CASE REPORT

Complete Response with Immunotherapy Alone after Discontinuing VEGF Inhibitor in Advanced Hepatocellular Carcinoma: A Case Report

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Abstract

Bevacizumab and atezolizumab combination is one of the preferred combinations for managing advanced hepatocellular carcinoma (HCC), while the evidence on monotherapy with either agent is not convincing. We present a case of a man in his 50s diagnosed with HCC with spinal metastases who showed a good response to combination therapy. However, he developed severe proteinuria and hypertension secondary to bevacizumab, which had to be discontinued after 18 cycles. After an informed decision, atezolizumab was continued and the patient showed a sustained response. Till date, he has received 16 additional cycles of atezolizumab monotherapy after discontinuation of bevacizumab and continues to show a persistent response, with a progression-free survival of over 30 months now. It needs to be prospectively evaluated if atezolizumab's effectiveness as monotherapy for extended periods, as in our report, is a residual effect of initial combination therapy or if HCC is intrinsically responsive to immunotherapy alone.

Keywords: Atezolizumab, Bevacizumab, Case report, Complete response, Hepatocellular carcinoma, Hypertension, Spinal decompression, Progression-free survival, Proteinuria.

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Introduction

Hepatocellular carcinoma (HCC) is the most common malignancy of the liver and is the third-biggest contributor to cancer-related mortality worldwide.[1] Certain regions, notably East Asian countries, exhibit a high incidence, with China recording the highest global rate of HCC.[2,3] It has been proposed that this high rate in these countries corresponds directly to the geographical incidence of Hepatitis B viral infection, with some regions having a prevalence of as high as 18% compared to 1% in the United States.[4,5]

Early-stage hepatocellular carcinoma is amenable to curative methods and carries a good prognosis, with transplantation, resection, or local ablative techniques.[6] In contrast, advanced HCC carries a poor prognosis owing to limited effective treatment options and diminished liver and functional capacity of the patient in most cases.[7] In the rapidly evolving landscape of the use of immunotherapy in oncology, a landmark study was the IMbrave 150 trial, published in 2020. It highlighted the combined use of Bevacizumab and Atezolizumab for the treatment of advanced HCC and its superiority compared to Sorafenib which at the time was the standard of care.[8]

Atezolizumab is a programmed death ligand (PDL-1) inhibitor and bevacizumab is a recombinant humanized monoclonal antibody that blocks angiogenesis by inhibiting vascular endothelial growth factor A (VEGF-A).[9,10] The anti-PD-L1 activity of atezolizumab is enhanced by bevacizumab's reversal of VEGF immunosuppression and this in turn promotes T-cell infiltration of tumors.[11] Concurrently, this combination demonstrated a better response rate and overall survival (with 29.8% and 19.2 months vs 11.3% and 13.4 months, respectively) and a more acceptable side effect profile.[8] Since then, the above combination has been accepted worldwide and has been included in various guidelines as the first line treatment of advanced HCC.

Well-documented side effects of VEGF inhibitors include hypertension and proteinuria. Proteinuria associated with Bevacizumab occurs at a rate of 21–64% in various reports.[12] However, nephrotic range proteinuria, which is a more severe form of proteinuria, is considerably less common, occurring in only 1–2% of cases. This distinction is important as it highlights the severity of the condition when it does occur, despite its low incidence rate. It is hypothesized that nephrotic range proteinuria arises through multiple pathways, with the most well-documented mechanism being the decreased production of VEGF at the podocyte level.[13,14] This leads to a loss of endothelial fenestrations and proliferation, which in turn can cause profound thrombotic glomerular

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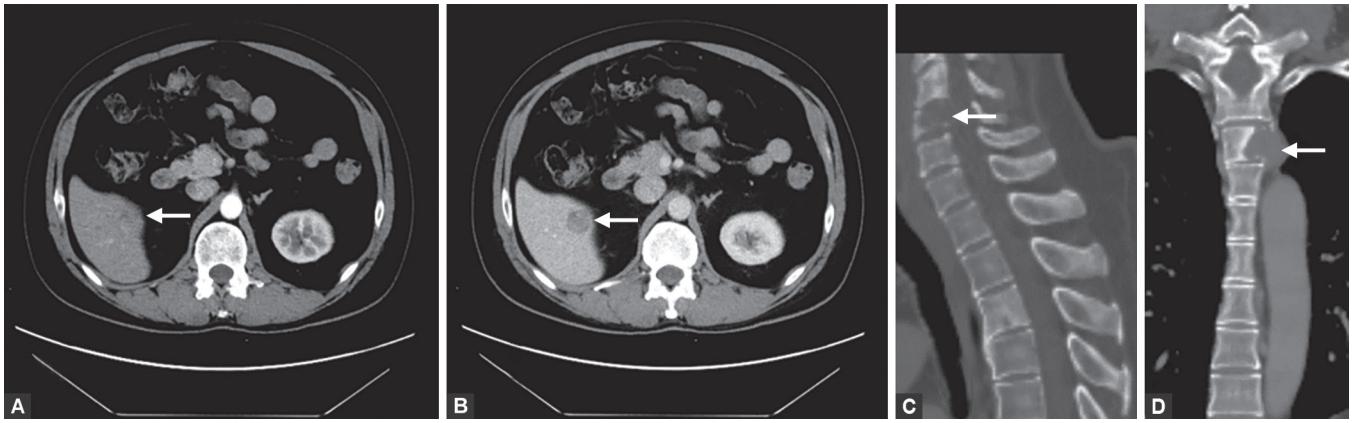


Figs 1A to D: (A) Contrast enhanced axial images in arterial and portal venous; (B) Phases show a lesion in segment VI of liver (denoted by white arrows) showing mild patchy arterial enhancement and washout on the portal venous phase, consistent with hepatocellular carcinoma; (C) Sagittal and coronal; (D) Reformat images from the same patient show lytic lesions (denoted by white arrows) in C5 and T3 vertebral bodies respectively with soft tissue component representing metastatic deposits

injury, serving as the pathophysiology behind thrombotic microangiopathy.[15]

Case Presentation

A man in his 50s, having comorbidities of hypertension and hyperlipidemia, and an Eastern Cooperative Oncology Group (ECOG) performance status score of 1, presented to our institution with complaints of neck pain radiating to both shoulders for one month. His pain was poorly controlled with analgesia and was progressively increasing in severity, hampering his daily activities. Further questioning did not reveal any other systemic symptoms or significant event in his prior medical and family history. On physical examination, he was of average build and all his vital parameters were within reference ranges. Regional examination of the neck and shoulders was normal, and a focused neurological examination did not demonstrate any sensory or motor deficits. Examination of the remaining systems was unremarkable as well.

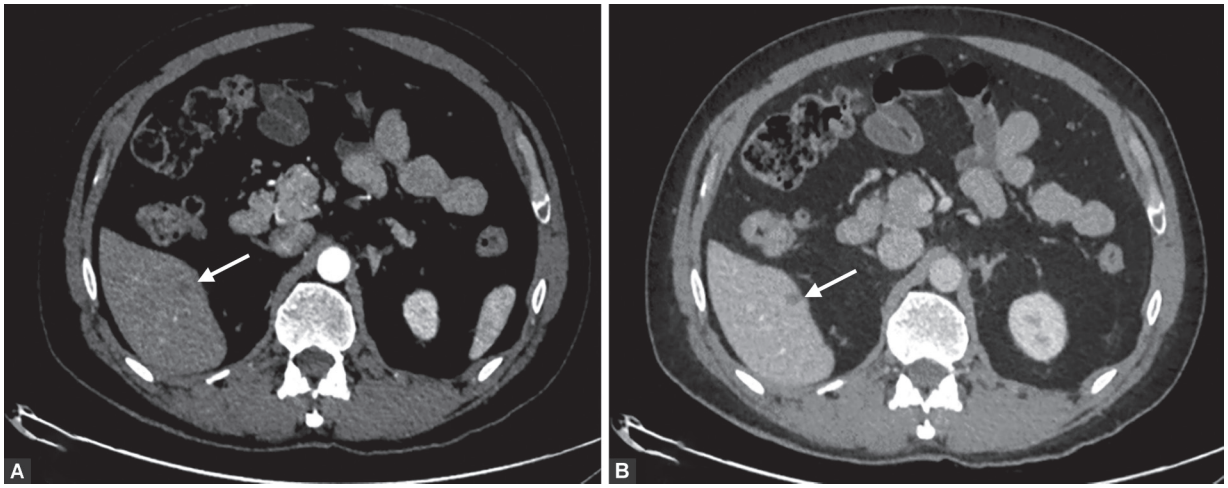
He had been assessed earlier at an outside healthcare facility, where a computed tomography (CT) scan of the chest, abdomen, and pelvis (CAP) was advised. It revealed a solitary lesion in segment VI of the liver with arterial enhancement and portovenous phase washout. Along with this, a large paraspinal lytic lesion with an associated soft tissue component was seen at C5 and another lesion at T3 spinal level. Image findings at initial diagnosis are shown in Figure 1. Following these findings, he underwent an image-guided biopsy of the T3 lesion, confirming the diagnosis of hepatocellular carcinoma, as indicated by morphology and immune histochemical markers, notably Hep-Par1 positivity. Further diagnostic tests revealed an elevated alpha-fetoprotein level of 13.1 IU/mL (Normal <6.7 IU/mL). The patient's liver function was evaluated using the Child-Pugh score, resulting in a classification of child class A. For disease staging, the Barcelona Clinic Liver Cancer (BCLC) staging system was applied, categorizing his condition as advanced stage BCLC-C, owing to extrahepatic spread with preserved liver function and performance status.

A dedicated magnetic resonance imaging (MRI) study of the spine was undertaken to rule out cord compression, which demonstrated lesions at C5 and T3 levels along with a lesion at T10 and another deposit at the right scapular blade. A comprehensive approach was undertaken for the patient's treatment, involving both neurosurgical and radiation oncology consultations. Initially, radiation therapy was recommended. However, during the radiation planning phase, the patient exhibited left arm motor weakness, with a strength assessment revealing a power of 3/5 in the left upper limb. This prompted an urgent neurosurgical evaluation, leading to a decision for surgical intervention. The patient underwent a successful C4, C5 complete, and C6 partial laminectomy for spinal decompression and stabilization. Subsequently, the patient received a targeted course of radiation therapy, consisting of 10 fractions totaling 30 gray (Gy), to further support treatment outcomes.

After discussion of treatment options, systemic therapy was initiated with atezolizumab (at a standard dose of 1200 mg) and bevacizumab (at a dose of 15mg/kg) every three weeks. This regimen was continued with monthly to two monthly scheduled follow-up visits. A CT CAP was repeated after cycle 3 which demonstrated stable disease as per response evaluation criteria in solid tumor (RECIST) criteria. A repeat CT scan after cycle 7 showed improvement, and a sustained complete response was seen here onwards on all interim scans. Figure 2 shows latest CT findings.

By the time cycle 18 was given, a trend was observed in the clinic visits. Routine vital monitoring revealed a persistently raised blood pressure, particularly systolic hypertension (ranging from 150 to 180 mm Hg). A physical examination revealed generalized edema. A dipstick urinalysis revealed proteinuria of 4+. 24-hour urine protein quantification showed 8.4 g/24 hour of proteinuria. Further treatment was suspended, and an urgent expert opinion from nephrology was sought. He was started on diuretics and valsartan. In addition to this, a renal biopsy was performed, and histopathology with direct immunofluorescence revealed segmental thickening of the capillary wall due to endothelial swelling with accumulation of material between endothelial cells, and underlying basement membrane, IgM and C3 were positive in subendothelial region, as shown in Figure 3. These features were suggestive of thrombotic microangiopathy.

Following the diagnosis, the patient was informed, and it was decided to permanently discontinue bevacizumab and continue exclusively with atezolizumab for the treatment. Within a month of discontinuation of bevacizumab, blood pressure returned to normal systolic ranges. Serial monitoring of urine protein levels over the next 6 months showed a significant decline, with the last value being 448 mg/24 hours.



Figs 2A and B: (A) Axial contrast-enhanced arterial, and (B) Portal venous phase images from the latest follow-up scan show a non-enhancing hypodense focus (denoted by white arrows) in segment VI of liver, consistent with healed lesion. This appears unchanged in interval on follow-up imaging performed over a period of 2 years

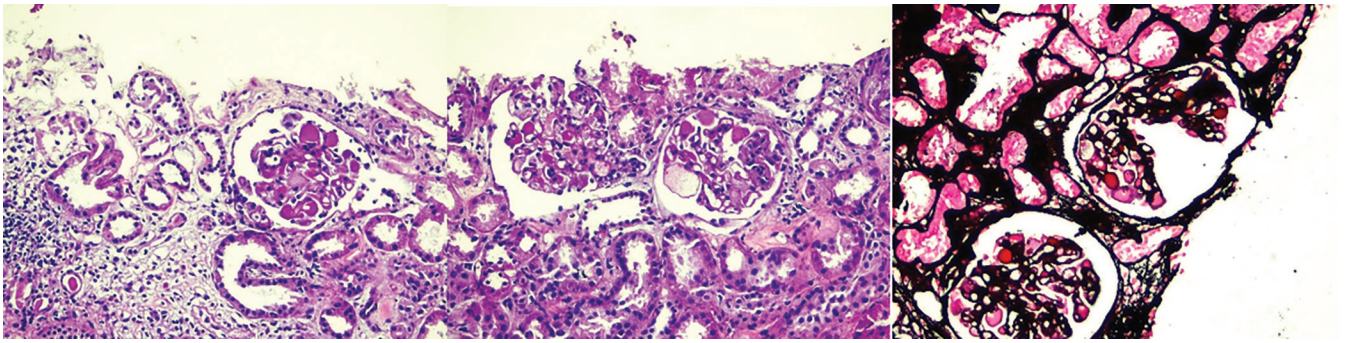


Fig. 3: Renal biopsy with subendothelial swelling, segmental thickening of the glomerular capillary walls, and focal double contours with wrinkling of the basement membrane

The utilization of atezolizumab alone raised concerns regarding the likelihood of a continued response due to the paucity of convincing evidence. However, an informed decision was made after explaining to the patient to continue single agent immunotherapy, with the intent to change therapy as soon as any signs of progression appear.

All subsequent imaging scans consistently showed that the disease remained stable. To date, the patient has completed a total of 34 treatment cycles. The first 18 cycles were administered in combination with bevacizumab, and the subsequent 16 cycles were administered as atezolizumab monotherapy. Imaging scans were performed every 3 months. Impressively, the most recent CT scan, conducted after the 34th cycle, showed a complete response to the treatment (Fig. 2). This means that from the point of diagnosis to the most recent treatment cycle, the patient has achieved a progression-free survival of over thirty months, including the period after Bevacizumab was discontinued, ultimately resulting in a complete response.

Discussion

The immune microenvironment of HCC exhibits complex interplay of immune cells, cytokines, and tumor signaling pathways.[16] Combining antiangiogenic drugs with immune checkpoint inhibitors has shown effectiveness in enhancing outcomes by improving drug delivery and immune cell infiltration. IMBrave150 have proven the benefit of combination therapy and resulted in the expansion of treatment approaches for advanced liver cancer, moving beyond traditional tyrosine kinase inhibitors like sorafenib, with improvements in progression-free survival and overall survival.[8,17] Monotherapy using either bevacizumab or atezolizumab has shown limited effectiveness, with response rates of 15–20%.[18–20] Despite the introduction of more effective treatment modalities, the prognosis for patients with unresectable conditions remains challenging. Issues such as liver failure, comorbidities and treatment-related toxicities, worsening Child-Pugh score and declining performance status frequently render these patients' ineligible for many therapeutic options.[21] These patient groups are regularly excluded from clinical trials, further limiting their access to potentially beneficial therapies.[22]

The rapid evolution of the therapeutic landscape for patients with advanced HCC has left many unanswered questions that will need to be addressed in future research. These include the choice and sequencing of treatments, the identification of biomarkers, combinations with locoregional therapies, and the development of newer agents. Furthermore, immunotherapy and bevacizumab possess a unique spectrum of adverse effects, which can sometimes restrict their utilization. This was shown in our

case, where the patient developed nephrotic syndrome, leading to the discontinuation of bevacizumab. The subsequent choice to proceed with monotherapy using an immunotherapeutic agent represented a well-considered decision made jointly by the physician and the patient. Hypertension and proteinuria stand out as the principal adverse effects associated with bevacizumab treatment. A comprehensive meta-analysis shows the incidence of proteinuria to be 13.3%.[23] Given the high risk of serious proteinuria, it's crucial to regularly monitor patients with cancer who are receiving bevacizumab. Utilizing spot urine protein and creatinine levels for screening, and 24-hour urine collection for quantification, is a reasonable approach. Additionally, it is important to seek advice from a nephrologist, consider antihypertensive treatment, and get a renal biopsy if proteinuria worsens or renal failure occurs.[24] Prompt management of side effects can help preserve the quality of life of the patient and allow them to consider alternate therapy.

Our case demonstrates the effectiveness of atezolizumab as a standalone immunotherapy in treating advanced hepatocellular carcinoma, persisting even after bevacizumab was discontinued. The patient has shown a consistent complete response in follow-up scans and remains in good health, marking an unusual scenario where sole immunotherapy achieves sustained disease control. As far as we are aware, this represents the first case report to describe such a response pattern with single-agent immunotherapy in this setting. This outcome suggests a need to reassess the role of monotherapy in HCC's therapeutic framework, validate these findings and determine their wider relevance. Additional aspects of our report include the rapid resolution of microangiopathy and nephrotic range proteinuria, adverse effects tied to VEGF inhibitors, and the drug's discontinuation.

The continued efficacy of atezolizumab as a monotherapy prompts debate regarding whether this represents a genuine long-term immunotherapeutic effect or an aftereffect of the previous VEGF inhibitor therapy. Future research is essential to evaluate the potential of single-agent therapies used in sequence or as continuous treatment modalities to lessen toxicity and expenditures, potentially enhancing patient outcomes. Identifying patients who would most benefit from such tailored monotherapy approaches remains a key area of interest.

Conclusion

In conclusion, this case highlights the potential of using single-agent therapies sequentially to manage HCC, offering a strategy that may reduce both toxicity and costs while maintaining therapeutic effectiveness. Close monitoring and accurate grading of proteinuria are essential when administering VEGF inhibitors, as discontinuing bevacizumab can alleviate adverse effects without diminishing the efficacy of subsequent immunotherapy. Further research is needed to identify which patients would most benefit from individualized monotherapy approaches and to determine the optimal sequencing of treatments in HCC management.

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