

[CASE REPORT]

Sinus Node Dysfunction Co-occurring with Immune Checkpoint Inhibitor-associated Myocarditis

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Abstract:

Immune checkpoint inhibitor (ICI)-induced myocarditis is a potentially life-threatening adverse event. We herein report a rare case of sick sinus syndrome (SSS) co-occurring with ICI-associated myocarditis. A 71-year-old woman with lung cancer undergoing pembrolizumab monotherapy was admitted owing to a fever, worsening kidney function, and sinus bradycardia. She was diagnosed with multi-organ immune-related adverse events, including myocarditis. Pulse steroid therapy was initiated immediately under the support of a temporary pacemaker, which resulted in the resolution of SSS in a few days. Biopsy specimens of the endomyocardium showed active myocarditis. Thus, we should be aware that SSS can co-occur with ICI-induced myocarditis.

Key words: case report, cardio-oncology, sick sinus syndrome, pembrolizumab, immune-related adverse event, myocarditis

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Introduction

Immune checkpoint inhibitors (ICIs) are widely used to treat various types of cancer, including lung, renal, gastrointestinal, and head/neck cancers, in addition to lymphomas and malignant melanomas. Due to the increasing number of cancer patients being treated with ICIs, there has been an increase in immune-related adverse events (irAEs).

Among irAEs, ICI-induced cardiovascular toxicity is a major problem in cancer patients. Cardiovascular toxicities often manifest as myocarditis, complete heart block, atrial fibrillation (AF), ventricular arrhythmia, and heart failure (1, 2). Notably, because immune-related myocarditis is potentially lethal, oncologists and cardio-oncologists cautiously monitor for these events. ICI-induced myocarditis is often identified due to arrhythmia or an increase in the levels of various biomarkers, such as troponin T/I and brain natriu-

retic peptide (BNP)/N-terminal pro-B-type natriuretic peptide (NT-proBNP) (3). AF and ventricular arrhythmia commonly co-occur with ICI-induced myocarditis. However, sick sinus syndrome (SSS) seems to be an extremely rare manifestation of ICI-cardiotoxicity, with only one study reporting a case without clinical features of myocarditis (4).

We herein report a case of pembrolizumab-induced SSS with histopathological evidence for ICI-induced myocarditis.

Case Report

A 71-year-old woman was diagnosed with cT4N2M1 squamous cell lung carcinoma at the Osaka International Cancer Institute through a histopathological analysis of her lung tumor and systemic imaging studies, including enhanced computed tomography, brain magnetic resonance imaging, and fluorodeoxyglucose-positron emission tomography.

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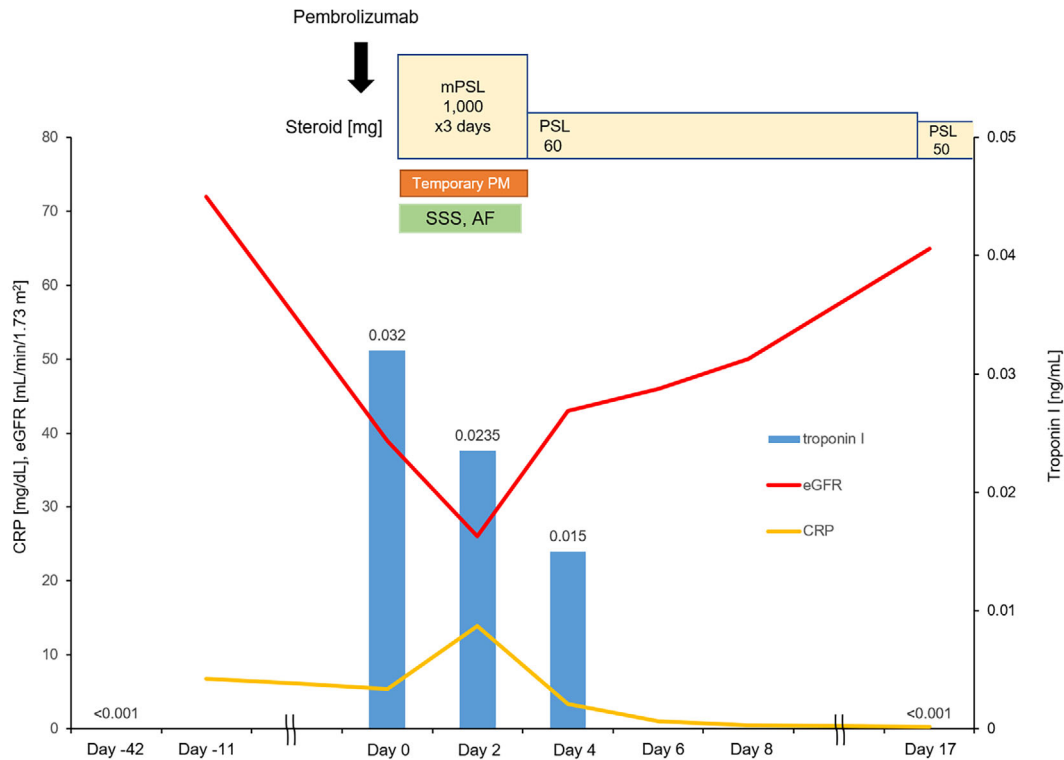


Figure 1. Clinical time course. Day 0 indicates the day of the second course of pembrolizumab. PSL: prednisolone, mPSL: methylprednisolone, SSS: sick sinus syndrome, PM: pacemaker, CRP: C-reactive protein, eGFR: estimated glomerular filtration rate

For the treatment of advanced squamous cell lung carcinoma, the patient had been administered combination therapy of carboplatin, nab-paclitaxel, and pembrolizumab as the first line therapy; however, she experienced severe pulmonary infection. After recovery from the AE, her treatment was switched to pembrolizumab monotherapy. Subsequently, after the second course of chemotherapy with pembrolizumab monotherapy, she developed a high fever [Common Terminology Criteria for Adverse Events (CTCAE) (5) grade 1], and her kidney function worsened [estimated glomerular filtration rate (eGFR) declined from a baseline of 72 mL/min/1.73 m² to 39 mL/min/1.73 m²; CTCAE grade 3]. Thus, she was admitted to our hospital for observation.

The following evening, frequent sinus pauses of approximately 5 s (Fig. 1) and paroxysmal AF were observed upon electrocardiogram monitoring. These frequent sinus pauses were observed both during sinus rhythm and between paroxysmal AF (bradycardia-tachycardia syndrome). Consequently, we diagnosed the patient with SSS (CTCAE grade 3).

She had no history of cardiovascular disease or arrhythmia and was not being treated with bradycardia-inducing drugs, such as β -blockers or anticholinergic drugs. There were no prior viral infectious symptoms or suspected laboratory data for viral myocarditis. In addition, laboratory data showed a normal thyroid and adrenal function. Although the hemodynamics were preserved (blood pressure was 105/65 mmHg with heart rate of 90-120 bpm), she exhibited symptoms of palpitation and discomfort. Therefore, we decided to

insert a transvenous temporary pacemaker to treat the SSS.

At this point, the levels of cardiac biomarkers, such as troponin I (0.032 ng/mL; normal range \leq 0.026 ng/mL) and NT-proBNP (1,724 pg/mL; normal range \leq 125 pg/mL), were found to be elevated above the normal ranges, although no suspected ischemic changes in the electrocardiography or typical chest pain were observed. Echocardiography showed no decline in the left ventricular ejection fraction (60-65%), local asynergy, pericardial effusion, or any valvular disease. Based on the clinical features of a fever, worsening kidney function, and newly diagnosed arrhythmia with increasing levels of cardiac biomarkers, we clinically diagnosed these medical conditions as being associated with multi-organ irAEs, including myocarditis. Therefore, we started pulse steroid therapy with an initial dose of 1 g of methylprednisolone for 3 days from the day of the diagnosis, followed by 1 mg/kg of prednisolone as maintenance therapy.

From the second day of pulse steroid therapy, an increase in the eGFR, a decrease in the troponin I and NT-proBNP levels, and a reduction in the frequency of sinus pauses were observed. In addition, AF disappeared completely and never recurred. Even when sinus rhythm was maintained, temporary pacing was frequently observed (Fig. 2C), indicating that SSS was not caused by AF alone. Since AF did not affect the symptoms or blood pressure, we did not introduce any medication for either rate or rhythm control. Furthermore, we did not introduce anticoagulation therapy, as AF did not recur following the day after steroid therapy initiation.

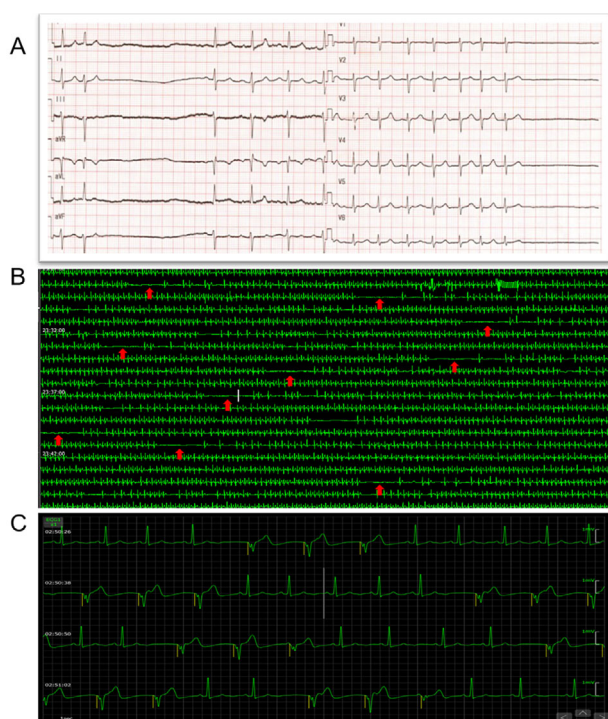


Figure 2. Electrocardiogram images. (A) A 12-lead electrocardiogram generated following the diagnosis of sick sinus syndrome. (B) An electrocardiogram showing frequent sinus pauses. One row indicates one minute. Sinus pauses (red arrows). (C) An electrocardiogram showing ventricular pacing by the temporary pacemaker during sinus rhythm.

Although steroid therapy was initiated, further cardiac investigations were necessary to identify the cause of arrhythmias on the fourth day after steroid pulse therapy initiation. Since cardiac magnetic resonance imaging was not suitable under transvenous temporary pacing, we performed cardiac catheterization. Coronary angiography confirmed no coronary artery stenosis; therefore, we performed an endomyocardial biopsy of the right ventricular septum. This revealed that CD3-positive lymphocytes and CD163-positive macrophages had infiltrated the interstitium adjacent to the degenerated and necrotic myocytes, which showed localized immunopositivity for programmed death-ligand 1 (PD-L1) (Fig. 3). In addition, immunostaining for tenascin-C, a known marker for inflammation, was positive in the interstitium adjacent to the necrotic myocytes (Fig. 3).

As electrocardiogram monitoring revealed that the patient had no SSS after steroid therapy, we removed the temporary pacemaker. Furthermore, because there were no symptoms or documentation of SSS thereafter, we concluded that the sinus node damage had most likely been caused by ICI-induced myocarditis, and the dysfunction was limited and could be reversed by steroid therapy. Thus, the patient did not require permanent pacemaker implantation according to clinical guidelines (6), and she did not experience any arrhythmia or cardiac failure upon hospital discharge or during the six months of follow-up performed until transition to palliative care.

Discussion

This is the first report of the co-occurrence of SSS and ICI-induced myocarditis with pathological evidence. Myocarditis is a critical irAE in cancer patients treated with ICIs. Ventricular arrhythmia and AF are also widely known adverse events that occur following ICI treatment. However, to our knowledge, there is no pathological evidence for SSS co-occurring with ICI-induced myocarditis. In a previous study, SSS was observed after ICI treatment, which was assumed to be due to immune- or adrenal insufficiency-mediated sinus node dysfunction, without clinical signs or laboratory findings suggesting myocarditis (4). In the present case, no adrenal dysfunction was observed on laboratory tests. Since we obtained samples of the right ventricular septum by an endomyocardial biopsy, we were unable to directly prove the presence of inflammation in the sinus node. Recent studies have revealed many ICI-related myocarditis cases with a small number of infiltrated lymphocytes as cases of low-grade myocarditis (7). Although this might be because of the initiation of steroid therapy, low-grade focal lymphocyte infiltration is consistent with ICI-related myocarditis.

Considering the age of the patient, sinus node dysfunction may have occurred. However, the clinical course, in which SSS and AF occurred on the most active day of irAE, SSS was observed for a short duration during sinus rhythm, and neither SSS nor AF recurred after steroid therapy initiation, suggests that SSS likely occurred due to myocarditis, including related inflammation around the sinus node. Furthermore, although SSS caused by myocarditis is rare, several previous studies have reported its occurrence. ICI-associated or viral myocarditis in mouse models has been shown to induce sinus arrest (8, 9). According to a multicenter study of fulminant myocarditis with venoarterial extracorporeal membrane oxygenation, two patients were documented to have SSS during their treatments (10). More recently, SSS was reported to be passively caused by cardiac inflammation as a result of coronavirus disease (11). In the present case, at the initial diagnosis of SSS, the levels of the cardiac biomarkers troponin I and NT-proBNP were significantly elevated. After steroid pulse treatment, a histopathological analysis of an endomyocardial biopsy revealed persistent mild but noticeable myocarditis. PD-L1 was detected in degenerated and necrotic myocytes, consistent with the findings of studies on ICI-related myocarditis. In addition, positive immunostaining of interstitial tenascin-C, a known marker for inflammation and fibrosis in the myocardium (12-15), was recently reported in ICI-related myocarditis cases (16). Because the present patient was diagnosed with SSS induced by ICI-associated myocarditis, we considered the sinus node inflammation observed during SSS to potentially be reversible with appropriate steroid therapy.

Weber et al. (17) reported that 85% of irAEs occur within 16 weeks in patients treated with nivolumab. Furthermore,

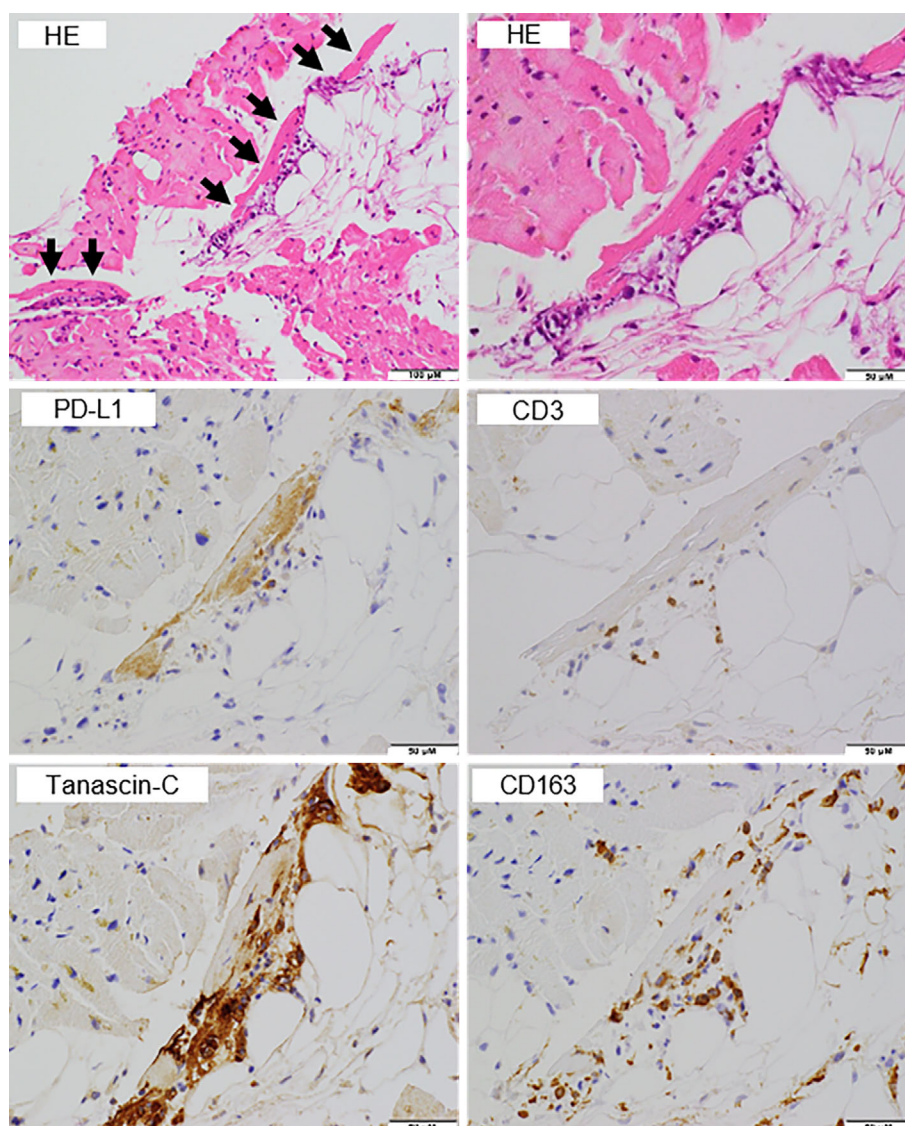


Figure 3. Histopathological and immunohistological findings of the right ventricular endomyocardial biopsy sample. Degenerated necrotic myocytes with inflammatory infiltrates (black arrows). Immunostaining shows CD3-positive T-lymphocytes and CD163-positive macrophages around the PD-L1-positive necrotic myocytes, with the surrounding interstitium positive for tenascin-C. The scale bar corresponds to 100 μm in the top left image showing Hematoxylin and Eosin staining and 50 μm in the other images. PD-L1: programmed death-ligand 1

Wang et al. (18) reported that fatal and toxic effects associated with ICIs occur early after treatment initiation, regardless of the type of therapy [median time of 40 days, 40 days, and 14.5 days for ipilimumab, anti-programmed death-1 (PD-1)/PD-L1, and a combination of the two therapies, respectively]. Among the fatal irAEs caused by anti-PD-1/PD-L1 treatment, cardiac toxicity was observed in 8% of cases, whereas combination therapy of ipilimumab and anti-PD-1/PD-L1 caused cardiac toxicity in 25% of cases (18). Furthermore, the fatality rate of ICI-induced myocarditis was 39.7%. Jiang et al. (19) reported that 10% of fatal AEs caused by ICIs were cardiac toxicity. These findings are consistent with those of the present case, in which the patient suffered from potentially fatal myocarditis for 43 days following the initiation of pembrolizumab therapy.

Recently, in a retrospective cohort study, Zhang et al. (20) reported that corticosteroid introduction within 24 h of admission for patients with ICI-related myocarditis may result in a reduced incidence of major adverse cardiac events (MACEs). Similarly, in the present case, the patient was treated with corticosteroids within 24 h after the clinical diagnosis of ICI-induced myocarditis and did not experience any MACEs. Furthermore, as ICI-related myocarditis was diagnosed during her hospital admission, we were able to introduce steroid therapy immediately. However, most cases of myocarditis appear in outpatients; therefore, it is important during the early phase after ICI therapy initiation for oncologists, onco-cardiologists, and pathologists to maintain close communication with their cancer patients. In addition, self-monitoring of vital signs, such as pulse rate or rhythm,

might be beneficial for ICI-treated patients.

Further studies on the incidence and prognosis of SSS co-occurring with ICI-induced myocarditis should be performed on a large-scale, prospective registry basis. SSS is considered an irAE that can co-occur with myocarditis. Oncologists and cardio-oncologists should be aware of the signs of myocarditis that might appear as arrhythmia.

The authors state that they have no Conflict of Interest (COI).

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