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Case Report

Two Cases of Immune-Related ACTH Deficiency after the Initiation of Atezolizumab plus Bevacizumab for Multiple Hepatocellular Carcinoma

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Abstract

Background: There have been a few case reports of immune-related Adrenocorticotropic Hormone (ACTH) deficiency in cases of atezolizumab plus bevacizumab therapy for unresectable HCC. Our report aims to enhance comprehension of immune-related ACTH deficiency, its management, and its impact on clinical outcomes. **Case Report:** We present two cases of immune-related ACTH deficiency. The patient of Case 1 is an 81-year-old man with a history of hepatitis B. He complained of fatigue and loss of appetite after 5 cycles of atezolizumab plus bevacizumab therapy and was diagnosed with isolated ACTH deficiency. His symptoms are well controlled with oral hydrocortisone, and he continues the treatment. The patient of Case 2 is a 65-year-old man with a history of alcoholic cirrhosis. On the fifth-cycle day, he complained of fatigue and had ACTH deficiency and low cortisol levels. However, since the fatigue was mild, treatment was continued without interruption. ACTH and cortisol levels had returned to normal on the sixth-cycle day without hydrocortisone. After six cycles, CT revealed multiple new lesions of HCC. Therefore, atezolizumab plus bevacizumab was discontinued. **Conclusion:** Atezolizumab can be safely continued with hydrocortisone when immune-related ACTH deficiency occurs. Case 2 shows the possibility of that immune-related ACTH deficiency may recover spontaneously on follow-up.

Keywords: Adrenal Insufficiency; Hepatocellular Carcinoma; Immune Checkpoint Inhibitors; Immune-Related Adverse Events; Isolated ACTH Deficiency.

Introduction

Immune Checkpoint Inhibitors (ICIs) are a type of treatment that uses antibodies to boost the immune system. These agents have had a significant impact on improving the prognosis for patients with advanced cancers. Hepatocellular Carcinoma (HCC) has become the third leading cause of cancer death worldwide, and the number of patients with HCC continues to rise [1]. Atezolizumab plus bevacizumab have been recommended as the first line in patients with unresectable HCC since 2020 [2]. Based on the positive results of the phase 3 trial of durvalumab plus tremelimumab [3], a combination of anti-PD-L1 and CTLA-4 antibodies is also considered as the first line. Thus, immune-combination therapy is the mainstream in systemic therapy for unresectable HCC. ICIs offer significant clinical benefits. However, they can also cause a specific range of side effects called immune-related adverse events (irAEs) [4]. The overall rate of endocrinopathy-related irAEs is about 10% of patients receiving ICI treatments [5]. Endocrinopathy-related irAEs include hypothyroidism, hyperthyroidism, hypophysitis, and adrenal insufficiency, in which thyroid disorders are the most common AEs [5,6]. Hypophysitis and adrenal insufficiency can be fatal even though the number of cases is small [7]. However, there have been few case reports of immune-related Adrenocorticotropic Hormone (ACTH) deficiency in atezolizumab plus bevacizumab therapy for unresectable HCC. This report aims to develop a better understanding of immune-related ACTH deficiency, its management, and the impact on clinical outcomes in patients with unresectable HCC treated with atezolizumab plus bevacizumab.

Case Presentation

Case 1: An 81-year-old man with a history of hepatitis B underwent hepatectomy for HCC 13 years prior and subsequently received Radiofrequency Ablation (RFA) and Transcatheter Arterial Chemoembolization (TACE) twice each. A Gd-EOB-DTPA MRI scan showed multiple hypointense lesions on the hepatobiliary phase in both the right and left hepatic lobes, indicating a recurrence of HCC. As the Child-Pugh score was 5(A) without any distant metastasis, it was classified as intermediate stage (B) HCC according to the Barcelona Clinic Liver Cancer (BCLC) staging system. Since the lesions did not meet the Up-to-seven criteria and with no invasion of the portal vein, first-line chemotherapy was initiated with intravenous administration of atezolizumab at a dose of 1,200 mg/body and bevacizumab at 15 mg/kg of body weight every 3 weeks. After three cycles of atezolizumab plus bevacizumab, the patient achieved Stable Disease (SD) according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria. However, after five cycles of atezolizumab plus bevacizumab (15 weeks from the administration), the patient complained of fatigue and loss of appetite and had low blood pressure; thus, atezolizumab plus bevacizumab was interrupted. Six days after discontinuation, an abnormal endocrinologic finding was detected, and the patient was immediately hospitalized. Blood examinations showed increased values of eosinophils (11.0%) and decreased values of ACTH (1.6 pg/mL) and cortisol (1.0 μg/dL), and the values of the Luteinizing Hormone (LH), thyroid stimulating hormone (TSH), Follicle-Stimulating Hormone (FSH), Prolactin (PRL) and Vasopressin (AVP) were higher than the upper limits of normal, and the Growth Hormone (GH) and Insulin-Like Growth Factor-1 (IGF-Ⅰ)were within the normal range, which suggested secondary adrenal insufficiency (Table 1). The MRI of the pituitary gland showed no obvious abnormalities in the anterior pituitary (Figure 1), indicating atezolizumab-induced Isolated ACTH Deficiency (IAD). Blood tests showed serum TSH, Free Triiodothyronine (FT3), Free Thyroxine (FT4), and Anti-Thyroid Peroxidase Antibody (anti-TPO) levels of 11.6 μIU/mL, 3.60 pg/mL, 0.86 ng/mL and 3.7 IU/mL, respectively. Thyroid ultrasound sonography showed no morphological abnormalities and anti-thyroglobulin antibodies were negative, indicating atezolizumab-induced hypothyroidism. After the intravenous administration of hydrocortisone (100mg/body), the fatigue and loss of appetite were promptly improved.

TP	7.1	g/dL	cortisol	1.0	μg/dL
Alb	3.7	g/dL	FT3	3.60	ng/dL
T-Bil	1.0	IU/L	FT4	0.86	ng/dL
AST	27	IU/L	TSH	11.6	μIU/mL
ALT	14	IU/L	ACTH	1.6	pg/mL
LDH	266	IU/L	GH	1.04	ng/mL
Na	136	mEq/L	LH	14.4	mIU/mL
K	4.4	mEq/L	FSH	28.2	mIU/mL
Cl	101	mEq/L	PRL	25.2	ng/mL
CRP	1.14	mg/dL	IGF-I	34	ng/mL
BUN	27.2	mg/dL	AVP	5.2	pg/mL
Cre	1.42	mg/dL			
WBC	7.3	$\times 10^3/\mu L$			
Seg	43.0	%			
Eosino	11.0	%			
RBC	4.36	$\times 10^6/\mu L$			
Hb	13.6	g/dL			
PLT	26.1	$\times 10^4/\mu L$			

TP: total protein, Alb: albumin, T-Bil: total bilirubin, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, Na natrium, K: kalium, Cl: chlorine, CRP: C-reactive protein, BUN: blood urea nitrogen, Cre: creatinine, WBC: white blood cells, RBC: red blood cells, Hb: hemoglobin, PLT: platelets, ACTH: adrenocorticotropic hormone, FT3: free triiodothyronine, FT4: free thyroxine, GH: growth hormone, LH: luteinizing hormone, FSH: follicle stimulating hormone, PRL: prolactin, IGF-1: insulin-like growth factor 1, AVP: Arginine Vasopressin, TSH: Thyroid Stimulating Hormone

Table 1: The patient's laboratory findings on hospital admission (Case1).

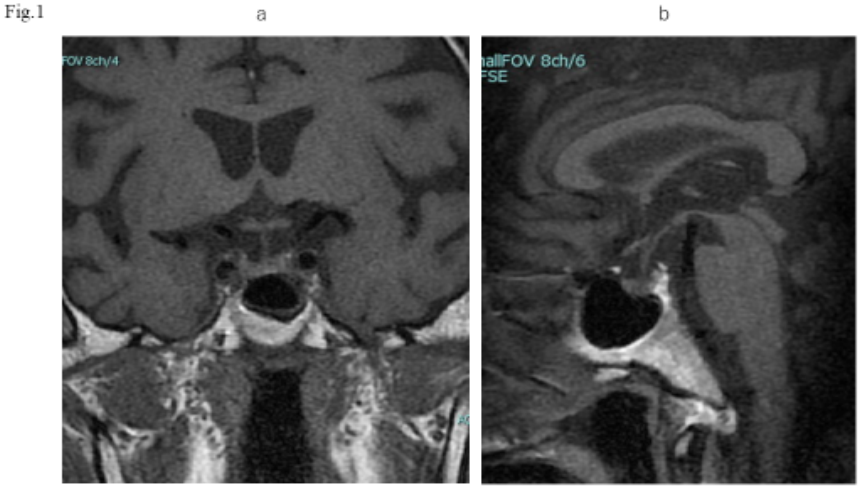

Figure 1: The Magnetic Resonance Imaging (MRI) of pituitary gland (Case1). a-b The MRI showed no pituitary enlargement.

Following the intravenous administration, oral hydrocortisone at a dose of 60mg/day (0.8mg/kg/day) was started. On the fifth hospital day, the serum cortisol level improved (12.7μg/dL), and the oral dose was reduced to 40 mg/day. After 2 more days, it was reduced to 20 mg/day (Figure 2). After the patient's symptoms had completely resolved, atezolizumab plus bevacizumab were reintroduced based on the recommendation of the endocrinologists. Gd-EOB-DTPA MRI showed stable disease after seven cycles of treatment (two cycles after the onset of IAD) (Fig.3). Atezolizumab plus bevacizumab was continued for 11 cycles with 20 mg of oral hydrocortisone daily. No recurrence of IAD or other adverse events was observed after the administration of hydrocortisone.

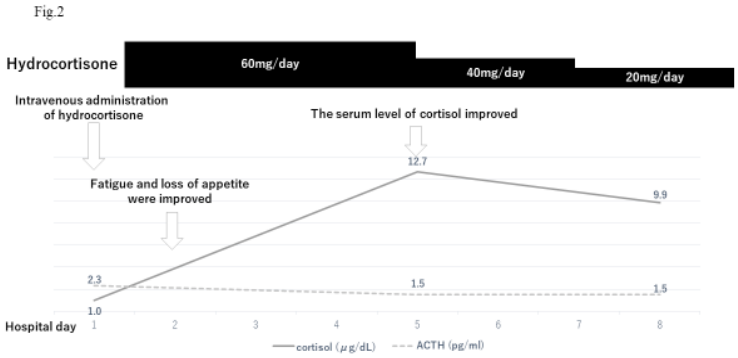

Figure 2: Clinical Course (Case 1).

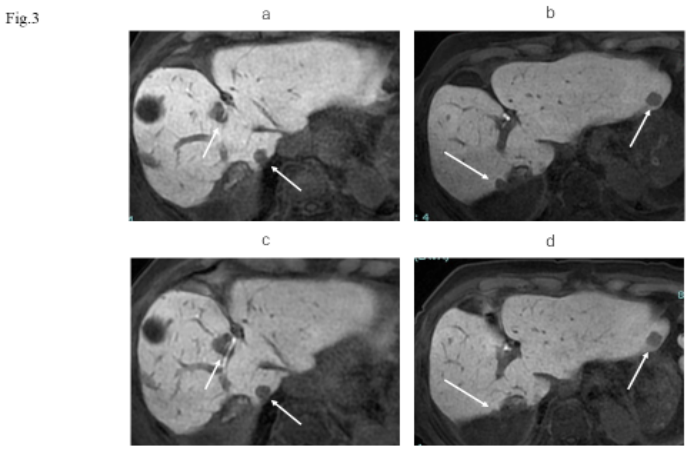

Figure 3: Changes in Magnetic Resonance Imaging (MRI) with the course of treatment (Case1). a-d Liver Gd-EOB-DTPA MRI. a-b Initial examination. Multiple lesions are seen in S1, S2, S7, S8 and hepatic portal region hilum of liver, with high signal on diffusion-weighted imagaing (DWI) and on the arterial phase. c-d After IAD. The size of the lesions did not change.

Case 2: A 65-year-old man with a history of alcoholic cirrhosis was initially diagnosed with HCC in 2013. He had histories of hypertension, diabetes, and a duodenal ulcer and took Esomeprazole Magnesium Hydrate 20mg, Rifaximin 1200mg, Amlodipine Besilate 2.5 mg, Sitagliptin Phosphate Hydrate 25mg and Atenolol 25mg. He reported no relevant family history. He had been a two-pack-per-day cigarette smoker for forty years and consumed 70g of alcohol every other day. He received six TACEs, two RFAs, and one cyberknife treatment. Even though he had no extrahepatic metastasis or major portal invasion, he was diagnosed as TACE refractory and started receiving lenvatinib as first-line systemic therapy in November 2018. In April 2019, he underwent Transcatheter Arterial Embolization (TAE), and in June 2020, he underwent TACE. However, a contrast enhancement CT (CECT) performed in October 2020 showed a recurrence of HCC in S8 with adrenal metastasis, which indicated PD, and lenvatinib was discontinued. Since the Child-Pugh score was 6 (A) with an extrahepatic lesion, it was classified as advanced stage (C) according to the BCLC staging system. Second-line chemotherapy with atezolizumab plus bevacizumab was initiated every three weeks. After three cycles of chemotherapy, the patient archived SD according to RECIST criteria. On the day of the fifth cycle of atezolizumab plus bevacizumab (12 weeks from the initial chemotherapy session), the patient complained of fatigue.

Although blood examinations showed decreased values of ACTH (<1.5 pg/mL) and cortisol (0.9 μg/dL), the patient only had fatigue as a symptom (Table 2). As the fatigue was classified as Grade 1 according to Common Terminology Criteria for Adverse Events ver 5.0 (CTCAE ver 5.0), atezolizumab plus bevacizumab was continued based on the recommendation of the endocrinologists. His hormone levels were carefully monitored without any treatment for adrenal deficiency, and blood tests on the day of the sixth cycle showed that the ACTH and cortisol levels had returned to normal (93pg/ml and 9.2 μg/dL, respectably) (Figure 4). Therefore, the sixth cycle was administered without a dose reduction. After six sessions (one cycle after the onset of ACTH deficiency), a CECT performed in March 2021 revealed new multiple HCC lesions in both the right and left hepatic lobes. As a result, atezolizumab plus bevacizumab was discontinued, and the patient was switched to sorafenib as third-line chemotherapy.

TP	6.9	g/dL	cortisol	0.9	μg/dL
Alb	3.1	g/dL	FT3	2.3	ng/dL
T-Bil	1.5	IU/L	FT4	1.0	ng/dL
AST	47	IU/L	TSH	1.1	μIU/mL
ALT	25	IU/L	ACTH	<1.5	pg/mL
LDH	237	IU/L			

Na	142	mEq/L	
K	3.9	mEq/L	
Cl	107	mEq/L	
CRP	0.72	mg/dL	
BUN	11.2	mg/dL	
Cre	0.79	mg/dL	
WBC	3.3	$\times 10^3/\mu L$	
Seg	70.0	%	
Eosino	5.0	%	
RBC	4.49	$\times 10^6/\mu L$	
Hb	12.9	g/dL	
PLT	60	$\times 10^4/\mu L$	
ICI: Immune Checkpoint Inhibitor, IAD: Isolated ACTH Deficiency, NSCLC: Non-Small Cell Lung Cance, HCC: Hepatocellular Carcinoma			

Table 2: The patient's laboratory findings on the day of the fifth course (Case 2).

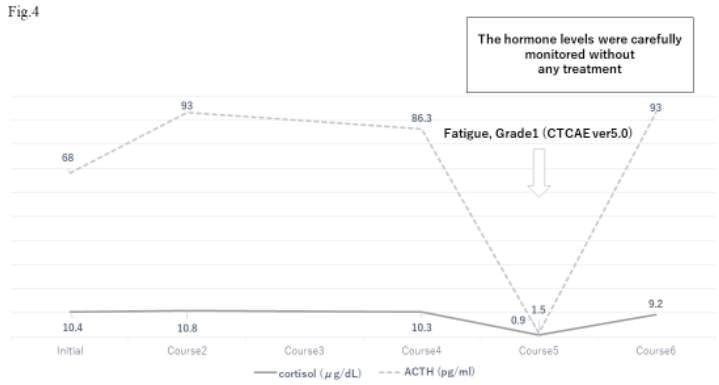

Figure 4: Clinical Course (Case2).

Discussion

We are reporting two cases of ACTH deficiency during atezolizumab plus bevacizumab therapy for HCC. The first case was identified as IAD with normal levels of other pituitary hormones and no abnormalities found in the pituitary gland. The second case was diagnosed as ACTH deficiency, as no testing of other hormones or pituitary imaging was conducted.

ICI-related IAD is rare [5]. Among 1615 patients with ICI treatment, fourteen (0.87%) patients developed IAD [8]. Among some types of ICIs, such as anti-CTLA4 and anti-PD-1/PD-L1, atezolizumab-related IAD has been infrequently reported. IMbrave 150 trial reported only one case of hypopituitarism [2]. Out of 1,548 patients with non-small cell lung cancer who were treated with atezolizumab monotherapy, 85 patients developed endocrinopathy irAEs, and 4.7% of them had adrenal gland-related AEs [9]. In a systematic review of 60 IAD cases induced by ICI, no case was reported due to atezolizumab [10]. Out of 206 patients with ICI-induced adrenal deficiency, 191 had secondary AD. The distribution of the causes of secondary adrenal deficiency was as follows: ipilimumab (anti-CTLA-4)

53(27.7%), nivolumab (anti-PD-1) 69(36.1%), pembrolizumab (anti-PD-1) 22(11.5%), and atezolizumab (anti-PD-L1) 2(1.0%) [11].

Atezolizumab-related IAD has only been described as case reports [12,13] (Table 3). All cases required the continuation of corticosteroids as hormonal replacement therapy (HRT), which aligns with findings from previous studies [14]. In our report, case 1 continued HRT, while case 2 showed a rapid improvement in the levels of ACTH and cortisol without HRT. Case 2 had mild symptoms, and no additional examination was performed, such as imaging or testing of other hormones, so it was not classified as IAD, but it might be hypophysitis. Although careful observation and continuing ICI are recommended for patients with Grade 1 (mild) hypophysitis [15], hypophysitis sometimes evolves into IAD [16]. If case 2 were IAD, this would be the first report suggesting that follow-up without HRT is a viable option for IAD with Grade 1 (mild) symptoms.

Author	Case	Sex	Age	ICI	Cancer type	Cycles of ICI to the onset of IAD	Time to the onset of IAD	Symptoms	Initial Management	Reinitiated ICI/ continuation of replacement therapy
Kanie	1	M	65	Atezolizumab	NSCLC	19	56 weeks	malaise, loss of appetite, diarrhea	hydrocortisone	Atezolizumab/ hydrocortisone
Kanie	2	M	70	Atezolizumab	NSCLC	18	52 weeks	malaise, loss of appetite	hydrocortisone	no information/ hydrocortisone
Hayashi	3	M	63	Atezolizumab+Bevacizumab	HCC	4	21 weeks	fatigue, loss of appetite	hydrocortisone	Atezolizuma+Bevacizumab/ hydrocortisone
Our case	4	M	81	Atezolizumab+Bevacizumab	HCC	5	15 weeks	fatigue, loss of appetite	hydrocortisone	Atezolizuma+Bevacizumab/ hydrocortisone
Our case	5	M	65	Atezolizumab+Bevacizumab	HCC	4	12 weeks	fatigue	no replacement treatment	Atezolizuma+Bevacizumab/ none

Table 3: The Clinical Characteristics of Atezolizumab-induced Isolated ACTH Deficiency.

It is now well established from a variety of studies that irAEs are linked to either enhanced effectiveness of immunotherapy (such as increased response rates and prolonged survival) [9,17] or similar effectiveness as compared to those who do not experience irAEs [18]. Therefore, it is crucial to continue treatment with appropriate management of side effects. Prior studies and our case have demonstrated that atezolizumab-induced IAD can be managed with corticosteroids [12,13], and therapy can be continued. However, since cancer patients, particularly those receiving ICIs, often report non-specific symptoms of cortisol deficiency, such as weakness and loss of appetite, early detection of cortisol and ACTH abnormalities is important. Ideally, regular endocrinologic testing should be conducted. However, this can be challenging in practice due to limitations in insurance coverage or facility capabilities. It has been found that relatively basic tests, such as sodium and eosinophil levels, can predict these endocrinologic abnormalities. Cho et al. reported that hyponatremia (sodium <135 mEq/l) occurs early in IAD caused by ICIs and that comparison of sodium levels before and after treatment is useful as a monitoring indicator [19]. Ariyasu et al. showed eosinophilia in 4 of 5 patients with IAD caused by anti-PD-1 and anti-CTLA-4 antibodies, 3 of whom had eosinophilia more than 1 month before the onset of clinical symptoms [20]. These findings reflect those of Iglesias P et al. (2021), who also found that hyponatremia (68%) and eosinophilia (31.8%) were the laboratory abnormalities most frequently associated with IAD [10]. Our case also presented with eosinophilia in addition to the non-specific symptoms of cortisol deficiency.

The phase 3 trial of durvalumab plus tremelimumab was successful [3], and the combination therapy has been recently approved in Japan, the United States, and Europe. The incidence of IAD would increase up to 5%-8% with combination therapy from 1%-2% with ICI monotherapy. Therefore, earlier diagnosis and rapid intervention for IAD become more important in real-world practice.

In this report, we present two cases of IAD that occurred during treatment with atezolizumab and bevacizumab for HCC. Atezolizumab-induced IAD is uncommon, and further research is needed to establish appropriate management, its impact on long-term outcomes, and treatment effectiveness. Case 1 and several earlier studies indicate that oral corticosteroids may allow for the safe continuation of atezolizumab; case 2 suggests that ICI-related ACTH deficiency may also be viable for follow-up, although only limited examination was conducted.

Conclusion

We reported two cases of ACTH deficiency during atezolizumab plus bevacizumab therapy for HCC. Atezolizumab-induced IAD is uncommon, and our reports have indicated that oral corticosteroids may allow for the safe continuation of atezolizumab. Additionally, there is a possibility that ICI-related ACTH deficiency may recover spontaneously on follow-up. Further research is needed to establish appropriate management, impact on long-term outcomes, and treatment effectiveness.

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Conflicts of Interest

Kaoru Tsuchiya, Masayuki Kurosaki, and Namiki Izumi received advisory board fees and honoraria for the speakers' bureau from Eli Lilly Japan, Chugai Pharmaceutical Company, Takeda, and Eisai. The Japanese Ministry of Health, Labour and Welfare had no role in the study design, data collection, data analysis, data interpretation, manuscript writing, or the publication of results.

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