CASE REPORT

Rapid Onset of Takotsubo Cardiomyopathy Induced by an Infusion Reaction to Pembrolizumab in a Patient with NSCLC

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Introduction

Pembrolizumab, an antiprogrammed cell death protein-1 monoclonal antibody, is predominantly administered in patients with advanced NSCLC. Recently, a few cases of immune checkpoint inhibitor (ICI)–induced Takotsubo cardiomyopathy (TC) were reported.[1] However, it is difficult to clarify the correlation between ICI administration and TC because patients with cancer have several risk factors of TC. Here, we describe a case of a patient who was strongly suspected to have TC caused by an infusion reaction immediately after pembrolizumab administration.

Case Report

A 76-year-old woman, who had had left pneumonectomy for pulmonary tuberculosis at the age of 21 years, presented with anemia. She was an ex-smoker but had no history of cardiovascular disease. Chest computed tomography results revealed a mass in the lower lobe. She was diagnosed to have stage IIIC (cT3N3M0) lung adenocarcinoma (programmed death-ligand 1 tumor proportion score of 80%) with microcytic hypochromic anemia and high ferritin levels by chronic inflammation (Fig. 1*A–C*). She received pembrolizumab monotherapy. Six hours after pembrolizumab administration, she developed an infusion reaction to pembrolizumab that presented as fever, dyspnea, and wheezing. Despite the management of the infusion reaction, respiratory failure rapidly progressed. Electrocardiography results revealed ST elevation in leads V4 to V5 (Fig. 2*B*), and qualitative troponin test yielded positive results clearly. Echocardiography results also detected left ventricular apical segment akinesis and ventricular base hyperconstriction with apical ballooning (Fig. 3*A*). Deeper negative T waves were observed in leads II, III, aVF, and V3 to 6 the next day (Fig. 2*C*), but the peak elevation of creatine kinase was very mild and normalized quickly (Supplementary Fig. 1), which was not consistent with a wide range of myocardial ischemia by left anterior descending coronary artery stenosis. These findings suggested TC owing to a pembrolizumab-induced infusion reaction. The patient was intubated and ventilated with systemic corticosteroid therapy and vasopressor administration. Without the cardiac medications, her symptoms and negative T waves improved (Fig. 2*E*) and the abnormal heart wall motion normalized 1 month after the onset (Fig. 3*B–D*). However, the patient's lung cancer progressed rapidly, and she died 62 days after the admission.

Discussion

Patients with cancer have a high prevalence of TC with a poorer prognosis than those with TC without

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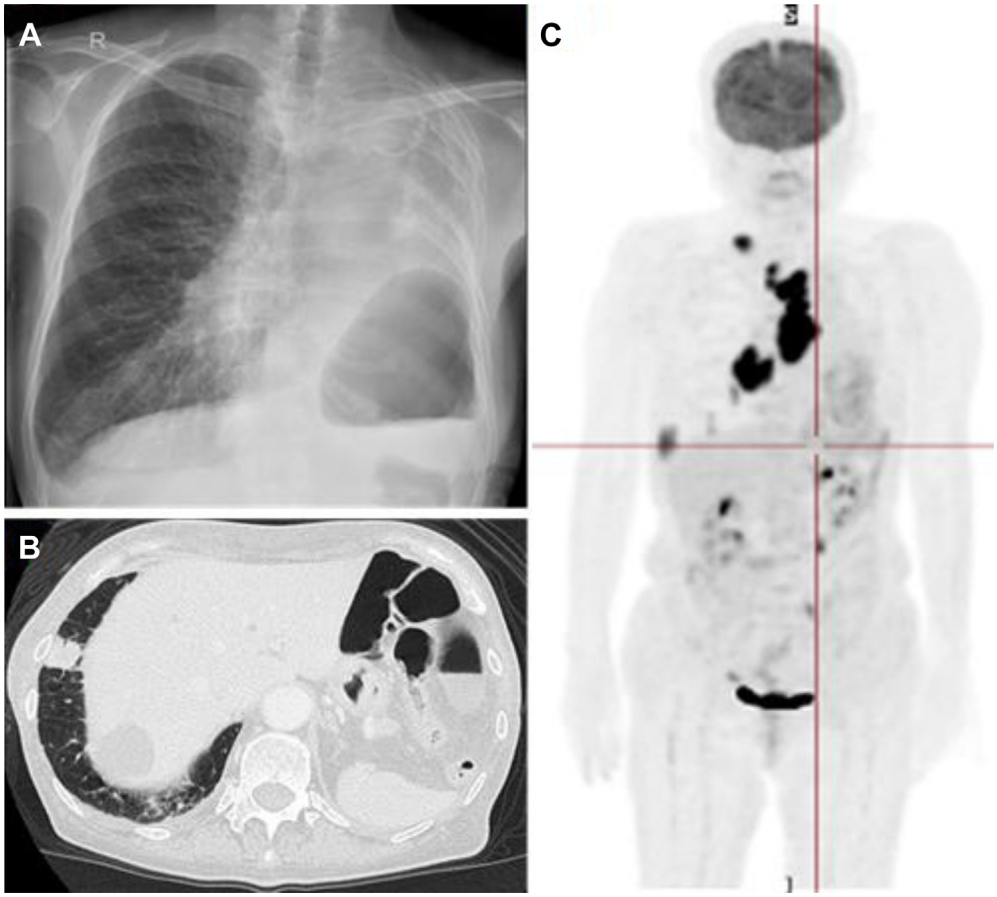

Figure 1. (*A*) Chest radiograph results after left pneumonectomy for pulmonary tuberculosis revealing a mass in the right lower lung field. (*B*) Primary tumor on chest computed tomography scan. (*C*) Primary tumor and N3 lymph node metastasis on positron emission tomography.

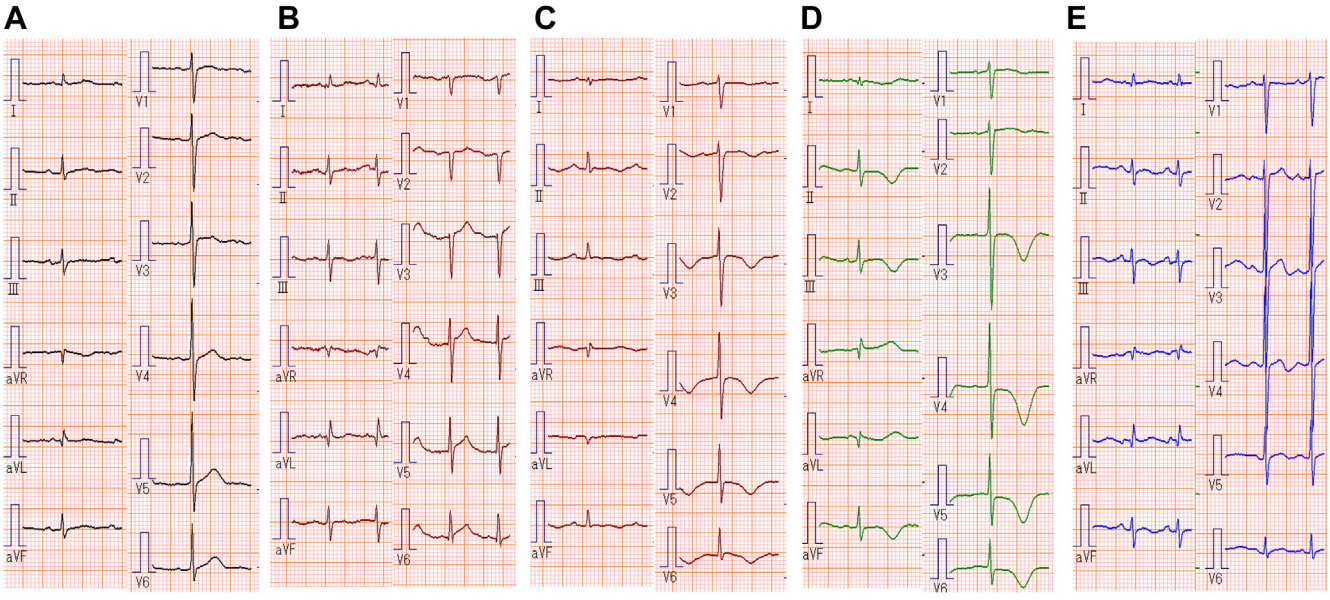

Figure 2. Electrocardiography results (*A*) on admission, (*B*) at the onset of Takotsubo cardiomyopathy, (*C*) on the day after the onset, (*D*) 1 week after the onset, and (*E*) 11 days after the onset.

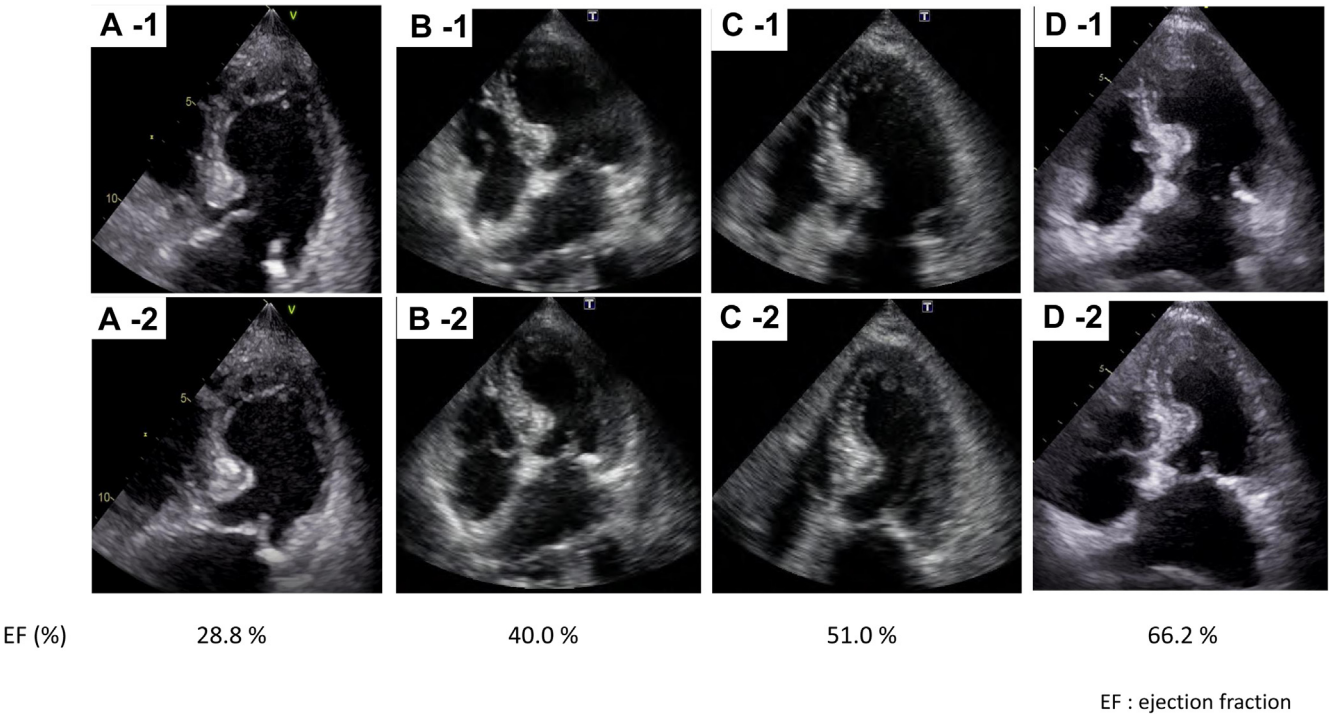

Figure 3. Transthoracic echocardiogram results (*A*) during (*A1*) diastole and (*A2*) systole at the onset of Takotsubo cardiomyopathy revealing apical hypokinesis; (*B*) during (*B1*) diastole and (*B2*) systole 1 week after the onset revealing the improvement of cardiac function; (*C*) during (*C1*) diastole and (*C2*) systole 9 days after the onset; and (*D*) during (*D1*) diastole and (*D2*) systole 1 month after the onset revealing the improvement to reference range.

malignancy.[1] Although the pathogenesis of TC is widely described, it still remains unclear. The most credited hypothesis involves the stress-induced release of catecholamines resulting in microvascular dysfunction or direct myocardial toxicity and finally leading to myocardial stunning.[2] The potential triggers for TC in patients with cancer include distress on cancer diagnosis, systemic inflammation owing to cancer, and physical stress of various cancer treatments, including chemotherapy.[3] In previous cases of ICI-related TC, the onset of TC occurred later in the treatment course (between 5 days and 8 months after treatment initiation).[1] In contrast, our case was characterized by the rapid onset of TC, suggesting a clear association between pembrolizumab administration and TC. The increase in physical stress and the elevation of inflammatory cytokine levels associated with an infusion reaction to pembrolizumab were considered to have led to TC, as reflected by a marked increase in the patient's ferritin level from 916 ng/mL to 30,248 ng/mL on the day after pembrolizumab administration. ICI-induced infusion reactions are very rare and are mostly mild to moderate in severity. Infusion reactions with ICIs have been reported to account for less than 1% of the adverse events.[4] Nevertheless, the infusion reaction-induced TC made our patient's condition serious. This case was strongly suspected to have TC triggered by an infusion reaction to ICI monotherapy. Our findings suggest that it is necessary to pay particular attention to infusion reactions and the potential for TC development while administering chemotherapy, including ICIs.

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The authors obtained appropriate consent for the publication of this manuscript.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology Clinical and Research Reports* at www.jtocrr.org and at https://doi.org/10.1016/j.jtocrr.2020.100055.

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