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【 CASE REPORT 】

A Successful Case of Hepatocellular Carcinoma Treated with Atezolizumab Plus Bevacizumab with Multisystem Immune-related Adverse Events

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Abstract:
A 63-year-old man with hepatitis C was treated with atezolizumab plus bevacizumab for unresectable diffuse hepatocellular carcinoma (HCC). After four cycles of atezolizumab plus bevacizumab, the diffuse HCC markedly shrank; however, he complained of general fatigue, loss of appetite, and slight loss of muscle strength in the lower legs. He was diagnosed with isolated adrenocorticotropic hormone deficiency (IAD), hypothyroidism, and myopathy, suggesting multisystem immune-related adverse events (irAEs). After administration of hydrocortisone, the clinical symptoms rapidly disappeared. Patients with multisystem irAEs can have favorable outcomes; thus, to continue immune-checkpoint inhibitors therapy, a correct diagnosis and management of multisystem irAEs are important.

Key words: hepatocellular carcinoma, atezolizumab, isolated adrenocorticotropic hormone deficiency, multisystem immune-related adverse effects

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Introduction

Immune-checkpoint inhibitors (ICIs) have drastically improved the outcomes of various cancers; however, specific adverse events such as immune-related adverse events (irAEs) often occur in various organs (1). Investigations of single-organ irAEs have reported single-organ irAE incidences of 30% with programmed cell death-1 (PD-1)/programmed cell death-ligand 1 (PD-L1) inhibitors (2), 72% with ipilimumab (3), and 88% with combination therapy (4). In contrast, little is known about multisystem irAEs, which are characterized by a combination of individual irAEs or involved organ systems in the same patient. This is likely due to underrecognition of such irAEs and a lack of reporting (5).

Two recent reports indicated that the incidences of multisystem irAEs range from 5.4% to 9.3% (5, 6); specifically, the incidences of irAEs affecting 2, 3, and 4 organs systems are 4.5%, 0.8%, and 0.06%, respectively (5). The predominant organs affected are the skin, lung, liver, and thyroid and, rarely, the pituitary. In addition, the development of multisystem irAEs is associated with survival benefits among patients with various cancers (5, 6).

In November 2020, therapy with the PD-L1 inhibitor atezolizumab plus bevacizumab was approved for unresectable hepatocellular carcinoma (HCC). This therapy is highly effective and considered a first-line systemic therapy for unresectable HCC (7). A recent network meta-analysis demonstrated that atezolizumab had the best safety profile in general compared with other ICIs (8); however, irAEs occasionally occurred in the pituitary (7). Furthermore, whether or not atezolizumab plus bevacizumab therapy causes multisystem irAEs is unclear.

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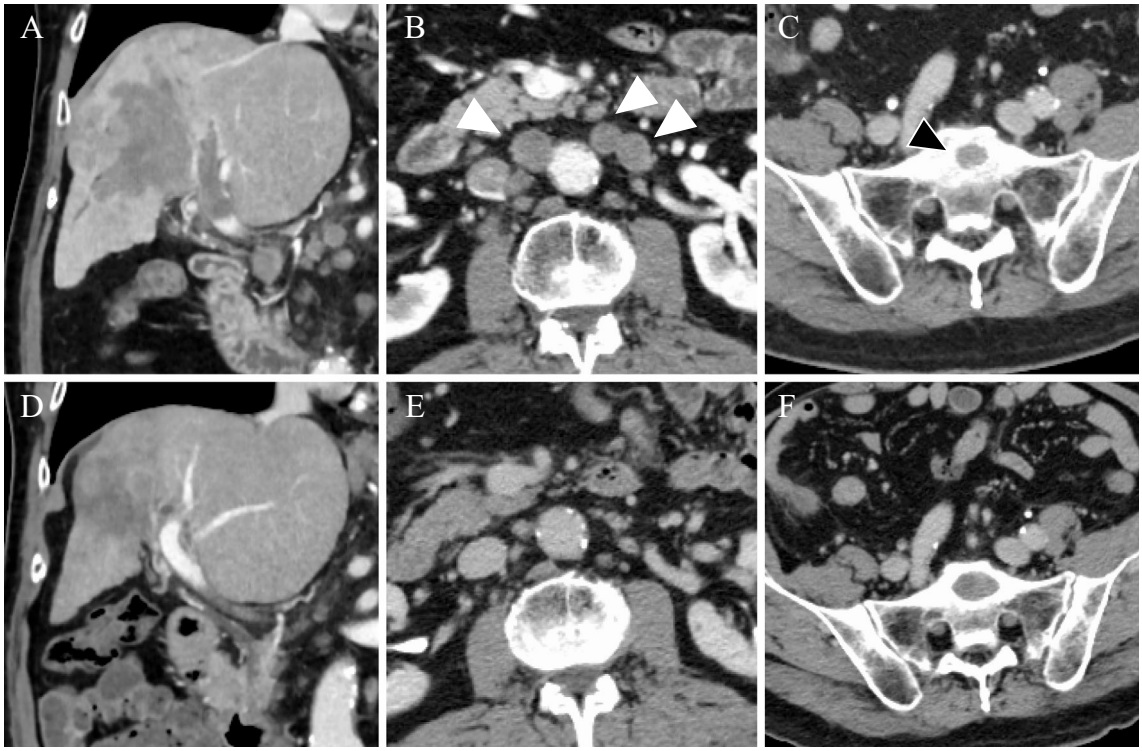

Figure 1. Computed tomography (CT) of hepatocellular carcinoma (HCC). (A) CT revealed diffuse-type HCC at both the right and portal vein tumor thrombi at the main portal trunk. (B) Multiple para-aortic lymph nodes were swollen (white arrowheads). (C) CT revealed osteolytic changes, indicating sacrum metastasis (black arrowhead). (D, E) After four cycles of atezolizumab plus bevacizumab, CT revealed that the intrahepatic lesions and lymph node metastases had markedly shrunk, and the portal vein thrombus had disappeared. (F) CT revealed slight progression of sacrum metastasis.

We herein report the first case of HCC treated with atezolizumab plus bevacizumab therapy complicated by multisystem irAEs, including isolated adrenocorticotropic hormone (ACTH) deficiency (IAD), hypothyroidism, and myopathy. Atezolizumab plus bevacizumab therapy produced a rapid HCC response, and the patient was able to continue therapy thanks to the immediate recognition and management of multisystem irAEs.

Case Report

A 63-year-old man with hepatitis C who was treated with lenvatinib for 1 year due to unresectable HCC was referred to our hospital because of HCC progression. Computed tomography (CT) revealed diffuse-type HCC at both the right and medial hepatic lobes, portal vein tumor thrombus, and both lymph node and sacrum metastases (Fig. 1A-C). Blood examinations showed no abnormalities in the serum ACTH or cortisol level (ACTH: 29.4 pg/mL, cortisol: 17.9 μg/dL) (Table 1). Therefore, intravenous treatment with atezolizumab at 1,200 mg and bevacizumab at 15 mg/kg of body weight every 3 weeks was started as second-line chemotherapy. After two cycles of atezolizumab plus bevacizumab (seven weeks from the initiation of therapy), the intrahepatic lesions and lymph node metastases had markedly shrunk, and the portal vein thrombus had disappeared, although the sacrum metastasis had progressed. After 4 cycles of atezolizumab plus bevacizumab (13 weeks from the initial therapy), the antitumor effect persisted (Fig. 1D-F).

However, after four cycles of atezolizumab plus bevacizumab, the patient complained of tarry stool due to hemorrhagic gastric ulcer; thus, chemotherapy was discontinued. Seventy-four days after the last chemotherapy session (21 weeks from the initial chemotherapy session), he complained of general fatigue, loss of appetite, and slight loss of muscle strength in the lower legs. Blood examinations showed increased values of eosinophils (9.4%) and creatinine phosphokinase (CPK) (691 U/L) and decreased values of ACTH (10.6 pg/mL) and cortisol (0.50 μg/dL). The findings of the Luteinizing hormone-releasing hormone, Thyrotropin-releasing hormone, and Corticotropin-releasing hormone stimulating tests suggested secondary adrenal insufficiency. The arginine stimulation test and growth hormone-releasing peptide 2 loading test (GHRH-2 test) did not indicate GH deficiency (Table 2). Thus, based on the findings from stimulating tests, our patient was diagnosed with IAD. Magnetic resonance imaging (MRI) of the pituitary gland showed no obvious abnormalities in the anterior pituitary (Fig. 2A), indicating atezolizumab-induced IAD.

Sixty-two days after the last chemotherapy session, blood

Table 1. Laboratory Data.

WBC	4,270 /μL	ALP	423 U/L	IgG	1,341.2 mg/dL
Neut	72.5 %	LDH	510 U/L	IgA	499.3 mg/dL
Lymp	19.0 %	γGTP	837 U/L	IgM	83.6 mg/dL
Mono	6.6 %	ChE	201 U/L	ANA	<40
Eos	1.9 %	BUN	15.8 mg/dL	AMA	(-)
Baso	0.0 %	Cre	0.86 mg/dL	HBs Ag	0.01 IU/mL
RBC	3.57 $\times 10^6$/μL	Na	143 mmol/L	HBc Ab	6.36 S/CO
Hb	12.0 g/dL	K	3.7 mmol/L	HBV-DNA	<1.0 LogIU/mL
PLT	7.6 $\times 10^4$/μL	Cl	110 mmol/L	HCV Ab	14.19 S/CO
T.P.	7.2 g/dL	FT4	1.17 ng/dL	AFP	384 ng/mL
Alb	3.4 g/dL	TSH	5.59 μIU/mL	PIVKA-II	6,654 mAU/mL
T. Bil	1.1 mg/dL	Cortisol	17.9 μg/dL		
D. Bil	0.3 mg/dL	ACTH	29.4 pg/mL		
AST	46 U/L				
ALT	28 U/L				

ACTH: adrenocorticotropic hormone, ANA: anti-nuclear antibody, AMA: anti-mitochondrial antibody, HBs Ag: hepatitis B surface antigen, HBc Ab: hepatitis B core antibody, HCV Ab: hepatitis C virus antibody, S/CO: sample cut off, AFP: α fetoprotein, PIVKA-II: protein induced by vitamin K absence or antagonists-II

Table 2. Pituitary-related Endocrinological Examinations.

LHRH, TRH, and CRH stimulation tests						
	Normal range	Pre	Post 30 min	Post 60 min	Post 90 min	Post 120 min
THS (μIU/mL)	0.5-5.00	2.52	18.10	17.40	15.20	12.80
LH (μIU/mL)	2.2-8.4	9.83	34.80	35.80	33.20	30.60
FSH (U/mL)	1.8-12.0	7.00	13.20	15.00	15.20	14.90
PRL (ng/mL)	4.29-13.69	11.70	33.50	28.70	22.90	19.00
ACTH (pg/mL)	7.2-63.3	10.00	15.90	14.50	10.90	9.97
Cortisol (μg/dL)	6.24-18.0	1.12	1.47	1.59	1.20	0.98
Arginine stimulation test						
	Normal range	Pre	Post 30 min	Post 60 min	Post 90 min	Post 120 min
GH (ng/mL)	≤2.47	3.12	5.44	12.00	9.57	7.27
GHRP-2 loading test						
	Normal range	Pre	Post 15 min	Post 30 min	Post 45 min	Post 60 min
GH (ng/mL)	≤2.47	5.68	47.60	49.60	40.60	32.40

LHRH: luteinizing hormone-releasing hormone, THR: thyrotropin-releasing hormone, CRH: corticotropin-releasing hormone, TSH: thyroid-stimulating hormone, LH: luteinizing hormone, FSH: follicle-stimulating hormone, PRL: prolactin, ACTH: adrenocorticotropic hormone, GH: growth hormone, GHRP-2: GH-releasing peptide 2

examinations showed serum Thyroid stimulating hormone (TSH), FT3, and FT4 levels of 10.4 μIU/mL, 3.35 pg/mL, and 1.19 ng/mL, respectively. Thyroid ultrasound sonography did not show abnormalities, and thyroid disorder-related antibodies, such as anti-thyroglobulin antibody and anti-thyroid peroxidase antibody, were negative, indicating atezolizumab-induced hypothyroidism.

Fat suppression T2-weighted imaging of the thigh revealed diffuse high intensity at the quadriceps muscle (Fig. 2B). Inflammatory myopathy-related autoantibodies, such as anti-ARS antibody, anti-TIF-1γ antibody, anti-Mi-2 antibody, and anti-MDA5 antibody were negative, indicating atezolizumab-induced myopathy according to the diagnosis of a neurologist. Based on these findings, our patient was diagnosed with atezolizumab plus bevacizumab therapy-associated multisystem irAEs.

After the administration of hydrocortisone (15 mg/day) and 25 μg/day levothyroxine, the clinical symptoms rapidly disappeared, and the endocrinological abnormalities and serum CPK levels improved. One month later, he was able to resume atezolizumab plus bevacizumab therapy. Although the serum CPK levels were slightly elevated (255-351 U/L) after resuming atezolizumab plus bevacizumab therapy, the therapy was able to be continued because there were no clinical symptoms.

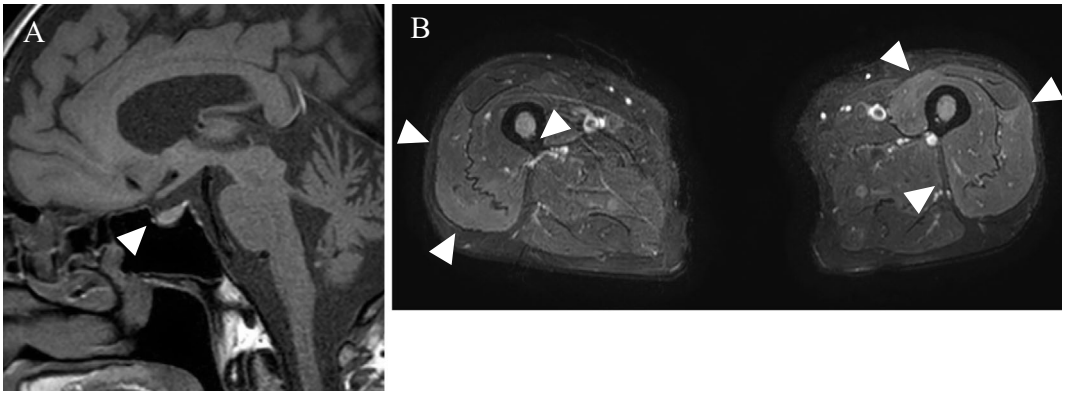

Figure 2. **The findings of magnetic resonance imaging at the pituitary gland and quadriceps muscle. (A) T1-weighted imaging of the pituitary gland showed no obvious abnormalities in the anterior pituitary gland (arrowhead). (B) Fat suppression T2-weighted imaging of the thigh revealed diffuse high intensity at the quadriceps muscle (arrowheads).**

Table 3. **Clinical and Pathological Features of Atezolizumab-induced Isolated ACTH Deficiency.**

Case (Reference)	Sex	Age	Primary cancer type	Time from atezolizumab to IAD	Cycle of onset	Symptoms	Laboratory findings	Other irAEs
1 (9)	M	65	NSCLC	56 weeks	19	General malaise, appetite loss, diarrhea	Eosinophils 14.0% ACTH 3.5 pg/mL Cortisol 0.2 μg/dL	None
2 (9)	M	70	NSCLC	52 weeks	18	General malaise, appetite loss	Eosinophils 7.5% ACTH 13.7 pg/mL Cortisol 4.9 μg/dL	None
3	M	63	HCC	21 weeks	4	General fatigue, appetite loss	Eosinophils 9.4% ACTH 10.6 pg/mL Cortisol 0.5 μg/dL	Hypothyroidism myopathy

IAD: isolated adrenocorticotropic hormone deficiency, irAEs: immune-related adverse events, M: male, NSCLC: non-small cell lung cancer, HCC: hepatocellular carcinoma, ACTH: adrenocorticotropic hormone

Discussion

We herein report a case of multisystem irAEs, including IAD, hypothyroidism, and myopathy, after atezolizumab plus bevacizumab therapy for HCC. Among patients with other cancer types, there have been only three cases of atezolizumab-induced IAD (9), and our case was the first involving multisystem irAEs with IAD (Table 3).

Among pituitary irAEs, ICI-induced hypophysitis, which is usually associated with frequent hormonal deficiencies at the diagnosis and rare yet threatening pituitary-adrenal dysfunction (10, 11), is particularly common with cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitors or combination therapy with CTLA-4 inhibitors and PD-1 inhibitors. Its frequency is 4.53% with CTLA-4 inhibitors and less than 1% with PD-1/PD-L1 inhibitors (10). Pituitary MRI exhibits mild to moderately diffuse pituitary enlargement as radiological evidence of both pituitary inflammation and pituitary dysfunction with multiple deficits in anterior pituitary hormones (12, 13).

In contrast, ICI-induced IAD is a rare irAE (0.87%); however, the number of patients diagnosed with IAD associated with immunotherapy has recently increased. A systematic review revealed that 60 patients were diagnosed with IAD induced by ICIs, mostly due to PD-1 inhibitors (60% had nivolumab; 18.3% had pembrolizumab), whereas there were no patients with IAD due to atezolizumab in this systematic review (14). Pituitary MRI was normal in most patients and rarely showed slight atrophy of the anterior pituitary (9, 14, 15). In our case, pituitary-related endocrine examinations (Table 1) suggested secondary adrenal insufficiency due to IAD, and the findings of pituitary MRI supported the diagnosis of IAD.

ICI-induced thyroid disorder is the most common endocrine irAE in patients treated with ICIs (16); in particular, PD-1 inhibitors are associated with higher rates of thyroid dysfunction (7-21%) than CTLA-4 inhibitors (0-6%) (17). Recently, a clinical trial and comprehensive study revealed that PD-L1 inhibitors were associated with a 10-25% risk of thyroid irAEs (6, 17, 18), which is similar to PD-1 inhibitors. In most cases, management is supportive without requiring steroids or discontinuation of ICIs, and thyroid dysfunction is considerably reversible (19).

ICI-induced musculoskeletal irAEs present with a wide range of clinical manifestations, such as myalgia, asymptomatic increasing of serum CPK levels, muscle weakness, myopathy, myasthenia gravis, necrotizing myopathy, and lethal cardiomyopathy (20, 21). Although the prevalence of myalgia is a common clinical symptom with a 2-21% risk, myopathy and myasthenia gravis are rare irAEs (22, 23). PD-1/PD-L1 inhibitors appear to be more tightly associated with musculoskeletal irAEs than CTLA-4 inhibitors. Most studies have reported a median time of ≤12 weeks from the first ICI administration to the symptom onset. As in our case, most patients with musculoskeletal irAEs do not have autoantibodies (24). A diagnosis of myopathy is classified as definitive, probable, and possible. Definite myopathy is designated for patients who have histopathological evidence of myopathy or who meet all three of the following criteria: (i) elevated serum CPK, (ii) electrodiagnostic findings of myopathic motor unit potentials, and (iii) imaging abnormalities observed in the clinically affected muscle. Probable myopathy is diagnosed if the patients meet two of the criteria, and possible myopathy is diagnosed when one criterion is met (25). Although we did not perform a muscle biopsy, our case met the first and third criteria, suggesting probable myopathy. In addition, the elevation in serum CPK levels after resuming atezolizumab plus bevacizumab therapy supported atezolizumab plus bevacizumab-induced myopathy.

Some human leukocyte antigen (HLA) haplotypes are reported as risk factors in irAEs (26-28). We performed an analysis of HLA haplotypes to test genetic susceptibility to irAEs. HLA typing in our case revealed HLA-DR15, which has been reported as a possible predictive marker of ICI-induced IAD in Japanese individuals (26, 27). These findings suggest that our patient exhibited a genetic susceptibility to ICI-induced IAD.

After the initiation of atezolizumab plus bevacizumab therapy in our case, the intrahepatic lesions, portal vein thrombi, and lymph node metastases rapidly shrank, suggesting that atezolizumab plus bevacizumab therapy was highly effective in this patient. The overall survival has been shown to be better in patients with certain endocrine irAEs, such as ipilimumab-induced hypophysitis (29) and PD-1/PD-L1-induced thyroiditis (17, 30). In addition, recent reports suggest that patients with multisystem irAEs demonstrate incrementally an improved disease control rate, progression-free survival, and overall survival (5, 6). These findings may support the high effectiveness of atezolizumab plus bevacizumab and multisystem irAEs in our case.

Our case developed multisystem irAEs approximately 10 weeks after the discontinuation of atezolizumab plus bevacizumab therapy. Most cases of nivolumab-induced IAD occur four to eight months after the initiation of therapy and during the course of or within one month of the discontinuation of therapy (15); however, ICI-induced IAD has rarely but occasionally occurred several months after the discontinuation of therapy, as in our case (15). Unlike our case, the onset of ICI-induced myopathy is usually acute or subacute, occurring in most cases after two infusions of ICI therapy (21). We monitored the levels of TSH, FT3, FT4, ACTH, and cortisol every three to six weeks and the levels of CPK every one to two weeks after the discontinuation of atezolizumab plus bevacizumab therapy. Nine weeks before the onset of IAD and myopathy, the levels of ACTH, cortisol, and CPK were 46.6 pg/mL, 3.39 μg/dL, and 296 U/L, respectively, and 3 weeks before the onset, these were 18.8 pg/mL, 0.99 μg/dL, and 678 U/L, respectively, without symptoms. We were unable to diagnose IAD and myopathy early because there were no symptoms in our patient. In addition, 6 weeks before the onset of hypothyroidism, the level of TSH was slightly elevated (6.69 μIU/mL). Thus, we recommend performing monitoring every six weeks to diagnose IAD, myopathy, and hypothyroidism early, even if ICI therapy has been discontinued.

In conclusion, we herein report the first case of multisystem irAEs, including IAD, hypothyroidism, and myopathy, after atezolizumab-plus-bevacizumab therapy for HCC. Because patients with multisystemic irAEs can have favorable outcomes, a correct diagnosis and management for multisystemic irAEs are important for allowing patients to resume ICI therapy. In addition, our case suggests that oncologists should be aware of the potential for the development of multisystem irAEs several months after discontinuation of ICI therapy.

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

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