



## Case Report

# A Case of Lung Cancer with Very-Late-Onset Immune Checkpoint Inhibitor-Related Myocarditis

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### ABSTRACT

Immune checkpoint inhibitor (ICI)-related myocarditis has been reported to appear in the early phase after ICI initiation. Herein, we report the case of a 78-year-old man with non-small cell lung cancer. Pembrolizumab was introduced as first-line therapy. After 9 months, second-line therapy, including bevacizumab, was initiated. After another 7 months, echocardiography showed diffuse left ventricular dysfunction. Based on the histopathologic examination of the myocardium, the patient was diagnosed with ICI-related myocarditis. Initiation of prednisolone therapy improved cardiac function. This case of late-onset ICI-related myocarditis illustrates that endomyocardial biopsy can be useful in the differential diagnosis of cancer-related left ventricular dysfunction.

### RÉSUMÉ

Il a été rapporté qu'une myocardite pouvait survenir peu après l'instauration d'un traitement par des inhibiteurs des points de contrôle immunitaire (ICI). Nous présentons le cas d'un homme de 78 ans atteint d'un cancer du poumon non à petites cellules. Le pembrolizumab a été administré comme traitement de première intention. Neuf mois plus tard, un traitement de deuxième intention par le bévacizumab a été instauré. Après sept autres mois, l'échocardiographie a montré une dysfonction ventriculaire gauche diffuse. À la suite des résultats de l'examen histopathologique du myocarde, une myocardite liée aux ICI a été diagnostiquée. L'instauration d'un traitement par la prednisolone a amélioré la fonction cardiaque du patient. Ce cas de myocardite tardive liée aux ICI montre l'utilité éventuelle de la biopsie de l'endomyocarde dans le diagnostic différentiel d'une dysfonction ventriculaire gauche liée au cancer.

With the increasing use of immune checkpoint inhibitors (ICIs) for treating various cancers, immune-related adverse events (irAEs) have become a growing problem. Among irAEs, myocarditis is considered to be rare but potentially lethal. Therefore, cardiologists and oncologists are cautious regarding cardiac events. Severe life-threatening irAEs, including myocarditis, tend to occur in the early phases after ICI

initiation.<sup>1</sup> Herein, we present a rare case of ICI-related myocarditis with very late onset.

### Case

A 78-year-old man was diagnosed with non-small cell lung cancer (adenocarcinoma). After curative surgical lobar resection, his pathologic cancer stage was IIb (pT3N0M0). After 8 months, liver metastasis was discovered, diagnosed, and confirmed by liver biopsy (thyroid transcription factor-1, diffuse positive; programmed cell death 1-ligand 1 tumor proportion score, 70%); however, no driver mutations were detected. Based on the diagnosis of the postoperative recurrence of lung cancer, pembrolizumab monotherapy was administered every 3 weeks. After 9 months, positron emission tomography showed new cancer lesions in the mediastinal lymph nodes, despite pembrolizumab having achieved a partial response to liver metastasis. Therefore, combination

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
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See page 654 for disclosure information.

### Novel Teaching Points


- ICI-related myocarditis can occur as late as 7 months after discontinuation of ICI.
- Endomyocardial biopsy may be useful for differential diagnosis of cancer treatment-related cardiac dysfunction.

chemotherapy, including carboplatin, pemetrexed, and bevacizumab, was initiated as second-line therapy following pembrolizumab discontinuation.

Four months after initiating second-line therapy (13 months after ICI therapy initiation), although pemetrexed and bevacizumab resulted in a partial response, the patient reported slight fatigue and had worsening kidney dysfunction (estimated glomerular filtration rate decreased from a baseline of  $> 60$  mL/min per  $1.72$  m<sup>2</sup> to  $29$  mL/min per  $1.72$  m<sup>2</sup>). We considered this an adverse effect of second-line chemotherapy; therefore,  $1$  mg of betamethasone was administered to relieve the symptoms. However, after another 3 months (7 months from second-line therapy initiation, 16 months from ICI therapy initiation), the patient began experiencing severe fatigue and dyspnea on exertion. At this point, his peak serum brain natriuretic peptide level was  $293$  pg/mL (normal range:  $\leq 125$  pg/mL), and his cardiac troponin I level had increased slightly, to  $0.031$  ng/mL (normal range:  $\leq 0.026$  ng/mL). His 12-lead electrocardiogram revealed slightly widened QRS waves (90 ms at the baseline to 108 ms at the diagnosis of myocarditis) and no specific ST-T change (Fig. 1, A and B). Furthermore, echocardiography revealed a left ventricular end-diastolic diameter (LVDd) of  $47$  mm, left ventricular end-systolic diameter (LVDs) of  $39$  mm, and left ventricular ejection fraction (LVEF) of  $37\%$ , with newly appearing mild pericardial effusion (Fig. 1C; Video 1 , view video online). At baseline, echocardiography revealed an LVDd of  $43$  mm, an LVDs of  $26$  mm, and an LVEF of  $70\%$  (Video 2 , view video online). The patient was admitted to the hospital with a diagnosis of acute heart failure.

On admission, the patient's blood pressure and heart rate were  $160/98$  mm Hg and  $86$  beats per minute, respectively. During admission, administration of angiotensin-converting enzyme inhibitors and beta-blockers to control hypertension helped in relieving the patient's symptoms. Cardiac catheterization was performed to assess the LV dysfunction etiology, but no significant stenosis was revealed. Then, myocardial biopsy of the right ventricular septum was performed. Histopathology revealed significant lymphocyte infiltration, with evidence of cluster of differentiation (CD)8-positive cells and mild fibrosis on Masson's trichrome staining (Fig. 2). CD68-positive macrophages and tenascin-C (typically noted after cardiac inflammation) were also observed.

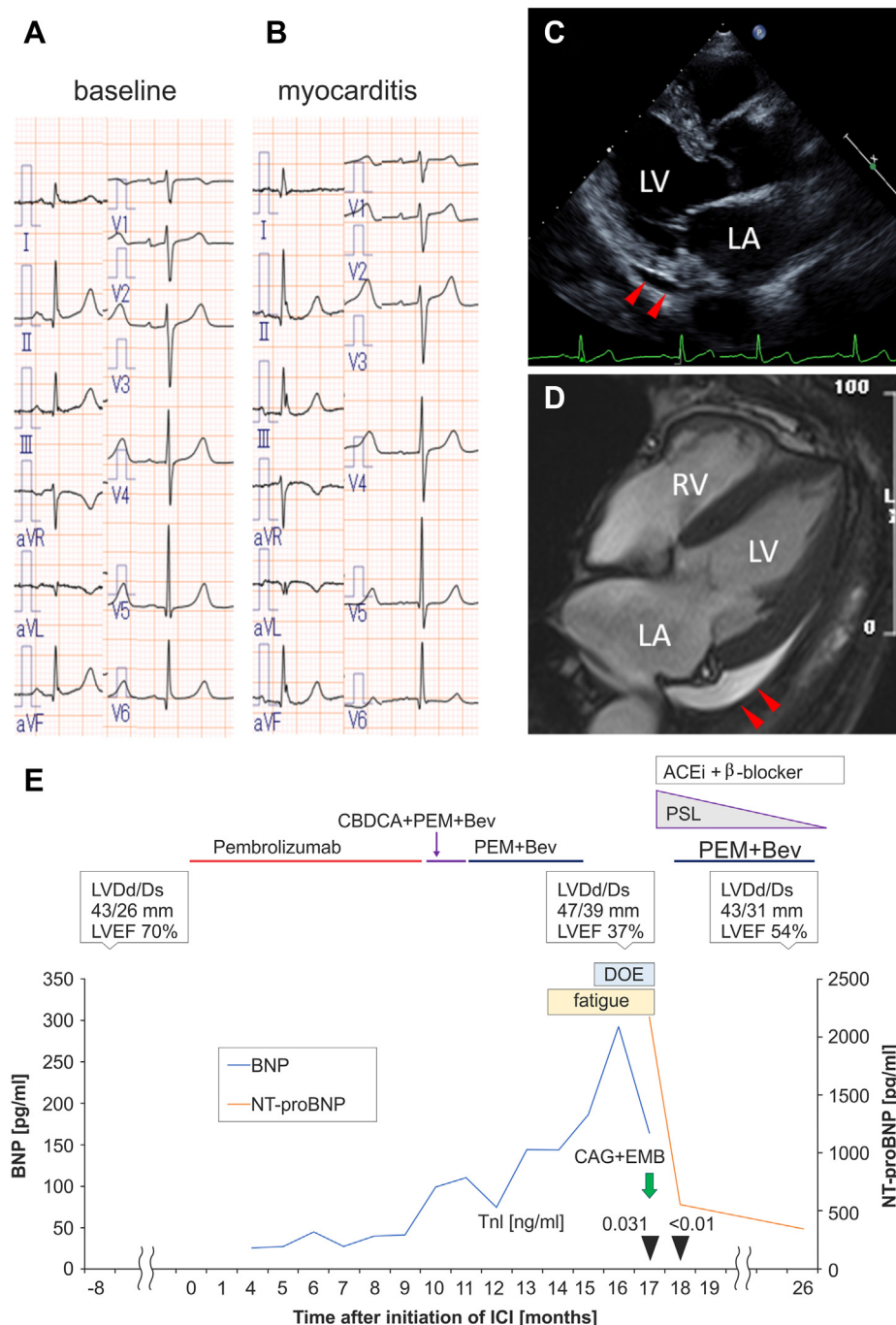
In our patient, cardiac magnetic resonance imaging showed no obvious dilatation of the left ventricle or typical evidence of inflammation via T2-weighted imaging. Diffuse hypokinetic wall motion of the left ventricle and pericardial effusion were observed (Fig. 1D). Furthermore, no clinical or symptomatic sign of viral infection was present, leading to no suspicion of viral myocarditis. In addition, although the mechanism of bevacizumab-related cardiomyopathy is not

clear yet, it is not reported to involve myocardial inflammation.<sup>2</sup> Therefore, by excluding other myocardial diseases, we assumed that very-late-onset immune-related myocarditis induced by pembrolizumab was the cause of his myocardial dysfunction. Myocarditis developed 16 months after pembrolizumab therapy initiation and 7 months after pembrolizumab therapy discontinuation. Given that the myocarditis was not fulminant, we initiated  $1$  mg/kg ( $50$  mg/d) prednisolone therapy, as indicated in the American Society of Clinical Oncology practice guidelines. The patient's symptoms were significantly relieved, and his N-terminal pro-brain natriuretic peptide level was reduced significantly (Fig. 1E). We reduced the dose of prednisolone by  $5$  mg every 2 weeks, and at 6 weeks after steroid therapy initiation, with  $30$  mg/d of prednisolone, the patient's LVEF improved to  $53\%$ , as revealed on echocardiography. At the time of writing, at 9 months after steroid therapy initiation (26 months from ICI therapy initiation), his echocardiographic data were as follows: LVDd,  $43$  mm; LVDs,  $31$  mm; and LVEF,  $54\%$  (Video 3 , view video online). Therefore, we are gradually reducing the prednisolone to  $10$  mg/d. The second-line therapy, including bevacizumab, has been restarted 2 months after steroid therapy initiation, and myocarditis or worsening of cardiac function has not recurred. The clinical time course is shown in Figure 1E.

### Discussion

The remarkable findings of our case were that very-late-onset ICI-related myocarditis was diagnosed after ICI discontinuation—16 months from ICI therapy initiation—and that endomyocardial biopsy was useful in diagnosing ICI-related myocarditis and distinguishing cardiac dysfunction from other drug-induced cardiomyopathies. According to recent studies, the incidence of myocarditis is  $0.27\%$ - $1.14\%$ .<sup>3</sup> Mahmood et al. reported that the prevalence of myocarditis in patients receiving the programmed cell death 1-ligand 1 inhibitor was as high as  $2.4\%$ , which is higher than that reported in patients receiving the programmed cell death 1 inhibitor ( $0.52\%$ ).<sup>4</sup> ICI-related myocarditis is reported to occur in the early phase after ICI therapy initiation.<sup>3,4</sup> A previous report indicates that the median time from ICI therapy initiation to the onset of myocarditis is 34 days.<sup>4</sup> In the latter study, the longest duration from ICI therapy initiation to myocarditis onset was  $> 400$  days. Recently, Moriyama et al. reported that ICI-related pericarditis was clinically diagnosed 18 months after ICI therapy initiation<sup>5</sup>; however, all reported cases were noted while ICI therapy was continuing. In our case, the patient had been treated with ICIs for 9 months, with myocarditis diagnosed 7 months after ICI therapy discontinuation; therefore, this case is considered extremely rare. Given that we had not performed echocardiography sequentially after ICI therapy initiation in this case, we could not determine the exact point at which myocarditis occurred. However, the appearance of dyspnea on exertion and increasing levels of brain natriuretic peptide seem to be closely related (Fig. 1E). Thus, we determined that the myocarditis had occurred approximately 16 months after ICI therapy initiation.

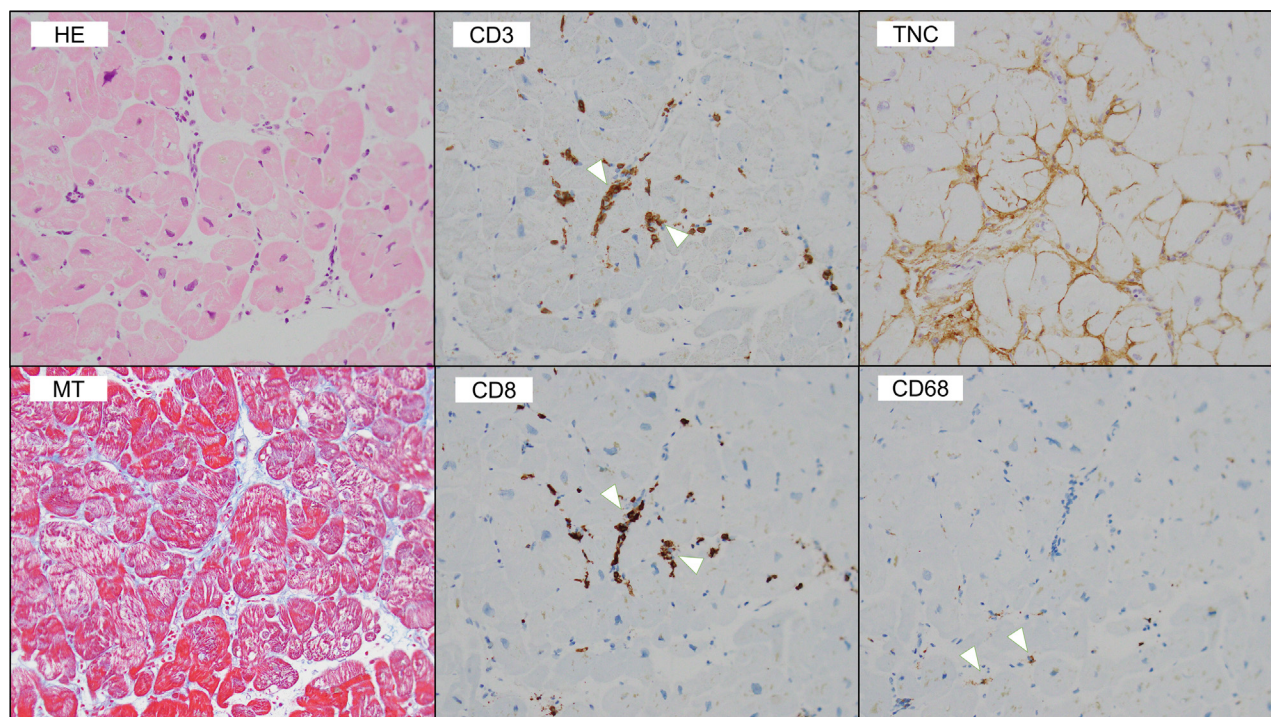
In our patient, we first inferred that myocardial dysfunction was caused by bevacizumab, as it is a vascular endothelial



**Figure 1.** Electrocardiography findings at (A) baseline and (B) the time of diagnosis of immune checkpoint inhibitor (ICI)-related myocarditis. (C) Echocardiogram and (D) cardiac magnetic resonance image at the time of diagnosis of ICI-related myocarditis revealing new small pericardial effusion but no left ventricular dilatation or wall thickness. (E) The clinical time course is also noted. ACEi, angiotensin-converting enzyme inhibitor; Bev, bevacizumab; BNP, brain natriuretic peptide; CAG, coronary angiography; CBDCA, carboplatin; DOE, dyspnea of exertion; EMB, endomyocardial biopsy; ICI, immune checkpoint inhibitor; LA, left atrium; LV, left ventricle; LVDd/Ds, left ventricular diastolic diameter/systolic diameter; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-BNP; PEM, pemetrexed; PSL, prednisolone; RV, right ventricle; TnI, troponin I.

growth factor inhibitor with known cardiac toxicity. In fact, the mechanism of myocardial toxicity of vascular endothelial growth factor inhibitor has not been elucidated completely yet. However, tyrosine kinase inhibitor-related cardiomyopathy does not show specific histopathologic characteristics in the myocardium. Therefore, among cancer treatment-related

cardiac dysfunctions, myocardial inflammation might be a specific characteristic of ICI-related myocarditis. In our case, bevacizumab had been continued after the diagnosis of ICI-related myocarditis, and the patient showed no worsening of clinical conditions. Therefore, we diagnosed the heart failure as ICI-related myocarditis (Fig. 2). Most infiltrated



**Figure 2.** Histopathologic findings of specimens of the right ventricular (RV) septum obtained during the endomyocardial biopsy. Mild fibrosis is observed on Masson-trichrome (MT) staining. Immunostaining of cluster of differentiation (CD)3 and CD8 reveals significant lymphocyte infiltration (**white arrowheads**). Immunostaining of CD68 shows mild infiltration of macrophages (**white arrowheads**). All images are at  $\times 200$  original magnification. HE, hematoxylin-eosin, TNC, tenascin-C.

lymphocytes were CD8+ cells, suggestive of ICI-related myocarditis. In our case, histopathologic examination was both useful and necessary for a more accurate diagnosis.

The mechanism of the pathogenesis of ICI-related myocarditis has not yet been elucidated. Meanwhile, several mechanisms have been proposed for the development of irAEs in other organs. Johnson et al. suggested a mechanism for the pathogenesis.<sup>6</sup> In that study, the suggestion was made that T cells were activated through shared antigens, which are proteins expressed in both cancer tissues and the myocardium. T-cell infiltration causes myocardial damage. The histopathologic examination in our case was consistent with the results of this prior study.<sup>7</sup>

According to a previous study, nivolumab-bound T-cells were detected  $> 20$  weeks after the last infusion.<sup>7</sup> The duration that T-cells spend bound to other ICIs remains unknown; however, pembrolizumab used in our case, may bind to T-cells for several months. Therefore, we should acknowledge the differential diagnosis of ICI-related myocarditis even several months after ICI discontinuation.

Furthermore, in terms of immunosuppressive therapy for ICI-related myocarditis, corticosteroids are the first choice.<sup>3</sup> We tapered the amount of oral corticosteroid very slowly, as re-emergence of myocarditis after cessation of corticosteroids has been reported.<sup>8</sup> Patients with myocarditis may need to be monitored even after the discontinuation of corticosteroids.

## Conclusion

ICI-related myocarditis may occur even 7 months after ICI therapy discontinuation. In cases of sequential treatment with

ICIs and other potentially cardiotoxic chemotherapy, such as bevacizumab, all these drugs should be considered to be potential causes of cardiac dysfunction. In such cases, a clinical course and cardiac biopsy may be useful to distinguish ICI-related myocarditis from other drug-induced cardiomyopathies.

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## Disclosures

The authors have no conflicts of interest to disclose.

## References

1. Wang DY, Salem JE, Cohen JV, et al. Fatal toxic effects associated with immune checkpoint inhibitors: a systematic review and meta-analysis. *JAMA Oncol* 2018;4:1721-8.
2. Bordun KA, Premez S, daSilva M, et al. The utility of cardiac biomarkers and echocardiography for the early detection of bevacizumab- and sunitinib-mediated cardiotoxicity. *Am J Physiol Heart Circ Physiol* 2015;309:H692-701.
3. Hu JR, Florido R, Lipson EJ, et al. Cardiovascular toxicities associated with immune checkpoint inhibitors. *Cardiovasc Res* 2019;115:854-68.
4. Mahmood SS, Fradley MG, Cohen JV, et al. Myocarditis in patients treated with immune checkpoint inhibitors. *J Am Coll Cardiol* 2018;71:1755-64.

5. Moriyama S, Fukata M, Tatsumoto R, Kono M. Refractory constrictive pericarditis caused by an immune checkpoint inhibitor properly managed with infliximab: a case report. *Eur Heart J Case Rep* 2021;5:ytab002.
6. Johnson DB, Balko JM, Compton ML, et al. Fulminant myocarditis with combination immune checkpoint blockade. *N Engl J Med* 2016;375:1749-55.
7. Osa A, Uenami T, Koyama S, et al. Clinical implications of monitoring nivolumab immunokinetics in non-small cell lung cancer patients. *JCI Insight* 2018;3:e59125.
8. Li Y, Hu Y, Yang B, et al. Immunotherapy-related cardiotoxicity re-emergence in non-small cell lung cancer—a case report. *Onco Targets Ther* 2021;14:5309-14.

### **Supplementary Material**

To access the supplementary material accompanying this article, visit *CJC Open* at <https://www.cjcopen.ca/> and at <https://doi.org/10.1016/j.cjco.2022.03.007>.