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Case Report

Abscopal downstaging of intermediate stage hepatocellular via combination cryoablation and immunotherapy with complete pathologic response ☆

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ABSTRACT

The abscopal effect is a rare phenomenon characterized by disease regression in distant sites after tumoral locoregional therapy. Locoregional therapy, such as cryoablation, can induce an antitumor immunological response, potentially improving outcomes in cancer patients receiving immunotherapy. This report describes a patient with multifocal hepatocellular carcinoma who progressed through multiple locoregional therapies, was initially unresponsive to immunotherapy, and later achieved rapid and sustained disease regression with a combination cryoablation and immunotherapy. A 5-year sustained complete tumor response successfully bridged to liver transplantation.

Introduction

Liver transplantation is offered to patients with hepatocellular carcinoma (HCC) if they meet Milan criteria, which are based on imaging features of tumor size and number, and absence of vascular invasion. Liver transplant is oncologically sound in those who present outside these criteria if they can be successfully downstaged. In addition to anatomic features, tumor biology will determine recurrence rates after transplantation. The aggressiveness of the tumor is difficult to quantify, but extrahepatic or macrovascular extension, recurrence after locoregional therapy, poor histologic differentiation and vascular invasion, and persistently elevated alpha-fetoprotein (AFP) are among the indicators of unfavorable tumor biology [1].

☆ Competing Interests: Beau Toskich reports a relationship with Boston Scientific Corp that includes: consulting or advisory. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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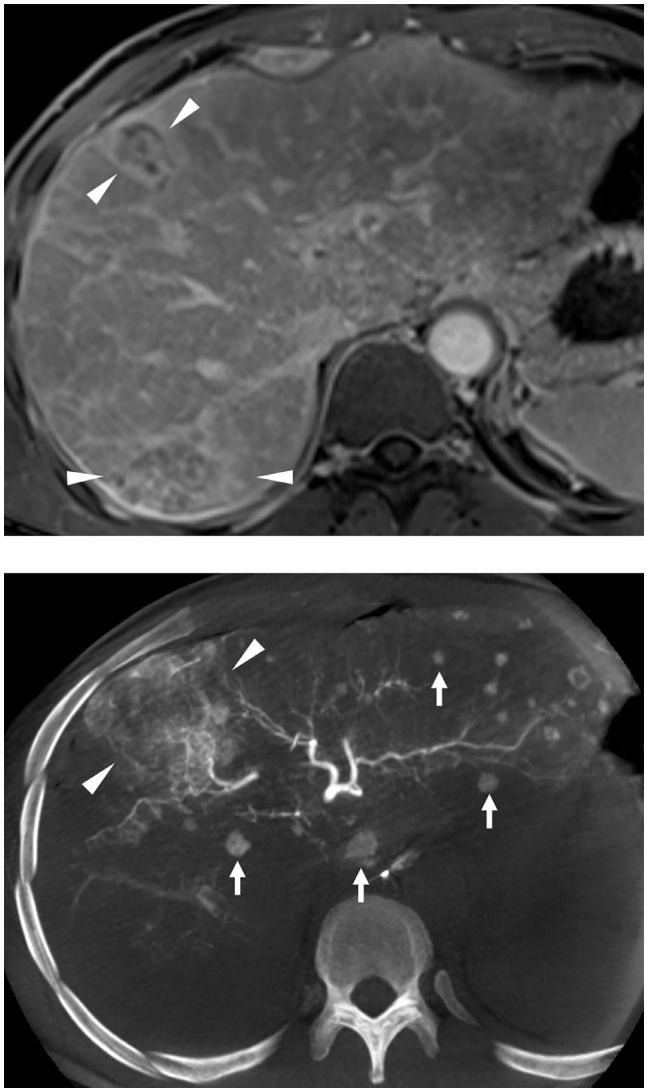

Fig. 1 – (A) MRI delayed postcontrast axial image shows 2 sites of hepatocellular carcinoma (arrowheads). (B) Cone-beam CT during angiographic evaluation of the liver done 6 weeks later shows rapid enlargement of HCC (arrowheads) and numerous enhancing nodules of multifocal HCC in both lobes of the liver (arrows) compared to the MRI. This pattern of disease is not well suited for locoregional therapy.

Downstaging is typically achieved with locoregional therapy (LRT). When this fails, the treatment is escalated to systemic agents [2], and the likelihood of successful downstaging significantly decreases.

This report presents a case of multifocal HCC with multiple recurrences despite repeated locoregional therapy that generated a strong abscopal effect with combination therapy of percutaneous cryoablation and an anti-PD-1 check-point inhibitor (Opdivo, nivolumab, Bristol Myers Squibb, NY). Liver transplantation was successfully performed after a prolonged complete anatomic and biochemical response with no viable tumor identified within the explanted liver.

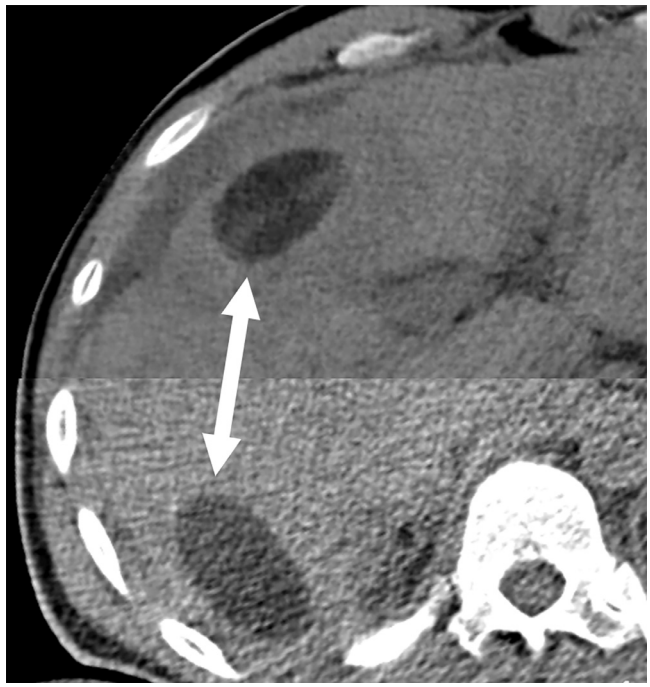

Fig. 2 – Composite of 2 CT scan images obtained immediately after partial cryoablation of 2 sites of multifocal HCC. The ice balls produced by the treatment (double arrow) appeared as ovoid hypodense zones that were smaller than the targeted zones of malignancy.

Case report

In 2017 a 43-year-old male was referred for LRT of multifocal HCC in the setting of hepatitis B virus treated with entecavir (HBV DNA undetectable) and HIV co-infection treated with efavirenz/emtricitabine/tenofovir (HIV-1 RNA undetectable). In 2007 cirrhosis was confirmed with biopsy. In 2016 he developed multifocal bilobar BCLC-B stage HCC and was treated with multiple percutaneous ablations and chemoembolizations over the following 2 years. He did not qualify for Yttrium-90 radioembolization because of extensive HCC multifocality. The tumor was outside Milan criteria and liver transplantation was denied.

At the end of 2017, he developed infiltrative hepatic progression that was not amenable to LRT (Fig. 1A). The serum AFP level was 45 ng/mL, sorafenib was started, and bland embolization of the liver was done while on sorafenib. Sorafenib was discontinued after 3 months because of disease progression, and nivolumab was started (immunotherapy standard of care at that time). The patient's AFP continued rising to 1014 ng/mL while on nivolumab (Fig. 1B). Six weeks after the nivolumab was started (no imaging obtained at that time) a partial cryoablation of 2 sites of HCC was performed with the specific objective of augmenting immune response by means of antigen presentation and local inflammation (Fig. 2). The AFP peaked at 1873 ng/mL. Two weeks after cryoablation AFP decreased to 593 and normalized 3 months after cryoablation. Four years after the cryoablation, the AFP remained normal at

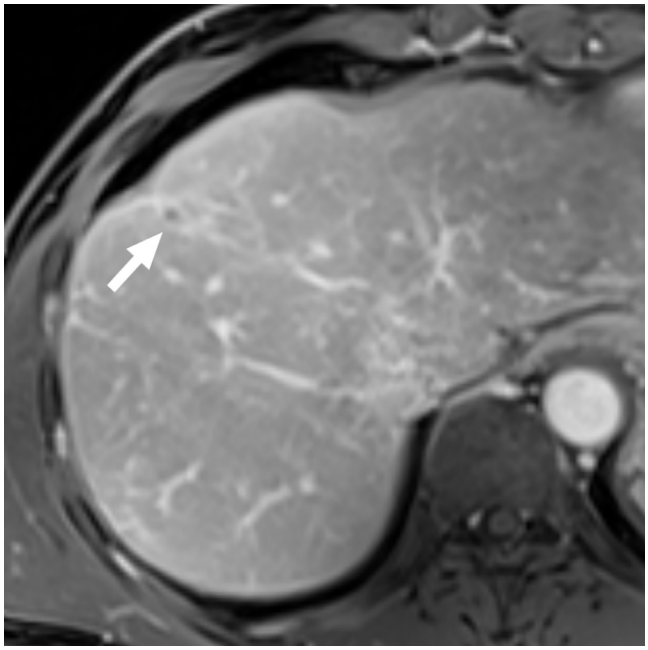

Fig. 3 – Axial MRI image after intravenous contrast obtained almost 5 years after cryoablation/immunotherapy shows a scar where a large tumor was partially treated with ablation (arrow). The liver was free of viable HCC.

1.3 ng/mL, the liver MRI showed a complete tumor response by mRECIST criteria, and imaging did not uncover any evidence for extrahepatic HCC (Figs. 3 and 4).

After more than 4 years without evidence of malignancy, he was placed on the active waitlist for liver transplantation. Five years after the liver cryoablation the patient received a full-sized orthotopic liver transplant with duct-to-duct biliary anastomosis, donated after circulatory death. Elevation of total bilirubin and alkaline phosphatase led to the diagnosis of ischemic cholangiopathy. A biliary anastomotic stricture was managed endoscopically with a fully covered metallic stent. Five months after transplantation the patient remained free of biochemical or imaging evidence for recurrent HCC.

Discussion

The abscopal effect refers to the regression of distant tumor induced by an immune-mediated effect of local tumor therapy. This phenomenon has been known since the 1950s, first observed after radiation therapy, but also seen with various LRT [3]. Preclinical data indicate that cryoablation has the potential to induce an immune response towards tumors by releasing tumor antigens and activating antitumor immunity. The mechanisms are under investigation, but it appears that changes in tumor microenvironment occur in association with an increase in effector cells and a decrease in immunosuppressive cells [4]. Cryoablation induces the release of multiple cytokines and leads to a tumor-specific immune response mediated by dendritic cells [5].

Cryoablation is a safe and effective therapy. In a randomized controlled trial, cryoablation for HCC ≤4 cm was shown to be similarly effective as radiofrequency ablation for tumors <3 cm but was shown to have a more favorable local tumor progression rate for tumors >3 cm (7.7% vs 18.2%). For cryoablation, the local tumor progression rates at 1, 2, and 3 years were 3%, 7%, and 7%. The recurrence-free survival, overall survival, and complication rates were comparable for cryoablation versus radiofrequency ablation [6]. It is generally acknowledged that cryoablation can rarely induce abscopal effects, but the combination with immunotherapy holds a promise that a systemic anticancer immune response can be potentiated by such combination, and abscopal effect can be seen with greater frequency [5].

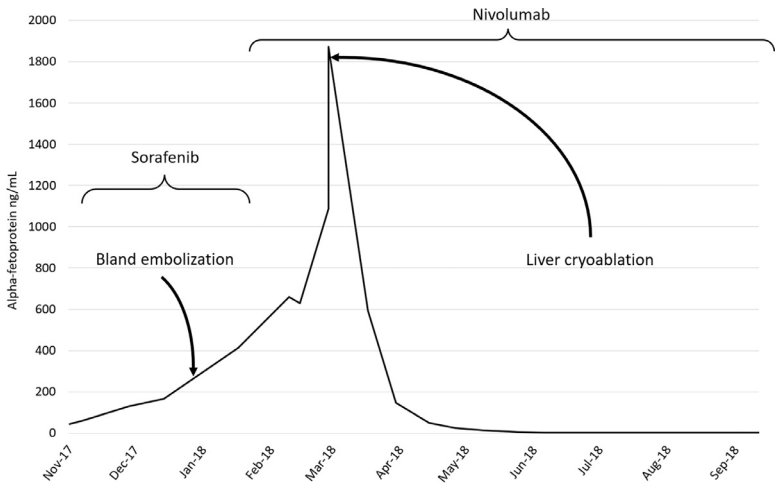

Fig. 4 – Annotated 10-month timeline of alpha-fetoprotein (AFP) levels. Notice the exponential increase in AFP despite combination sorafenib/bland embolization and later initiation of nivolumab. Immediately after cryoablation of HCC, without other changes in therapy, a rapid and sustained biochemical response was elicited. Follow-up imaging confirmed the complete response by mRECIST criteria. The timeline excludes most of the 5-year period before liver transplantation with consistently normal AFP and no imaging findings of tumor recurrence.

Current NCCN Guidelines for the management of unresectable HCC in those who do not qualify for transplant state that LRT is preferred. Systemic therapy, clinical trials, and best supportive care can be offered when LRT is not a consideration [2]. The current first-line systemic therapy, according to the BCLC guidelines, for infiltrative intermediate-stage, and advanced stage HCC is a combination of immunotherapy and antiangiogenesis with atezolizumab and bevacizumab. The reported objective response rate for atezolizumab + bevacizumab versus sorafenib is 29.8% versus 11.3% by RECIST 1.1 and 35.4% versus 13.9 by mRECIST criteria [7]. Even though the combined use of atezolizumab and bevacizumab results in better overall survival compared to sorafenib, most patients do not respond, and median survival remains less than 2 years [7]. The phase III HIMALAYA trial found that a combination of tremelimumab and durvalumab had a 22% decrease in risk of death compared to sorafenib and is another first-line systemic therapy option [8].

LRT has the potential to reverse the immunologic anergy that prevents response to immunotherapy in many patients and its use can be justified if done safely [9].

This case demonstrates that LRT, in addition to its direct tumoricidal effect, can trigger an immunological antitumor response, which can be considered an abscopal effect because of the response seen in intrahepatic multifocal tumors that were not subjected to cryoablation. Thawing after cryoablation releases antigens, which are taken up by dendritic cells, leading to further acquired immune activation [10]. When compared to other thermal ablation techniques, cryoablation is found to induce a higher immune response [11].

Given the immunological repercussions of LRT, some studies have assessed their potential combination with immunotherapy. Ghodara et al. reported the case of an 80-year-old male with squamous cell lung carcinoma stage IV with metastatic liver disease. Three months after hepatic Yttrium-90 ablative radioembolization a metastasis outside of the treatment field had regressed completely, indicating an abscopal effect [12]. In a single-center retrospective study of patients with intermediate/advanced HCC, the combination of LRT (TACE or radioembolization) and nivolumab was shown to be safe [13]. Another study determined that LRT and tremelimumab result in positive outcomes and can be considered a potential new treatment protocol for advanced HCC [14]. Initial reports of pulsed electric field therapy inducing the formation of tumor tertiary lymphoid structures suggest that new developments in LRT have the potential to achieve a more effective immune response and are expected to stimulate more investigation [15]. The case presented is unusual because the abscopal event was so profound and sustained for 5 years that the patient was declared eligible for liver transplantation, and in the short-term has remained without HCC recurrence.

Conclusion

Liver transplant eligibility can potentially be expanded with novel combination therapy capable of enhancing the immune response towards HCC. Although systemic therapy advances have been achieved, most patients are nonresponders. While abscopal events are rare, the addition of local therapy to immunotherapy is safe and can reverse immunologic anergy. The benefit of this therapeutic approach would be challenging to demonstrate in clinical trials and biomarkers to properly select patients are needed. Combination LRT and immunotherapy should be considered in patients who are refractory to standard-of-care systemic treatments after multidisciplinary tumor board discussion.

Patient consent

The patient's consent for the use of de-identified medical information for education and research purposes was filed in written form in the electronic medical record.

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