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Hepatocellular Carcinoma Regression After Cessation of Immunosuppressive Therapy

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Introduction

Hepatocellular carcinoma (HCC) is most often associated with underlying liver disease, such as chronic viral hepatitis, alcohol-induced liver injury, toxic hepatitis, and metabolic disorders. Approximately 70% to 80% of HCCs develop in patients with liver cirrhosis.¹ We here describe two patients who developed HCC while receiving immunosuppressive therapy for Crohn's disease and rheumatoid arthritis. Both patients showed measurable tumor regression, α -fetoprotein (AFP) decline, and prolonged survival after withdrawal of immunosuppressive therapy.

Case 1

The patient, a 40-year-old white man, had a 20-year history of Crohn's disease. During the course of his disease, he underwent multiple surgeries for strictures and a perforation. He had been treated with many medications, including infliximab, a chimeric (mouse/human) tumor necrosis factor (TNF) α antibody, and adalimumab, a fully human monoclonal anti-TNF- α antibody. After 11 years of treatment, the patient was noted to have elevated aminotransferases with negative hepatitis serologies. A few months later, he presented with abdominal pain. A computed tomography (CT) scan showed bleeding from the liver into the peritoneal cavity, for which he underwent a coil embolization. A month later, he returned to the hospital with worsening abdominal pain. A repeat CT showed an increasing hematoma. A laparoscopic left lateral segmentectomy was performed. Pathology revealed a 2.5-cm, moderately differentiated HCC with 40% necrosis and no vascular invasion. The margins were grossly negative. Serial imaging and AFP levels showed no evidence of recurrence until 5 years later, when the patient presented with rising AFP titers (172 ng/mL) and recurrent disease in his liver. A second resection confirmed poorly differentiated HCC in segments 2, 3, and 5. The AFP level was 2 ng/mL after the operation. During the next 2 years, his AFP increased to a peak of 832 ng/mL, and CT imaging showed progressive pulmonary nodules and liver lesions. Because of the patient's underlying Crohn's disease, he

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was initially watched. However, given continued disease progression, the patient began receiving sorafenib. After 5 months of therapy, he presented with a bowel perforation that required bowel resection, which resulted in a prolonged hospital course and recovery. His AFP level was 379 ng/mL at this time. Adalimumab was also discontinued at this time. Seven months later, his AFP decreased to 2 ng/mL, and a CT scan showed marked regression of his liver and lung lesions (Table 1). These areas remained quiescent for more than 12 months. The patient recently presented with a single focus of biopsy-proven HCC in a rib lesion and has since undergone localized radiation therapy.

Case 2

The second patient, a 74-year-old white man, had a 10-year history of rheumatoid arthritis and ulcerative colitis. For the treatment of his rheumatoid arthritis, he had received etanercept, a soluble TNF- α receptor fusion protein, for 5 years, followed by abatacept (cytotoxic T-lymphocyte antigen immunoglobulin [CTLA-4 Ig]), a fusion protein, which consists of CTLA that is linked to a modified heavy chain–constant region of human IgG1v, for 4 years. For his ulcerative colitis, he had been receiving mesalamine for 1 year. Four years into the abatacept treatment, the patient noted an 11-pound weight loss over a span of a few months. He also complained of right upper quadrant pain, night sweats, and increasing fatigue. This prompted an ultrasound, which showed numerous hepatic lesions; a CT scan of the abdomen confirmed liver masses that were highly suggestive of metastases, with the largest one in the right lobe measuring 56 cm. Biopsy of the lesions showed poorly differentiated HCC. Hepatitis serologies were negative. At this time, his AFP level was 97,932 ng/mL.

At the time of the diagnosis, abatacept was discontinued. Two months later, the patient's AFP level decreased to 38,000 ng/mL; in the two consecutive months, the AFP decreased to 2,623 ng/mL and then to 1,385 ng/mL. A CT scan performed at that time also showed a reduction in size of the right hepatic dominant lesion. The patient continued to be observed, with serial AFPs, and once the AFP plateaued, he was offered transarterial chemoembolization. Eight months after the diagnosis of HCC, the patient is asymptomatic; his most recent magnetic resonance imaging showed stable disease, with an AFP level of 820 ng/mL.

Discussion

HCC has been reported in at least two patients with Crohn's disease who received infliximab therapy. Similar to our patients, neither patient was reported to have cirrhosis or hepatitis.^{2,3} Immunosuppression has long been associated with various forms of malignancy. However, there are multiple reports refuting the notion that biologic agents, including infliximab, adalimumab,^{4,7} and abatacept,^{8–11} have any increased incidence of malignancy. Yet in the Wegener's Granulomatosis Etanercept Trial (WGET), patients with Wegener's granulomatosis had a statistically significant increase in the incidence of solid malignancies when treated with the TNF fusion protein etanercept (six solid cancers in 89 patients treated with etanercept plus cyclophosphamide versus no malignancy in 91 control patients treated with cyclophosphamide alone).¹² Also, a meta-analysis of studies using anti-TNF in patients

with rheumatoid arthritis reported an odds ratio for risk of malignancy of 3.3 (95% CI, 1.2 to 9.1)¹³ in patients treated with anti-TNF drugs versus those treated with placebo. TNF- α has been extensively studied as an anticancer agent (hence the name tumor necrosis factor), and there is substantial preclinical evidence that TNF- α has cytostatic and growth inhibitory effects on various tumors, including HCC.^{14,15} Unfortunately, systemic therapy with TNF- α has not been widely effective and has been associated with significant toxicity in clinical models.^{16,17} However, this may point to an underlying increased susceptibility in some patients, for whom TNF- α may be cytostatic and inhibition by anti-TNF agents may promote malignancy.

Targeting CTLA-4 has implications in both the treatment of autoimmunity and cancer. Abatacept is a fusion protein that is composed of the Fc region of IgG1 and CTLA-4. By binding to costimulatory molecules on antigen-presenting cells, abatacept prevents T cells from receiving these costimulatory signals during interaction with antigen-presenting cells, resulting in immune suppression. Conversely, ipilimumab, a CTLA-4 antagonist antibody, binds to activated T cells and inhibits the down regulatory signals, resulting in activation of T cells. As evidenced by the success of ipilimumab in the treatment of melanoma, alterations in the pathway can have significant effects on tumor immunity.¹⁸ In the case of abatacept, loss of costimulatory effects to cytotoxic T cells may be altering the effect on immune surveillance and hence promoting tumor growth.

There also could be other explanations for the regression that was observed in our patients, including spontaneous regression of HCC, which has been extensively reported in the literature as resulting from various causes, including ischemia,¹⁹ anoxia, and herbal medicines.²⁰ Interestingly, Ohba et al²¹ suggested a role for increased TNF- α in cases of spontaneous regression of hepatoma after radiotherapy as well.

In our two patients, HCC developed during receipt of potent immunosuppressive therapies for autoimmune diseases. Furthermore, our patients' tumors partially or near completely regressed when these agents were withdrawn. This suggests that immune surveillance played a role in the development of their cases of HCC. Both patients had a history of inflammatory bowel disease, which could theoretically put them at higher risk for GI-related complications from sorafenib, the most commonly prescribed drug for HCC. The first patient developed a bowel perforation, and the disease regression was a fortuitous finding after medications were stopped in the context of a severe complication. In the second patient, a deliberate decision was made to watch for regression while the patient was not receiving therapy. Both patients have achieved prolonged disease stability. On the basis of these patient cases, we believe that in patients receiving immunosuppressive agents during treatment of HCC and perhaps other malignancies, a trial period without immunosuppressive agents as anticancer therapy may be appropriate if the patient presents in a noncurative paradigm.

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Table 1

Clinical Responses

Characteristic/Response	June 2008	September 2009	January/February 2011	July 2011	February 2012	June/July 2012
Patient 1						
AFP (ng/mL)	6	3	832	379	2	2
Tumor size (mm)	0	0	26	20	0	0
Response assessment	NA	NA	Baseline	Stable disease	Complete response	Complete response
Patient 2	May/June 2012	July 2012	August 2012	September 2012	January 2013	
AFP (ng/mL)	97,932	38,000	2,623	1,385	722	
Tumor size (mm)	56	38	NA	42	40	
Response assessment	Baseline	Partial response	NA	Partial response	Partial response	

Abbreviations: AFP, α -fetoprotein; NA, not available.