CASE REPORT

Asymptomatic Myocarditis with Mild Cardiac Marker Elevation Following Nivolumab-Induced Myositis

Akito Shindo,1,2 MD, Masataka Yamasaki,1 MD, Keita Uchino,3 MD and Masao Yamasaki,1 MD

Summary

Although myocarditis following immune checkpoint inhibitor (ICI) therapy is rarely reported, it is considered clinically important because of its high mortality rate. Although various tests may be used for early diagnosis, abnormalities suggestive of myocarditis may not be detected. We report a case of ICI-induced myositis and concurrent asymptomatic myocarditis with mild cardiac marker elevation following nivolumab therapy in a 79-year-old man with metastatic gastric cancer. In this case, cardiac magnetic resonance imaging was useful for diagnosis. Treatment with oral prednisolone rapidly improved the patient’s symptoms and creatine kinase levels. Follow-up examination revealed no flare-up of myositis and exacerbation of myocarditis. Since ICI-induced myositis is often complicated by myocarditis, this case report highlights the importance of detecting concurrent myocarditis in patients with ICI-induced myositis through intensive cardiac assessments to improve clinical outcomes.

Key words: Immune checkpoint inhibitor, Immune-related adverse events, Onco-cardiology, Cardio-oncology

Immune checkpoint inhibitors (ICIs) have dramatically improved the clinical outcomes of patients with advanced or refractory cancers. However, immune-related adverse events that may affect any organ have been commonly reported following ICI therapy, prompting subsequent management. Among these, myocarditis is particularly important because of its high mortality. Nevertheless, the diagnosis of ICI-induced myocarditis is often difficult to establish because some cases are asymptomatic and often detected via laboratory examinations at late stages. In this paper, we present a case of ICI-induced myositis and asymptomatic myocarditis with slightly elevated cardiac biomarkers following nivolumab therapy in a patient with metastatic gastric cancer.

Case Report

A 79-year-old man with gastric cancer and peritoneal metastasis presented with lower extremity muscle weakness 11 days after nivolumab therapy. Four months before the consultation, he was treated with oral fluorouracil for 4 months. Nevertheless, the tumor size increased, which prompted treatment modification to paclitaxel. Although paclitaxel was effective, nivolumab was started as a third-line therapy because the patient presented with paclitaxel-induced peripheral neuropathy. However, 11 days after nivolumab therapy, the patient complained of lower extremity muscle weakness, which prompted consultation with our hospital.

Blood tests revealed elevated levels of creatine kinase (CK) (1015 U/L, reference: ≤ 248 U/L) and highsensitivity troponin T (hs-TnT) (31 pg/mL, reference: ≤ 14 pg/mL) with normal CK-myocardial band (CK-MB) levels (2.9 ng/mL, reference: ≤ 3.1 ng/mL). Despite this, the patient did not report any chest symptoms. Electrocardiography (ECG) revealed no abnormalities (Figure 1). Serologic tests confirmed the absence of anti-acetylcholine receptor antibodies, which excluded the possibility of myasthenia gravis. These findings were consistent with a diagnosis of ICI-induced myositis, which prompted the discontinuation of nivolumab.

Treatment with oral prednisolone (30 mg) rapidly improved the patient’s symptoms and CK levels. However, his hs-TnT levels remained slightly elevated, which prompted a referral to the cardiology department for further evaluation. Transthoracic echocardiography showed a normal left ventricular global longitudinal strain (GLS) of −17.0% with no wall motion abnormalities and pericardial effusion (Figure 2). Levels of high-sensitivity troponin I (hs-TnI), a more specific myocardial marker compared with hs-TnT, were not elevated (3.38 pg/mL, reference: ≤ 26.2 pg/mL). This suggests that the elevated hs-TnT levels were likely due to myositis. Cardiac magnetic resonance imaging (MRI) was performed because of the high rates of concurrent myocarditis in patients with ICI-induced myositis. T2-weighted imaging demonstrated a hyperintense signal at the basal anterior wall septum of the left ventricle. Late gadolinium enhancement imaging...
Figure 1. Electrocardiogram (ECG) showing no remarkable ST-T change or arrhythmias before and after nivolumab administration. “Day −7,” “Day 12,” and “Day 35” represent the ECG before nivolumab administration, when myositis is diagnosed, and when myocarditis is diagnosed, respectively.

Figure 2. Echocardiography showing no wall motion abnormality or decreased global longitudinal strain (GLS).

Figure 3. Cardiac magnetic resonance imaging showing a high-intensity area on T2-weighted image (A, white arrows) and late gadolinium enhancement (B, C, white arrows) at the left ventricular basal anterior wall septum.

demonstrated hyperenhancement in the same area (Figure 3), suggestive of myocardial edema and inflammation. Magnetic resonance coronary angiography showed no significant stenosis and perfusion defects in the coronary arteries, which ruled out acute coronary syndrome. These findings were consistent with a diagnosis of ICI-induced...
myocarditis.

Since the patient was asymptomatic, the prednisolone therapy was tapered off with careful monitoring. Follow-up examination revealed no flare-up of myositis and exacerbation of myocarditis (Figure 4).

Unfortunately, 2 months after the diagnosis of myositis, contrast-enhanced computed tomography showed an increase in tumor size. Because of concerns about the recurrence of myositis and myocarditis, nivolumab was not reintroduced and palliative care was selected. The patient died 2 months later because of the progression of gastric cancer.

Discussion

We have described a case of ICI-induced myositis and asymptomatic myocarditis with slightly elevated cardiac biomarkers. Our findings indicate that even a slight increase in cardiac markers may be indicative of myocarditis, especially in presence of myositis. Although ICI-induced myocarditis is rare, it is considered clinically important because of its high mortality.1 The incidence of ICI-induced myocarditis was 0.06% when used as monotherapy and 0.27% when used in combination with ipilimumab.5 A single-center registry estimated the incidence to be as high as 1.14%. With the increasing number of patients receiving ICIs, more cases of ICI-induced myositis are being reported. Moreover, the fatality rate of this condition is 39.7%, which is particularly higher when compared with other immune-related adverse events,6 highlighting the importance of early diagnosis and therapeutic intervention.

Currently, there is no consensus regarding the diagnosis and treatment of ICI-induced myocarditis. However, a cardio-oncology expert panel from the French Working Group of Cardio-Oncology proposed a pragmatic approach to ICI-induced myocarditis.3 It suggested that myocarditis should be suspected in patients who have cardiovascular symptoms, troponin elevation, and ECG abnormalities. In these patients, a thorough examination with cardiac MRI is necessary.

Although troponin measurements are simple and objective, the results should be interpreted with caution.6 Although troponin T is elevated in most patients with myositis, troponin I is considered to be more myocardial-specific.5 A study showed that 24 of 214 patients who received ICIs had elevated troponin I and among these, only three patients were diagnosed with myocarditis.8 Thus, the troponin levels should be judged carefully on the basis of the patient’s clinical background. In our case, although the hs-TnT levels were only slightly elevated, the hs-TnI and CK-MB levels were within normal limits. This suggests that the hs-TnT elevation was not of myocardial origin but mainly of skeletal muscle origin. Considering that the patient was asymptomatic with no abnormalities on ECG and echocardiography, myocarditis would have been overlooked if cardiac MRI was not performed.

It has been reported that patients with ICI-induced myocarditis often present with concomitant immune-related adverse events affecting other organ systems, such as myositis (25%) and myasthenia gravis (11%).9 A study reported that 12.9% of patients with ICI-induced myositis developed myocarditis and 56.7% of these patients died.10 Recently, a case of ICI-induced myositis leading to fatal myocarditis has been reported in Japan.11 As such, patients with ICI-induced myositis should be referred to cardiologists for a thorough examination with cardiac MRI, even in the absence of abnormalities, such as elevated troponin levels.

Echocardiography, cardiac MRI, and myocardial biopsy are some of the cardiac tests that can be performed when myocarditis is suspected. When performing echocardiography, it is advisable to measure GLS and evaluate for pericardial effusion and left ventricular wall motion. It
has been reported that GLS is decreased in patients with ICI-induced myocarditis, even in those without decreased cardiac systolic function.\(^{[12]}\) Although cardiac MRI is becoming the gold standard for the diagnosis of ICI-induced myocarditis, it should be noted that the absence of radiologic findings suggestive of myocarditis alone is not sufficient to exclude the diagnosis. One study has shown that 43% of patients did not present with late gadolinium enhancement and hyperintense cardiac T2 signals.\(^{[13]}\) Recently, a case of asymptomatic myocarditis with unremarkable MRI findings was diagnosed via a myocardial biopsy.\(^{[14]}\) Considering the high frequency of myocarditis in patients with ICI-induced myositis, a myocardial biopsy may be considered if the diagnosis cannot be established by noninvasive tests.

Steroids are used in the treatment of ICI-induced myocarditis. A retrospective study reported that patients treated with steroids earlier and at higher doses had fewer major adverse cardiac events.\(^{[5]}\) Thus, in patients diagnosed with myocarditis, treatment with pulse methylprednisolone (1000 mg/day for 3-5 days) or high-dose prednisone (2 mg/kg) is recommended.\(^{[13,16]}\) By contrast, the recommended management options for ICI-induced myositis are careful monitoring and prednisolone therapy (1-2 mg/kg) for mild and moderate/severe cases, respectively.\(^{[13,16]}\) Moreover, lifelong discontinuation of ICI is recommended regardless of the grade of myocarditis. However, in the case of myositis, ICI can be re-administered if the patient improves to grade 1.\(^{[13,16]}\) Thus, it is important to detect myocarditis in patients with ICI-induced myositis.

In our case, because the hs-TnI and GLS measurements were performed 3 weeks after the initiation of prednisolone therapy, the results of these laboratory parameters may have been affected. However, considering that myocardial edema and inflammation were detected on cardiac MRI taken at the same time, the impact of prednisolone use on the test results seems to be limited. Nonetheless, the frequency and clinical importance of asymptomatic myocarditis are unknown. Hence, further studies are warranted.

In conclusion, we encountered a case of ICI-induced myositis and myocarditis without significant elevation of cardiac markers diagnosed by cardiac MRI. This study highlights the importance of detecting concurrent myocarditis in patients with ICI-induced myositis through intensive cardiac assessments.

**Disclosure**

**Conflicts of interest:** None.