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Nivolumab Plus Ipilimumab in Primary Clear Cell Hepatocellular Carcinoma (CCHCC): A Case Report and Literature Review

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Abstract

Primary clear cell carcinoma of the liver is an uncommon morphologic variant of Hepatocellular Carcinoma (HCC). Management of advanced clear cell variant of HCC is challenging with no established treatment guidelines. We report a case of advanced clear cell HCC in a 55-year-old male presenting with a large liver mass measuring 22 cm × 12 cm × 15 cm with tumor thrombi extending to Inferior Vena Cava (IVC) and the right atrium with acute tumor bleeding causing hemoperitoneum, required emergent embolization of hepatic artery. Immunostains show the tumor to be positive for HepPar1, focally positive for CEA (Carcino Embryonic Antigen)-p (canalicular pattern), and focally and weakly positive for pan-cytokeratins, establishing the diagnosis of primary hepatocellular clear cell carcinoma.

Positron Emission Tomography-Computed Tomography (PET CT) demonstrated the liver mass with tumor thrombi and lung nodules consistent with metastasis. Tumor profiling showed combined positive score 5 for Programmed Death Ligand 1 (PD-L1) on tumor determined by IHC 22C3 PharmDx test. He was started on combination immunotherapy with Nivolumab plus ipilimumab with an ongoing response after completion of four cycles followed by nivolumab every two weeks without any clinical symptoms and radiologically stable disease.

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Introduction

Hepatocellular carcinoma is an aggressive tumor typically associated with chronic liver disease most commonly related viral hepatitis B and C infection [1]. Other risk factors that have been associated with development of HCC includes hereditary hemochromatosis, cirrhosis of any cause, environmental toxins, tobacco and alcohol abuse, nonalcoholic fatty liver disease. Primary clear cell HCC is an uncommon variant of hepatocellular carcinoma, though previous studies reported favorable prognosis compared to non-clear cell HCC, there is no general consensus on in the management due to rarity of the disease [2]. We present a unique case of a patient with no prior history of liver disease diagnosed with clear cell HCC with large tumor burden in the liver, with portal vein and left atrial tumor thrombus associated with massive intra tumoral bleeding. Given no clear guidelines in the management of advanced clear cell HCC patient was treated with dual check point immunotherapy with nivolumab plus ipilimumab.

Case Presentation

A 61 year-old male patient with a history of atrial fibrillation, coronary artery disease self-palpated a mass in the epigastric area. Labs revealed AST 100 u/L, ALT 143 u/L, albumin 4 g/dL, total bilirubin 1 g/dL. Serology for HBV, HCV non-reactive. CT abdomen and pelvis revealed a large 20 cm × 17 cm × 14 cm mass replacing the left lobe of liver extending into the segment VII of the right lobe associated with a filling defect extending to intrahepatic inferior vena cava and right atrium, most likely a tumor thrombus (Figure 1). Transthoracic echocardiogram revealed a large 4.9 cm × 2.7 cm mass in the right atrium as well as large mass extending through the IVC (Figure 2).

A CT guided biopsy of the liver mass revealed sheets of malignant cells containing abundant clear cytoplasm with a round to oval hyperchromatic nuclei. Immunochemical stains showed malignant cells to be positive for HepPar1, CEA-p (canalicular pattern), pan-cytokeratin AE1/AE3

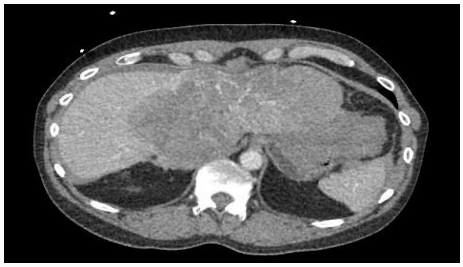

Figure 1: Large heterogeneous liver mass replacing the left lobe of liver.

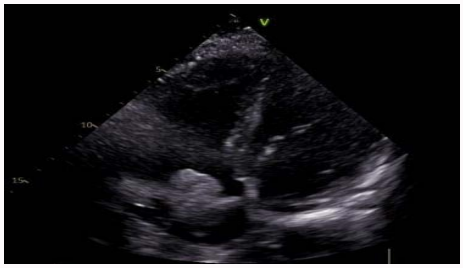

Figure 2: Large right atrial tumor thrombus on transthoracic echocardiogram.

(weak and focal) (Figure 3). Malignant cells were negative for *SOX10*, Inhibin, *PAX8*, and RCC, consistent with HCC, clear cell variant. CT abdomen pelvis confirmed no additional renal mass or adrenal masses, thus established diagnosis of primary clear cell carcinoma of the liver. The mass was staged as moderately differentiated cT4N0M1 (Stage IVB). Serum Alpha-Fetoprotein Level (AFP) was elevated, 24 ng/ml (normal <9 ng/ml).

Positron Emission Tomography Computed Tomography (PET CT) demonstrated liver mass, omental metastasis, IVC, and right atrial tumor thrombus as well as bilateral pulmonary metastasis. MRI brain did not show any metastasis. A week after diagnosis, he was hospitalized due to a sudden worsening of abdominal pain with acute anemia, Hb dropped to 7.5 g/dL from 13 g/dL a week prior. A CT angiogram abdomen and pelvis demonstrated left hepatic tumor bleeding with a large amount of hemoperitoneum. Hemostasis was achieved with an emergent visceral angiogram with successful embolization of right phrenic and left hepatic artery. The patient received palliative radiation to liver and IVC tumor thrombus for a total of 3600 cGy in 600 cGy daily fractions.

Due to ongoing bleeding and transaminitis, sorafenib was not considered in first-line therapy. Due to the rarity of the tumor, no established treatments guidelines exist to treat clear cell variant HCC. Therefore, we extrapolated data from phase 3 Checkmate 214 trials, the immune blockade in advanced previously untreated renal cell carcinoma with Nivolumab plus ipilimumab *vs.* sunitinib, an objective response rate of 42% *vs.* 27% and complete response rate of 9% with immune therapy [2].

Patient's tumor PD L-1 Combined Positive Score (CPS) is >1, he was started on a combination of systemic immune therapy with nivolumab plus ipilimumab every three weeks for four cycles followed by nivolumab 240 mg every two weeks. Interval PET CT imaging at the end of 4 cycles of immune therapy revealed partial response in the left hepatic lobe mass with interval development of areas of decreased uptake likely represent tumor necrosis (Standard Uptake Value [SUV], 6.5) which represent residual tumor. There is some concern for progression *vs.* pseudo progression of pulmonary

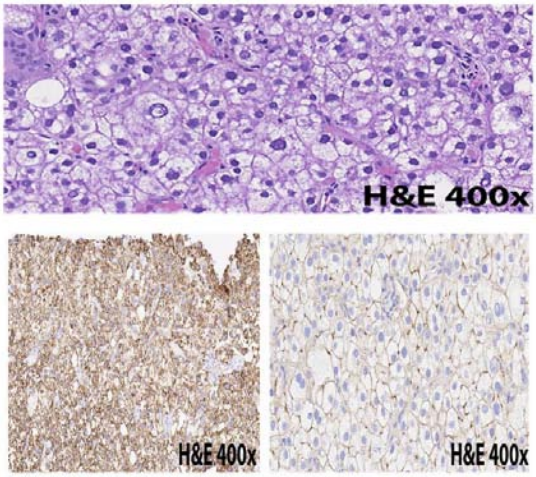

Figure 3: Malignant cell with clear cytoplasm with hyperchromatic nuclei.

metastasis; however, no new lesions or lymphadenopathy noted. Repeat transthoracic echocardiogram showed a mass in the right atrium is smaller compared to a prior echocardiogram.

After completion of 4 cycles of nivolumab and ipilimumab, labs demonstrated grade 3 immune therapy-induced hepatitis. Immune therapy was temporarily held, the patient was treated with high dose prednisone 1 mg/kg with the resolution of hepatitis. Other than mild fatigue, the patient remained asymptomatic. To date, his symptoms (abdominal pain) completely resolved, and immunotherapy was resumed with single agent nivolumab every two weeks with close monitoring of liver function tests with minimal adverse events except grade 1 fatigue.

Discussion

Primary clear cell carcinoma of the liver is usually rare histological type of liver cancers which accounts for less than 10% of HCC. It is commonly associated with hepatitis c and cirrhosis with female predominance. It is morphologically similar to other clear cell tumors with renal clear cell carcinoma indistinguishable morphologically from it [1,2].

If diagnostic criteria for HCC are absent, hepatocyte antibody as a screening immunostain distinguishes primary clear cell carcinoma of the liver from other clear cell malignancies with sensitivity and specificity of 90% and 100% respectively. Alternative method using in situ hybridization from albumin mRNA can also distinguishes primary liver clear cell carcinoma from other metastatic clear cell tumors to the liver [2].

Generally the prognosis is better than other type of liver cancers and factors such as higher clear cell ratio, no vascular invasion, capsule formation and improved liver function associated with better prognosis.

ICIs (Immunotherapy) have transformed the management of a variety of advanced and metastatic tumors, such as melanoma and Non-Small Cell Lung Cancer (NSCLC). PD-L1 expression is the most commonly used metric to initiate immune therapy treatment.

The efficacy of nivolumab in advanced HCC with Child-Pugh A or B cirrhosis, who had progressed on sorafenib or intolerant to the drug. Checkmate 040 is a phase I/II dose-escalation, and expansion trial which included 48 patients in the dose escalation phase and

214 patients in dose expansion phase. Nivolumab was given every two weeks. Forty-nine of 255 patients had an objective response to immune therapy, and two patients had a complete response. An additional 50 percent of the patients had stable disease. The median duration of response was 17 months (95% CI 6-24), and median OS was 15 months. Based on this data, the FDA has expanded the indication for nivolumab to patients with HCC who were treated with sorafenib in the first-line setting [3].

Since the approval of nivolumab, a phase III KEYNOTE-240 trial of best supportive care plus either pembrolizumab or placebo for second-line therapy of advanced HCC after progression or intolerance of sorafenib. In a preliminary report presented at the 2019 annual ASCO meeting. Total of 413 patients was randomly assigned to pembrolizumab or placebo. The objective response rate was higher for pembrolizumab (16.9 *vs.* 2.2 percent), there were more complete responders with pembrolizumab (six *vs.* none), and responses were durable (median duration of response 13.8 months, range 1.5 to 23.6+ months) [4].

Simultaneously blocking both PD-1 and CTLA-4 signals has been another strategy in solid tumors, currently being used to achieve a stronger effect than monotherapy. Inhibition of the PD-1/PD-L1, as well as simultaneous inhibition of the B7-CTLA-4 pathway by an anti-CTLA-4 antibody, can increase the number of activated CD+T cells infiltrating into tumor tissues, thereby enhancing antitumor effects. This strategy has been proved in malignant melanoma, and clear cell advanced renal cell carcinoma, respectively [5,6].

In the Checkmate 040 HCC trial combination cohort has been added to evaluate the safety and tolerability of nivolumab with ipilimumab with advanced HCC [7]. Overall, nivolumab plus ipilimumab was well tolerated with clinically meaningful responses and acceptable safety profile, with an overall response rate twice that of nivolumab monotherapy (31% and 14% respectively) with median overall survival of 23 months. Another phase III ongoing HIMALAYA study is looking at the combination of durvalumab (anti-PDL-1 antibody) and tremelimumab (anti-CTLA-4 antibody) as initial treatment in a patient with inoperable liver cancer [8].

Future Prospects

HCC is heterogeneous cancer without any driver mutation and cannot be treated with agents that cause hepatic dysfunction. There is an unmet need for treatment for HCC, such as neoadjuvant therapy and adjuvants after resection and ablation [9,10] or combination therapy with trans catheter arterial Chemoembolisation [11,12] and first and second-line treatments. Novel antibodies against PD-1and PD-L1 may be beneficial at these stages. Their combination with other anti-angiogenic agents, locoregional therapy, another checkpoint inhibitor such as an anti-CTLA-4 antibody (ipilimumab or tremelimumab), or with molecularly targeted agents (e.g. sorafenib or lenvatinib) appears promising.

The development of combination immunotherapy is rapidly advancing. Immune checkpoint inhibitors, in combination with locoregional and systemic therapies as treatment strategies, will soon become the mainstay of anticancer treatment for liver cancer.

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