Nivolumab-induced Myocarditis Successfully Treated with Corticosteroid Therapy: A Case Report and Review of the Literature

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Abstract:
A 62-year-old man presented to our hospital for the further evaluation and treatment of his back pain, general fatigue, and dyspnea, which had developed 4 days after the 29th administration of nivolumab to treat his lung cancer. Based on his clinical history, elevated serum cardiac enzyme values, and cardiac magnetic resonance (CMR) imaging and myocardial biopsy findings, he was diagnosed with myocarditis induced by nivolumab. Corticosteroid therapy improved his condition, and CMR performed on hospital day 11 also showed remarkable improvement. Although nivolumab-induced myocarditis is rare, cardiologists should consider it when encountering patients treated with such a drug for malignant disease.

Key words: cardiac magnetic resonance imaging, corticosteroid, lung cancer, myocarditis, nivolumab

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Introduction
Nivolumab is an immune checkpoint inhibitor (ICI) that has become a new treatment option for malignant tumors. While initially proven effective for melanoma, the diseases for which this agent is administered have been expanding. However, a number of immune-related adverse events (ir-AEs), which are rarely seen in conventional chemotherapy, have been reported with this drug, and as the frequency of its use increases, there are concerns that the number of side effects will also increase.

We experienced a case of myocarditis induced by nivolumab. To our knowledge, only 13 such cases have been reported (1-12). In this case, the onset was delayed until one year after the introduction of nivolumab, and cardiac magnetic resonance imaging (CMR) findings were useful for its differentiation from viral myocarditis. We report this case and review the literature.

Case Report
A 62-year-old man with an unresectable lung adenocarcinoma of clinical stage cT1bN2M0 of the Eighth Lung Cancer Stage Classification (13) diagnosed in August 2013 presented to Saitama Cardiovascular and Respiratory Center complaining of back pain, chest discomfort, general fatigue, and dyspnea in September 2018 and was admitted for a further evaluation. Because of mild fibrosis for which the possibility of interstitial lung diseases on CT could not be ruled out, he had been receiving chemotherapy without radiation therapy since the diagnosis of adenocarcinoma. Since September 2013, he had undergone chemotherapy with cisplatin plus pemetrexed followed by maintenance chemotherapy with pemetrexed and docetaxel. In May 2017, because the contralateral mediastinal lymph node was enlarged, recurrence was diagnosed, and nivolumab was started biweekly. The swollen lymph nodes decreased in size, and no abnormal shadows were noted, so he was considered to be in remission. However, 4 days after the 29th administration of nivolumab, he became febrile, his back pain worsened, and he complained of general malaise and dyspnea. His blood pressure was 124/76 mmHg, heart rate was 98 beats/min, respiratory rate was 20 breaths/min, and his body temperature was 38.3°C. There was no rash, scleral icterus, or photophobia. The left lower lung field crackles were audible, and his jugular venous pressure was normal. Heart sounds were normal, and there were no murmurs or gallops. In the legs, no edema was noted. In the back, the lumbar paravertebral muscles were spastic, and tenderness was noted on palpation. Laboratory tests revealed increased C-reactive protein (1.8 mg/dL) and cardiac enzymes. The troponin T level was 0.014 ng/mL, but the creatine kinase MB isoenzyme level was normal. The serum levels of alanine transaminase and aspartate transaminase were also normal. The creatinine level was 0.8 mg/dL, and the glomerular filtration rate was 69.1 mL/min/1.73 m². The hemoglobin level was 12.6 g/dL, and the white blood cell count was 4,700 cells/µL. The blood platelet count was 207,000 cells/µL, and the prothrombin time was 13.0 seconds. Cardiac magnetic resonance imaging (CMR) showed left ventricular wall motion abnormalities, and the left ventricular ejection fraction was 42.7% with a mildly dilated left ventricle. There was also increased signal intensity in the anterior and inferior wall of the left ventricle consistent with myocardial edema. The left atrium was normal, and there were no pericardial effusions. The left ventricular end-diastolic volume index was 96.1 mL/m², and the left ventricular end-systolic volume index was 58.1 mL/m². Cardiac biopsy showed diffuse interstitial myocardial edema with myocarditis. On electron microscopy, there were focal areas of lymphocyte infiltration. The myocardium was edematous, and electron microscopic examination showed focal areas of myofibrillar degeneration. The diagnosis of myocarditis was made.

Corticosteroid therapy was started. Prednisolone was given at a dose of 1 mg/kg/day, starting at the time of admission. By day 3, the patient’s dyspnea and back pain had improved. On day 11, CMR showed no increase in the left ventricular end-diastolic volume index or left ventricular end-systolic volume index. The left ventricular ejection fraction had improved to 55.7%. The patient was discharged on day 11.

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coronary angiography was performed, but no significant stenosis of the coronary arteries was found. We also performed various CMR examinations (Fig. 2). Cine images showed diffuse moderately reduced wall motion abnormality with mild wall hypertrophy, and T2-weighted short-tau inversion recovery (STIR) black-blood (BB) (T2w-STIR-BB) imaging showed diffuse high signal intensity (SI) equal to or greater than the spleen SI. Early gadolinium-enhanced (EGE) imaging showed diffuse hyper-enhancement of the myocardium, and late gadolinium-enhanced imaging showed diffuse patchy enhancement. Given the above findings, we diagnosed him with myocarditis with diffuse myocardial edema.

We performed a myocardial biopsy from the endocardial side of the left ventricle. The biopsy revealed fibrosis of the myocardial tissue, infiltration of inflammatory cells, and T cell-dominant lymphocyte infiltration, which were consistent with lymphocytic myocarditis (Fig. 3). Viral PCR testing using myocardial specimens for influenza virus, adenovirus, respiratory syncytial virus, corona virus, parainfluenza virus, bocavirus, echovirus, coxsackie virus echovirus, and enterovirus were all negative. Serum antibodies measured in the convalescent phase against echovirus, coxsackie virus, enterovirus, adenovirus, influenza virus, parainfluenza virus, and respiratory syncytial virus were not increased compared with those measured in the acute phase. We subsequently considered nivolumab-induced myocarditis. We also detected transient complete atrioventricular block during the myocardial biopsy and inserted a temporary pacemaker. Because of these new findings, we diagnosed the patient with nivolumab-induced myocarditis and started administration of methylprednisolone 1 g daily for 3 days.

From hospital day 4, the internal corticosteroid dose (prednisolone) was reduced to 60 mg daily (1 mg/kg). The patient’s condition subsequently improved. His serum creatine kinase value decreased to the normal range within a week after admission. The ejection fraction measured by the transthoracic cardiac ultrasound examination performed on hospital day 9 improved to 55%, and asynergy of the car-

In November 2017, decreased FT3 and FT4 values and an elevated thyroid-stimulating hormone value indicating hypothyroidism were found, but there were no clinical symptoms, and we followed him without treatment. In July 2018, he developed general fatigue, and we considered the symptoms due to hypothyroidism and stopped the nivolumab. By August 2018, his general fatigue had improved, and we restarted the nivolumab. However, in September 2018, 4 days after the 29th administration of nivolumab, he developed back pain, chest discomfort, general fatigue, and dyspnea. His vital signs were as follows: blood pressure of 92/62 mmHg, heart rate of 85 beats/min, and respiratory rate of 20/min. Chest auscultation revealed an irregular heartbeat without murmurs or rales. Pitting edema was found in his lower extremities. The electrocardiogram showed wide QRS waves (Fig. 1A). A transthoracic cardiac ultrasound examination showed an attenuated left ventricular ejection fraction of 45% compared with that of 70% in February 2014 and a decrease in the left ventricular wall motion in the posterior, inferior, and lateral walls. Laboratory data showed white blood cells of 6,200/mm³, hemoglobin of 13.1 g/dL, platelets of 205,000/mm³, serum creatine kinase value of 970 IU/L (normal 56 to 244), and increases in creatine kinase-myocardial band to 78 ng/mL (normal <5 ng/mL) and cardiac troponin T to 4.81 ng/mL (normal <0.1 ng/mL). The C-reactive protein value was also increased to 2.06 mg/dL. Autoantibodies, including antinuclear antibodies, anti-Acl-70 antibodies, anti-ARS antibodies, anti-ds DNA antibodies, anti-RNP antibodies, anti-SS-A/Ro, and anti-SS-B/La antibodies, were all negative. BNP was increased to 466 pg/mL, and chest X-ray showed cardiac enlargement with right-sided pleural effusion (Fig. 1B).

We initially suspected acute myocardial infarction, and a Swan-Ganz catheter was inserted to assist in management in the intensive care unit. The pulmonary artery pressure [systolic/diastolic (mean)] was 28/19 (23) mmHg. Emergency coronary angiography was performed, but no significant complete remission.

Figure 1. Electrocardiogram and chest X-ray findings on admission. The electrocardiogram showed irregular and wide QRS waves (A). Chest X-ray showed cardiomegaly and right-sided pleural effusion (B).
Figure 2. Cardiac magnetic resonance imaging. Day 1, T2-weighted short-tau inversion recovery (STIR) black-blood (BB) \( (T2w\text{-STIR-BB}) \) MRI showed diffuse high signal intensity (SI) equal to or greater than the spleen SI. (a) Day 1, early gadolinium-enhanced (EGE) imaging showed diffuse hyper-enhancement of the myocardium. (b) Day 1, late gadolinium-enhanced (LGE) imaging showed diffuse patchy enhancement. (c) Given the above, myocarditis with diffuse myocardial edema was diagnosed. Day 11, T2w-STIR-BB (d) and EGE (e) images showed improvement of edematous findings, and late gadolinium enhancement (f) of the myocardium was decreased.

Figure 3. Histology of the myocardial biopsy specimen. Myocardial tissue fibrosis, inflammatory cell infiltration \( (a: \text{Hematoxylin and Eosin staining}) \), and T cell-dominant lymphocyte infiltration \( (b: \text{immunohistochemical staining for CD3 cells}) \) were found. Infiltration of B cells was minimal \( (c: \text{immunohistochemical staining for CD20 cells}) \).
to cause several ir-AEs, including thyroid dysfunction, colitis, immune responses (14). Treatment with nivolumab is known of several cancers by releasing restrained antitumor face of cancer cells. Nivolumab has transformed the treat-
cytes by suppressing the expression of PD-1 on the cell sur-
mors that promotes the attack of cancer cells by lympho-
carditis has not recurred.
he has been regularly followed up on an outpatient basis. He
in three cases, after the third administration in three cases,
in one case. Our patient developed myocarditis even if one year has
Nivolumab to
onset of myocarditis

| Age/ Sex | Primary disease | Duration from initiation of nivolumab to onset of myocarditis | Treatment | Outcome | Reference |
|----------|-----------------|-------------------------------------------------------------|-----------|---------|-----------|
| 75/M     | Lung cancer     | 3 days after the ninth administration                       | Prednisolone (1 mg/kg/day) | Alive   | 1         |
| 64/F     | Glioblastoma    | 8 days after the second administration                      | Mycophenolate (1 g twice daily) | Alive   | 2         |
| 68/F     | Lung cancer     | One week after the second administration                    | Myethylprednisolone (250 mg/day) | Died    | 3         |
| 69/M     | Melanoma        | Two weeks after the third administration                    | Prednisolone (2 mg/kg/day) | Alive   | 4         |
| 72/M     | Melanoma        | After the tenth administration                               | Prednisolone (1 mg/kg/day) | Alive   | 5         |
| 49/M     | Melanoma        | Two weeks after the initial administration                   | Prednisolone (10 mg/day) | Alive   | 6         |
| 68/M     | Melanoma        | Two weeks after the initial administration                   | Methylprednisolone (1 mg/kg/day) | Died    | 7         |
| 65/F     | Melanoma        | 12 days after the initial administration                     | Methylprednisolone (2 mg/kg/day) | Died    | 8         |
| 63/M     | Melanoma        | 15 days after the initial administration                     | Methylprednisolone (1,000 mg/day) plus ifliximab (5 mg/kg/day) | Died    | 8         |
| 80/M     | Melanoma        | Two weeks after the initial administration                   | Methylprednisolone (1,000 mg/day) plus IVlg (400 mg/kg/day) | Alive   | 9         |
| 72/M     | Melanoma        | After the third administration                               | Prednisolone (1 mg/kg/day) | Alive Effective | 10        |
| 55/M     | Lung cancer     | 21 days after the second administration                      | Unknown | Died    | 11        |
| 69/F     | Lung cancer     | One week after the third administration                      | Methylprednisolone (1,000 mg/day) | Alive    | 12        |
| 62/M     | Lung cancer     | 4 days after the third administration                        | Methylprednisolone (1,000 mg/day) | Alive    | Our case  |

Table. Characteristics of Reported Cases of Nivolumab-induced Myocarditis.

M: male; F: female; IVlg: intravenous immunoglobulin

Discussion

We herein report a case of nivolumab-induced myocarditis that developed one year after its administration. A cardiac muscle biopsy specimen showed T cell-dominant lymphocyte infiltration, which was successfully improved by corticosteroid therapy.

As an ICI, nivolumab is a novel remedy for malignant tu-
mors that promotes the attack of cancer cells by lympho-
carditis, in Japan are reported to be 3 in 4,259 patients (0.07%) (15) and 2 in 2,800 patients (0.07%) (16), respec-
tively. Although its probability of occurrence is not high, myocarditis is an ir-AE that cannot be ignored due to the possibility of a fatal outcome. To our knowledge, only 13 cases of myocarditis induced by nivolumab have been re-
ported (Table). Among these 13 cases, the patients’ ages ranged from 49 to 80 years, and 9 men were included. Ma-
lignancies for which nivolumab was administered included melanoma in eight cases, lung cancer in four cases, and glioblastoma in one case. Development of nivolumab-induced myocarditis occurred after the initial administration of nivolumab in five cases, after the second administration in three cases, after the third administration in three cases, after the ninth administration in one case, and after the tenth administration in one case. Our patient developed myocarditis one year after the initiation of nivolumab but during the third readministration after a two-month period of drug ces-
sation due to hypothyroidism. As our case indicates, nivolumab-induced myocarditis can develop even one year after its administration. Thus, clinicians should consider nivolumab as a cause of myocarditis even if one year has passed from its introduction.

Nine of the 13 patients underwent a myocardial biopsy or autopsy (2, 4-6, 8-12). All patients had myocardial tissue fi-
brosis, inflammatory cell infiltration, and T cell-dominant lymphocyte infiltration, findings that were also found in our patient. From previous reports, the characteristic histological finding of nivolumab-induced myocarditis is T-cell inflam-
mation. Four potential mechanisms of ir-AE have been pro-
posed (17). First, ICIs (monoclonal antibodies) binding di-
rectly to cell surface proteins, such as cytotoxic T lympho-
cyte antigen 4 (CTLA4), which is expressed on normal tis-
sues, can cause T-cell infiltration and injury to tissues due to complement mediation. Second, circulating T cells that rec-
diac wall also improved. Electrocardiography performed on hospital day 10 showed narrowing of the QRS. CMR im-
ingar was performed on hospital day 11 and one month fol-
owing the start of methylprednisolone administration. Cine images showed gradual improvement of the wall motion ab-
normality with recovery of the left ventricular ejection frac-
tion. T2w-STIR-BB and EGE images showed improvement of edema findings, and late gadolinium enhancement of the myocardium was decreased.

The patient was discharged on hospital day 19. After dis-
charge, the corticosteroid dose was gradually tapered (pred-
nisolone 60 mg daily for 1 week, 50 mg daily for 2 weeks,
40 mg daily for 2 weeks, and 30 mg daily thereafter), and he has been regularly followed up on an outpatient basis. He continues to take prednisolone 30 mg daily, and his myo-
carditis has not recurred.
no Conflict of Interest (COI).

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