CASE REPORT

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A case of severe immune-related adverse events, myocarditis with myositis, and myasthenia gravis overlap syndrome following adjuvant nivolumab administration for muscle-invasive bladder cancer

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ABSTRACT

Herein, we present a case of severe immune-related adverse events (irAEs), myocarditis with myositis, and myasthenia gravis overlap syndrome (IM3OS) in a patient receiving an immune checkpoint inhibitor (ICI), as adjuvant therapy after surgery for muscle-invasive bladder cancer. An 80-year-old woman who had undergone a total cystectomy for bladder cancer presented with ptosis, diplopia, and paralysis 18 days after receiving nivolumab, an anti-programmed cell death-1 (PD-1) monoclonal antibody, as adjuvant therapy for the first time. Initial testing revealed positive findings on the ice pack test; elevated troponin, creatine kinase, and aldolase levels; and an abnormal electrocardiogram, suggesting that the patient had developed ICI-related myocarditis, myositis, and myasthenia gravis. Despite treatment with intravenous immunoglobulin (IVIG) and high-dose corticosteroids, her condition worsened, leading to a complete atrioventricular block. After cardiac pacemaker insertion and intensive treatment with repeated high-dose corticosteroids, IVIG, plasma exchange, and tacrolimus, left ventricular function and myositis symptoms improved. However, the patient developed a respiratory infection and renal failure, leading to death on day 99. Although ICIs are considered relatively safe with few side effects, they can cause serious complications and lead to death. In particular, when severe irAEs occur in multiple organs, such as IM3OS, the prognosis is poor. Although IM3OS has no specific diagnostic biomarker, making early detection difficult, clinicians should always pay attention to patient symptoms when using ICI and evaluate other pathologies with IM3OS when conditions such as myositis or myocarditis are suspected. Further research is needed to elucidate the pathophysiology and risk factors of IM3OS.

Keywords: immune checkpoint inhibitors, immune-related adverse events, IM3OS, bladder cancer, adjuvant therapy

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Abbreviations:
CK: creatine kinase
ECG: electrocardiogram
ICI: immune checkpoint inhibitor
IM3OS: ICI-induced myocarditis with myositis and/or myasthenia gravis overlap syndrome

INTRODUCTION

Urothelial carcinoma (UC), including bladder cancer, is a common cancer associated with a poor prognosis in patients with muscle-invasive tumor and/or metastatic disease. Platinum-based chemotherapy has remained the cornerstone of systemic anticancer treatment for many years, and recent developments in the treatment landscape have improved outcomes. In particular, in patients with newly diagnosed muscle-invasive bladder cancer, neoadjuvant cisplatin-based chemotherapy before radical cystectomy is recommended. In addition, the administration of nivolumab (up to 12 months), an anti-programmed cell death-1 (PD-1) monoclonal antibody, as adjuvant immune checkpoint inhibitor (ICI) therapy, has been reported to significantly improve prognosis in patients with high-risk muscle-invasive UC.

In general, ICI therapy is considered to have a low incidence of serious adverse events and can be administered easily in an outpatient setting. However, we experienced a case of severe immune-related adverse events (irAEs), including myositis, myocarditis, and myasthenia gravis, during adjuvant therapy after surgery for muscle-invasive bladder cancer.

Here, with the consent of the patient's family, we report this case to assist in the treatment of similar cases in the future.

CASE PRESENTATION

An 80-year-old Japanese woman was hospitalized to receive nivolumab as adjuvant therapy after total cystectomy for muscle-invasive bladder cancer. She was discharged from our hospital on the fourth day of administration with no apparent adverse effects. At a routine outpatient visit 14 days after the first nivolumab administration, only serum creatine kinase (CK) level was elevated to 1,180 U/L, common terminology criteria for adverse events (CTCAE) version 5.0 grade 3, (normal range: 41–153 U/L); however, there were no ancillary symptoms including myalgia or chest pain, external injury, or fever. The second course of nivolumab was postponed, and the patient was under strict observation. On the 18th day after nivolumab administration, she presented to the emergency department of our hospital with ptosis, diplopia, and paresis. Her past medical history was significant for hypertension and thyroid cancer, for which she received treatment over 10 years ago and was in remission. She had no history of autoimmune diseases. Vital signs on admission were as follows: temperature, 36.7°C; heart rate, 100 bpm; blood pressure, 118/47 mmHg; respiratory rate, 20/min; and oxygen saturation, 99% on room air. On physical examination, manual muscle tests were 5/5 on most measures; however, the ice pack test result was positive. Additionally, eye movement disorder and proximal muscle paresis were observed. Troponin T, CK, and aldolase levels were elevated to 2.2 ng/mL (grade 3, normal range: <0.014 ng/mL), 6,417 U/L (grade 4), and 83.5 U/L (normal range: 2.1–6.1 U/L), respectively. The anti-acetylcholine receptor antibody titer revealed a slightly elevated value of 2.60 nmol/L (normal range: <0.2 nmol/L). Other laboratory data were within the normal range.

An electrocardiogram (ECG) demonstrated a new-onset complete right bundle branch block.

Based on the patient's clinical presentation and the investigations described above, ICI-induced myocarditis (grade 3) with myositis (grade 3), and myasthenia gravis (grade 3) overlap syndrome (IM3OS) were suspected. The clinical course and treatments are shown in Figure 1. Intravenous immunoglobulin (IVIG, 25 mg daily for 5 days) was initiated on day 19. The next day, the ECG demonstrated a new-onset complete atrioventricular (AV) block, and the troponin T level increased to 3.57 ng/mL. A worsening myocarditis was suspected. The patient was transferred to the intensive care unit (ICU) after undergoing coronary angiography (CAG) and an endomyocardial biopsy. CAG revealed no evidence of coronary artery disease, and the biopsy revealed lymphocyte-induced myocarditis (Figure 2). Thus, intravenous methylprednisolone (1000 mg/day for 3 days followed by 1 mg/kg/day) was administered on day 20. CK levels recovered to the normal range within 3 days. On day 33, the ventricular tachycardia (VT) arose into severe left ventricular hypokinesis. ECG revealed various arrhythmias, including right branch bundle block, complete AV block, and premature ventricular contraction. Worsening myocarditis was a serious concern, and a cardiac pacemaker was inserted. After a second endomyocardial biopsy was conducted to evaluate the effectiveness of the first treatment, second-line treatment was initiated. On day 35, a combination of a second dose of intravenous methylprednisolone (1000 mg/day), plasma exchange, tacrolimus, and a second dose of IVIG was administered. Antiarrhythmic medication (amiodarone) and a cardiovascular agonist (dobutamine) were administered. The VT

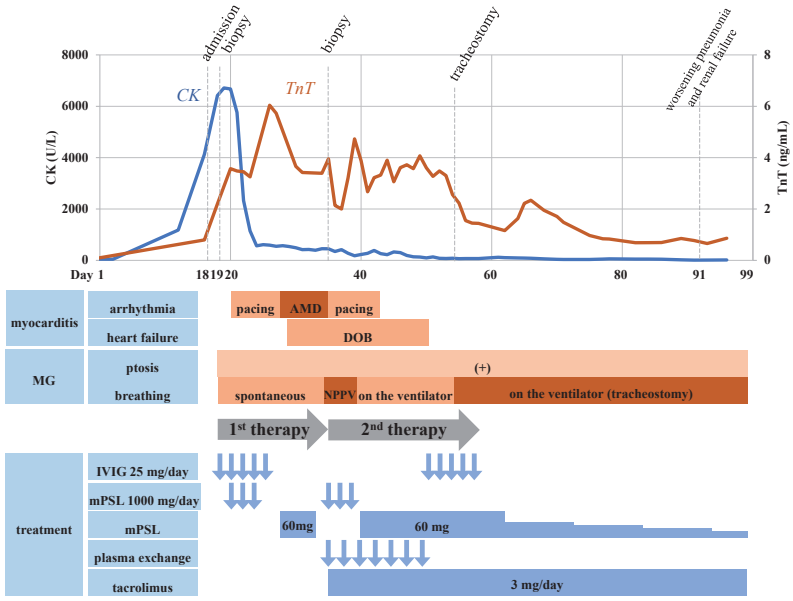

Fig. 1 Clinical course and treatment of the patient

AMD: amiodarone
CK: creatine kinase
DOB: dobutamine
IVIG: intravenous immunoglobulin
MG: myasthenia gravis
mPSL: methylprednisolone
NPPV: non-invasive positive pressureventilation
TnT: troponin T

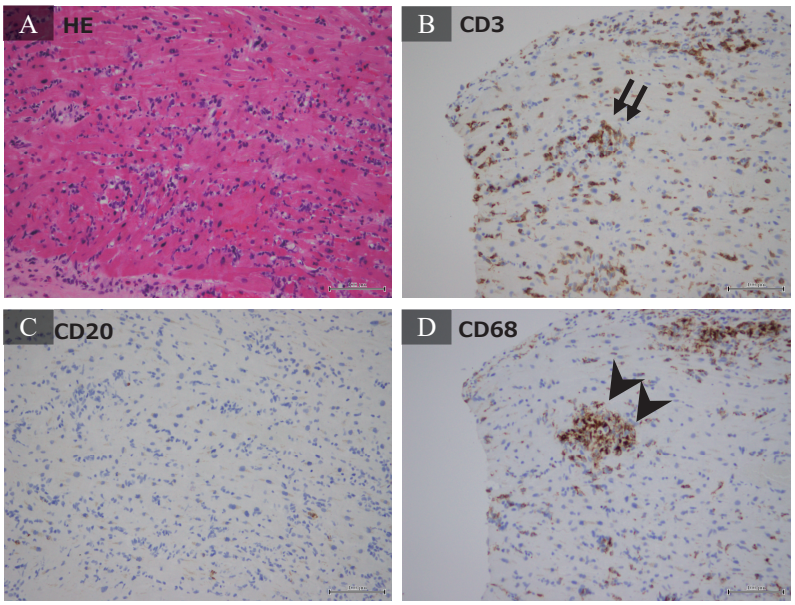

Fig. 2 First endomyocardial biopsy
The first endomyocardial biopsy revealed lymphocytic myocarditis. Hematoxylin and eosin (HE), CD3, CD20, and CD68 staining are shown in (A), (B), (C), and (D), respectively. Infiltration of the inflammatory cells into the myocardial cells can be also observed (A). CD3 staining indicates the presence of T lymphocytes (B). CD20 staining indicates the absence of B lymphocytes (C). Infiltration of CD68-positive macrophages was also confirmed (D).
Arrows: T lymphocytes
Arrowheads: CD68-positive macrophages

and left ventricular ejection fraction (LVEF) improved with these treatments. However, ptosis and paresis persisted, and the patient required continued ventilatory support. She was discharged from the ICU and transferred to the ward 58 days after the tracheostomy.

Thereafter, maintenance therapy was continued; however, the patient's general condition deteriorated with progressive disuse syndrome, worsening pneumonia and renal failure, and increased pleural effusion and ascitic fluid. Her family did not want additional invasive treatment, including renal replacement therapy, and emphasized their desire for the patient's best comfort. The patient died 99 days after the initial nivolumab administration.

DISCUSSION

The gemcitabine-cisplatin therapy, which has been used as standard neoadjuvant/adjuvant chemotherapy for UC, has been reported to cause grade 3 or greater neutropenia in 71.1% of the patients, grade 3 or greater thrombocytopenia in 57% of the patients, and grade 3 nausea in 22% of the patients.[1] However, Bajorin et al reported the efficacy of adjuvant nivolumab therapy for the treatment of bladder cancer with few adverse events (approximately 1% or more).[2] Thus, ICIs were considered relatively safe drugs that did not exhibit these hematological toxicities. However, ICIs can occasionally cause serious immune-related complications. In a systematic review of irAEs, a mortality rate of 57% was reported in patients who developed IM3OS.[3]

To the best of our knowledge, this is the first report of IM3OS in a patient receiving adjuvant nivolumab therapy for muscle-invasive bladder cancer, and the diagnosis and treatment of this disease have been challenging. The mechanisms, diagnoses, and treatments for IM3OS are discussed below.

Mechanism of IM3OS development

Generally, the following mechanisms are thought to be responsible for the development of irAEs: i) antigen cross-reactivity between tumor and healthy tissue, ii) release of tumor and healthy tissue antigens following tumor destruction, or iii) direct toxicity from ICI.[4] Recently, it was reported that some patients with ICI-induced myasthenia gravis had autoimmune antibodies against cardiac and skeletal muscle as well as acetylcholine receptors.[5] Johnson et al also reported that IM3OS cases had a common high-frequency T-cell receptor sequence in the myocardium, skeletal muscle, and infiltrates from tumors,[6] suggesting that IM3OS may not be a pure combination of myocarditis, myositis, and myasthenia gravis, but may develop through common antibody responses. In particular, the presence of anti-acetylcholine receptor antibodies, a biological indicator of thymic-associated autoimmunity, is implicated in the development of ICI-related myocarditis and myasthenia gravis.[7] In the present case, the anti-acetylcholine receptor antibody titer was also slightly elevated. Although the risk factors for the development of IM3OS and the mechanism of its severity are unknown, the antibody titer of anti-acetylcholine may be an indicator of the disease.

Diagnosis of IM3OS

There is no promising biomarker to diagnose IM3OS. Therefore, if either myocarditis, myositis, or myasthenia gravis is suspected, it is essential to screen for other conditions that may not be apparent and proceed with examinations simultaneously.

Myocarditis

There are several examinations to diagnose myocarditis including elevated serum cardiac muscle troponin T and natriuretic peptide levels, positive ECG, echocardiogram, and endomyocardial biopsy findings.[8] It has been reported that 85% of patients with IM3OS developed arrhythmias on ECG and 23% had developed a decrease in LVEF on echocardiography.[3] However, among these parameters, serum cardiac muscle troponin T level is elevated early in the development of myocarditis, as observed in this case, and should always be measured as a screening evaluation when ICI therapy is introduced.

Myocardial biopsy is a useful examination for the definitive diagnosis of myocarditis, which is characterized by two main components: inflammatory infiltrate and myocardial necrosis.[9] As observed in our case (Figure 2), myocardial biopsy shows a significant presence of CD3+ T cells and CD68+ macrophages, with few CD20+ B cells in ICI-induced myocarditis.[10] In addition, late gadolinium enhancement in the cardiovascular magnetic resonance (CMR) represents the localization of pathological lymphocytic infiltration.[11] In the future, CMR may help diagnose myocarditis.

Myositis

Patients with myositis typically present with progressive proximal upper and lower extremity weakness, myalgia, and fatigue. Occasionally, ptosis, ophthalmoplegia, and dysphagia were observed. On laboratory tests, elevated CK, liver transaminases, lactate dehydrogenase, aldolase, and inflammatory markers (erythrocyte sedimentation rate, C-reactive protein) suggest myositis.[12] Although the presence of endomysial inflammatory infiltrates on muscle biopsy and necrosis or myophagocytosis in a multifocal pattern is typical of ICI-related myositis, no biological and

clinical markers are pathognomonic for ICI-related myositis.[4,13] In the present case, elevated CK was observed even before the onset of muscle weakness in the upper and lower extremities, and CK measurement after ICI treatment may be a useful screening test for myositis.

Myasthenia gravis

The distinctive characteristics of myasthenia gravis are fluctuating fatigability and weakness affecting the ocular, bulbar, and (proximal) limb skeletal muscle groups. Positive findings on electromyography, repetitive nerve stimulation, and single-fiber electromyography suggest myasthenia gravis.[3] Autoantibodies against the acetylcholine receptor or another target on the surface of the muscle membrane, such as low-density lipoprotein receptor-related protein, have been reported in some patients treated with ICI.[14] The anti-acetylcholine receptor antibody titer were also elevated in this patient from the time of the onset of muscle weakness. This antibody is thought to be involved in the development of other ICI-related complications, such as myocarditis and myositis, and should be measured as soon as possible when muscle weakness and dyspnea are observed after ICI treatment.

Treatment of IM3OS

Although there are no definitive treatments for IM3OS, several reports have been published. A systematic review reported that all IM3OS patients received high-dose corticosteroid therapy, and many patients received upfront IVIG and plasmapheresis to prevent the paradoxical exacerbation of myasthenia symptoms observed with steroids alone.[3] For refractory cases, corticosteroids were supplemented with other immunosuppressive drugs such as tacrolimus, infliximab, mycophenolate mofetil, or antithymocyte globulin.[3] Our patient also showed improvement in myocarditis and myositis with the above combination therapies; however, the improvement was not adequate to wean the patient off ventilation. Patients with severe symptoms such as those seen in our patient appear to be resistant to treatment.

CONCLUSION

Here, we reported the case of a patient who developed severe IM3OS after nivolumab administration as adjuvant therapy. The patient received intensive treatment but ultimately died. Postoperative adjuvant therapy intended to reduce postoperative recurrence and cancer-specific mortality has occasionally resulted in premature death due to serious complications. Because the development of IM3OS after ICI therapy is rare but fatal, clinicians must provide adequate information to the patient and obtain consent before ICI therapy is introduced. Additionally, IM3OS should be recognized when a patient develops muscle weakness or elevated myocardial enzyme levels and serum CK during treatment, and prompt diagnosis and treatment should be conducted. Further research is needed to elucidate the pathophysiology and risk factors of IM3OS.

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CONFLICT OF INTEREST STATEMENT

The authors state that they have no conflict of interest.

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