Postprint: Diagnostic and Therapeutic Approach for Multisystem Immune-Related Adverse Events Induced by Immune Checkpoint Inhibitors

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Abstract

Immune checkpoint inhibitors (ICIs), as a novel class of anticancer therapeutics, have transformed the treatment landscape for multiple cancers. However, these therapies are associated with numerous potential complications, termed immune-related adverse events (irAEs). These complications may involve the nervous, cardiac, pulmonary, integumentary, renal, gastrointestinal, hepatic, and hematologic systems, among others. Although a series of guidelines for the management of immune-related adverse events have been issued domestically and internationally, clinicians' levels of awareness and attention to these conditions vary, and the early recognition, diagnosis, and treatment of immune-related adverse events in clinical practice remain inadequately standardized. This study reports the clinical data of a patient who developed severe multi-system irAEs following treatment with sintilimab, analyzes the case in conjunction with relevant literature, summarizes experiences worthy of reference as well as existing limitations, and provides insights for clinicians to better manage multi-system immune-related adverse events.

Full Text

Diagnostic and Therapeutic Approaches for Multiorgan Immune-Related Adverse Events Caused by Immune Checkpoint Inhibitors

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Abstract

Immune checkpoint inhibitors (ICIs) have transformed the therapeutic landscape for multiple cancers as a novel class of anticancer agents. However, these therapies carry potential complications known as immune-related adverse events (irAEs), which may affect the nervous, cardiac, pulmonary, cutaneous, renal, gastrointestinal, hepatic, and hematologic systems. Although numerous guidelines for managing irAEs have been issued domestically and internationally, clinical awareness and attention to these conditions vary among physicians, resulting in insufficient standardization in the early identification, diagnosis, and treatment of irAEs in clinical practice. This study reports the clinical course of a patient who developed severe multiorgan irAEs following treatment with sintilimab. Through case analysis integrated with relevant literature, we summarize valuable experiences and existing limitations to provide clinicians with insights for better management of multiorgan immune-related adverse events.

Keywords: Multiorgan; Immune-Related Adverse Events; Immune Checkpoint Inhibitors; Glucocorticoids; Sintilimab

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Immunotherapy has revolutionized established cancer treatments. As a primary immunotherapeutic approach, ICIs have achieved remarkable success in treating malignant tumors. These human-derived monoclonal antibodies restore antitumor immune function by blocking the programmed cell death 1 (PD-1)/programmed death-ligand 1 (PD-L1) pathway, thereby disrupting tumor immune evasion. In recent years, ICIs have been approved for antitumor therapy in China. However, clinical physicians across various specialties—including medical oncology, emergency medicine, internal medicine, and general practice—have relatively limited experience in recognizing and managing their associated adverse reactions. Additionally, some patients may require drug infusion in non-specialized medical settings, necessitating that emergency physicians, general practitioners, and community physicians understand the unique and sometimes fatal toxicological characteristics associated with immunotherapy to ensure timely diagnosis and treatment. Literature reports indicate that mild irAEs often require only symptomatic management, whereas severe irAEs may necessitate discontinuation of ICIs and initiation of immunosuppressive therapy, with multidisciplinary treatment implemented according to patient condition [**?**]. This report presents a case of severe multiorgan irAEs manifesting as myocarditis, myasthenia gravis, hepatic dysfunction, and hyperthyroidism, which ultimately resulted in clinical death following treatment with methylprednisolone and immunosuppressive therapy, complicated by severe pneumonia.

1.1 Patient Information

Chief Complaint: A 67-year-old male retiree was admitted 20 days after completing one cycle of chemotherapy for esophagogastric junction cancer.

Present Illness: In September 2021, the patient developed progressive dysphagia without apparent cause. Gastroscopic biopsy from an external hospital, reviewed at our institution, revealed poorly differentiated adenocarcinoma of the esophagogastric junction with signet ring cell carcinoma, MSS, HER-2(-). Chest, upper abdominal, and pelvic CT with contrast demonstrated: (1) thickened walls at the cardia, gastric fundus, and lesser curvature of the gastric body, consistent with carcinoma involving the distal esophagus; enlarged pericardial lymph nodes suspicious for metastasis; and slightly enlarged bilateral inguinal lymph nodes; (2) fatty liver with multiple hepatic cysts and small bilateral renal cysts; (3) prostatic hyperplasia; (4) increased markings in bilateral lower lungs, with linear opacities and small consolidations in the right middle lobe and left lingular segment, consistent with chronic lesions; (5) focal increased bone density in some thoracic vertebrae, requiring correlation with relevant examinations. With a definitive diagnosis of esophagogastric junction adenocarcinoma with lymph node metastasis, the patient received one cycle of PD-1 plus SOX regimen chemotherapy on October 26, 2021, consisting of sintilimab 200 mg on day 1, oxaliplatin 260 mg on day 1, and tegafur 60 mg twice daily on days 1-14, repeated every 3 weeks. The chemotherapy course was uneventful, and the patient was admitted for further management. Three days prior to admission, the patient intermittently experienced chest discomfort with fatigue and right eyelid ptosis. He reported no significant abnormalities on brain MRI at an external hospital. Mental status and bowel movements were normal.

Past Medical History: Hypertension for over 5 years, well-controlled with regular antihypertensive medication. No history of hepatitis, tuberculosis, or other infectious diseases. No diabetes or coronary artery disease. No surgical history.

Family History: No family history of genetic diseases.

1.2.1 Physical Examination

Physical examination revealed: temperature 36.5°C, pulse 79 beats/min, respiration 16 breaths/min, blood pressure 200/130 mmHg, height 1.72 m, weight 92 kg, body surface area 2.1 m^2. The patient exhibited normal development and moderate nutrition. No jaundice of skin or mucous membranes. Coarse breath sounds in both lungs without rales. No precordial prominence or thrill. Heart sounds were strong and regular, without pathological murmurs in any valvular auscultation area. Abdomen was flat and soft, without tenderness, rebound tenderness, or palpable masses.

1.2.2 Laboratory Findings

(1) Complete blood count, renal function, and electrolytes were normal.

(2) Liver function: ALT 234 U/L (↑), AST 599 U/L (↑).

(3) Thyroid function: T4 182 nmol/L (↑).

(4) Cardiac biomarkers: BNP <10 pg/ml, high-sensitivity troponin (hsTnl) 1323.28 pg/ml (↑), lactate dehydrogenase (LDH) 1297 U/L (↑), LDH isoenzyme (LDH1) 389 U/L (↑), creatine kinase (CK) 6729 U/L (↑), CK-MB >300 g/L (↑), myoglobin (MB) >3000 g/L (↑).

2. Treatment Process and Clinical Reasoning

2.1 Clinical Reasoning 1: Treatment Contraindications

Based on the patient' s history and prior medication regimen, could chemotherapy combined with immunotherapy be continued? What are the contraindications for chemotherapy and immunotherapy in cancer patients?

For cancer patients, standardized and individualized treatment plans are formulated according to disease characteristics. Before initiating a new treatment cycle, comprehensive assessments including complete blood count, hepatic and renal function, and cardiac function must be performed to confirm the patient' s general condition: (1) Performance status: Karnofsky score should generally be $ $70, and PS score $ $2 to consider chemotherapy; (2) Hematologic parameters: total white blood cell count $ 3.0×10^{9}$/L or platelet count $ 100×10^{9}$/L; (3) Major organs including heart, lungs, liver, and kidneys should be essentially normal; (4) No grade III or higher severe toxic reactions to drugs in the previous regimen.

Based on the patient' s current condition—blood pressure 200/130 mmHg, intermittent chest discomfort, hyperhidrosis with fatigue, right eyelid ptosis, markedly elevated cardiac biomarkers, and liver function abnormalities exceeding 2 times the upper limit of normal—multiorgan irAEs were suspected, including immune myocarditis, immune myasthenia, and immune hepatitis. These findings constituted treatment contraindications, requiring immediate suspension of combined chemotherapy and immunotherapy. Symptomatic supportive care was initiated with methylprednisolone 2 mg/kg, along with hepatoprotective agents (magnesium isoglycyrrhizinate, polyene phosphatidylcholine, and bicyclol) and omeprazole for stress ulcer prophylaxis.

2.2 Clinical Reasoning 2: Diagnosis and Assessment of irAEs

How are irAEs diagnosed and assessed? Why is grading necessary? What was this patient' s irAE grade?

IrAEs fall under the category of adverse drug reactions (ADRs). According to the *Technical Guidelines for the Evaluation of Immune-Related Adverse Events of Antitumor Therapy* [**?**], determining that this patient's irAE was caused by sintilimab requires consideration of: (1) whether systemic steroids, other immunosuppressants, or endocrine replacement therapy were administered for the target irAE and the subsequent outcome—the patient received methylprednisolone and mycophenolate mofetil with improvement in chest discomfort, cardiac biomarkers, and liver injury, which is consistent; (2) pathological examination results—not available; (3) target immunologic mechanism—consistent; (4) temporal relationship between the event and treatment—consistent; (5) whether the event has been reported and clearly identified as an irAE for the same target drug —consistent; (6) severity of the target irAE and whether single or multiple organ/system involvement—consistent; (7) patient history of autoimmune disease and baseline disease status—the patient had no autoimmune disease history and baseline examinations before ICI therapy were normal, which is consistent; (8) support from safety-related biomarkers—the patient' s high-sensitivity troponin and myoglobin were markedly elevated, which is consistent; (9) exclusion of other etiologies and important clinical differential diagnoses for non-immune events with similar manifestations—consistent; (10) exclusion of other reasonable explanations for the target adverse event (e.g., infection, concomitant medications, and underlying diseases)—consistent. In summary, the patient was definitively diagnosed with multiorgan irAE caused by sintilimab.

According to the Chinese Society of Clinical Oncology (CSCO) *Guidelines for the Management of Immune Checkpoint Inhibitor-Related Toxicities* (2021) [**?**], irAEs are classified into four grades, with clinical management based on grading principles. For grade 1 toxicity, ICI therapy may continue with close monitoring, except for certain hematologic, cardiac, and neurologic toxicities. For grade 2 toxicity, consider suspending ICI therapy, which may resume when symptoms recover to grade 1 or lower. If symptoms persist beyond one week, corticosteroids are administered. For grade 3 toxicity, suspend ICI and initiate high-dose corticosteroids. Refractory cases without response within 48-72 hours may require immunosuppressive therapy with agents such as infliximab, with specialist consultation encouraged for refractory cases. When toxicity decreases to grade 1, consider rechallenge with caution, particularly in cases with early-onset toxicity. For grade 4 toxicity, ICI should be permanently discontinued, except for endocrine disorders controlled by hormone replacement.

This patient' s multiorgan irAE involved the heart, nervous system, liver, and thyroid. During ICI therapy: (1) The patient developed fatigue, palpitations, and intermittent chest discomfort accompanied by other irAEs such as hepatic dysfunction and thyroid dysfunction. After excluding pulmonary embolism and exacerbation of primary cardiovascular disease, myocarditis grade 3-4 was considered; (2) Right eyelid ptosis and fatigue symptoms were present, with a myasthenia gravis severity score of 1, accompanied by elevated CK and CK-MB, suggesting grade 2 myasthenia gravis. However, comprehensive neurologic examination and exclusion of other central and peripheral nervous system etiolo-

gies are required for diagnosing myasthenia gravis, with biopsy when necessary —this patient did not undergo such evaluation; (3) Elevated ALT and/or AST with or without bilirubin elevation suggests ICI-related hepatotoxicity. This patient' s ALT was 234 U/L and AST 599 U/L (>10×ULN), indicating grade 3 hepatotoxicity; (4) Unexplained palpitations, sweating, increased bowel movements, and weight loss warrant consideration of hyperthyroidism, confirmed by elevated free T4 or T3 with normal or decreased TSH. This patient' s serum T4 was 182 nmol/L without obvious physical symptoms, suggesting grade 1 hyperthyroidism. Comprehensive assessment determined the multiorgan irAE as grade 3-4.

2.3 Clinical Reasoning 3: Glucocorticoid Use

What are the appropriate dose, duration, and discontinuation protocols for glucocorticoids? Was glucocorticoid use appropriate in this patient?

On hospital day 1, the patient received intravenous methylprednisolone 200 mg. On days 2-6, the dose was increased to 400 mg/day with mycophenolate mofetil 1000 mg twice daily. On day 7, despite persistent fatigue, the methylprednisolone dose was reduced to 200 mg/day after improvement in chest discomfort. Several issues were identified: (1) **Insufficient initial dose.** Zhang et al. [**?**] collected data from 126 patients with irAEs treated with corticosteroids, categorizing them into low (<60 mg/day), medium (60-500 mg/day), and high (501-1000 mg/day) dose groups based on initial methylprednisolone equivalent on day 1. Higher initial doses (i.e., intravenous methylprednisolone 1000 mg/day) were closely associated with improved cardiac outcomes in ICI-related myocarditis. Although consensus on glucocorticoid dosing for fatal irAEs such as myocarditis and pneumonitis is lacking, existing reports and studies support a trend that higher initial immunosuppressive doses correlate with lower rates of major adverse cardiac events [**?**]. This patient with multiorgan irAE grade 3-4 involving vital organs (e.g., heart) received an inadequate initial steroid dose. (2) **Overly rapid taper.** To prevent toxicity recurrence, glucocorticoid tapering should be gradual (>4 weeks, sometimes requiring 6-8 weeks or longer). While no definitive rules for dose reduction exist, steroids are typically decreased by 10 mg every 1-2 weeks until symptoms improve to mild levels, then gradually tapered over 4-6 weeks. After reducing the dose below 30 mg, the steroid dose is decreased by 2.5-5 mg every 1-2 weeks [**?**]. This patient' s methylprednisolone dose was directly reduced from 400 mg to 200 mg, representing an overly rapid taper. In summary, the glucocorticoid regimen was suboptimal.

2.4 Clinical Reasoning 4: Outcome After Glucocorticoid and Immunosuppressant Therapy

Did the patient improve after glucocorticoid and immunosuppressant therapy? What should be the next management step?

Nine days after initiating glucocorticoid and immunosuppressant therapy, the

patient suddenly developed altered consciousness. Following cardiopulmonary resuscitation, his oxygenation index was 52 mmHg, white blood cell count $32.98\$\times10\hat{}\{9\}/L.Chestradiographyshowedpatchyinfiltratesintheleftlowerlungwithincreasedmarkingsand$ $6, severepneumoniacouldnotbeexcluded.VitalsignswereHR80-90beats/min, BP100-120/50-60mmHg, RR22breaths/min, SpO\_\{2\}\$$ 87-90%. Auscultation revealed diminished breath sounds bilaterally. Arterial blood gas showed pH 7.374, $PaCO_2$ 66.9 mmHg, PaO_2 52 mmHg, BE 12 mmol/L, SaO_2 82%. Fiberoptic bronchoscopy revealed slightly congested and edematous airway mucosa with abundant grayish-yellow grade I-II secretions in bilateral lower lungs (approximately 5-8 ml), which were thoroughly cleared, and deep airway secretions were collected for culture. Given multiorgan irAE involvement of vital systems with high toxicity grade, multidisciplinary consultation and ICU-level monitoring were warranted. Blood gas analysis indicated type II respiratory failure, prompting ICU transfer.

2.5 Clinical Reasoning 5: ICU Management Strategy

What treatment strategy should ICU physicians formulate for this patient' s complex condition?

2.5.1 Comprehensive Analysis and Reassessment

(1) The patient was an elderly male (67 years) who presented for the second cycle of esophagogastric junction adenocarcinoma treatment, having experienced intermittent chest discomfort with fatigue and right eyelid ptosis for three days prior to admission. (2) The patient was obese (weight 92 kg, BMI=31.10 kg/m^2) with admission blood pressure of 200/130 mmHg. (3) Laboratory findings at ICU admission: Inflammatory markers: WBC $34.21\$\times10^{\{9\}/L, neutrophils31.92\times10}\{9\}/L, IL-6120.3pg/ml, PCT0.39ng/ml.Biochemistry: ALT133U/L, AST144U/L, TBIL19.6\mu mol/L, DBIL10.4\mu$ $C2.35mg/L, K\hat{}\{+\}\$$ 4.3 mmol/L, Na^+ 136 mmol/L, lactate 4 mmol/L, BNP 28.52 pg/ml, hsTnI 2483.29 pg/ml, Pcv-aCO_2 4.2 mmHg, $Scvo_2$ 59%. Blood gas: pH 7.389, Pco_2 62.3 mmHg, Po_2 57 mmHg, BE 13 mmol/L, HCO_3 37.2 mmol/L, SaO_2 86%. At 24 hours after ICU admission, APACHE II score was 44 with a mortality risk coefficient of 82%, and SOFA score was 14.

2.5.2 Management Strategy

(1) The patient had definitive diagnoses of immune myocarditis, cardiogenic shock, and heart failure following immunotherapy. Given critical condition requiring high-dose dopamine combined with norepinephrine for blood pressure maintenance, fluid resuscitation was guided by hemodynamic parameters including intake/output, blood pressure, and blood gas analysis to ensure tissue perfusion. (2) Progressive elevation of hsTnI suggested inadequate response to methylprednisolone 2 mg/kg/day. Therefore, methylprednisolone 1000 mg daily pulse therapy was initiated com-

bined with immunoglobulin 0.5 g/kg/day and mycophenolate mofetil 1000 mg every 12 hours for irAE management, with regular efficacy assessment. (3) The patient developed pneumonia with elevated inflammatory markers and fever. Considering hemodynamic instability and high-dose steroid use, high risk for severe infection was recognized. Fungal workup was completed. Bronchoalveolar lavage NGS returned positive for *Candida albicans* and *Aspergillus fumigatus*; blood NGS returned positive for *Acinetobacter*. Antimicrobial therapy with meropenem 1 g every 8 hours, vancomycin 1.5 g every 12 hours, and voriconazole 400 mg every 12 hours was initiated. Changes in inflammatory markers are shown in Figure 1, other parameters in Figure 2, and cardiac biomarker hsTnI in Figure 3.

[Figure 1: see original paper]
[Figure 2: see original paper]
[Figure 3: see original paper]

2.6 Follow-up and Outcome

Despite symptomatic supportive care and antimicrobial therapy, the patient' s inflammatory markers improved but respiratory status did not. After family discussion, they elected to forgo further treatment and requested discharge. Telephone follow-up on December 5, 2021 confirmed the patient had died.

Discussion

IrAEs are common and diverse in clinical practice, yet the incidence, clinical characteristics, and predisposing factors of multiorgan irAEs require further investigation. Multiorgan irAEs are defined as involving more than one organ system, driven by multiple components of the immune system with varying incidence, timing, and severity. Clinicians should pay greater attention to multiorgan irAEs to enable more effective monitoring and management of this increasingly common condition.

This report describes a case of multiorgan irAEs including myocarditis, myasthenia gravis, hepatitis, and hyperthyroidism occurring after only one cycle of sintilimab, which ultimately resulted in death despite treatment with corticosteroids, immunosuppressants, and supportive care. Reviewing the entire disease management process yields the following insights: (1) **Early recognition of irAEs with prompt treatment discontinuation.** The patient' s clinical symptoms were not ignored to continue chemotherapy. IrAEs differ pathophysiologically from conventional anticancer drug toxicities due to their involvement in physiological process activation, making predisposing factors less clear and early identification challenging. Predictive and sensitive biomarkers serve as effective tools for identifying and comprehensively characterizing irAEs. Mahmood et al. [**?**] compared data from patients with and without immune-mediated myocarditis after ICI therapy, finding that discharge/final cTnT $ 1.5ng/mlincreasedtheriskofmajorcardiacadverseeventsfourfold.AlthoughcTnTisamyocardialinjurymar

$organ - specificirAEbiomarkersincludecytokines, CRP, andinterferon-$ \$, whose abnormalities should prompt consideration of irAEs after excluding primary diseases. (2) **Timely antimicrobial therapy.** This patient developed ventilator-associated pneumonia after high-dose steroids and immunosuppressants. Appropriate antibiotic therapy critically determines hospital stay and recovery. As a hospital-acquired pneumonia occurring \$ \$5 days after admission, the likely pathogens were multidrug-resistant organisms including *Klebsiella pneumoniae* and other Enterobacteriaceae, *Pseudomonas aeruginosa*, *Acinetobacter* species, MRSA, and *Legionella pneumophila*. According to the *Guidelines for Clinical Application of Antimicrobial Agents* [**?**], anti-pseudomonal β-lactams or carbapenems are recommended, combined with anti-pseudomonal fluoroquinolones or aminoglycosides when necessary. If MRSA is suspected, glycopeptides or linezolid should be added. Additionally, invasive fungal infections are important causes of mortality in ICU patients [**?**], with *Aspergillus* and *Candida* as primary pathogens. Prophylactic voriconazole reduces *Aspergillus* infections in allogeneic stem cell transplant patients. This patient received appropriate therapy with vancomycin, meropenem, and voriconazole, resulting in gradual improvement of inflammatory markers. (3) **Treatment limitations.** The patient did not undergo evaluation or treatment for myasthenia gravis symptoms. Myasthenia gravis management typically includes symptomatic and immunosuppressive therapy, with pyridostigmine bromide, an acetylcholinesterase inhibitor, considered initial therapy for most patients. All myasthenia gravis patients receiving adequate pyridostigmine bromide who fail to achieve treatment goals should receive glucocorticoids or immunosuppressants [**?**]. For multiorgan irAEs, particularly those involving vital organs, insufficient attention was paid to initial steroid dosing, which was inadequate, and the taper was overly rapid, potentially contributing to the poor outcome.

Yanase et al. [**?**] reported a successfully treated case of myocarditis and myasthenia gravis induced by combined nivolumab and ipilimumab therapy for renal cell carcinoma. The patient received initial treatment in the ICU to prevent myasthenia gravis deterioration or cardiac arrest. Intravenous methylprednisolone pulse therapy began at 1000 mg/day for three days. Complete atrioventricular block resolved on day 2, with sinus rhythm restoration. CPK levels steadily decreased to 778 ng/mL by day 3. Methylprednisolone was reduced to 200 mg on day 4. With poor neurologic improvement, plasma exchange was performed every other day for four sessions, resolving eyelid ptosis. CPK normalized. At 4 weeks, CPK rose again to 1014 ng/mL, but normal ECG and troponin T indicated myasthenia gravis rather than myocarditis recurrence. Intravenous immunoglobulin 400 mg/kg was administered for 4 days, normalizing CPK. Steroids were subsequently tapered, and after 6 months, myocarditis and myasthenia gravis remained inactive despite steroid discontinuation, with good outcome. Notably, steroids can cause acute clinical deterioration in approximately 50% of myasthenia gravis patients, progressing to respiratory failure. Therefore, steroids alone as first-line therapy may be suboptimal for multiorgan irAEs including

myasthenia gravis. Evidence suggests [**?**] that intravenous immunoglobulin and plasma exchange as first-line therapy may yield better outcomes than steroids alone, recommended before or concurrent with steroids to overcome transient deterioration risk. Kazuma et al. [**?**] reported a head and neck cancer patient with multiple severe simultaneous irAEs managed through multidisciplinary collaboration: dermatologists addressed skin issues, gastroenterologists managed digestive symptoms, ophthalmologists improved ocular symptoms, and endocrinologists monitored diabetes and hypothyroidism. Hydrocortisone 1 mg/kg/day (50 mg) was initiated immediately after irAE diagnosis for 7 days, then tapered to 40 mg/7 days, 30 mg/7 days, 20 mg/14 days, and 15 mg/14 days, with multidisciplinary care throughout. Dermatitis and inflammation of tracheal membranes and digestive tract gradually improved after steroids; ocular conjunctivitis was treated with steroid eye drops; hypothyroidism was managed with levothyroxine sodium; and hyperglycemia from type I diabetes was well-controlled with insulin within weeks. The patient began oral intake on day 41 and was discharged on day 58. Experienced multidisciplinary team involvement in customizing treatment strategies may positively impact prognosis.

Finally, clinicians should note several key points regarding irAEs: (1) **Potential mechanisms** driving irAEs [**?**] include: activation of cytotoxic T cells; B cell activation and increased autoantibody production; direct molecular mimicry and off-target toxicity; activation of intracellular signaling and proinflammatory cytokine production; environmental regulation of immune system activation, including host gut microbiome composition. These mechanisms may help identify predictive biomarkers and targeted therapeutic strategies. (2) **Population risk factors:** Current research indicates [**?**] that gender, age, smoking, prior disease, BMI, and ECOG performance status are associated with irAE development, though no unified conclusions exist. Retrospective studies of cardiac events during ICI therapy report higher risks of irAE myocarditis, pericarditis, arrhythmias, CAD, and MI in males [**?**]. Wong et al. [**?**] found that while ICIs appear similarly effective in younger and older patients, adults $ $65 years have significantly increased irAE incidence compared to patients aged 18-64 receiving ICI monotherapy or combination therapy, with fatal irAEs occurring in older patients (median age 70 vs. 62 years). Patients with cardiovascular risk factors (hypertension, CAD, HF, MI) are more susceptible to cardiac irAEs [**?**]. A Korean study [**?**] found significantly increased irAE risk in patients receiving pembrolizumab with BMI $ $25kg/m\hat{}\{2\}$, with high BMI patients having greater irAE risk even with lower metabolic risk. Japanese research [**?**] reported higher-grade irAEs in lung cancer patients with smoking history and poor performance status (ECOG $ $2). This elderly male patient with hypertension and obesity represented a high-risk profile requiring close monitoring during ICI therapy. (3) **Timing of irAEs:** Successful irAE management requires understanding general patterns. Reports indicate [**?**] that cutaneous irAEs occur earliest (median 2-6 weeks), followed by gastrointestinal events (6-7 weeks), immune-related hepatitis (6-9 weeks), and endocrine irAEs relatively later (28 weeks). Immune-mediated myocarditis occurs at a median of 30 days, and

immune-mediated myasthenia gravis at 2-6 weeks. However, irAEs can occur anytime after ICI therapy, typically within 1-6 months, but also within days or over 1 year after treatment completion. The possibility of early irAEs must not be overlooked—this patient developed multiorgan irAEs including myocarditis, myasthenia gravis, hepatitis, and hyperthyroidism after only one sintilimab cycle. (4) **Patient education importance:** Comprehensive patient education is fundamental to toxicity management and high-quality cancer care. Enhanced awareness of expectations during treatment can improve coping skills and resilience, ultimately enhancing treatment adherence and health outcomes. Effective irAE management [**?**] requires early recognition and timely reporting of signs and symptoms. Key information includes treatment response and irAE timing, early irAE identification, and the unique ability of ICIs to continue affecting immune responses after treatment discontinuation. Before initiating ICIs, physicians must assess patient susceptibility to toxicities and provide information to patients and caregivers regarding signs and symptoms heralding irAE onset. Some patients may hesitate to report symptoms for fear of discontinuing anticancer therapy, and high-quality patient education can alleviate these concerns. This patient experienced irAE symptoms for several days before admission without adequate attention—earlier presentation might have altered the outcome.

Given the remarkable clinical outcomes across tumor types, immune checkpoint inhibitor use continues to increase significantly in oncology. While emphasizing tumor eradication with ICIs, clinicians must also focus on alerting patients to autoimmune complications. However, irAEs reported in clinical trials are typically limited to single organs, preventing accurate information on multiorgan irAE incidence and timeline. Multiorgan irAEs in the same patient may affect treatment decisions for both adverse reactions and cancer, requiring multiple medications and various specialists for management. Therefore, thorough understanding of multiorgan irAEs caused by ICIs is crucial. This case demonstrates that multiorgan irAEs generally appear early and progress rapidly, potentially evolving to fatal outcomes without timely recognition and management. Corticosteroids are the cornerstone of irAE therapy, with severe cases also requiring intravenous immunoglobulin, plasma exchange, and other immunomodulatory treatments. Close multidisciplinary collaboration may further enhance the benefits of immunotherapy.

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Note: Figure translations are in progress. See original paper for figures.