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## Case report

## Hypothyroidism as an immune-related adverse event caused by atezolizumab in a patient with muscle spasms: a case report

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## ABSTRACT

A 60-year-old man with a history of 4 cycles of atezolizumab treatment for non-small cell lung cancer presented to our hospital with a chief complaint of proximal muscle-dominant spasms. Blood tests showed elevated creatine phosphokinase (CPK) of 8450 U/L and hypothyroidism. There was little improvement even after stopping levetiracetam and pregabalin, and no subspinous physical findings of myositis. After levothyroxine was started for hypothyroidism, his muscle cramps and serum CPK level improved. Hypothyroidism as an immune-related adverse event can cause muscle spasms and is important in the differential diagnosis of muscle spasms in patients treated with immune checkpoint inhibitors.

## 1. Introduction

Indications are expanding for the use of immune checkpoint inhibitors (ICIs) in the treatment of various malignant tumors such as lung cancer, breast cancer, malignant melanoma, and renal cell carcinoma, and opportunities for the use of these agents are thus increasing. ICIs suppress the pathway that stops anti-tumor T-cell responses and enhance their anti-tumor effects. Immune checkpoints, on the other hand, play important roles in suppressing the development of autoimmune diseases, and ICIs can trigger immune-related adverse events (irAEs) [1]. Since irAEs can cause systemic organ damage, including endocrine disorders, appropriate follow-up is necessary when ICIs are prescribed [2]. Thyroid dysfunction (hyperthyroidism and hypothyroidism) is the most frequent endocrine irAE caused by ICIs, and the symptoms are often nonspecific [3]. We report herein a relatively rare case of hypothyroidism as an irAE induced by atezolizumab, in which the diagnosis was made after the patient complained of muscle spasms.

## 2. Case presentation

A 60-year-old man undergoing chemotherapy for non-small cell lung cancer (clinical stage T2bN1M1b, stage IVA) had a history of craniectomy for a single brain metastasis followed by radiotherapy to prevent recurrence. He had been treated with atezolizumab as a 5th-line treatment. No thyroid function abnormalities were observed before the induction of atezolizumab. After 4 cycles of treatment, computed tomography showed enlargement of the primary tumor. He was therefore changed to nab-paclitaxel as a 6th-line treatment. Around the same time, he began to notice bilateral upper and lower limb spasms and pain with a proximal muscle predominance and visited our hospital. Examination revealed mild proximal muscle grasping pain without muscle weakness or paralysis, and no dyspnea. No skin rash was observed on the face or trunk. Blood tests showed that levels of creatine phosphokinase (CPK) were elevated, at 8450

*Abbreviations:* irAEs, immune-related adverse events; ICIs, immune checkpoint inhibitors; CPK, creatine phosphokinase; TSH, thyroid stimulating hormone; TPO Ab, Antithyroperoxidase antibody; TRAB, Antithyrotropin receptor antibody; nab-PTX, nab-paclitaxel.

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U/L (Table 1). The patient was therefore admitted for further investigation. Creatine phosphokinase-MB (CPK-MB) and troponin-I were negative, and electrocardiography showed no changes. Potassium concentration was 3.8 mmol/L, within the normal range. No urine occult blood or myoglobinuria was identified. The patient was taking levetiracetam, pregabalin, acetaminophen, dextromethorphan, and dimethorphan phosphate. Levetiracetam and pregabalin were stopped due to the possibility of drug-induced CPK elevation, but improvement remained poor, and muscle spasms continued for several weeks. Magnetic Resonance Imaging (MRI) of the upper extremities with muscle spasms and pain showed no findings suggestive of myositis, and MRI of the head showed no new metastatic lesions. Since the patient was in a state of clear consciousness, electroencephalography was not performed. Thyroid function evaluation on admission showed a thyroid-stimulating hormone (TSH) concentration of 93.2  $\mu$ IU/mL and a thyroxine concentration of  $<0.04$  ng/dL (Table 1), so hypothyroidism was diagnosed. No evidence of thyroid metastasis was seen on thyroid echography and the patient did not show any development of goiter. Positive results were obtained for antithyrotropin receptor antibody (TRAb). Levothyroxine was started at 25  $\mu$ g/day for hypothyroidism after confirming that the patient did not have adrenal insufficiency. The dose of levothyroxine was then increased, and a slow decrease in TSH was obtained (Fig. 1). Improvements in both muscle spasms and CPK levels were observed, and no increase in CPK was seen with resumption of nab-paclitaxel. Rhabdomyolysis and muscle spasms as a result of hypothyroidism were therefore diagnosed as an irAE caused by atezolizumab.

### 3. Discussion

Atezolizumab, an anti-PD-L1 antibody, is known to cause hypothyroidism, but the diagnosis of hypothyroidism based on muscle spasms appears uncommon. Hypothyroidism is an important differential diagnosis for muscle spasms in patients treated with ICIs, as muscle spasms represent an important physical manifestation of hypothyroidism.

Thyroid dysfunction is the most common endocrine irAE [3], but no previous reports have described cases in which this pathology has been diagnosed as a cause of muscle spasms. Symptoms and signs associated with abnormal thyroid function are often nonspecific [1]. Muscle symptoms such as rigidity, myalgia, and muscle spasms are known to result from hypothyroidism, and rhabdomyolysis has also been reported [4]. Hypothyroidism can cause peripheral nerve and skeletal muscle disorders, and causes metabolic myopathy due to abnormalities in mitochondrial oxidative metabolism and glycogenolysis. In addition, decreased  $\text{Na}^+/\text{K}^+$  ATPase in skeletal muscle leads to abnormal membrane excitability. Furthermore, a lack of aerobic energy pathways causes anaerobic pathway metabolism and a rapid decrease in pH, representing one hypothesized mechanism of pathological muscle impairment [5]. Myopathy lowers the threshold for muscle contraction, resulting in muscle spasms and rhabdomyolysis.

The most common blood test finding in ICI-induced thyroid dysfunction is a transition from hyperthyroidism to hypothyroidism, but this often goes unrecognized due to a lack of symptomatic presentations during the hyperthyroid period (thyrotoxicosis), and this dysfunction is therefore typically diagnosed after the onset of symptoms. Spontaneous improvement is difficult in patients who have progressed from hyperthyroidism to severe hypothyroidism [6]. Thyroid dysfunction as an irAE caused by anti-PD-L1 often occurs early in the course of ICI treatment, at a median of about 6 weeks after ICI initiation [7]. In addition, the time required for hyperthyroidism to progress to hypothyroidism is relatively short, ranging from 16 to 45 days in ICI cases, compared to several weeks to months in conventional painless thyroiditis [8]. In the present case, hypothyroidism was not diagnosed until 4 months after starting ICI treatment. However, triiodothyronine levels were mildly elevated between 1 and 2 months after the start of treatment, suggesting that the patient had developed mild thyrotoxicosis at that time and then transitioned to hypothyroidism. Antithyroperoxidase antibody (TPOAb)-positive and antithyrotropin receptor antibody (TRAb)-positive cases have often been reported in irAE-related thyroid dysfunction. However, whether a positive result for TPOAb before ICI induction is associated with the risk of irAE development remains unclear [6].

The most common drugs causing myalgia and cramps are steroids, statins, fibrates, colchicine, beta blockers, calcium blockers, and

**Table 1**  
Laboratory data on admission.

<b>Hematologic tests</b>					
White blood cells	7,400	/ $\mu$ L	Creatinine	0.97	mg/dL
Neutrophils	43.5	%	Sodium	138	mmol/L
Lymphocytes	40.4	%	Potassium	3.8	mmol/L
Red blood cells	$4.25 \times 10^6$	/ $\mu$ L	Chloride	101	mmol/L
Hemoglobin	13.1	g/dL	CPK	12,022	U/L
Platelet count	$21.7 \times 10^4$	/ $\mu$ L	CPK-MB	19.1	ng/mL
<b>Chemistry</b>					
Total protein	7.0	g/dL	Troponin I	$<0.010$	ng/mL
Albumin	4.4	g/dL	T-chol	408	mg/dL
Total bilirubin	0.4	mg/dL	CRP	0.26	mg/dL
<b>Thyroid function</b>					
AST	126	U/L	TSH	93.28	$\mu$ IU/mL
ALT	53	U/L	ft4	$<0.40$	ng/dL
ALP	80	U/L	ft3	$<1.50$	pg/mL
$\gamma$ -GTP	145	U/L	Thyroglobulin	226	ng/mL
LDH	633	U/L	TPO Ab	13	IU/mL
BUN	16	mg/dL	TRAb	112	IU/mL

AST: aspartate aminotransferase, ALT: alanine aminotransferase, ALP: alkaline phosphatase,  $\gamma$ -GTP:  $\gamma$ -glutamyl transpeptidase, LDH: lactate dehydrogenase, BUN: blood urea nitrogen, CPK: creatine phosphokinase, CPK-MB: Creatine phosphokinase-MB, T-chol: Total cholesterol, CRP: C-reactive protein, TSH: thyroid stimulating hormone, ft4: free thyroxine, ft3: free triiodothyronine, TPO Ab: antithyroperoxidase antibody, TRAb: antithyrotropin receptor antibody.

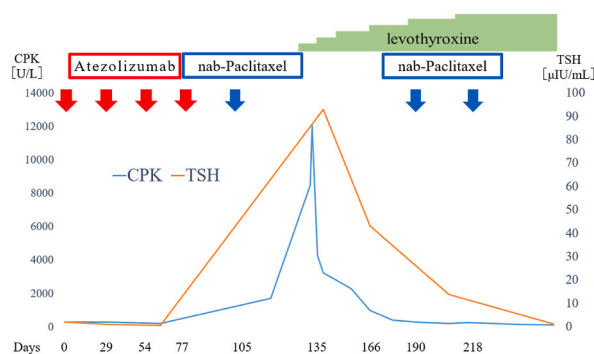


Fig. 1. Clinical course of hypothyroidism as an irAE caused by atezolizumab.

diuretics [5]. However, the present patient had no history of using any of those agents. Some case reports have described hyperCKemia and rhabdomyolysis caused by levetiracetam, one of the drugs discontinued in this case, but these are quite rare [9]. A single-center, retrospective study of levetiracetam use in children identified CPK elevation in about 1.9% of cases [10]. Cases of hyperCKemia and rhabdomyolysis have been reported for pregabalin in combination with other drugs [11], but those are likewise considered quite rare. No previous reports have described pregabalin as the single cause of hyperCKemia or rhabdomyolysis. In the present case, little improvement in CPK was seen even after discontinuing levetiracetam and pregabalin. Since most of the improvement in CPK levels in this case was observed in parallel with improvements in hypothyroidism, a drug-induced mechanism was considered unlikely. Some reports have described neuroleptic malignant syndrome caused by dextromethorphan, resulting in elevated CPK [12]. However, the present case showed no symptoms such as muscle stiffness, fever, sweating, or tachycardia that could be attributed to neuroleptic malignant syndrome. A few case reports have described rhabdomyolysis caused by regimens including paclitaxel, but this is also rare [13]. In the present case, paclitaxel was resumed after CPK improved with treatment of hypothyroidism, but no subsequent increase in CPK was observed. From the disease course in this case, a drug-induced effect was considered unlikely.

Myositis due to irAEs has also been reported, especially myocarditis, which is known to have a high fatality rate [14]. In addition, some reports have described Guillain-Barre syndrome or myasthenia gravis developing as an irAE due to ICIs, and these diagnoses need to be ruled out when symptoms of muscle weakness are present [15]. In the present case, muscle cramps and grasping pain were observed, but no symptoms such as muscle weakness, decreased swallowing function, or dyspnea were apparent, so Guillain-Barre syndrome and myasthenia gravis were not suspected. In irAE-related myocarditis, electrocardiographic abnormalities and troponin elevation are seen in 89% and 94% of patients, respectively [16]. In the present case, the CK-MB fraction represented less than 5% of CK, and troponin was negative on admission. No abnormalities were observed on electrocardiography, and myocarditis due to an irAE was therefore considered unlikely.

MRI of musculoskeletal disorders in irAEs induced by ICIs typically show findings of myofasciitis and synovitis [17]. Inclusion body myositis is characterized by adipose tissue infiltration [18]. In addition, MRI findings in dermatomyositis and polymyositis often show signal hyperintensity in the fascia, with peripheral predominance in the muscles [19]. In the present case, muscle spasms were mainly seen in the proximal muscles, and MRI was performed on the right upper arm where the grasping pain was strong, but findings consistent with dermatomyositis or polymyositis were not seen, and apparently random areas of high signal intensity were evident on fat-suppressed T2-weighted imaging, making myositis difficult to suspect. No muscle biopsy was performed, because muscle damage after muscle spasms was thought to be more likely as a result. In addition, most cases of ICI-related myositis are treated with steroids or immunosuppressive drugs [20]. However, in the present case, those drugs were not used, and hyperCKemia was improved by treating the hypothyroidism. The possibility of myositis was therefore considered low.

#### 4. Conclusion

We have described a case of hypothyroidism due to an atezolizumab-induced irAE, which was diagnosed as a result of muscle spasms. Muscle spasms represent an important physical manifestation of hypothyroidism in patients treated with ICIs.

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#### Author contributions (credit roles)

Yosuke Nakanishi: conceptualization, Toshihide Yokoyama: supervision, Tadashi Ishida: writing-review and editing.

#### Declaration of competing interest

None.

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