A Fatal Case of Myocarditis Following Myositis Induced by Pembrolizumab Treatment for Metastatic Upper Urinary Tract Urothelial Carcinoma

Hotaka Matsui, MD, Taketo Kawai, MD, Yusuke Sato, MD, Junichi Ishida, MD, Hiroshi Kadowaki, MD, Yoshiyuki Akiyama, MD, Yuta Yamada, MD, Masaki Nakamura, MD, Daisuke Yamada, MD, Hiroshi Akazawa, MD, Motofumi Suzuki, MD, Issei Komuro, MD and Haruki Kume, MD

Summary

We report a case of lethal myocarditis and myositis after pembrolizumab treatment for advanced upper urinary tract urothelial carcinoma. A 69-year-old man underwent pembrolizumab therapy as a second-line treatment. He had myalgia and a slightly elevated creatinine kinase (CK) on the day of the second administration of pembrolizumab. Five days later, the patient was admitted with severe fatigue and an abnormal gait. Physical examination revealed reduced muscle reflexes and proximal muscle weakness. An electrocardiogram (ECG) demonstrated a wide QRS complex ventricular rhythm. A marked elevation of cardiac enzymes, including CK, myoglobin, and cardiac troponin I, was detected. Myocardial biopsy revealed inflammatory cell infiltration and the partial impairment of myocardial tissue. The electromyogram was normal, but inflammation in myofibers was noted in a muscle biopsy. Myocarditis and myositis as immune-related adverse events (irAEs) were suspected, and the patient began intravenous steroid therapy and plasma exchange. However, the patient underwent cardiac arrest three days after admission and began extracorporeal membrane oxygenation and intra-aortic balloon pumping therapy. Despite steroid pulse therapy, the patient demonstrated no sign of improvement and subsequently died 17 days after admission. Immune-mediated myocarditis is a rare but fatal irAE of an immune checkpoint inhibitor (ICI). The present case suggests that myositis precedes myocarditis. Therefore, if myositis is suspected, subsequent myocarditis may need attention. In conclusion, we found that myositis and myocarditis developed in a patient with advanced urothelial carcinoma after pembrolizumab treatment. A routine follow-up of CK and cardiac troponin I, as well as an ECG, should be performed to identify any possible ICI-induced myocarditis and myositis quickly.

Key words: Immune checkpoint inhibitor, Immune-related adverse event, Creatinine kinase, Cardiac troponin I, Myocardial biopsy, Steroid pulse therapy

Case Report

The patient was a 69-year-old man with multiple metastases to the liver, lung, and lymph nodes from left renal pelvic cancer. He underwent pembrolizumab treatment, at a dose of 200 mg/body, after the failure of ten courses of first-line salvage chemotherapy with gemcitabine and carboplatin. All blood tests, physiological tests, including electrocardiogram (ECG; Figure 1A), and a chest X-ray (Figure 2A) were within normal limits before the patient began pembrolizumab therapy. Three weeks after the first administration, the patient complained of myalgia. A subsequent biochemical blood test revealed a slight elevation of creatinine kinase (CK; 498 U/L). However, the pembrolizumab was administered as scheduled because the pa-
The patient reported that he had recently exercised excessively. The patient presented to the emergency room for severe fatigue and an abnormal gait five days after the second treatment of pembrolizumab. A physical examination revealed bilateral diplopia, bilateral ptosis, and decreased brachioradialis, triceps, patellar tendon, and Achilles’ tendon reflexes. Dysesthesia was found bilaterally in the hands and feet. Weakness was noted in bilateral iliopsoas and neck muscles. The patient was not able to squat. Although a chest X-ray did not show any pulmonary congestion (Figure 2B), an ECG showed a wide QRS complex ventricular rhythm (Figure 1B). Myocarditis and myositis were suspected as irAEs of pembrolizumab. The patient was admitted to the hospital for further evaluation and close monitoring of vital signs (Figure 3).

Biochemical blood tests revealed elevations of CK (3,887 U/L), CK-myocardial band (CK-Mb; 143 U/L), myoglobin (3,800 ng/mL), and high-sensitive cardiac troponin I (10,318 pg/mL) (Figure 3). Anti-acetylcholine receptor and anti-muscle specific tyrosine kinase antibodies were negative.

An echocardiogram revealed that systolic cardiac function was preserved (a left ventricular ejection fraction of 50%) without significant edema in the ventricular wall and pericardial effusion (Figure 4A). The coronary angiogram showed no evidence of coronary artery disease. A myocardial biopsy was performed. Histological findings showed infiltration of lymphocytes and eosinophils into the myocardial extracellular space with partial impairment of myocardial tissues (Figure 5), which led to a histopathological diagnosis of myocarditis.

An electromyogram was recorded at the right deltoid, biceps, and iliopsoas muscles, which were within normal limits. A muscle biopsy was taken from the left bicep,
which demonstrated no infiltration of inflammatory cells or necrosis. However, immunostaining for human leukocyte antigens (HLA)-A, B, and C revealed an increase in HLA-positive cells on myofibers in muscle bundles, suggesting an inflammatory background of muscle weakness.

The patient was transferred to a coronary care unit because a wider QRS complex ventricular rhythm was recorded on an ECG compared with that on admission (Figure 1C), which suggested worsening myocarditis. A chest X-ray revealed no pulmonary congestion (Figure 2C). The patient began intravenous prednisolone (PSL) therapy (15 mg/day/body) for ICI-induced myocarditis and myositis. At this time, steroid pulse therapy was not initiated, and plasma exchange was performed, because the possibility of myasthenia gravis could not be ruled out. However, the patient developed ventricular arrhythmia (an echocardiogram indicated severe impairment of systolic cardiac function; Figure 4B), and subsequent cardiac arrest three days after admission. The patient was revived after cardiopulmonary resuscitation and began extracorporeal membrane oxygenation (ECMO) as well as intra-aortic balloon pumping therapy (IABP). Four days after admission, steroid pulse therapy with methylprednisolone (mPSL) 1000 mg/day was started and continued for three days, followed by 1 mg/kg/day PSL. Cardiac enzyme levels, including cardiac troponin I, began decreasing five days after admission (Figure 3). However, six days after admission, an ECG demonstrated a complete atrioventricular block, suggesting worsened myocarditis. Therefore, a temporary pacemaker was inserted into the right ventricle. Although
cardiac enzyme values continued to decrease, there was no sign of recovery of cardiac function, and the patient continued to require ECMO and IABP. Seventeen days after admission, the patient died.

Discussion

The use of pembrolizumab as second-line therapy has improved the prognosis of advanced urothelial carcinoma. However, irAEs are often reported. Myocarditis, in particular, is lethal as an irAE. The prevalence of myocarditis after ICI is around 1% with a median time of onset of 34 days after starting ICI. Combination ICI therapy (e.g., nivolumab plus ipilimumab) has a higher risk of myocarditis than monotherapy. An elevated troponin level and an abnormal ECG are highly specific for myocarditis after ICI. Currently, there is no established consensus for treating myocarditis following ICI therapy. Mahmood, et al. reported that 31 out of 35 cases of myocarditis with immune checkpoint inhibitors received steroid therapy, with a mean steroid dose of 120 mg/body; even with a high initial steroid dose of 1000 mg mPSL, two patients experienced major adverse cardiac events (MACEs). Immunosuppression therapy with other agents was also attempted, such as with infliximab, immunoglobulin, mycophenolate, and anti-thymocyte globulin. Nevertheless, myocarditis was treated successfully in only 30-50% of patients administered nonsteroidal immunosuppressive agents.

The present case also received a high dose of mPSL (1000 mg/body); however, the myocarditis progressed, and plasma cardiac enzyme values became elevated, including cardiac troponin I (Figure 3), which suggested massive

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Figure 5. Histological findings of myocardial biopsy. Infiltration of lymphocytes and eosinophils into the myocardial extracellular space was observed (arrow). Myocyte damage was also found (arrowhead). Bar indicates 200 μm.

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Figure 6. Proposed diagnostic algorithm for screening and diagnosis of an immune checkpoint inhibitor (ICI)-related myocarditis. In patients receiving ICIs, an electrocardiogram (ECG) should be recorded, and cardiac troponin I should be measured before every ICI administration, particularly within two months of ICI initiation. When abnormal ECG findings and/or elevated cardiac troponin I are detected, the patient should be referred to the Department of Cardiovascular Medicine. In the case of suspected myocarditis, ICI termination, the cardiac catheter, including endomyocardial biopsy and coronary care unit administration, can be considered. BNP indicates B-type natriuretic peptide; CCU, coronary care unit; ECG, electrocardiogram; and ICI, immune checkpoint inhibitors.
necrosis of myocardial tissues. As a result, the patient was unable to recover from a MACE.

Myositis is another rare irAE of ICIs and is often accompanied by myocarditis. Several case reports exist on myositis after pembrolizumab therapy, including at least three publications that described fatal cases of pembrolizumab-induced myopathy. Myositis was observed after two cycles of pembrolizumab treatment in most cases, which is comparable with the present case. Currently, no consensus has been reached on the histopathological features of ICI-induced myositis since histopathological findings have been varied. Furthermore, electromyogram findings were not necessarily abnormal in some reported cases of ICI-induced myositis. The present case indicated no abnormality in the electromyogram or any obvious necrosis suggesting myositis in the muscle biopsy specimen. However, HLA-ABC staining suggested inflammation in the muscle bundle; the patient was subsequently treated with plasma exchange in addition to systemic steroid therapy for myositis. Nevertheless, the patient was not saved from a combination of myositis and myocarditis.

Several previous reports on the use of pembrolizumab have described the co-existence of myositis and myocarditis; myositis is associated with 20-40% of myocarditis cases. However, reports are lacking on which develops first: myositis or myocarditis. The present case suggests that myositis precedes myocarditis because myalgia and a slight elevation of CK were already observed on the second pembrolizumab administration. Discrepancies in the degree of elevation between CK and CK-Mb at admission may support this hypothesis. If our hypothesis is correct, subsequent myocarditis may need attention in cases in which myositis is suspected.

Previous reports and the findings of the current case suggest that the combination of myositis and myocarditis can aggravate the mortality rate of irAEs. A marked increase in CK and cardiac troponin I, and an abnormal ECG were detected in the present case at admission. We have created an algorithm for the initiation of ICI therapy and follow-up to avoid the risk of developing fatal myocarditis in future patients under ICI therapy at our hospital (Figure 6).

In conclusion, we found that myositis and myocarditis developed in a patient with advanced urothelial carcinoma after pembrolizumab treatment. We suggest that a routine follow-up of CK and cardiac troponin I, as well as an ECG, should be performed to identify any possible ICI-induced myocarditis and myositis promptly.

Disclosure

Conflicts of interest: The authors declare no conflict of interest.

Ethical approval and consent for publication: The Ethics Committee at the University of Tokyo Hospital approved this report (Approval number: 3124). The patient and family provided written consent to the publication of clinical data. A review of the present case was performed according to the ethical principles of the Declaration of Helsinki.

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