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Complete Pathological Response in Advanced Hepatocellular Carcinoma: *Be Brave*

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Abstract

Hepatocellular carcinoma (HCC) is the fourth most common malignancy and the third leading cause of cancer-related deaths among males in Macao population. Despite active preventative and screening measures, a majority of HCC patients present with advanced, unresectable disease. The treatment landscape for advanced HCC (aHCC) is rapidly evolving with the availability of novel agents. However, real-world evidence on the management of aHCC remains sparse, especially across different geographic areas, and there is currently no consensus guideline on optimal treatment sequence. In this report, we present the case of a male patient with large, multifocal aHCC, developing a complete pathological response (pCR) after a multidisciplinary onco-surgical approach.

Keywords

Advanced hepatocellular carcinoma; multidisciplinary; complete pathological response

1. Case Presentation

In January 2022, a 64-year-old Chinese male patient presented to the Emergency Department of our Center with a complaint of abdominal distension and constipation for 2 days. He had previously been informed of abnormal findings of elevated serum alpha-fetoprotein (AFP) levels and a suspicious liver lesion identified during a community health center screening ultrasound scan. The patient had a medical history significant for chronic hepatitis B and denied alcohol intake, drug use, or transfusions. Serologic testing confirmed hepatitis B surface antigen positive, with a HBV-DNA viral load of 959 IU/mL, and an AFP level of 118,310 ng/ml (reference <7.0 ng/mL). Computed tomography (CT) scan revealed a cirrhotic liver with a 17.4 × 11.7 cm contrast-enhanced mass in the right lobe involving segments 4, 5, 7, and 8, as well as a similar nodule about 1.2 × 1.0 cm in segment 6 **(Figure 1)**. The portal vein was patent, and multiple enlarged lymph nodes up to 1.3 × 0.9 cm were observed in the retroperitoneal space, along with a small amount of ascites and right pleural effusion. The patient had a Child-Pugh class A score of 5, a Model for End-Stage Liver Disease (MELD) score of 6, and an Eastern Cooperative Oncology Group (ECOG) performance score of 0. Upper gastrointestinal endoscopy did not reveal esophageal or gastric varices. The patient was initiated on entecavir at a daily dose of 0.5 mg. The multidisciplinary evaluation considered an aHCC not amenable to primary surgical resection and decided on an antiangiogenic plus immunotherapy combination approach. Treatment was started in March 2022, with atezolizumab, at a dose of 1200 mg intravenously paired with bevacizumab, at a dose of 7.5 mg/kg intravenously every 3 weeks. After 6 cycles, the patient's AFP level decreased from 118,310 to 19,923 ng/mL and further declined to 45.6 ng/mL after 14 cycles **(Figure 2)**. Atezolizumab was temporarily withheld for one cycle (cycle 7) due to an episode of diarrhea in August 2022. The dimensions of the liver tumor remained stable for the initial 3 months, and tumor reduction became evident only after 6

months of treatment, with a further reduction of the contrast-enhanced component after 9 months **(Figure 3)**.

Given the partial response observed with the antiangiogenic plus immunotherapy combination, the multidisciplinary evaluation decided to proceed with tumor resection. with an interval trans-arterial chemoembolization (TACE) and one cycle of bridge chemotherapy with intravenous oxaliplatin (85 mg/m^2) and low-dose oral capecitabine for tumor control during the pre-operative bevacizumab suspension. The calculated remnant liver volume was 29% of the total liver volume, and the functional remnant after excluding the tumor volume was 35%. Surgical resection was performed in July 2023. Intraoperative findings included a large exophytic tumor measuring 10 × 7 × 5 cm, occupying the surface of S4a, S8, and S7 with tight adhesion/invasion of the right hemidiaphragm. There was no ascites or peritoneal carcinomatosis. An extended right hepatectomy with en-bloc resection of the right hemidiaphragmatic area and cholecystectomy were performed. Pathology revealed tumor necrosis with irregular fibrous bands, without identified viable tissue in all planes of tumor section. The hepatic capsule was intact, and the raw surface was free of tumor. These findings confirmed a pCR **(Figure 4)**. To date, the AFP level has remained within the normal range **(Figure 2)**. However, 3 months post-surgery imaging was suspicious of local recurrence in the surgical margin, with an AFP level of 1.06 ng/mL, and a PIVKA-II level of 12.40 ng/mL (reference <28.6 ng/mL). The multidisciplinary evaluation decided to resume the antiangiogenic plus immunotherapy combination therapy. Under close monitoring, 7 months post-surgery, magnetic resonance imaging (MRI) showed no evidence of tumor recurrence. The patient remains asymptomatic at the time of writing this report in March 2024.

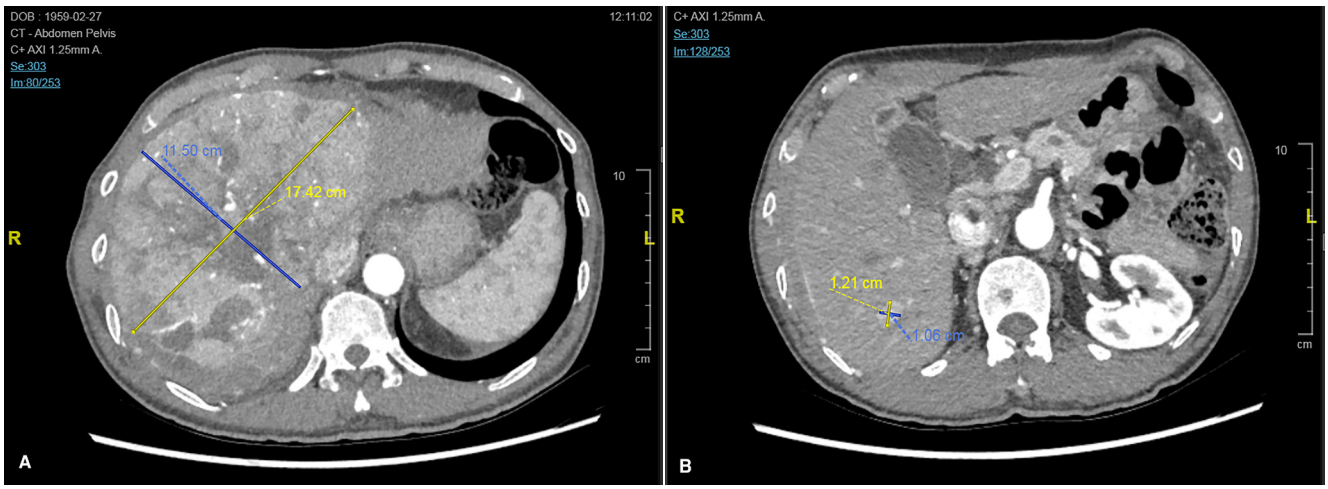

Figure 1: **(A)** CT showed a cirrhotic liver with a 17.4 × 11.7 cm contrast-enhanced mass in the right lobe involving segments 4, 5, 7, and 8 **(B)** A similar 1.2 × 1.0 cm nodule in segment 6.

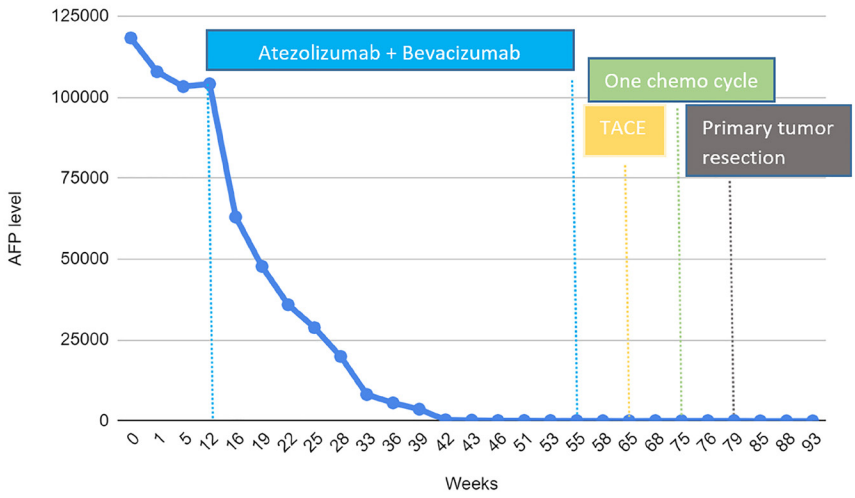

Figure 2: The level of alpha-fetoprotein (ng/ml) sharply decreased after 4 months of treatment.

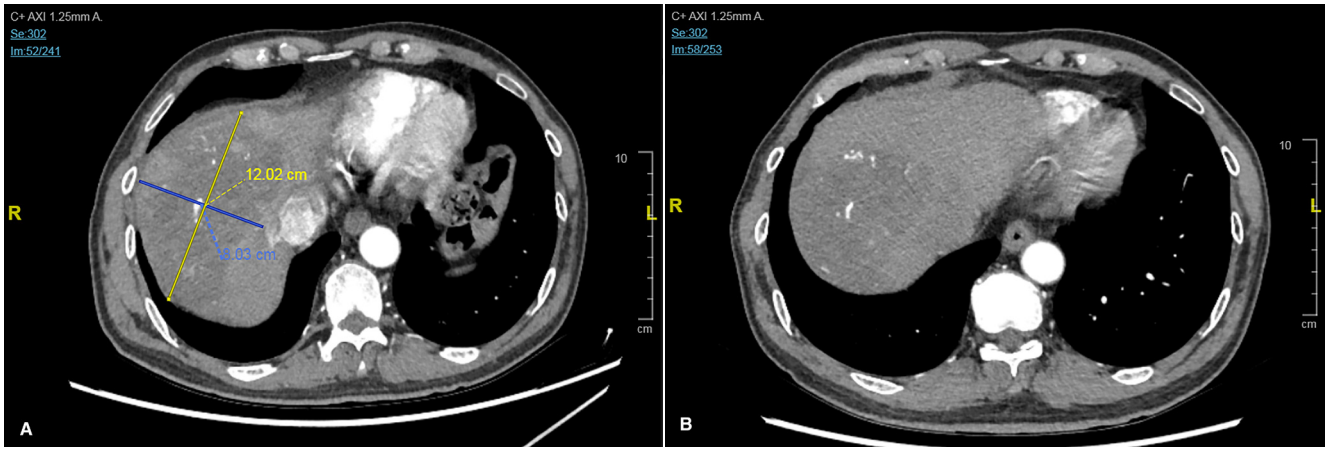

Figure 3: **(A)** Partial response after six months of treatment. The mass shrank to 12 × 8 cm **(B)** Further reduction of the contrast-enhanced component after nine months.

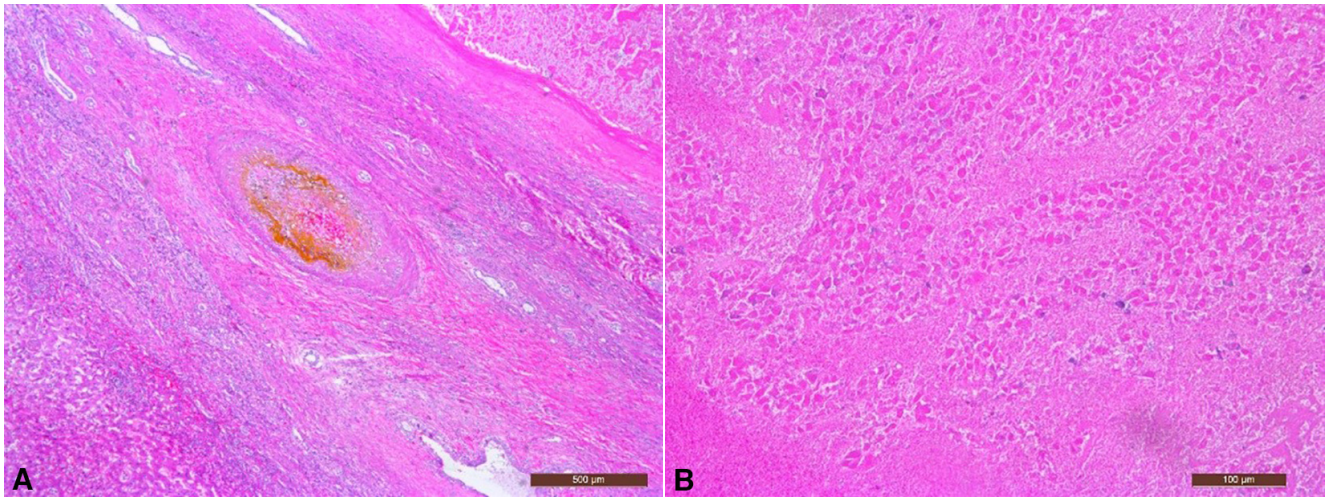

Figure 4: Histologic sections showed complete necrosis & fibrotic tissues with no viable tissue (hematoxylin-eosin stain) **(A)** 50x **(B)** 200x.

2. Discussion

HCC is a major health problem with a rising incidence in Macao [1], despite immunization programs being effective since 1989 [2]. The Macao Cancer Registry reports an incidence rate of 27.9 per 100,000 person-years, age-adjusted to the 2021 Macao male population, with a corresponding mortality rate of 22.6 per 100,000 person-years [1]. A majority of patients with HCC are diagnosed at an advanced, initially unresectable stage due to extensive extrahepatic spread, the presence of multifocal tumors, poor hepatic function, or major vessel involvement [3]. The treatment landscape for aHCC is rapidly evolving with the availability of novel agents, requiring a consensus therapeutic algorithm for optimum clinical outcomes [3]. An aHCC conversion rate of up to 13% has been reported for upfront systemic therapy [4]. This opens a window of opportunity for curative treatment despite an *ab initio* high tumor burden. However, almost 70% of HCC patients develop tumor recurrence within 5 years after surgery [5]. Complete pathological response is an infrequent occurrence in HCC [6], and even more rare in aHCC. Tyrosine kinase inhibitors (TKIs) alone were reported to yield CR (no imaging evidence of neoplastic disease) in 0.4% of aHCC cases [7]. A few single case reports in PubMed documented CR being achieved in aHCC treated with immunotherapy with PD-1 inhibition alone or in combination with TKIs [8–10]. The combination of immunotherapy with anti-angiogenesis has emerged as the standard therapy in aHCC, with an 8% CR rate [11]. In a real-world study from China, the combination of immunotherapy plus TKIs yielded pCR in 5% of initially unresectable HCC patients [12].

A French study showed that achieving a pCR versus non-pCR confers significantly improved outcomes with benefits in both overall survival (OS) and recurrence-free survival (RFS) in patients with HCC after liver resection (LR) and tends to be higher after liver transplantation (LT). Five-year OS rates were significantly higher in patients with pCR compared to those without (58% vs. 34% after LR; $p = 0.0006$ and 84% vs. 65% after LT; $p = 0.09$). The five-year RFS rates were also significantly higher in both groups (24% vs. 13% after LR; $p = 0.008$ and 94% vs. 73% after LT, $p = 0.007$) [13]. An American study showed that achieving a pCR versus non-pCR confers a significant improvement in both OS and RFS in patients with HCC after LT, with a mean five-year OS of 83.3% vs. 65.2% ($p < 0.05$), and five-year RFS of 80.6% vs. 62.5% ($p < 0.05$) [14]. Certainly, pCR can only be confirmed in resected or

transplanted patients for whom the curative treatment itself confers long-term survival benefits.

3. Conclusion

Devising policies on patient selection and sequencing of novel systemic therapies with prime concern for liver function preservation for aHCC is an unmet need. There is no single algorithm to achieve this goal [15]. Multidisciplinary management with an experienced, committed team is, therefore, imperative.

Authors' Contributions

I.K.S., C.V.H., J.C-M. conceptualization, methodology, data curation, writing—review and editing; I.K.S. writing—original draft preparation; I.K.S., C.V.H., systemic therapy; J.C-M. surgical resection; L.F.K. pathology report, slides review, and pathology pictures; all authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest

The authors declare no conflicts of interest.

Ethical Approval

The study has been approved by the national ethical committee and adhered to the guidelines of the Declaration of Helsinki.

Patient Consent

Informed written consent was obtained prior to submitting the manuscript.

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