

Seroconversion of Hbsag in Melanoma Patient with Hepatitis B Treated with Checkpoint Inhibitors: A Case Report

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Abstract

Based on remarkable and sustained antitumor activity, the anti-CTLA-4 antibody ipilimumab, and anti-PD1 antibodies nivolumab and pembrolizumab have been approved for treatment of advanced melanoma. As checkpoint blockade is associated with potentially serious immune-related adverse events, including autoimmune hepatitis, clinical trials evaluating these agents have excluded patients with chronic hepatitis B virus infection. Herein, we describe one patient with advanced melanoma and concomitant HBV infections experiencing seroconversion of HBsAg after treatment with combination of PD-1 and CTLA-4 blockade.

Keywords: Anti-CTLA-4; Anti-PD-1; Ipilimumab; Melanoma; Pembrolizumab; HBV; Safety

Abbreviations: ALT: Alanine Transaminase; AST: Aspartate Aminotransferase; CTLA-4: Cytotoxic T-lymphocyte-Associated Protein 4; CR: Complete Response; HBV: Hepatitis B Virus; HCV: Hepatitis C Virus; HIV: Human Immunodeficiency Virus; HBsAb: anti-HBs Antibodies; HBsAg: Hepatitis B Virus Surface Antigen; HBeAg: Hepatitis B Virus e Antigen; HBeAb: anti-HBe antibodies; HBcAb: anti-hepatitis B virus c Antibody; IFN: Interferon; MRI: Magnetic Resonance Imaging; PET: Positron Emission Tomography; PD-1: Programmed Cell Death Protein-1; PD-L1: Programmed Death Ligand-1

Introduction

The combination of PD-1 and CTLA-4 blockade appeared to outperform each as a single agent in regards to response rate and progression free survival as first line treatment of advanced melanoma [1,2]. CTLA-4 and PD-1/PD-L1 play important roles in regulating the immune system; hence, patients with autoimmune diseases requiring systemic immunosuppression or patients with HBV/HCV or HIV infection have been excluded from studies evaluating these agents over concerns about inadvertent augmentation of infectious or inflammatory activity. We report one patient with advanced melanoma and concomitant HBV infection treated with combination of pembrolizumab and ipilimumab. The patient obtained complete remission and were well tolerated. No exacerbation of underlying HBV infection was observed. It's more exciting that seroconversion of HBsAg was observed after 4 cycles of therapy, which is infrequently achievable with the currently available anti-HBV agents [3]. To our knowledge, this is the first report of advanced melanoma patient with HBV infection to be treated with combination of PD-1 and CTLA-4 blockade.

Case Report

A 32-year-old man was diagnosed with malignant melanoma in situ on his left dorsal hand in January 2014. Following negative wide excision, no adjuvant therapy was offered. He was followed closely and presented with subcutaneous nodule of the left forearm in July 2014. PET/CT scan confirmed active metabolically left axillary lymph nodes. The patient underwent re-excision of a local recurrence and lymph node dissection that revealed metastatic melanoma in 1 of 22 lymph nodes without extracapsular extension. Molecular testing confirmed BRAF V600E mutation.

Prior history was notable for HBV infection documented in July 2014 following mildly elevated ALT (49.5 IU/L; normal range, 0 to 40 IU/L) with AST in normal range. HBV specific characteristics manifested as

positive HBsAg, positive HBeAb, positive HBcAb and negative HBeAg. HBV DNA was undetectable by polymerase chain reaction.

He received adjuvant high-dose interferon (IFN) between August 2014 and February 2015. During which time liver transaminases elevated: ALT 90.1 IU/L (normal range, 0-40 IU/L), AST 60.8 IU/L (normal range, 0-45 IU/L), which was considered to be secondary to interferon as HBV serological markers and DNA level remained unchanged. The transaminase returned to normal after discontinuation of IFN due to development of multiple lung metastases.

He was offered 1 doses of ipilimumab (3 mg/kg every 3 weeks) on March 27; 2015. As pembrolizumab was available in Hong Kong, China, he then received four cycles of pembrolizumab combined with ipilimumab therapy during April to July in 2015. Pembrolizumab 1 mg/kg was given on day 1 followed by ipilimumab 3 mg/kg on day 2. Treatment was repeated every 3 weeks.

Patient experienced grade 2 rash and pruritus after the first cycle of combined therapy. Liver function test indicated grade 2 elevation of AST (77.9 U/L), ALT (132 U/L) after 2 cycles of combined therapy, which was believed to be autoimmune and unrelated to his HBV as HBV serological markers remained unchanged and no viral replication was detected (Table 1 and Figure 1). Transaminase levels soon recovered

Time	HBsAg	HBsAb (IU/L)	HBeAg	HBeAb	HBcAb
2015-03-27	+	-	-	+	+
2015-04-15	+	-	-	+	+
2015-04-23	+	-	-	+	+
2015-06-02	+	7.0(-)	-	+	+
2015-07-14	-	10.1(+)	-	+	+
2015-09-15	-	10.6(+)	-	+	+
2015-11-10	-	18.3(+)	-	+	+
2016-01-25	-	21.53(+)	-	+	+

Table 1: Change of HBV serological markers.

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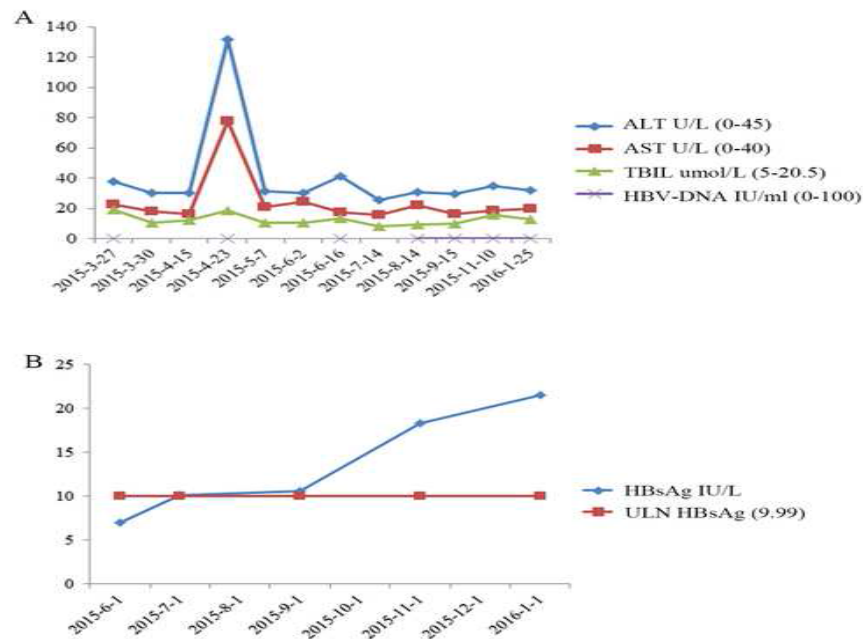


Figure 1: A: Changes of liver function and HBV-DNA load during the treatment; B: With the treatment, HBsAg converted from negative to positive, and increased gradually.

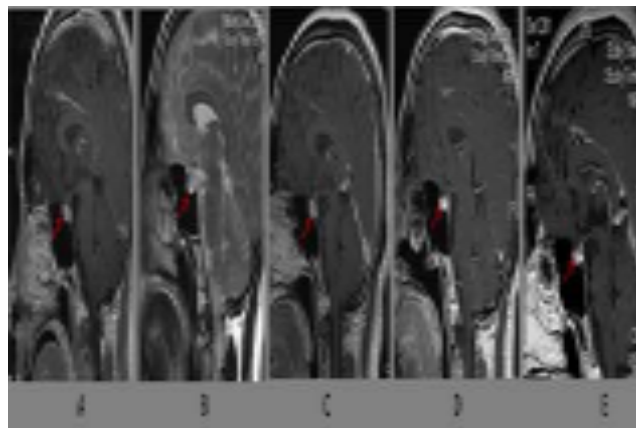


Figure 2: A: normal size of the pituitary gland in baseline; B: enlarged pituitary after 2 cycles of combined therapy; C: Enlarged pituitary gland after 4 cycles of combined therapy; C and D: Pituitary gland returned to normal size during the maintenance therapy.

and remained normal throughout the remainder of the therapy without special treatment. The patient complained of a headache and fatigue after the second infusion. Brain metastases were ruled out using magnetic resonance imaging (MRI). MRI did reveal a small nodule on the enlarged pituitary gland (Figure 2). An endocrine function test revealed a decrease in thyroid-stimulating hormone, adrenocorticotropic hormone, and plasma cortisol levels. However, triiodothyronine (T3) and thyroxin (T4) were in normal range. Immune-related hypophysitis was diagnosed; symptoms relieved soon after hormone replacement therapy with prednisone. After 3 doses of combined therapy, serological test showed that HBsAg disappeared and HBsAb turned to be positive. This indicates the recovery from the chronic HBV infection and is associated with a life-long immunity against HBV [4]. Restaging scans showed significant reduction in size and number of pulmonary lesions after 4 doses of combined therapy (Figure 3).

Considering the treatment is effective, he accepted maintenance

therapy with pembrolizumab 2 mg/kg Q8W for three doses during September to January in 2016. He was well tolerated without other adverse event except for secondary adrenocortical insufficiency and pruritus. HBsAg seroconversion was maintained during follow-up. He obtained complete response (CR) in November 2015 and CR was confirmed in January 2016. He is still being followed up.

Discussion

As patients with chronic viral (HBV, HCV, and HIV) infection have been excluded from clinical trials, the application of CTLA-4 inhibitor or PD-1 inhibitors in that patient population has been reported only in sporadic cases [5-8]. Combined immune checkpoint blockade is considered to be more effective but much more toxic, especially hepatic toxic events which is autoimmune related [1,2]. We report a melanoma patient with HBV infection treated with combination of pembrolizumab and ipilimumab who obtained complete remission and with good

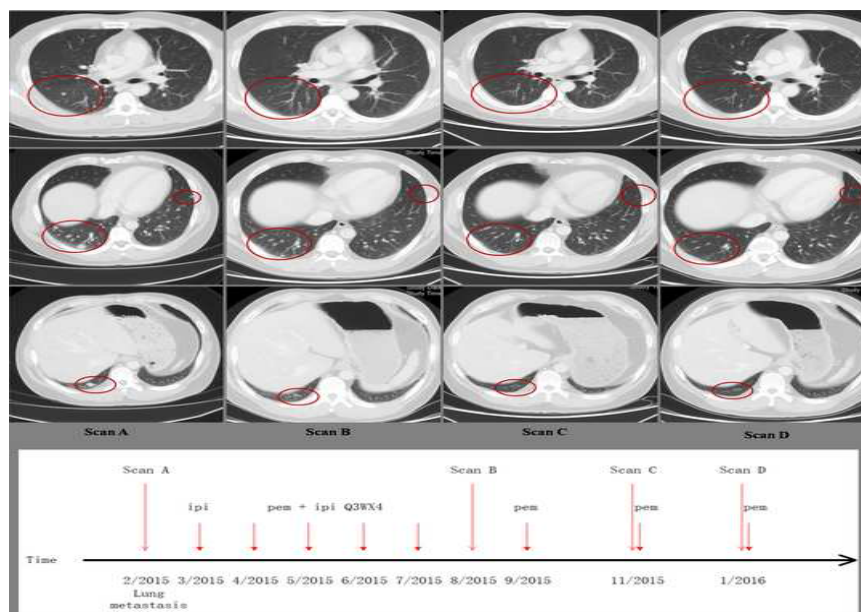


Figure 3: Changes in tumor size and Treatment schedule. After 4 cycles of combined therapy, metastatic lung lesions had decreased in size and number significantly (A-B). After 1 cycle of maintenance therapy, lung metastases have disappeared on CT scan (B-C). CR is maintained during the maintenance therapy (C-D).

tolerance. No severe hepatic toxicity and virus reactivation occurred. On the contrary, he recovered from the chronic HBV infection. To our knowledge, this is the first report of advanced melanoma patients with HBV infection to be treated with combination of PD-1 and CTLA-4 blockade.

The clearance of HBsAg and the appearance of HBsAb, defined as seroconversion, are now considered to be the most desirable clinical endpoints in patients with chronic HBV infection [3]. Unfortunately, with the currently available anti-HBV agents, the probability of HBsAg clearance is not more than 7%, the probability of seroconversion is even lower, especially in HBeAg negative patients [3]. The CTLA-4 and PD-1/PD-L1 pathway are known to be upregulated in chronic HBV infection where it may attenuate T-cell or NK-cell mediated antiviral host immune responses, thereby sustaining chronic infection [9,10]. Blocking CTLA-4 and PD-1/PD-L1 signaling may have benefit in chronic HBV infection. We observed HBsAg seroconversion after CTLA-4 and PD-1 combined blocking in this HBeAg negative patient, which may be related to the above mechanisms. However, anecdotal reports are not substitutes for well-conducted clinical trials. Further clinical trials are warranted to confirm these intriguing observations.

Viral hepatitis is a global health scourge, which has an outsized impact on patients in developing countries [11]. Tumor complicated with hepatitis B in developing countries such as China is very common. Understanding the relative safety of checkpoint inhibitors in these patients is crucial in helping to establish treatment guidelines. A wealth of experience has been accumulated in how to prevent chemotherapy-induced reactivation of hepatitis [12]. However, compared with the chemotherapy, immune checkpoints blockade is a fully new treatment method with completely different toxicity profile [13]. The dilemma of simultaneously managing hepatitis and cancer will need to be further explored, so as not to inadvertently deny therapies that could be delivered safely.

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