

A case of sustained ventricular tachycardia due to pembrolizumab



Hiroyuki Toyoshi, MD, Kazuya Yumoto, MD, Kazuki Yamanaka, MD, Tomohiko Iwata, MD, Masahiko Koda, MD, PhD, Hisato Takatsu, MD, PhD

From the Department of Cardiovascular Medicine, Chuno kosei Hospital, Gifu, Japan.

Introduction

Pembrolizumab is administered in cases involving postoperative recurrence of primary lung cancer, which can lead to the onset of ventricular tachycardia. We report our experience with a rare case wherein steroid administration effectively prevented the recurrence of ventricular tachycardia.

Case report

A 75-year-old man was hospitalized to undergo immunotherapy for postoperative recurrence of primary lung cancer. On June 13, 2018, upper-right lobectomy was performed after the patient was diagnosed with stage IIb right upper-lobe lung cancer. Histologic analysis of the surgical specimen revealed a mixture of adenocarcinoma and squamous cell carcinoma, with the expression of PD-L1. Postoperative chemotherapy consisted of 3 courses of a combination of cisplatin (80 mg/m²) and vinorelbine (25 mg/m²). In January of the following year, computed tomography (CT) revealed findings indicative of right hilar lymphadenopathy, right pleural effusion, liver metastasis, and bone metastasis. Fluorodeoxyglucose-positron emission tomography, performed at the same sites examined with CT, revealed significant fluorodeoxyglucose accumulation, and serologic testing showed significantly elevated CYFRA levels. Based on these findings, the patient was diagnosed with postoperative recurrence of primary lung cancer.

A 12-lead electrocardiogram (ECG), acquired at admission, showed normal sinus rhythm and no ST-T abnormalities or prolonged QT intervals (Figure 1A). Moreover, an echocardiogram revealed normal left ventricular systolic function and no significant valvular heart disease (Figure 2A). The patient was administered pembrolizumab (200 mg) on day 2 of hospitalization. He developed palpitations on day 3, and a 12-lead ECG showed wide QRS tachycardia with a heart rate of

KEY TEACHING POINTS

- Pulse steroid therapy with methylprednisolone effectively prevented the recurrence of pembrolizumab-induced ventricular tachycardia in our patient.
- Ventricular tachycardia in our patient might have been triggered by the exaggerated immune response against the electrical conduction system of the heart. Steroid therapy has been previously reported to be useful in cases involving immune checkpoint inhibitor-induced autoimmune myocarditis.
- Further investigations into the pathogenesis and treatment of pembrolizumab-induced ventricular tachycardia are warranted.

170 beats per minute (Figure 1B). Adenosine triphosphate and verapamil were ineffective in resolving the symptoms of tachycardia; however, sinus rhythm was restored with cardioversion. No significant changes were seen in the ECG acquired after the episode of tachycardia compared with that acquired at admission. Findings from CT coronary angiography and cardiac magnetic resonance imaging (Figure 2B) and serum angiotensin-converting enzyme levels were also normal. On day 4, 2 similar episodes of tachycardia were observed, but elevated troponin I levels and significant increases in brain natriuretic protein levels were not observed for 3 consecutive days after the initial onset of ventricular tachycardia. Further, the levels of liver enzymes and inflammatory markers were not elevated. Based on this evidence, it was suspected that tachycardia was related to pembrolizumab use. Thus, pembrolizumab was discontinued and pulse-steroid therapy was observed to inhibit the ventricular tachycardia. Therefore, the tachycardia was determined to be an adverse reaction to the administration of pembrolizumab. Therefore, pulse steroid therapy (methylprednisolone, 1 g/day, over 3 days) was initiated from the same day.

KEYWORDS Lung cancer; Pembrolizumab; Pulse steroid therapy; Steroids; Ventricular tachycardia
(Heart Rhythm Case Reports 2019;5:570–572)

Address reprint requests and correspondence: Dr Hiroyuki Toyoshi, Department of Cardiovascular Medicine, Chuno kosei Hospital, Gifu, Wakakusa-dori 5-1 Seki, 501-3802 Japan. E-mail address: star.hiroyuki.wars@gmail.com.

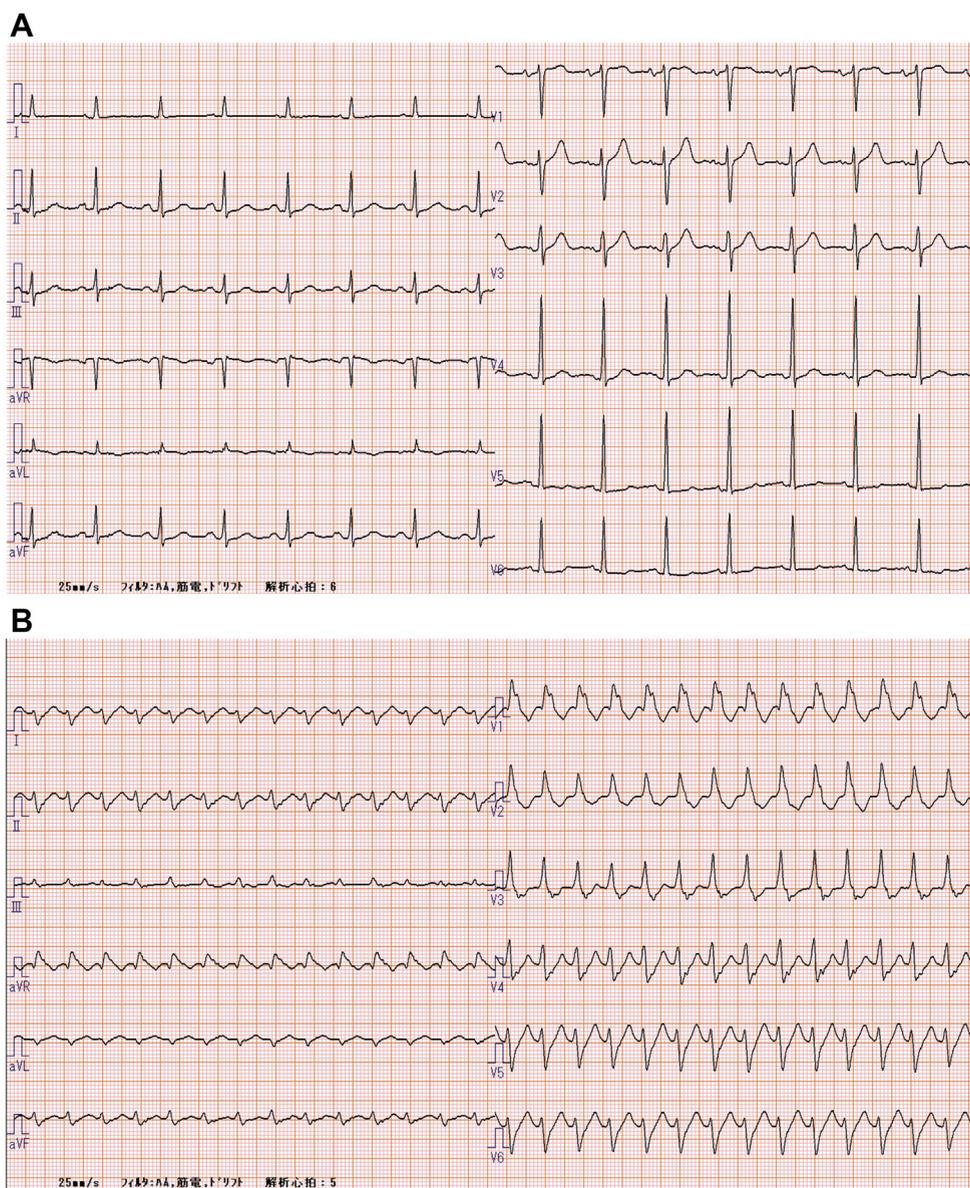


Figure 1 A: The 12-lead electrocardiogram (ECG) taken at admission showing heart rate of 66 beats/min (bpm), a normal sinus rhythm, and no ST-T abnormalities or prolonged QT intervals. B: The 12-lead ECG during the patient's palpitations showing heart rate of 170 bpm and wide QRS tachycardia with right axis.

Because the patient showed signs of interstitial pneumonia, amiodarone administration was considered highly risky, and bisoprolol 2.5 mg/day was administered. Symptoms of tachycardia did not recur after initiating steroid administration. The dose of methylprednisolone was tapered to 10 mg/day after pulse steroid therapy, and the patient was discharged on day 25. Outpatient follow-up did not show any signs of recurrence of ventricular tachycardia.

This patient provided oral informed consent for this case report.

Discussion

We have discussed a rare case of ventricular tachycardia caused by pembrolizumab and provided evidence suggesting that steroid administration can be effective for the treatment

of ventricular tachycardia resulting from pembrolizumab administration.

Because the ventricular tachycardia in our patient was of the relatively narrow right bundle branch block type, with a right axis, the reentry mechanism was estimated to involve the Purkinje fibers in the left posterior fascicle; however, the condition was unresponsive to verapamil. In addition, there were no organic heart diseases with an associated risk of inducing ventricular tachycardia, there were no blood biochemistry abnormalities, and the patient was not taking any medication (other than pembrolizumab), food, or beverages that might increase the risk of inducing ventricular tachycardia.

Cardiotoxicity owing to anticancer agents has been well known for some time, and these drugs, particularly anthracycline drugs, are known to cause left ventricular dysfunction.¹

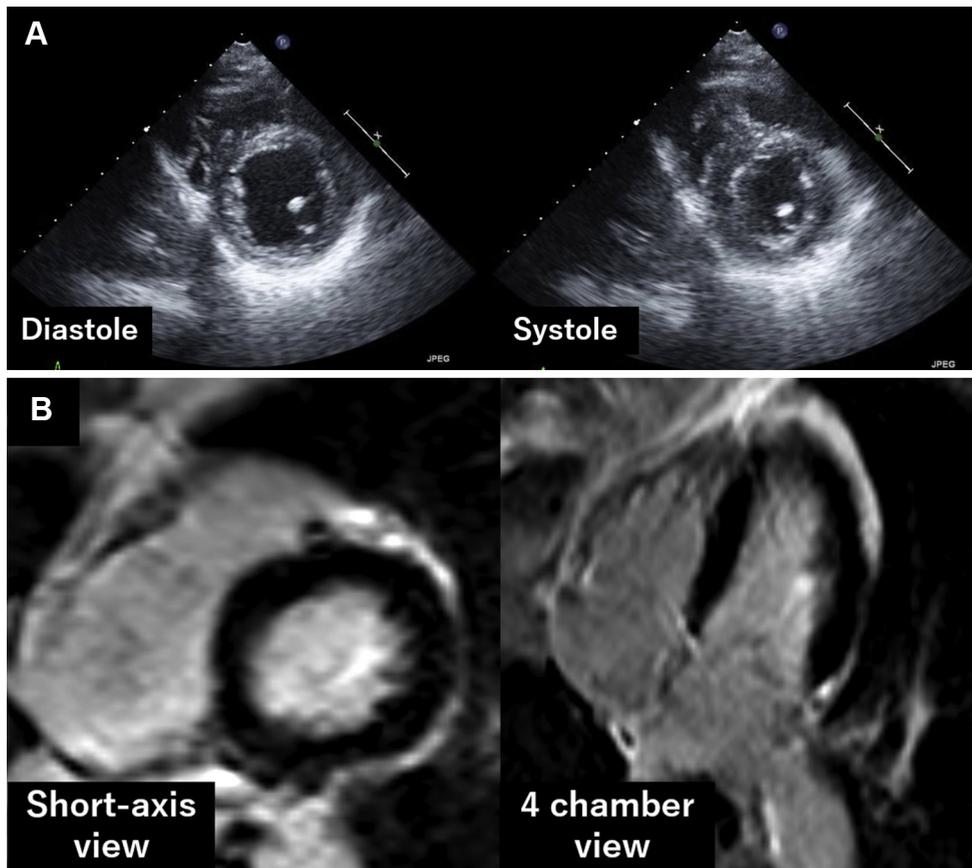


Figure 2 A: Echocardiogram (parasternal short-axis view) showing normal left ventricular function. B: Cardiac magnetic resonance imaging showing no significant delayed enhancement.

Immune checkpoint inhibitors have recently attracted attention as cancer drugs with a novel mechanism, but there have been some reports of nivolumab-associated myocarditis.^{2,3}

In this case report, elevated troponin I levels and significant increases in brain natriuretic protein levels were not observed for 3 consecutive days after the initial onset of ventricular tachycardia; therefore, acute heart failure, myocarditis, and epicarditis were ruled out as the cause of ventricular tachycardia. Based on the findings and the clinical course, the ventricular tachycardia in this case was strongly suspected to be a side effect of pembrolizumab.

There have been reports of pembrolizumab-associated myocarditis.⁴ Immune checkpoint inhibitors, such as pembrolizumab, are believed to trigger an excessively elevated immune response and cause various autoimmune diseases, such as myasthenia gravis and autoimmune myocarditis.^{5–7} In this report, ventricular tachycardia was believed to have been similarly triggered by the exaggerated immune response against the electrical conduction system of the heart, such as in the Purkinje fibers. This was because the ventricular tachycardia in our patient was suppressed by steroid pulse therapy, which was initiated as a diagnostic therapy. Indeed, Samara and colleagues⁸ previously reported the usefulness of steroid therapy in cases involving immune checkpoint inhibitor–induced autoimmune myocarditis.

Conclusion

This report describes a case involving pembrolizumab-induced ventricular tachycardia without myocarditis. We show evidence for preventing the recurrence of ventricular tachycardia with steroid administration; however, further investigations into the pathogenesis and treatment of pembrolizumab-induced ventricular tachycardia are warranted.

References

1. Senkus E, Jassem J. Cardiovascular effects of systemic cancer treatment. *Cancer Treat Rev* 2011;37:300–311.
2. Tadokoro T, Keshino E, Makiyama A, et al. Acute lymphocytic myocarditis with anti-PD-1 antibody nivolumab. *Circ Heart Fail* 2016;9:e003514.
3. Semper H, Muehlberg F, Schulz-Menger J, Allewelt M, Grohé C. Drug-induced myocarditis after nivolumab treatment in a patient with PDL1-negative squamous cell carcinoma of the lung. *Lung Cancer* 2016;99:117–119.
4. Inayat F, Masab M, Gupta S, Ullah W. New drugs and new toxicities: pembrolizumab-induced myocarditis. *BMJ Case Rep* 2018;2018. bcr-2017-223252.
5. Reck M, Rodríguez-Abreu D, Robinson AG, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. *N Engl J Med* 2016; 375:1823–1833.
6. Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med* 2010;363:711–723.
7. Ribas A, Puzanov I, Dummer R, et al. Pembrolizumab versus investigator-choice chemotherapy for ipilimumab-refractory melanoma (KEYNOTE-002): a randomized, controlled, phase 2 trial. *Lancet Oncol* 2015;16:908–918.
8. Samara Y, Yu CL, Dasanu CA. Acute autoimmune myocarditis and hepatitis due to ipilimumab monotherapy for malignant melanoma. *J Oncol Pharm Pract* 2019; 25:966–968.