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【 CASE REPORT 】

Fulminant Myocarditis for Non-small-cell Carcinoma of the Lung with Nivolumab and Ipilimumab Plus Chemotherapy

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Abstract:
A 59-year-old man with a high level of antinuclear antibody received nivolumab and ipilimumab plus chemotherapy for lung cancer. Two weeks after the second course, he was admitted with a fever and severe fatigue. Laboratory studies showed elevated markers of myocardial damage, and a myocardial biopsy showed inflammatory cell infiltration, damaged myocardial fibers. Myocarditis was diagnosed as an immune-related adverse event (irAE), and high-dose corticosteroids were initiated. However, his cardiac function rapidly worsened, and he died on the fifth day after admission. There is no established treatment strategy for fulminant myocarditis as an irAE, and the further exploration of viable treatment strategies is required.

Key words: myocarditis, nivolumab plus ipilimumab, irAE, case report

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Introduction

Immune checkpoint inhibitors (ICIs) are standard therapies for thoracic malignancies (1, 2). Novel combined immunotherapy, nivolumab plus ipilimumab, has demonstrated significant survival benefits in patients with non-small-cell lung cancer (NSCLC) (3) and malignant pleural mesothelioma (MPM) (4). However, it is well known that there are a wide variety of side effects, called immune-related adverse events (irAEs). The prevalence of fatal irAEs is considered rare; however, damage to major organ functions can be serious and fatal (5).

We herein report a case of fulminant myocarditis following nivolumab and ipilimumab plus chemotherapy in a patient with NSCLC.

Case Report

A 59-year-old man presented to our hospital with complaints of cough and respiratory distress over the past 2 months. Chest radiography revealed right pleural effusion (Fig. 1A). Computed tomography (CT) showed a 12-mm nodule in the right upper lobe of his lung (Fig. 1B) and multiple pleural thickening lesions, which showed the accumulation of ^{18}F-fluorodeoxyglucose (Fig. 1C). A right pleural biopsy was performed (Fig. 1D), and the histopathological diagnosis was metastasis of a poorly differentiated carcinoma (Fig. 1E). We clinically diagnosed stage IVA NSCLC.

A genomic analysis showed *PIK3CA* amplification and a *TP53 V173L* mutation, with no driver oncogenes. His tumor showed a high expression of programmed cell death ligand 1 (PD-L1) (Fig. 1F). Laboratory tests showed that the antinuclear antibody (ANA) level was high at 1:160 serum dilution. The serum NT-proBNP level was normal (73.5 pg/mL),

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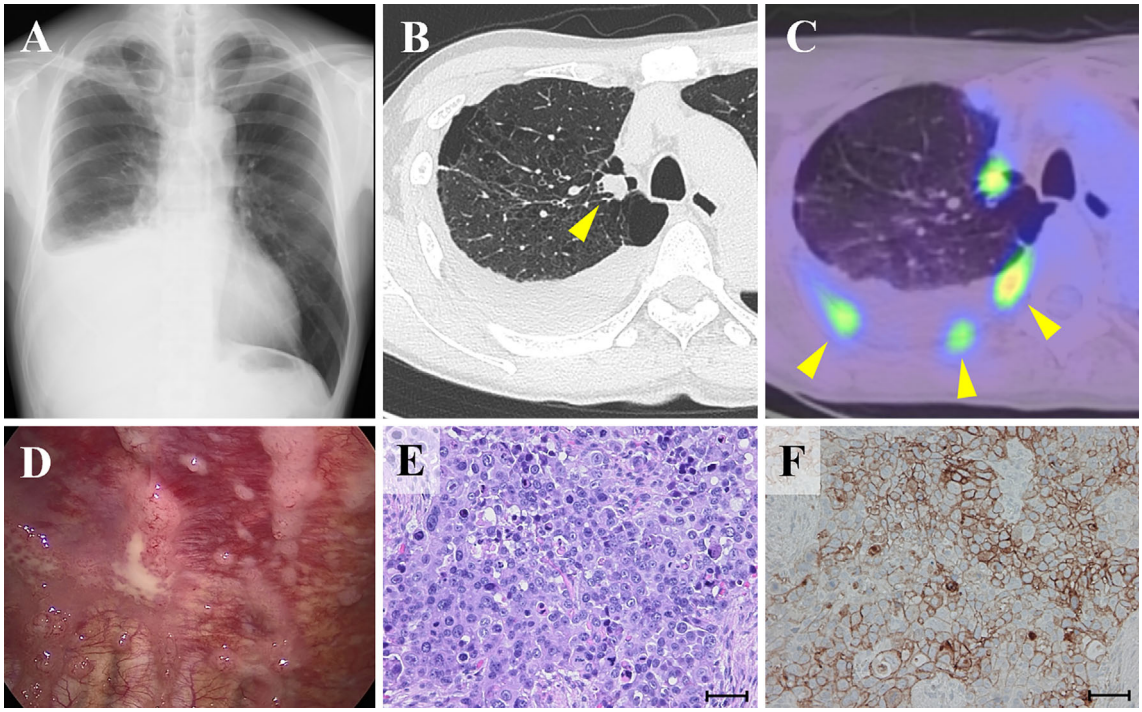

Figure 1. Findings at the diagnosis. Chest radiography shows right pleural effusion (A). CT and PET/CT show a primary lesion 12 mm in size on the right upper lobe of the patient's lung, pleural effusion, and multiple pleural thickening of the right (B, C, arrowheads). Thoracoscopy reveals multiple pleural nodules (D), and a biopsy of this area reveals poorly differentiated carcinoma (E). The tumor proportion score for PD-L1 expression (Dako 22C3 antibody) is 80-90% (F). Bars indicate 50 μm.

and his electrocardiogram showed sinus rhythm with no conduction abnormalities. He was treated with nivolumab (360 mg every 2 weeks) and ipilimumab (1 mg/kg every 6 weeks), as well as cytotoxic chemotherapy, cisplatin, and pemetrexed. One week after the first administration, the patient complained of a grade 2 rash that improved with topical corticosteroids. After three weeks of treatment, nivolumab plus chemotherapy was administered as scheduled.

Two weeks after the second dose of nivolumab plus chemotherapy, the patient was admitted with a fever and severe fatigue. A physical examination revealed a temperature of 38.8°C, pulse of 125 bpm, and blood pressure of 87/59 mmHg with pre-shock. He had no symptoms of muscle weakness or pain suggestive of myositis. Laboratory studies showed significant elevations in factors suggestive of myocarditis, including creatine kinase (CK; 349 U/L), CK-myocardial band (CK-MB; 21 U/L), troponin T (2.1 ng/mL), and brain natriuretic peptide (2,254.9 pg/mL).

Electrocardiography revealed atrial fibrillation with a right bundle branch block (Fig. 2A), and echocardiography showed marked thickening of the ventricular wall and pericardial effusion (Fig. 2B), with a particularly low left ventricular ejection fraction of 20%. Further blood examinations revealed negative results for enterovirus, adenovirus, and parvovirus, which did not suggest viral myocarditis. A histopathological examination of the myocardial biopsy of the right ventricle showed the large infiltration of inflammatory cells, mainly lymphocytes, between myocardial fibers, without invasive cancer cells (Fig. 2C). PD-L1 was strongly expressed on immune cells infiltrating the myocardium and on the membrane surface of injured cardiomyocytes (Fig. 2D). Based on these results, the patient was diagnosed with myocarditis induced by nivolumab and ipilimumab combination therapy.

He was immediately transferred to the intensive care unit and treated with high-dose corticosteroids (intravenous methylprednisolone administered at 1 g/day). In the evening, because his hemodynamic condition quickly deteriorated, intra-aortic balloon pumping therapy and veno-arterial extracorporeal membrane oxygenation were initiated. On the third day of glucocorticoid therapy, intravenous immunoglobulin was concomitantly administered. However, myocardial enzyme levels, such as CK-MB and troponin T, increased daily, and irreversible myocardial damage appeared on electrocardiography (Fig. 3). The patient did not respond to the treatments, his symptoms progressed rapidly, and he died on the fifth day of hospitalization.

Discussion

Novel combined immunotherapy with monoclonal antibodies targeting cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) and programmed cell death protein 1 (PD-1)

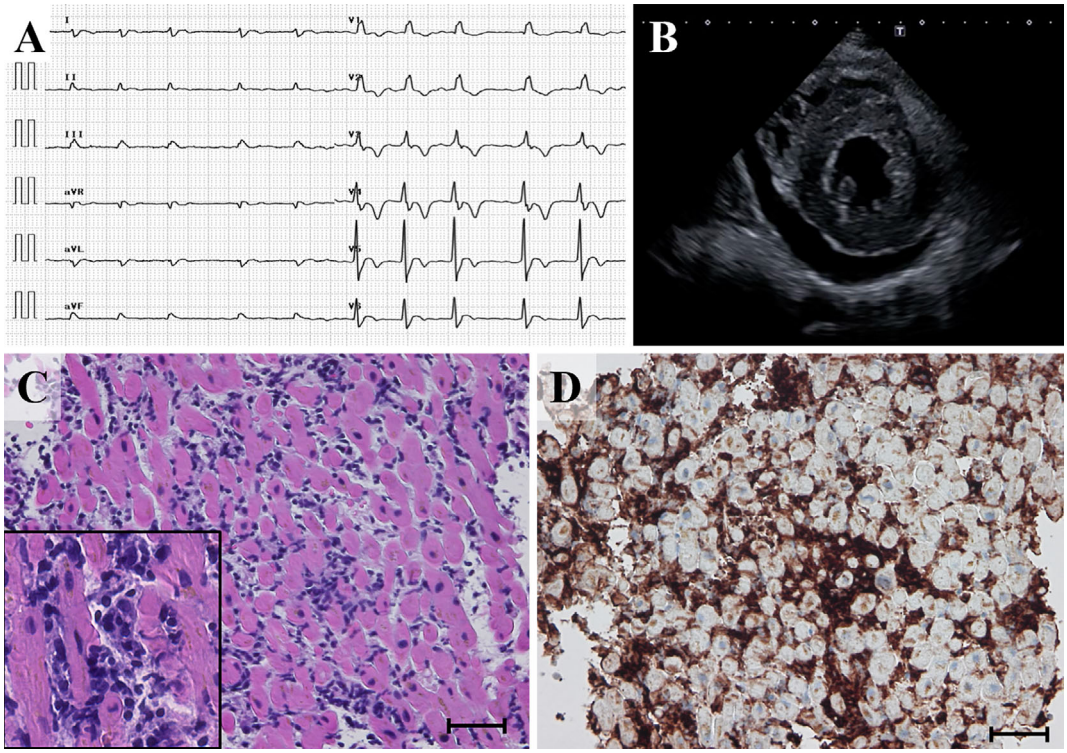

Figure 2. Findings at the onset of myocarditis. Electrocardiography shows atrial fibrillation with bundle branch block (A). Echocardiography shows a left ventricular ejection fraction of 20% with thickening of the ventricular wall and pericardial effusion (B). Histopathological findings of a myocardial biopsy show a high infiltration of lymphocytes into fibers, which are dissociated and miniaturized (C). Programmed cell death protein 1 expression (Dako 22C3 antibody) in damaged myocardial fibers and infiltrating immune cells (D). Bars indicate 50 μm.

has become standard care in the treatment of various malignancies. Therefore, an increasing number of patients are exposed to these drugs, subsequently being put at risk of developing irAEs. Although life-threatening irAEs are rare, cardiac irAEs can be fatal, and myocarditis has been associated with a high mortality rate of 25-50% (6). The prevalence of myocarditis with ICIs is very rare but appears to be higher when administered in combination with anti-PD-1 and anti-CTLA-4 antibodies (7); one treatment-related death due to myocarditis was reported in the CheckMate-227 trial with nivolumab plus ipilimumab in NSCLC (3). No cases of myocarditis were reported in the CheckMate-9LA trial with chemotherapy added to nivolumab plus ipilimumab (8). Thus, these results suggest that chemotherapy has little effect on the development of myocarditis.

The exact mechanism underlying ICI-induced myocarditis remains poorly understood. Johnson et al. found that, in fulminant myocarditis treated with anti-CTLA-4 plus anti-PD-1 combination therapy, a common T-cell clone was found in the tumor, myocardium, and skeletal muscle before and after treatment (7). This suggests that there is homology between T-cell targeted muscle antigens and tumor neoantigens. PD-1 inhibition may cause myocardial damage, as mice genetically deficient in PD-1 are known to develop cardiomyopathy due to the production of autoantibodies against cardiac troponin I (9). Myocardial PD-L1 expression has been reported to protect against cytotoxic T-lymphocyte-mediated myocarditis (10). Interestingly, in the present case, as in previous reports, the myocardial PD-L1 expression increased, suggesting that myocardial damage might have been further enhanced by the release of inhibition via the PD-1/PD-L1 pathway. However, basic research recently showed that the additional monoallelic loss of CTLA-4 in PD-1-deficient mice caused fulminant myocarditis (11). Salem et al. reported that the administration of the CTLA-4 agonist abatacept ameliorated corticosteroid-refractory myocarditis (12). In the present case, co-inhibition of CTLA-4 and PD-1 may have promoted the activation of PD-L1-positive immune cells within the myocardium, resulting in severe myocardial damage.

Several pretreatment biomarkers, such as troponin and electrocardiography, have been shown to be useful for cardiac irAE (6); however, predicting its onset is difficult. In the present case, the patient's ANA level was elevated, despite there being no clinical findings of arthralgia, myalgia, peripheral neuropathy, or rash to suspect collagen disease. Although previous reports suggest that the higher the titer of ANA is, the higher the incidence of irAEs is (13), the involvement of ANA titer in ICI-induced myocarditis has not been reported. Therefore, it is instructive that high ANA antibody titers may have been involved in the myocarditis in the present case.

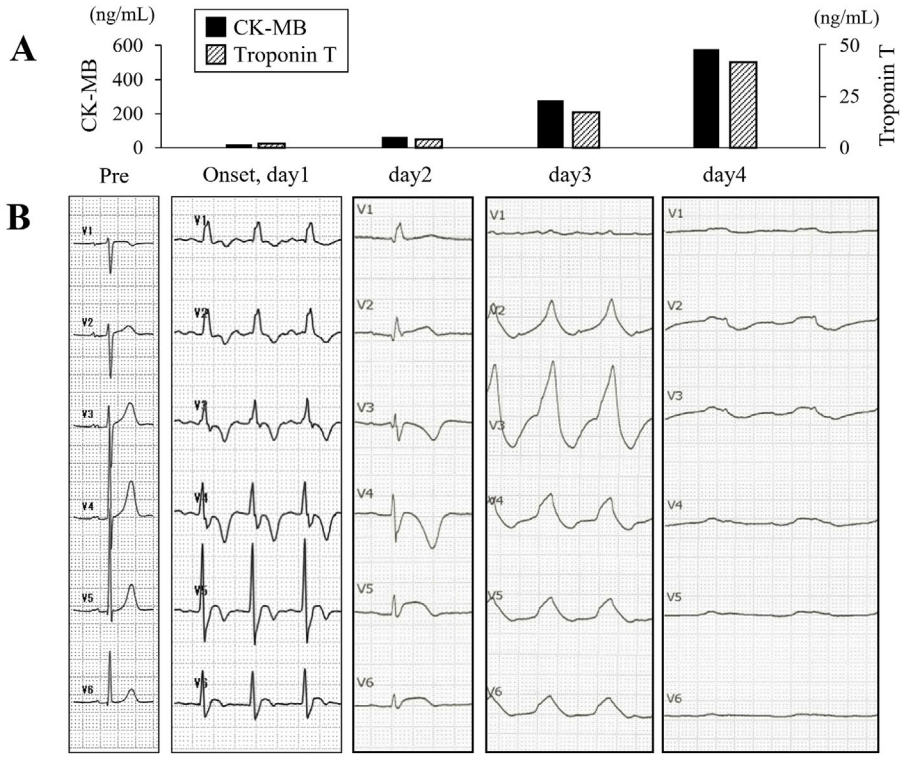

Figure 3. **Myocardial enzymes and electrocardiography changes after admission. CK-myocardial band and troponin T levels increase each day (A). Electrocardiography shows new atrial fibrillation with right bundle branch block on day 1. The QRS widened on day 3, and the electrical activity decreased on day 4 (B).**

In conclusion, we report a patient with NSCLC who developed fulminant myocarditis after nivolumab and ipilimumab plus chemotherapy and responded poorly to corticosteroid therapy. Novel treatment strategies are required for corticosteroid-resistant myocarditis caused by ICIs.

Author's disclosure of potential Conflicts of Interest (COI).
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