this patient’s tumor, we identified genes that may be implicated in this response mechanism, specifically mutations in MLH1. We propose study of the mechanisms of these genetic vulnerabilities so appropriately targeted therapies can be developed and tested.

Conclusion

To our targeted knowledge, this is the first documented case of MMR-deficient mRCC with a dramatic clinical benefit from anti-PD-1 immunotherapy, nivolumab. The impact of MMR-deficiency on PD-L1 inhibitor therapy for patients with mRCC deserves further investigation.

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