Rhabdomyolysis in a patient with lung cancer with sintilimab-induced overlap syndrome and hypothyroidism: A case report

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Abstract. The use of immune checkpoint inhibitors (ICIs) has significantly improved outcomes in advanced malignancies, although these may induce immune-related adverse events (irAEs) involving multiple organ systems. The present case study reported on a 65-year-old man with squamous cell lung carcinoma who developed bilateral limb edema, profound fatigue and muscle weakness following chemotherapy, immunosuppressive therapy and iodine-125 brachytherapy. Laboratory tests revealed markedly elevated levels of creatine kinase and other muscle enzymes, overt hypothyroidism and positive antinuclear antibodies, consistent with overlapping immune-mediated myopathy and endocrine dysfunction. The patient was treated with diuretics, levothyroxine and tapering glucocorticoids, which led to a resolution of the symptoms, the normalization of enzyme levels and restoration of thyroid function. The excessive immune activation associated with ICI therapy, in combination with the hypometabolic state caused by hypothyroidism, may have acted as a synergistic 'double-hit' to skeletal muscle, which thereby contributed to the development of rhabdomyolysis (RM). This case highlights the need for vigilant monitoring of both musculoskeletal and endocrine systems in patients on ICIs, as the early recognition of irAEs is crucial to prevent life-threatening complications such as RM.

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Introduction

Lung cancer represents a major global health burden and remains one of the leading causes of cancer-associated morbidity and mortality worldwide (1,2). Contemporary treatment strategies have evolved into multimodal approaches, with surgical resection for early-stage disease, and combinations of platinum-based chemotherapy, radiotherapy and immune checkpoint inhibitors (ICIs) administered for advanced or unresectable cases (3). In parallel with the development of these strategies, emerging studies have explored novel adjuvant strategies, including bioactive compounds derived from traditional Chinese herbal medicines and nanomedicine-based drug delivery systems, which have offered new insights into potential adjunctive therapies (4-6).

Even though ICIs have transformed the therapeutic landscape of advanced malignancies, they have the disadvantage of being associated with a broad spectrum of immune-related adverse events (irAEs) involving multiple organ systems (7). Rhabdomyolysis (RM) is a clinical syndrome characterized by skeletal muscle fiber necrosis and the release of intracellular components, including myoglobin (Mb) and creatine kinase (CK), into the circulation. Clinically, it typically presents with myalgia, fatigue and dark-colored urine, and is most commonly caused by trauma, strenuous exercise or drug and toxin exposure (8). The excessive immune activation associated with ICI therapy, in combination with the hypometabolic state caused by hypothyroidism, may serve to act as a synergistic 'double-hit' to the skeletal muscle, contributing to the development of RM. Although isolated cases of RM triggered by ICI-induced hypothyroidism or inflammatory myopathy have been reported, the concurrent occurrence of these two conditions acting synergistically to precipitate severe RM remains relatively uncommon (9,10). The present case study reported on a patient with squamous cell lung carcinoma who developed severe synergistic immune-endocrine toxicity following sintilimab therapy, manifesting as overt hypothyroidism and

an overlap syndrome, ultimately culminating in profound RM. With the administration of supportive care, prompt levothyroxine replacement and a tapering glucocorticoid regimen, the elevated cardiac enzyme levels were found to decrease, the estimated glomerular filtration rate (eGFR) improved and the RM-associated symptoms were largely resolved. This case report underscores the importance of vigilant monitoring for overlapping irAEs and also provides new insights into how endocrine and immune dysfunction may converge to cause severe tissue injury.

Case report

A 65-year-old male was admitted to the Department of Cardiovascular Diseases at the Affiliated Hospital of Shandong University of Traditional Chinese Medicine (Jinan, China) in December 2024 with the chief complaint of bilateral hand and foot swelling, accompanied by fatigue for 2 months. On admission, the patient presented with prominent pitting edema of the hands and feet. The affected skin appeared dark yellow, coarse and deeply wrinkled. The patient also reported marked fatigue, a sensation of distension and tightness in the limbs, and minimal response to previous use of oral diuretics, including furosemide (20 mg qd) and spironolactone (50 mg qd), which had been prescribed by the doctor of Shandong Provincial Qianfoshan Hospital (Jinan, China) due to oedema. Additional symptoms included cold extremities, profuse sweating and rough skin over the swollen areas.

The patient had a history of old myocardial infarction for >3 years, and dyslipidemia of a similar duration, for which no lipid-lowering medications had been taken. The patient also had a history of cerebral infarction for >3 years, which had resulted in residual dysarthria and left lower limb motor impairment. A diagnosis of right pulmonary squamous cell carcinoma had been made >6 months prior to admission to the Affiliated Hospital of Shandong University of Traditional Chinese Medicine (Jinan, China). Between May and August 2024, the patient had undergone four cycles of chemotherapy and immunotherapy at the Provincial Hospital Affiliated to Shandong First Medical University (Jinan, China). In September of the same year, the patient received CT-guided implantation of radioactive iodine-125 seeds for local control of the right lung tumor at Shandong Provincial Qianfoshan Hospital (Jinan, China). The patient had a history of alcohol consumption for >40 years and tobacco use for >50 years, but had ceased consuming both since his lung cancer diagnosis. The patient denied any history of drug allergies or other adverse personal habits.

Cardiac examination on admission revealed a mildly enlarged cardiac silhouette, with the point of maximal impulse displaced inferolaterally. The patient's heart rate was 81 bpm, which was within the normal range, with a regular rhythm and strong heart sounds. Percussion indicated leftward and downward extension of cardiac dullness, and auscultation revealed an ejective systolic murmur in the aortic valve area. No notable positive findings were identified in the examination of other systems.

The patient first presented in April 2024 with hemoptysis at Jinan Traditional Chinese Medicine Hospital (Jinan, China). Chest CT revealed a space-occupying lesion in the right upper lobe of the lung. Bronchoscopy and biopsy of the right main bronchus subsequently confirmed squamous cell carcinoma. According to the 8th edition of the American Joint Committee on Cancer TNM Staging System, the patient was diagnosed with right upper lobe squamous cell carcinoma (stage cT2bN2M0; IIIA) (11). Based on the medical records provided by the patient, considering his history of arteriosclerosis, lobectomy was not recommended; instead, a combination regimen was initiated, including albumin-bound paclitaxel (on days 1 and 5), nedaplatin (on days 2 and 3) and sintilimab (on day 4) for concurrent chemotherapy and immunotherapy (information on the doses could not be retrieved).

Following the second treatment cycle, the patient developed hypothyroidism, as detected by a thyroid function test, which was suspected to be an irAE associated with sintilimab, as indicated in the patient's medical records. As a result, sintilimab was discontinued in subsequent cycles and the patient completed the remaining two cycles of chemotherapy with albumin-bound paclitaxel and nedaplatin alone. Approximately 2 months after having completed the four-cycle regimen, follow-up imaging revealed inadequate tumor control. The patient subsequently underwent the CT-guided implantation of iodine-125 radioactive seeds at Shandong Provincial Qianfoshan Hospital (Jinan, China) for localized brachytherapy, a total of 14 particles, each containing 0.8 mCi, were implanted into the tumor in an effort to reduce the size of the primary lesion.

Upon admission to the hospital, the attending physician ordered a series of laboratory tests. Key findings included the following: Creatine kinase-myocardial brand (CK-MB), 37.44 ng/ml (reference range: 0-5 ng/ml); CK, 4,974 U/l (reference range: 50-310 U/l); lactate dehydrogenase (LDH), 556 U/l (reference range: 120-250 U/l); α-hydroxybutyrate dehydrogenase (α-HBDH), 361 U/l (reference range: 59-126.4 U/l); free tri-iodothyronine, <0.6 pmol/l (reference range: 3.1-6.8 pmol/l); free thyroxine, <0.5 pmol/l (reference range: 12.8-21.3 pmol/l); thyroid stimulating hormone (TSH), >100 μIU/ml (reference range: 0.27-4.2 μIU/ml); thyroglobulin, <0.04 ng/ml (reference range: 3.5-77 ng/ml); thyroglobulin antibodies (TGAb), 533 IU/ml (reference range: 0-115 IU/ml); and thyroid peroxidase antibody (TPOAb), 63.8 IU/ml (reference range: 0-34 IU/ml). Additional test results are shown in Table I.

The above abnormal findings indicated a pathological state of irreversible damage to thyroid tissue, as suggested by the patient's thyroid function tests revealing Hashimoto's thyroiditis and hypothyroidism, combined with diffuse thyroid changes demonstrated by thyroid color Doppler ultrasound (data not shown). CK levels were found to 4,974 U/l (reference range: 50-310 U/l), exceed the upper limit of normal by 15-fold, with a CK/CK-MB ratio exceeding 100, suggesting that skeletal muscle injury predominated over myocardial involvement. Given the patient's muscle weakness on admission, RM was considered. Elevated cardiac enzyme levels, including CK, CK-MB, LDH and α-HBDH, are indicative of potential cardiac complications, such as myocardial infarction or coronary artery disease. Renal function was also found to be impaired, with an eGFR of 47.87 ml/min (chronic kidney disease, stage G3a; normal reference range: 90-120 ml/min), along with elevated levels of blood urea nitrogen at 10.56 mmol/l (reference range: 50-310 mmol/l), serum creatinine at 134 μmol/l

Table I. Key laboratory parameters at admission and prior to discharge.

Day 40 after discharge	-	28.40	1.58	68.00	224.00	193.00	-	65.00	97.27	402.00	-
Day 12 after discharge	-	-	4.89	269.00	265.00	181.00	-	111.00	60.11	483.00	-
Day 17-18	61.00	-	6.58	795.00	352.00	240.00	-	87.00	80.70	449.00	89.80
Day 12	54.00	-	11.70	1931.00	428.00	287.00	-	113.00	58.83	621.00	>100
Day 7	-	76.60	16.18	2256.00	433.00	304.00	171.28	89.00	78.51	-	-
Day 5	-	68.37	18.66	3199.00	474.00	313.00	137.53	88.00	79.59	-	-
Day 3-4	53.00	68.31	22.19	4311.00	474.00	288.00	153.95	99.00	69.03	-	-
Day 2	-	80.82	25.60	5102.00	490.00	305.00	-	99.00	69.03	-	-
Day 1	-	113.90	37.44	4974.00	556.00	361.00	-	134.00	47.87	553.00	>100
Normal reference value	0-15 mm/h	0-14 ng/l	0-5 ng/ml	50-310 U/l	120-250 U/l	59-126.4	28-72	57-111	90-120	208-428	0.27-4.2
range and units						U/l	ng/ml	μmol/l	ml/min	μmol/l	μIU/ml
Test items	ESR	hs-cTnT	CK-MB	CK	LDH	α-HBDH	Mb	sCr	eGFR	UA	TSH

ESR, erythrocyte sedimentation rate; hs-cTnT, high-sensitivity cardiac troponin T; CK-MB, creatine kinase-myocardial band; CK, creatine kinase; LDH, lactate dehydrogenase; α-HBDH, α-hydroxybutyrate dehydrogenase; Mb, myoglobin; sCr, serum creatinine; eGFR, estimated glomerular filtration rate; UA, uric acid; TSH, thyroid-stimulating hormone.

(reference range: 57-111 μmol/l) and uric acid at 553 μmol/l (reference range: 208-428 μmol/l), which indicated glomerular filtration dysfunction and tubular reabsorption impairment.

Based on the patient's clinical history and ancillary investigations, the attending physician immediately initiated symptomatic treatment, including diuresis (furosemide injection 2 ml qd iv) and urine alkalinization (sodium bicarbonate tablets 1 g tid p.o.), alongside fundamental supportive measures such as antiplatelet therapy (clopidogrel hydrogen sulfate tablets 75 mg qd p.o.) and liver function protection (glutathione injection 1.2 g qd iv drip).

Given the presence of renal impairment and severe hypothyroidism, consultations with the nephrology and endocrinology departments were requested on the day of admission. The attending physician, guided by the consultation findings, conducted autoimmune marker tests, including anti-neutrophil cytoplasmic antibodies (ANCA) and antinuclear antibodies (ANA). Subsequent assessments of the levels of adrenocorticotropic hormone, 31.1 pg/ml (reference range: 7.2-63.3 pg/ml) and cortisol, 85.08 μg/l (reference range: 48.2-195 μg/l) ruled out adrenal insufficiency, and therefore, levothyroxine sodium tablets (25 mg qd p.o.) was initiated.

On the third day of hospitalization, edema in the hands and feet persisted, although joint pain had subsided and muscle strength had partially recovered. Follow-up cardiac enzyme marker tests showed improvements in their levels. Mb levels reached twice the upper limit of normal, further supporting the diagnosis of RM. Positive ANA results suggested the possibility of autoimmune diseases. Accordingly, with informed consent from the patient and his family, the patient was referred to the rheumatology department for further specialized treatment. The rheumatology team conducted additional limb electromyography (EMG) and myositis antibody testing. The results obtained from the EMG indicated peripheral nerve damage in the limbs, including the median, tibial and peroneal nerves, presenting as multiple, asymmetric lesions affecting both sensory and motor fibers. Specifically, the distal motor latency of the median nerve was prolonged to 6.8 msec on the right and 5.2 msec on the left. The compound muscle action potential amplitude of the right common peroneal nerve recorded over the extensor digitorum brevis was markedly reduced to 1.5 mV. In addition, the sensory nerve action potential (SNAP) of the right median nerve (digit-wrist segment) was absent, and the SNAP amplitudes of the bilateral sural and superficial peroneal nerves were all <5 μV. Antibody testing revealed positive results for anti-PM-Scl75 antibodies (++), anti-proteinase 3 antibodies (+) and anti-mitochondrial M2 antibodies (+). Following several days of diuretic therapy, the patient's edema had significantly subsided, revealing palmar hyperkeratosis with fissures (‘mechanic's hands’) and purple papules (Gottron's papules) (12). These findings further suggested that the patient likely presented with an overlapping syndrome dominated by inflammatory myopathy, superimposed by ANCA-associated vasculitis and subclinical primary biliary cholangitis. However, after the rheumatology attending physician proposed a muscle biopsy, the patient declined this invasive procedure, and a definitive diagnosis could not be established from a pathological perspective.

On the seventh day of hospitalization, with the aforementioned investigations completed, the rheumatology team

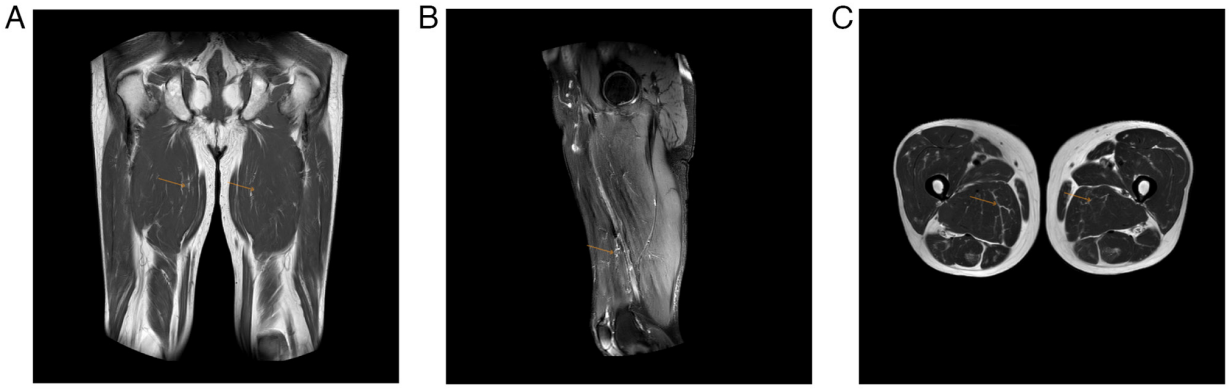

Figure 1. MRI of both thighs. The arrows indicate high signal intensity in the adductor muscle group and hamstring muscle group. (A) Oedema is seen in the vastus lateralis, intermedius femoris and semitendinosus muscles bilaterally. (B) Sagittal and (C) transverse angular views are shown.

prepared to initiate glucocorticoid pulse therapy to treat the inflammatory myopathy. Considering the patient's poor glycemic control, blindly adding corticosteroids might have had the effect of exacerbating the hyperglycemia risk (13). Therefore, treatment commenced with methylprednisolone sodium succinate (20 mg qd iv drip), while diuretic therapy and levothyroxine supplementation continued concurrently. An MRI of the lower limbs revealed persistent muscle edema with localized hematomas in multiple areas, including the biceps femoris and semitendinosus muscles, further supporting the radiological diagnosis of RM (Fig. 1). However, glucocorticoid use did induce significant hyperglycemia, with a randomly assessed blood glucose level reaching 15.9 mmol/l (reference range: 3.9-11.1 mmol/l); therefore, dapagliflozin (10 mg qd p.o.) and acarbose tablets (50 mg tid p.o.) were added to the regimen, and thereby, glycemic control was satisfactorily achieved.

The patient's condition gradually stabilized and improved, and plans were prepared for discharge and continued medication. Given the limited feasibility of intravenous administration outside the hospital, glucocorticoid therapy was to be switched to oral methylprednisolone tablets. In addition, the diuretic combination of drugs (furosemide plus spironolactone), blood glucose control medications (dapagliflozin plus acarbose) and hypothyroidism treatment (sodium levothyroxine) were all to remain unchanged.

At follow-up visits in January and February 2025, laboratory tests revealed that the myocardial enzyme levels had returned to near-normal levels and the eGFR had increased to 97.27 ml/min, indicating significant renal function recovery. The randomly assessed blood glucose level was 7.83 mmol/l and the hemoglobin A1c count was 8.6% (reference range: 4.0-6.0%), reflecting relatively stable glycemic control. The patient continued on the prescribed regimen, with sustained symptom relief and a favorable therapeutic response. Changes in the levels of cardiac enzymes, eGFR and thyroid function during the patient's hospitalization are shown in Fig. 2. The timeline of the patient's diagnosis and treatment process is shown in Fig. 3.

Discussion

This case report presents a highly complex multisystem toxicity event triggered by an ICI during the treatment of a patient with lung cancer. Following the administration of sintilimab, the patient sequentially developed severe hypothyroidism and overlap syndrome, which ultimately synergistically led to life-threatening RM. In reviewing the diagnostic and therapeutic course, it was observed that this sequence of events was not a simple superposition of single diseases; rather, it revealed that immune-endocrine axis dysregulation in the context of administering ICIs can produce synergistic effects, jointly attacking different target organs (14).

Cases where ICI-induced thyroiditis and myopathy sequentially occur in the same patient, and synergistically lead to severe RM, are relatively rare. In the present case, the elevation in the level of CK reached 4,974 U/l, ~15 times the upper limit of normal, far exceeding the levels commonly seen in myopathy associated with isolated hypothyroidism, which typically causes only a mild-to-moderate CK elevation (namely, <10 times the upper limit of normal) (15). CK=4,974 U/l supports the presence of dual pathological processes involving both immune-related inflammatory myopathy and hypothyroidism-associated endocrine myopathy. In addition, thyroid function testing revealed a TSH level >100 μIU/ml accompanied by a markedly reduced level of FT_4, consistent with severe primary hypothyroidism, a pattern that is commonly associated with destructive thyroiditis.

Recent evidence suggested that hypothyroidism significantly impairs muscle regenerative capacity and also alters metabolic homeostasis, which potentially diminishes myocyte resilience to additional injury (16). In hypothyroidism, the disruption of local thyroid hormone signaling pathways mediated by deiodinases (namely, D2 and D3) and thyroid hormone receptors (especially thyroid hormone receptor alpha) directly impairs satellite cell survival, myogenic differentiation and effective repair capacity (17,18). Under immune checkpoint inhibition, muscle cells may become more susceptible to T cell-mediated inflammatory attacks, leading to more extensive muscle necrosis.

The first-line chemotherapeutic regimen used (namely, nab-paclitaxel combined with nedaplatin administered to the patient) is representative of platinum-based concurrent chemoradiotherapy protocols for unresectable stage IIIB non-small cell lung cancer (19). Additionally, consolidation immunotherapy with sintilimab has been validated in clinical settings (20). However, clinical trials of sintilimab have reported that >10% of participants experienced

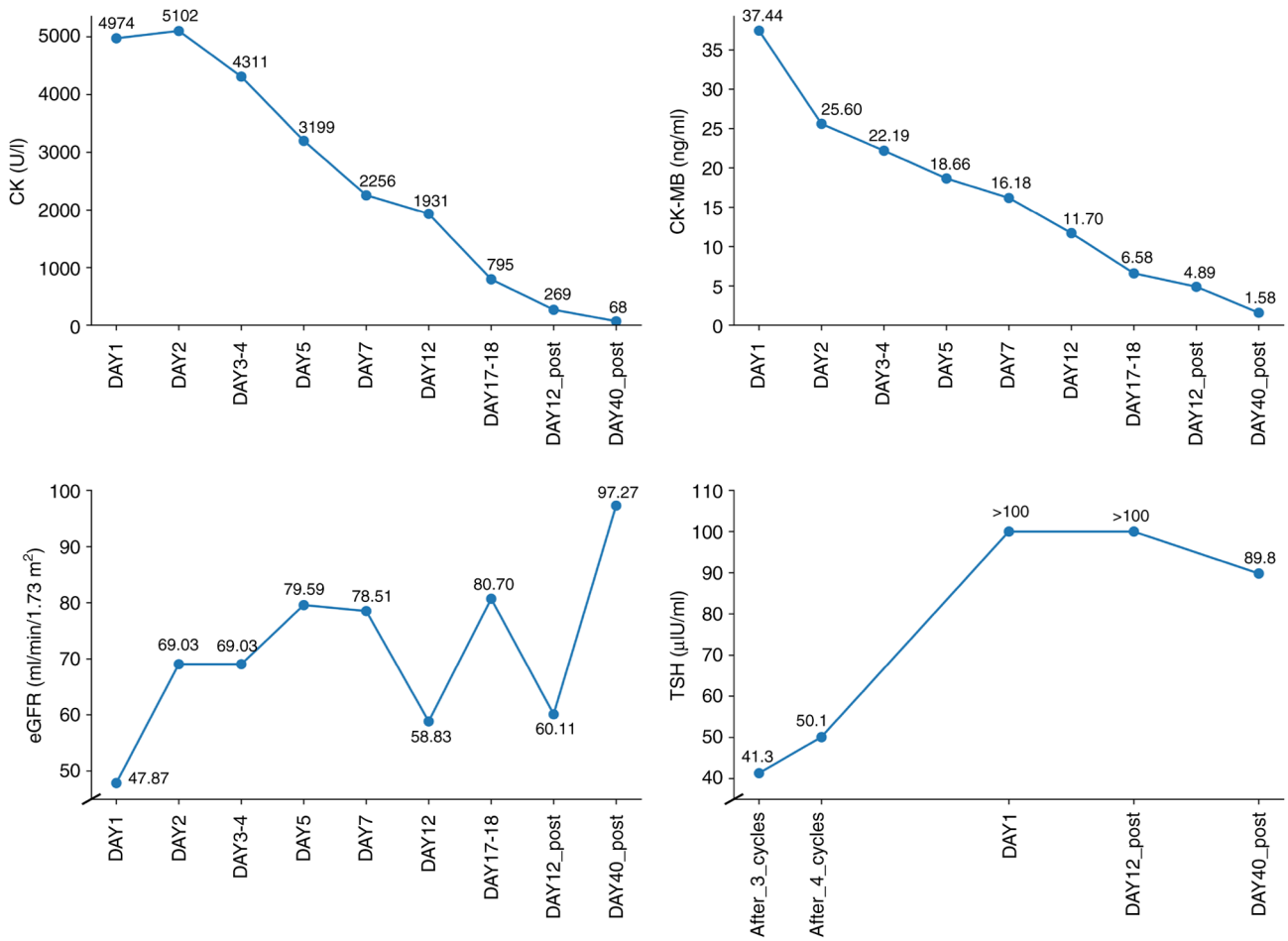

Figure 2. Dynamic changes in cardiac enzymes, and thyroid function during hospitalization and post-discharge review are shown. CK-MB, creatine kinase-myocardial band; eGFR, estimated glomerular filtration rate; TSH, thyroid-stimulating hormone.

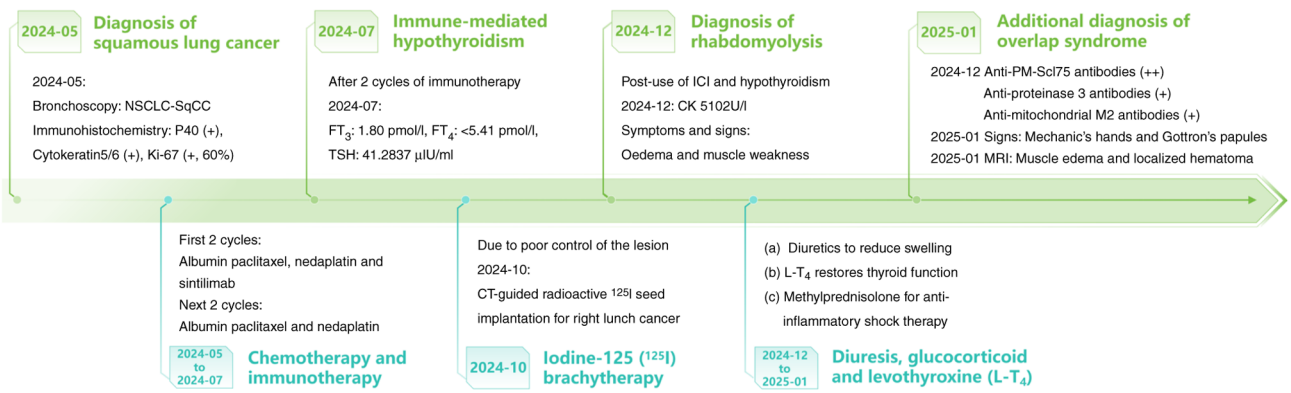

Figure 3. Timeline of disease progression and treatment interventions. NSCLC, non-small cell lung cancer; SqCC, squamous cell cancer; CK, creatine kinase; FT_3, free triiodothyronine; FT_4, free thyroxine; TSH, thyroid-stimulating hormone; ICI, immune checkpoint inhibitor; L-T_4, levothyroxine.

immune-associated endocrine dysfunction, including hypothyroidism (21). Programmed death-1 (PD-1) inhibitors are considered to cause destructive thyroiditis via activating T cells that infiltrate thyroid tissue and damage follicular cells, with this adverse reaction typically emerging after 1-3 treatment cycles. Concurrently, elevated levels of TPOAb and TGAb suggest the involvement of B cells, synergizing with T cell-mediated cytotoxicity to produce autoimmune thyroiditis, which typically precedes hypothyroidism (22). Regarding muscle damage, the presence of anti-PM-Scl75 antibodies similarly indicates B-cell involvement, suggesting an overlapping phenotype that ultimately manifests as an overlap syndrome characterized by inflammatory myopathy (23).

In the present case, both the thyroid and skeletal muscle became targets of immune attack, suggesting a systemic autoimmune storm at the cellular level driven by the core underlying mechanism of ICIs. PD-1 acts as a central 'brake' on peripheral T-cell activation, contributing to the maintenance

Table II. EULAR/ACR score sheet for the present patient.

EULAR/ACR item	Points	Evidence for the present patient
Onset age	2.1	Adult onset (age ≥40 years)
Symmetric proximal muscle weakness	2.4	Symmetrical proximal muscle weakness (affecting both upper and lower limbs), with proximal muscle weakness in the lower limbs being more pronounced than distal weakness.
Dysphagia	0	Absent
Gottron's papules / Gottron sign	2.1	Clinical exam: Gottron's papules become visible
CK elevation	1.3	Peak CK=5,102 U/l (document date: 2024.12)
EMG showing myopathic abnormalities	0	EMG did not demonstrate definite myopathic abnormalities, predominantly neuropathic features with spontaneous activity were noted.
Muscle biopsy consistent with IIM	0	Absent (patient declined)
Total score (without biopsy)	7.9	Total score=7.9 (without biopsy), exceeding the EULAR/ACR threshold for definite IIM classification.

According to the 2017 EULAR/ACR classification criteria, the following score thresholds correspond to the estimated probability of IIM: Without muscle biopsy: a) <5.3=exclude IIM (<50% probability); b) ≥5.3=suspicious IIM (≥50% probability); c) ≥5.5=probable IIM (≥55% probability); d) ≥7.5=definite IIM (≥90% probability). IIM, idiopathic inflammatory myopathy; CK, creatine kinase; EULAR/ACR, European League Against Rheumatism/American College of Rheumatology; EMG, electromyograph.

of self-tolerance through restraining effector T-cells and supporting the function of regulatory T-cells (Tregs) (24). As a PD-1 inhibitor, sintilimab not only promotes the expansion of $CD8^+$ T cells and tissue migration via releasing the inhibitory effect on T-cell activation, but it also exerts direct cytotoxic effects on parenchymal tissues, including thyroid follicular cells and skeletal muscle cells. Concurrently, it enhances $CD4^+$ T-cell-mediated support for B-cell responses and epitope spreading, thereby amplifying autoimmune reactions (25). This disrupts Treg-mediated autoimmune tolerance, thereby providing a common pathological basis for the simultaneous or sequential attack on multiple organs, clinically manifesting as clustered irAEs.

Under the influence of low thyroid hormone levels in severe hypothyroidism, mitochondrial oxidative phosphorylation in muscle cells is impaired, which leads to insufficient ATP production. Consequently, the activities of energy-dependent Na^+/K^+-ATPase and sarcoplasmic reticulum Ca^{2+}-ATPase are decreased, thereby impairing sarcoplasmic reticulum Ca^{2+} reuptake. This is accompanied by increased Ca^{2+} leakage mediated by rhabdomyolysis receptors, ultimately triggering cytoplasmic Ca^{2+} accumulation. This cytoplasmic Ca^{2+} overload further activates Ca^{2+}-dependent proteases, which both leads to an exacerbation of mitochondrial dysfunction and accelerates the disintegration of sarcolemma and myofibrils (26,27).

By contrast, immune-mediated myopathies primarily mediate muscle damage through immune effector mechanisms. Key pathways feature the activation and infiltration of $CD8^+$ T cells and macrophages, an abnormal upregulation of major histocompatibility complex class I molecules on muscle fiber surfaces, and the collaborative involvement of multiple autoantibody-dependent pathways. This process recruits and deposits the complement terminal complex (C5b-9) on to muscle capillary endothelium and myofibrillar structures, ultimately leading to focal myofibrillar necrosis and microvascular injury (28,29). These dual pathways of metabolic dysfunction and immune-mediated injury exhibit synergistic amplification effects at the skeletal muscle level, leading to extensive damage to myocyte membrane structures and significantly impaired repair capacity, ultimately precipitating myofibrillar destruction dominated by cell necrosis. The result is a massive release of intracellular components, which is manifested in laboratory tests as highly elevated CK levels (30). This provides mechanistic support for the critical role of the PD-1 inhibitor-associated dual-strike pathway in the occurrence of fulminant RM.

The mechanism of action of the aforementioned 'synergistic toxicity' has been well demonstrated in this case; however, although myositis-specific antibodies and myositis-associated autoantibodies provide important clues for diagnosing inflammatory myopathies, antibody positivity alone is insufficient to reliably distinguish between classic polymyositis, endocrine-associated myopathies, paraneoplastic inflammatory myopathies and ICI-associated myositis (31). The finding of neuropathic damage on EMG examination is not specific to idiopathic inflammatory myopathies (IIMs) and may also be observed in other neuromuscular disorders, such as chemotherapy-related or paraneoplastic peripheral neuropathies or chronic inflammatory demyelinating polyradiculoneuropathy. The patient's history of lung malignancy treated with radiotherapy, chemotherapy and immunotherapy suggests two non-mutually exclusive possibilities, either tumor-associated paraneoplastic myopathy or ICI-induced immune-mediated myopathy. Previous case reports and case series have confirmed that nivolumab and pembrolizumab may be associated with dermatomyositis/myositis and other myositis subtypes, suggesting that ICI therapy may either reveal underlying

paraneoplastic autoimmune phenomena or independently induce new-onset autoimmune myopathies (32-34).

A review of the patient's hospitalization records during antitumor therapy revealed that hypothyroidism had already developed in the course of immunotherapy. At that time, the attending physician diagnosed immune-related hypothyroidism and temporarily suspended the third and fourth cycles of ICI treatment. During the same period, ANA screening was negative and no further myositis-specific antibody testing was performed. Baseline thyroid function and rheumatologic autoantibody data prior to the initiation of immunotherapy were not available, which makes it difficult to definitively establish a causal relationship between immunotherapy and hypothyroidism. Notably, prior to the onset of endocrine dysfunction, the patient did not exhibit typical clinical manifestations suggestive of a paraneoplastic syndrome, such as characteristic rash or soft-tissue edema. Overall, while the possibility of a paraneoplastic process cannot be entirely ruled out, the temporal sequence and existing laboratory findings are more consistent with an immune-mediated mechanism.

Given the patient's refusal to undergo muscle biopsy during hospitalization, a definitive pathological diagnosis could not be obtained. Therefore, the classification of this case was primarily based on a comprehensive assessment of indirect evidence, including clinical symptoms and signs, laboratory findings and imaging data. According to the 2017 European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) classification criteria for adult IIMs, the patient presented with late-onset disease, which was clinically characterized by symmetric proximal muscle weakness and was accompanied by Gottron's papules, markedly elevated serum levels of CK and muscle edema, as revealed by muscle MRI imaging. In the 2017 EULAR/ACR scoring system without muscle biopsy, the cumulative score from these indicators reached 7.9 points, exceeding the threshold for a high probability of IIM. This suggested that the patient's comprehensive clinical presentation was highly consistent within the inflammatory myopathy spectrum (35). The specific points for each item in this scoring system are summarized in Table II.

The patient's complex antibody profile provided deeper diagnostic and differential diagnostic clues. In addition to anti-PM-Scl75 antibodies, positive anti-proteinase 3 and anti-mitochondrial M2 antibodies were detected, suggesting the potential for broader, or more latent, autoimmune activation following PD-1 blockade. During the clinical differential diagnosis process for the present case, a clear temporal correlation was noted between the onset of myopathic symptoms and serological abnormalities and the administration of sintilimab. Concurrently, the patient exhibited irAEs, including thyroid involvement and potential primary biliary cholangitis, and also demonstrated a marked response to glucocorticoid therapy. Further integration with the previously described history of sintilimab use, extensive autoantibody profile and multisystem involvement reveals pronounced overlapping features. Based on a comprehensive analysis of the above evidence, it was possible to classify this case as an ICI-associated overlap syndrome, primarily manifesting as inflammatory myopathy.

In the present case, during the course of diagnosis and treatment, it should be acknowledged that the absence of muscle biopsy imposed an inherent limitation on obtaining definitive histopathological confirmation. Although biopsy remains the gold standard for differentiating subtypes of immune-mediated myopathies and excluding non-inflammatory myopathies, the patient's refusal to undergo this invasive procedure reflects a common decision-making constraint encountered in real-world clinical practice. The term 'overlap syndrome' accurately reflects the complex clinical phenotype, and provides a coherent conceptual framework for understanding the unique pathophysiology of synergistic immune-endocrine toxicity.

In recent years, given the widespread use of ICIs, research on irAEs has increasingly shifted towards mechanistic elucidation and precision management. Distinct irAEs exhibit organ-specific immunological characteristics. In myositis-associated irAEs, large-scale transcriptomic analyses have demonstrated that different myositis subtypes harbor unique cytokine signatures and immune checkpoint gene expression profiles, thereby offering new insights into the biological heterogeneity of these conditions (36). In the context of thyroid toxicity, pre-existing antithyroid antibodies have been identified as important risk factors for the development of thyroid irAEs. For destructive thyroiditis, current management strategies have emphasized regular monitoring at monthly intervals during ICI therapy and the timely initiation of thyroid hormone replacement once hypothyroidism develops (37,38). Collectively, these advances have shown that contemporary irAE management is evolving towards a paradigm centered on risk stratification, early intervention and organ-specific therapeutic strategies. In parallel, efforts to identify the molecular pathways and predictive biomarkers for irAEs remain an active area of research (39). From a clinical practice perspective, current guidelines support a comprehensive approach: Patients with suspected ICI-associated inflammatory myopathy should undergo early evaluation, including cardiac enzyme assessment, muscle MRI, EMG and myositis-specific autoantibodies, with muscle biopsy also considered when feasible. For confirmed cases, multidisciplinary management involving oncology, rheumatology and endocrinology is recommended, together with timely initiation of stepwise immunosuppressive therapy, which is typically initiated with systemic corticosteroids (9,38,40).

In conclusion, through the diagnosis and management of this case, an irAE was used as the entry point to supplement existing knowledge regarding underlying mechanisms and real-world clinical decision-making. Building on prior descriptions of multisystem irAEs caused by ICIs, the concept of 'immune-endocrine synergy' may be proposed, whereby severe hypothyroidism and immune-mediated overlap myositis may act together to produce unusually marked creatine kinase elevations and RM. Future studies should further elucidate the shared genetic and immunological mechanisms underlying multisystem irAEs and prioritize the development of predictive biomarkers, thereby facilitating a transition from reactive management to precision prevention. From a clinical perspective, increased vigilance for irAEs during cancer immunotherapy is warranted. From a diagnostic standpoint, timely serologic testing is crucial, and particularly when muscle biopsy is not feasible, a composite strategy that integrates

targeted autoantibody panels, EMG, muscle MRI and early specialist consultation provides important practical guidance. Regarding prevention and treatment, the clinical course of this case underscores the need for proactive monitoring of cardiac enzymes together with thyroid function during ICI therapy, and for the timely initiation of immunomodulatory therapy and/or endocrine replacement when an irAE is identified. The occurrence of a single irAE should prompt consideration of potential overlapping events and the early initiation of coordinated multi-organ monitoring and multidisciplinary team-based management; such an approach may reduce the risk of severe complications and enable timely, pathophysiology-informed interventions that improve clinical outcomes.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

BC was involved in the conception and design of the study and drafted the manuscript. BC QZe and QZh were involved in the collection of data and clinical observations. BC and YL analyzed and interpreted the data. BC and QZe created and revised figures based on collected data. YL and SY acquired the medical images. BC, XL and QZh provided medical advice on patient treatment. YL and XL assisted in editing and revisions to the article. BC and QZh were involved in the follow-up of the patient after discharge from the hospital. BC, YL and QZh participated in the follow-up of the patient after discharge. BC and XL checked and confirmed the authenticity of the raw data. All authors confirmed the authenticity of all original data, and have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Written informed consent was obtained from the patient for the publication of this case report, including the images, data and treatment protocols generated during the course of treatment.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, artificial intelligence tools (ChatGPT version 4.0; https://chatgpt.com/) were used to improve the readability and language of the manuscript, and subsequently, the authors revised and edited the content produced by the artificial intelligence tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

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