Hyperprogression in a Patient With Hepatocellular Cancer Treated With Atezolizumab and Bevacizumab: A Case Report and Review of Literature

Balraj Singh, MD1, Parminder Kaur, MD1, and Michael Maroules, MD1

Abstract
Immune checkpoint inhibitors have emerged as a novel treatment in a wide variety of malignancies; however, it is associated with a distinctive array of side effects known as immune-related adverse events. Hyperprogression is defined as an accelerated growth of disease burden in patients treated with immunotherapy. Limited literature is available regarding hyperprogression in hepatocellular cancer. We report a case of a 36-year-old male with no past medical history who presented with nausea, vomiting, and abdominal pain and was diagnosed with unresectable hepatocellular cancer and thereby started on atezolizumab and bevacizumab. The patient got only 1 cycle of treatment and unfortunately had hyperprogression of disease.

Keywords
hepatocellular carcinoma, hyperprogression, immunotherapy, pseudo progression, tumor growth rate, atezolizumab, anti-PD-1, immune checkpoint inhibitors

Introduction
Hepatocellular carcinoma (HCC) is one of the major causes of cancer-related mortality worldwide.1 Risk factors include viral hepatitis B and C infections, alcohol abuse, and metabolic disorders.2 The prognosis of HCC is poor despite availability of many treatment modalities including surgical resection, transplantation, locoregional treatment (radiofrequency ablation, transcatheter arterial chemoembolization), and systemic therapy (tyrosine kinase inhibitors). In recent years, immune checkpoint inhibitors (ICIs) have expanded as an emerging treatment for HCC. Current approved treatment for advanced HCC includes atezolizumab (anti-PD-L1) with bevacizumab approved as first-line treatment option and pembrolizumab (anti-PD-1) and nivolumab (anti-PD-1) with or without ipilimumab (anti-CTLA4) approved as second-line therapy.3

Case Presentation
A 36-year-old male with no past medical history presented to emergency department (ED) for nausea, vomiting, and abdominal pain of 8 weeks duration. The patient had another emergency department visit 4 weeks prior to this presentation for similar complaints; imaging was done (Figure 1) and he was discharged from the ED to follow-up in oncology clinic. The patient was seen in the oncology clinic and plan was to biopsy of the liver mass; however, due to worsening of his symptoms, he came to the ED and was admitted. Review of system was positive for weight loss of 20 pounds over 6 weeks and negative for blood in stools, fever, shortness of breath, cough, chest pain, and night sweats. The patient denies any smoking or drug abuse and admitted to 1 to 2 beers sometimes over the weekend. No history of blood transfusion. Physical examination was normal. Initial laboratory evaluation showed complete blood count and basic metabolic profile within normal limits. Other blood work was as follows: lactate dehydrogenase 168 U/L (reference: 140-271 U/L), alkaline phosphatase 90 U/L (reference: 34-104 U/L), aspartate transaminase 35 U/L (reference: 13-39 U/L), alanine transaminase 58 U/L (reference: 7-52 U/L), bilirubin 0.6 mg/dL (reference: 0.3-1.1 mg/dL), prothrombin time 13.4 seconds (reference: 12.2-14.9 seconds), international normalized ratio 1 (reference: <1), partial thromboplastin time 27.7 seconds (reference: 21.3-35.1 seconds), calcium 9.7

1Saint Joseph’s University Medical Center, Paterson, NJ, USA

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Corresponding Author:
Balraj Singh, MD, Saint Joseph’s University Medical Center, 703 Main Street, Paterson, NJ 07503, USA.
Email: bsriar9@gmail.com
mg/dL (reference: 8.6-10.3 mg/dL), albumin 4.5 mg/dL (reference: 3.5-5.0 mg/dL), \( \alpha \)-fetoprotein 5037 ng/mL (reference: 0.5-9 ng/mL), and des gamma carboxy prothrombin 149.3 ng/mL (reference: 0-7.5 ng/mL). HIV, hepatitis B and C profile was negative. Computed tomography (CT) of the abdomen and pelvis with intravenous contrast showed large heterogeneous mass in the left lobe of the liver measuring 11 × 10 × 10 cm (Figure 2). The patient underwent CT-guided biopsy of the liver mass, and pathology was consistent with HCC. A hepatobiliary surgical consult was placed, and the patient underwent diagnostic laparoscopy, which showed left lobe mass involving segments 2 and 3, nodular lesion on the peritoneum overlying segment 2 of the liver (frozen pathology revealed the specimen sample was too small for evaluation, piece of peritoneum was removed in the same area and was sent as specimen), nodular area on the anterior surface of segment 4 (frozen pathology revealed carcinoma), and wedge resection of the posterior surface of segment 4 (3.0 × 2.2 × 1.7 cm). Final pathology of the wedge resection of segment 4 showed 3 separate nodules consistent with HCC and peritoneum biopsy was negative. The patient was discharged and seen at an outpatient clinic and started on atezolizumab and bevacizumab given unresectable disease. The patient got treatment on October 5, 2020. Three weeks later, the patient came to the ED for abdominal pain and CT
Singh et al

chest/abdomen/pelvis with contrast showed multiple bilateral lung nodules (all size less than 1 cm), large (21 × 10.9 × 16.5 cm) heterogeneously enhancing mass in the left lobe of the liver, and interval development of additional small multiple hypodense lesions in the right lobe of the liver suggesting multicentric HCC (Figures 3 and 4). The imaging findings of the patient were consistent with hyperprogressive disease (HPD). Summary of the patient’s course from presentation to HPD is provided in Figure 5. The patient performance status had declined to ECOG 3-4 (Eastern Cooperative Oncology Group). Palliative care was recommended and the patient went to his home country Peru.

Discussion

Checkpoint inhibition–based immunotherapy has become a primary treatment option in the management of wide range of malignancies and is associated with a distinctive array of side effects known as immune-related adverse events and can affect almost any organ in the human body. The most common adverse effects reported are pneumonitis, colitis, hepatitis, adrenocorticotropic hormone insufficiency, hypothyroidism, type 1 diabetes, acute kidney injury, and myocarditis.

Hyperprogression is characterized by accelerated growth in disease burden in patients treated with ICIs and is usually associated with a deteriorating clinical course. In reported literature hyperprogression incidence varied between 4% and 29% and has been reported with different types of cancer (head and neck squamous cell carcinoma, gastric cancer, non–small cell lung cancer, and melanoma). Limited literature is available regarding hyperprogression in HCC. HPD defining criteria, predictors, and mechanisms of hyperprogression are not completely understood at present. To define HPD, the following different criteria have been used in the literature: tumor growth kinetics, tumor growth rate, and time-to-treatment-failure. For the evaluation of HPD in our patient, we used Lo Russo and colleagues recommended criteria (diagnosis of HPD requires at least 3 of the following criteria): (1) time-to-treatment failure, which is defined as the time between the start and the discontinuation of immunotherapy of less than 2 months; (2) a ≥50% increase in the sum of the major diameters of the target lesions between baseline and first radiologic assessment; (3) the emergence of at least 2 new lesions in an already involved organ during the first radiologic assessment; (4) the involvement of a new organ revealed by the first radiologic assessment; and (5) an ECOG performance status score of ≥2 within the first 2 months of start of immunotherapy treatment. Furthermore, our patient met all the criteria.

Kim and colleagues reported an incidence of 12.7% (24/189) in advanced HCC patients treated with nivolumab.
Furthermore, HPD patients had worse progression-free survival and overall survival compared with patients with progressive disease without HPD, and more than 90% of HPD patients did not receive subsequent cancer treatment due to rapid decline of clinical status. Poor prognostic feature associated with HPD included elevated neutrophil-to-lymphocyte ratio (>4.125). In a retrospective study of 47 patients who got nivolumab as second- or third-line treatment, HPD was observed in 3 patients (6%) with metastatic HCC, metastatic lung adenocarcinoma, and metastatic urothelial transitional carcinoma.10 Wong and colleagues10 reported a case series of 6 patients with advanced HCC treated with ICIs who developed HPD. The immunotherapy drugs used were anti-PD-1 (nivolumab and durvalumab) and anti-CTLA4 (tremelimumab). Wang and colleagues11 reported HPD by serial F-fluorodeoxyglucose positron emission tomography in a patient with metastastic HCC patient during combined immunotherapy (pembrolizumab-ipilimumab-lenvatinib).

Vascular endothelial growth factor (VEGF-A) promotes tumor progression via angiogenesis and exhaustion of effector T-cells in the tumor microenvironment.12 Kim and colleagues8 analyzed 95 patients with advanced HCC treated with regorafenib (anti-VEGF therapy; along with 189 patients treated with immunotherapy) and observed that HPD occurred exclusively in patients treated with immunotherapy, thereby suggesting possible protective effect of anti-VEGF therapy against HPD. However, our patient received bevacizumab (anti-VEGF therapy) along with atezolizumab and still developed HPD. Further studies are needed regarding this aspect. As immunotherapy is being widely used for different types of cancer, it is of paramount importance to improve the knowledge of this novel phenomenon.

Conclusion

In conclusion, we report a patient with HCC treated with atezolizumab and bevacizumab for 1 cycle and developed HPD. Our case and review of literature suggest that health care providers should maintain a high index of suspicion to recognize HPD (accelerated progression with immunotherapy), and once the diagnosis is confirmed, immunotherapy should be stopped immediately.

Declaration of Conflicting Interests

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Ethics Approval

Our institution does not require ethical approval for reporting individual cases.

Informed Consent

Verbal informed consent was obtained from the patient for their anonymized information to be published in this article.

ORCID iD

Balraj Singh https://orcid.org/0000-0001-7986-6031

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