

[CASE REPORT]

Accelerated Progression of Hepatocellular Carcinoma during Immunosuppressive Therapy with Abatacept for Rheumatoid Arthritis

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Abstract:

Abatacept, a cytotoxic T lymphocyte antigen-4 immunoglobulin recombinant fusion protein, is an immunosuppressive agent indicated for rheumatoid arthritis. Although no significant increase in malignancy has been reported in abatacept-treated patients, whether or not abatacept accelerates tumor progression in specific cancer types remains unclear. We herein report a 66-year-old woman who showed unusually rapid progression of hepatocellular carcinoma following abatacept therapy for rheumatoid arthritis. Abatacept was speculated to have accelerated her hepatocellular carcinoma progression in the setting of her preexisting risk factors: autoimmune hepatitis and long-term methotrexate use. We propose close tumor surveillance be performed during abatacept therapy, especially for high-risk patients.

Key words: hepatocellular carcinoma, cancer immunity, immunosuppressive therapy, abatacept, cytotoxic T lymphocyte antigen-4 (CTLA-4)

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Introduction

Cytotoxic T lymphocyte antigen immunoglobulin-4 (CTLA-4) is one of the most studied checkpoint molecules that induce T-cell tolerance at the priming phase (1, 2). Strategies of targeting CTLA-4 have been clinically applied for controlling both autoimmune disease and cancer. Abatacept (a fusion protein of CTLA-4 and IgG1 Fc domain) and ipilimumab (anti-CTLA-4 antibody) are positive and negative modulators of the CTLA-4-mediated pathway, respectively; the former is indicated for rheumatoid arthritis (RA) and the latter for metastatic melanoma (3, 4). Despite no previous reports having described a significant increase in the risk for malignancy in association with abatacept (5-7), the immunosuppressive profile of abatacept should still be taken into account, especially for patients predisposed to

cancer.

We herein report a case of accelerated progression of hepatocellular carcinoma (HCC) during immunosuppressive therapy with abatacept for RA and discuss the possible etiology of the present case.

Case Report

The patient was a 66-year-old woman with an 8-year history of RA and Sjögren's syndrome. She had been treated with methotrexate (MTX) (4 mg/week) for 5 years and bucillamine (200 mg/day) for 4 years before she was referred to our department with abdominal distention at 65 years of age. She was diagnosed with liver cirrhosis classified as Child-Pugh class C (10 points). Laboratory tests revealed positive anti-nuclear antibodies (x84.7; normal range: <20) and elevated serum IgG levels (2,129 mg/dL; normal

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Table. Laboratory Values at the Time of Presentation to Our Department.

Variables	Present case	Normal range
PT (INR)	1.70	0.8-1.2
Albumin (g/dL)	2.3	3.9-5.1
Total bilirubin (mg/dL)	2.0	0.3-1.3
AST (IU/L)	34	12-30
ALT (IU/L)	17	7-27
γ -GTP (IU/L)	44	7-29
ALP (IU/L)	413	115-359
AFP (ng/mL)	4.7	<15
PIVKA-II (mAU/mL)	16	<40

PT: prothrombin time, AST: alanine aminotransferase, ALT: aspartate aminotransferase, γ -GTP: γ -glutamyltransferase, ALP: alkaline phosphatase, AFP: alpha-fetoprotein, PIVKA-II: protein induced by vitamin K absence or antagonist-II

range: 820-1,840 mg/dL). Viral serology was negative for hepatitis B surface antigen (HBsAg), anti-hepatitis B surface antibody (anti-HBs), anti-hepatitis B core antibody (anti-HBc), and anti-hepatitis C virus antibody (anti-HCV). Neither alpha-fetoprotein (AFP) nor protein induced by vitamin K absence-II (PIVKA-II) levels were elevated. The values of liver function tests and tumor markers at the time of presentation are summarized in Table.

Since her liver function had already deteriorated before the administration of MTX (data not shown), autoimmune hepatitis rather than the long-term use of MTX was considered as the primary etiology of liver cirrhosis. However, MTX was speculated to be involved in the worsening of her progressive liver dysfunction.

An initial imaging evaluation of her liver by abdominal ultrasound (US) showed hepatic surface nodularity, atrophy of the right lobe, hypertrophy of the left lobe, and abdominal fluid retention. Although contrast-enhanced computed tomography (CE-CT) revealed a slightly hyperdense lesion at segment VIII in the arterial phase (Fig. 1A), HCC was not suspected at this point because of the absence of a washout appearance in the delayed phase of CE-CT and no detection of tumor by CE-US (not shown). We decided to carefully watch the lesion. Because of the inadequate control of RA-related joint pain, MTX and bucillamine were discontinued and replaced with abatacept (10 mg/kg, every 4 weeks). Abatacept markedly improved the patient's joint pain and swelling. Six months after the administration of abatacept, however, CE-CT showed the progression of the above-mentioned hepatic lesion from 6 to 13 mm, which was clearly hyperdense in the arterial phase (Fig. 1B, upper panel) and hypodense in the delayed phase (Fig. 1B, middle panel). HCC was diagnosed, with confirmation made by CE-US (Fig. 1B, lower panel).

Radiofrequency ablation (RFA) was successfully performed. CE-CT performed three months after RFA confirmed no viable lesions (Fig. 2A). Six months later, however, follow-up CE-CT showed the marked recurrence of

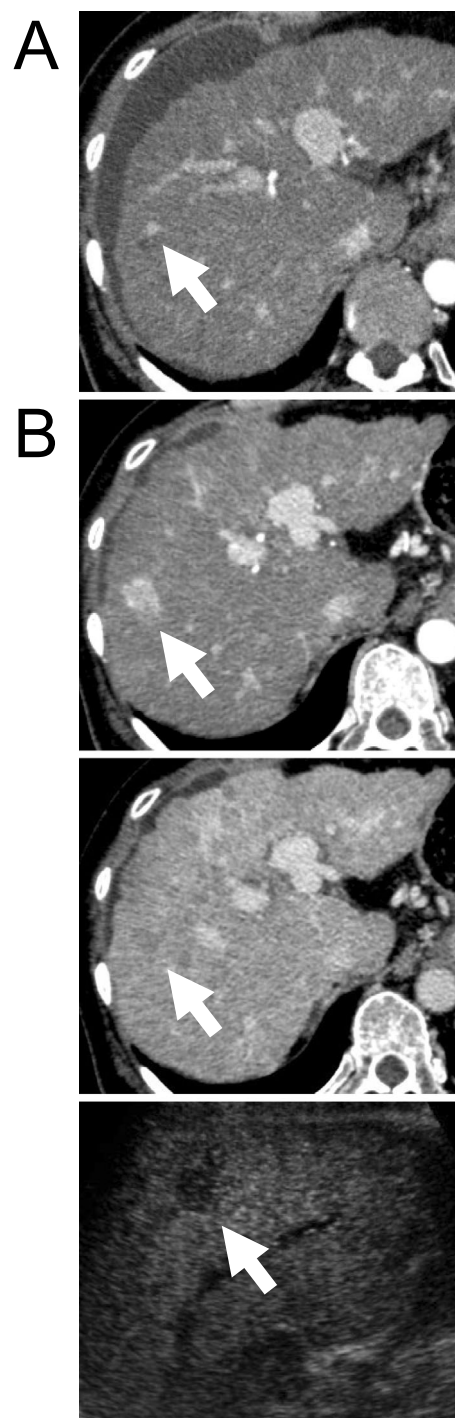


Figure 1. Development of HCC after initiating abatacept therapy. (A) Initial CE-CT showed a slight hyperdense lesion at segment VIII in the arterial phase (arrow). (B) Six months after initiating abatacept therapy, CE-CT showed a 13-mm liver lesion at segment VIII, which was clearly hyperdense in the arterial phase (arrow in the upper panel) and hypodense in the delayed phase (arrow in the middle panel). Kupffer-phase imaging by CE-US showed the corresponding lesion as a hypoechoic nodule (arrow in the lower panel). HCC: hepatocellular carcinoma, CE-CT: contrast-enhanced computed tomography, US: ultrasound

HCC near the ablated lesion (Fig. 2B). At this point, abatacept was discontinued due to the concern that it may have

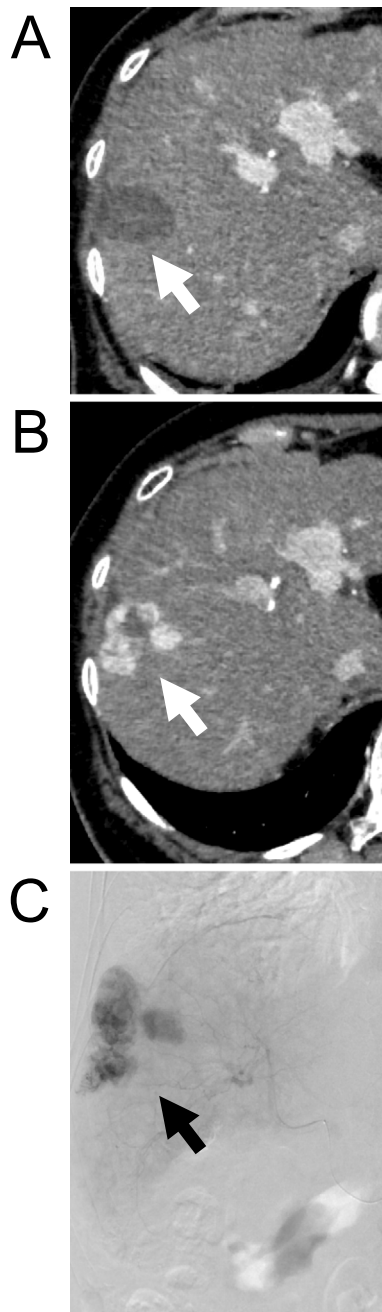


Figure 2. Early massive recurrence after RFA during continuation of abatacept. (A) Three months after RFA, CE-CT detected no recurrence (arrow). (B) Nine months after RFA, CE-CT revealed marked recurrence at the RFA site (arrow). (C) Hepatic arteriography demonstrated a large hypervascular tumor (arrow), a finding compatible with HCC recurrence. RFA: radiofrequency ablation, HCC: hepatocellular carcinoma

played a role in the progression of HCC. Transcatheter arterial chemoembolization (TACE) was performed (Fig. 2C). Two months later, the patient complained of exacerbated joint tenderness and swelling following the discontinuation of abatacept and strongly demanded that abatacept be resumed. After a careful discussion about the possible role of abatacept in the progression of HCC, abatacept was resumed to maximize her quality of life. One month after abatacept

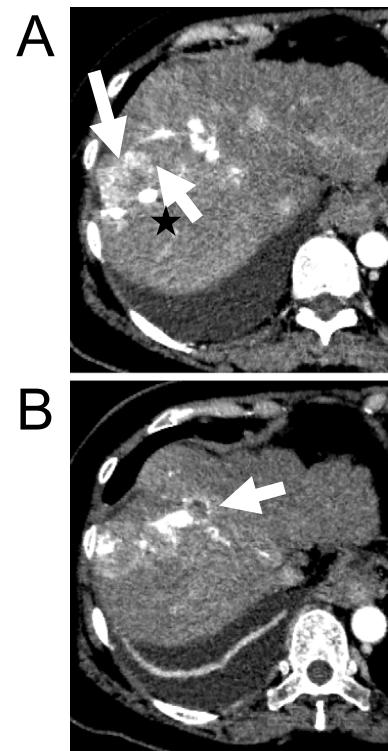


Figure 3. Rapid and aggressive progression of HCC. (A) Three months after TACE, CE-CT showed diffusely growing recurrent HCC (arrow). The black asterisk denotes a dense lipiodol deposit introduced by previous TACE. (B) Tumor invasion from the diffuse recurrent lesion to the intrahepatic portal vein was revealed by the same study (arrow). In both panels, massive ascites was demonstrated. HCC: hepatocellular carcinoma, TACE: transcatheter arterial chemoembolization

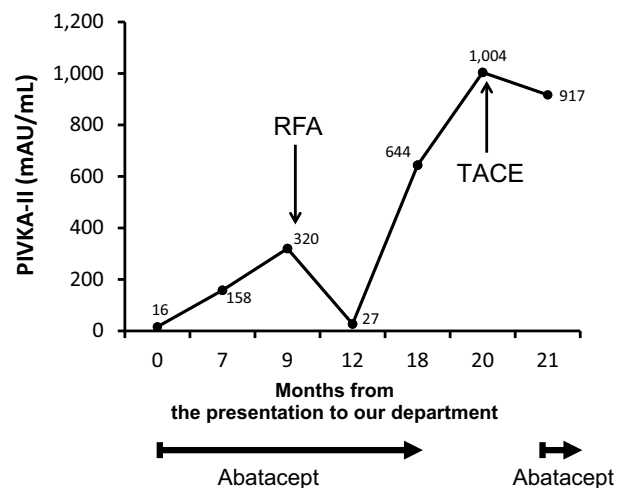


Figure 4. Serial changes in PIVKA-II in the present case. The PIVKA-II level increased parallel with HCC progression. PIVKA-II: protein induced by vitamin K absence-II, HCC: hepatocellular carcinoma

resumption, CT showed the unusually rapid progression of HCC, characterized by a diffusely growing viable lesion (Fig. 3A), aggressive invasion to intrahepatic portal vein

(Fig. 3B), and massive ascites (Fig. 3). As shown in Fig. 4, throughout the entire course, PIVKA-II increased substantially in parallel with the HCC progression. One month later, the patient presented to the emergency department with acute abdominal pain with hypovolemic shock and died the same day. A postmortem examination confirmed the ruptured HCC with hemorrhagic ascites, lung metastasis, and pelvic dissemination. Histopathology demonstrated poorly differentiated HCC. Sarcomatous changes that might have been caused by RFA and result in an aggressive clinical course (8) were not observed.

Discussion

Great clinical achievements in cancer immunotherapy have clearly proven the ability of the immune system to eradicate tumor cells (4). As such, the association between immunosuppressive therapy and an altered risk of malignancy has been actively discussed (5-7). In a recent study, the Wegener's granulomatosis etanercept trial research group showed that etanercept, a tumor necrosis factor antagonist, was associated with an increased incidence of solid malignancies (9).

Abatacept is a recombinant fusion protein comprising the extracellular domain of CTLA-4 and a fragment of the Fc domain of human IgG1 and is a member of a new class of drug used for the treatment of RA. Abatacept attenuates the co-stimulatory signal between T lymphocytes and antigen-presenting cells by selectively inhibiting the CD80 or CD86-CD28 co-stimulatory signal required for full T-cell activation (1, 2). The anti-CTLA-4-blocking antibody ipilimumab, a functional counterpart of abatacept, was shown to prolong the survival of patients with metastatic melanoma (4). Importantly, a recent report showed that another anti-CTLA-4 antibody, tremelimumab, also prolonged the survival for patients with HCC (10). Therefore, the immunosuppressive nature of abatacept, which is opposite that of ipilimumab and tremelimumab, may theoretically attenuate cancer immunosurveillance and lead to the acceleration of the progression of malignancy. Indeed, several case reports have documented the possible association of abatacept with tumor growth (11-14), although several studies have shown that abatacept was not associated with a statistically significant increase in the risk of malignancy (5-7). Regarding HCC, to our knowledge, there is only one report describing the spontaneous regression of HCC after the discontinuation of abatacept, and it unfortunately did not include any imaging results (14). In the present case, different imaging studies at multiple time points and a postmortem examination clearly demonstrated an unusually aggressive clinical course of HCC that contrasts with those in a previous report (15), suggesting the critical role of abatacept in rapid tumor progression, presumably by attenuating immune surveillance.

HCC most often develops as a consequence of chronic hepatitis or cirrhosis (16). Our patient had chronic hepatic inflammation caused by autoimmune hepatitis. The long-

term use of MTX may have contributed to the progression of liver damage and fibrosis, ultimately leading to cirrhosis. A strong immunosuppressive force driven by abatacept, combined with these predisposing factors, might accelerate the progression of HCC. Furthermore, because the immune environment of the liver is biased to tolerance (17), this inherent immunosuppressive property unique to the liver might also have an additive effect on abatacept.

Despite the limitations inherent to this single case report, we believe that our findings provide important information on the safety of abatacept for patients with underlying liver disease. During treatment with abatacept, close monitoring of the tumor and its progression should be considered, especially for the high-risk patients. The further accumulation of case reports is warranted to validate our observations and clarify the corresponding immunopathogenic mechanisms for HCC progression.

The authors state that they have no Conflict of Interest (COI).

References

1. Genovese MC, Becker JC, Schiff M, et al. Abatacept for rheumatoid arthritis refractory to tumor necrosis factor α inhibition. *New Engl J Med* **353**: 1114-1123, 2005.
2. Westhovens R, Robles M, Ximenes AC, et al. Clinical efficacy and safety of abatacept in methotrexate-naïve patients with early rheumatoid arthritis and poor prognostic factors. *Ann Rheum Dis* **68**: 1870-1877, 2009.
3. Gartlehner G, Hansen RA, Jonas BL, Thieda P, Lohr KN. The comparative efficacy and safety of biologics for the treatment of rheumatoid arthritis: a systematic review and metaanalysis. *J Rheumatol* **33**: 2398-2408, 2006.
4. Lipson EJ, Drake CG. Ipilimumab: an anti-CTLA-4 antibody for metastatic melanoma. *Clin Cancer Res* **17**: 6958-6962, 2011.
5. Weinblatt M, Combe B, Covucci A, Aranda R, Becker JC, Keystone E. Safety of the selective costimulation modulator abatacept in rheumatoid arthritis patients receiving background biologic and nonbiologic disease modifying antirheumatic drugs: a one year randomized, placebo-controlled study. *Arthritis Rheumatol* **54**: 2807-2816, 2006.
6. Kremer JM, Genant HK, Moreland LW, et al. Effects of abatacept in patients with methotrexate-resistant active rheumatoid arthritis: a randomized trial. *Ann Intern Med* **144**: 865-876, 2006.
7. Simon TA, Smitten AL, Franklin J, et al. Malignancies in the rheumatoid arthritis abatacept clinical development programme: an epidemiological assessment. *Ann Rheum Dis* **68**: 1819-1826, 2009.
8. Koda M, Maeda Y, Matsunaga Y, et al. Hepatocellular carcinoma with sarcomatous change arising after radiofrequency ablation for well-differentiated hepatocellular carcinoma. *Hepatol Res* **27**: 163-167, 2003.
9. Wegener's GE. Etanercept plus standard therapy for Wegener's granulomatosis. *New Engl J Med* **352**: 351-361, 2005.
10. Duffy AG, Ulahannan SV, Makorova-Rusher O, et al. Tremelimumab in combination with ablation in patients with advanced hepatocellular carcinoma. *J Hepatol* **66**: 545-551, 2017.
11. Corcoran MA, Olson JM, Hecht C, Knezevich S, Vary JC. Eruptive squamous cell carcinoma in a patient receiving abatacept for rheumatoid arthritis. *J Am Acad Dermatol* **69**: e178-e179, 2013.
12. Olivo D, Grembiale RD, Tallarigo F, Russo E, De Sarro G, Ursini F. Kaposi's sarcoma after T-cell costimulation blockade with

- abatacept in rheumatoid arthritis: a case report. *J Clin Pharm Ther* **42**: 367-369, 2017.
13. Deidda A, Pisanu C, Garau D, et al. Squamous cell carcinoma of the tongue following therapy of rheumatoid arthritis with abatacept. *Clin Case Rep* **2**: 66-69, 2014.
 14. Kumar A, Le DT. Hepatocellular carcinoma regression after cessation of immunosuppressive therapy. *J Clin Oncol* **34**: e90-e92, 2014.
 15. Shiina S, Teratani T, Obi S, et al. A randomized controlled trial of radiofrequency ablation with ethanol injection for small hepatocellular carcinoma. *Gastroenterology* **129**: 122-130, 2005.
 16. El-Serag HB. Epidemiology of viral hepatitis and hepatocellular carcinoma. *Gastroenterology* **142**: 1264-1273, 2012.
 17. Crispe IN. Immune tolerance in liver disease. *Hepatology* **60**: 2109-2117, 2014.

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