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Case Report

Immune Checkpoint Inhibitor-Associated Myocarditis: A Rare Presentation With Atrioventricular Block and Sinus Node Dysfunction

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Immune checkpoint inhibitors (ICIs) have emerged as promising therapies, allowing for durable responses in patients with various types of cancer. With the more widespread use of immunotherapy, cases of rare but often fatal ICI-associated myocarditis have captured the attention of oncologists and cardiologists.[1] Atypical presentations of this immune-mediated adverse event may delay the diagnosis and initiation of treatment, impacting patients' outcomes. We describe a case of pembrolizumab-associated myocarditis presenting with complete atrioventricular (AV) block and sinus node dysfunction in a patient with lung adenocarcinoma.

Case

A 54-year-old male patient with stage IV lung adenocarcinoma, presented with pulmonary, hepatic, bone, lymphatic, and left adrenal gland metastasis. As the tumour showed 50% expression of programmed death ligand-1 (PD-L1) without driver mutations, the decision was made to initiate first-line treatment with the ICI pembrolizumab. Prior to starting immunotherapy, the patient had been submitted to radiotherapy for lumbar pain control. He had a past history of a duodenal ulcer and was a previous smoker. He was not taking any medication.

After the ninth administration of pembrolizumab, he presented in the emergency department after several episodes of syncope. Initial evaluation showed a heart rate of 34 beats per minute, and the electrocardiogram (ECG) documented complete AV block (Fig. 1). He presented no signs of hemodynamic instability, and his peripherical oxygen saturation was normal.

His high-sensitivity troponin I (hsTnI) peak was 3220 pg/mL (upper limit of normal: 5 pg/mL), and his brain natrium peptide level was normal. The patient tested negative for severe acute respiratory syndrome (SARS)-CoV-2. The remaining blood tests and chest radiography were normal. Transthoracic echocardiogram (TTE) documented preserved left ventricular ejection fraction, mild hypokinesis of the inferior septum, preserved right ventricular function, no heart valve disease, and mild pericardial effusion (6 mm). Cardiac computed tomography showed a calcium score of 14 (percentile 59) and a nonobstructive lesion in the proximal circumflex artery.

Due to persistent AV block, and because cardiac magnetic resonance (CMR) imaging was not immediately available, the patient had a dual-chamber pacemaker implanted. Six weeks later, CMR imaging (1.5 Tesla) revealed preserved biventricular function, high native septal T1 values (1049 ms), and a normal signal on T2-weighted imaging. Intramural late gadolinium enhancement (LGE) was present in the interventricular septum and subepicardial LGE in the inferior wall (Fig. 2). The patient did not have any symptoms of recent viral illness, and Lyme disease was excluded.

Considering the AV block presenting with syncope, the findings of the CMR imaging, the elevation of troponin I level, the absence of obstructive coronary artery disease, and the concomitant immunotherapy with pembrolizumab, a diagnosis of ICI-associated myocarditis was made.[2]. Additionally, the Naranjo scale score, which estimates the probability of an adverse drug reaction, was found to be 5, indicating a probable causal relationship between the drug and the cardiac side effect.[3]

Given that the patient was stable at the time of diagnosis and the criteria for ICI-associated myocarditis were met, the decision was made not to perform a biopsy. Due to the delayed diagnosis and the patient's clinical stability, therapy

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Novel Teaching Points

- ICI-associated myocarditis can present as a combination of sick sinus syndrome and/or complete AV block.
- Timing of onset for ICI-associated myocarditis varies significantly; late cardiovascular events tend to carry a greater risk of noninflammatory heart failure and a higher mortality rate.

with steroids was not considered. During follow-up, the patient remained asymptomatic, with normalization of serum troponin levels.

The cardio-oncology and oncology teams decided on the suspension of pembrolizumab, and no rechallenge was attempted. Despite the suspension of immunotherapy, no oncologic disease progression occurred. Follow-up evaluation of the pacemaker revealed 0.3% of ventricular pacing and 21% of atrial pacing. The presence of a high percentage of atrial pacing caught the attention of the cardio-oncology team, as the patient had no signs or symptoms suggestive of sinus node disfunction prior to the episode. Taking this into account, the team concluded that the sinus node damage most likely had been caused by ICI-induced myocarditis.

Discussion

This case illustrates the variety of presentations of ICI-associated myocarditis and the inherent challenge of diagnosing it. ICIs are the most common form of immunotherapy, resulting in the activation of the patient's T cells to target and destroy cancer cells. Despite their significant benefits, a noteworthy concern arises from the potential overactivation of T cells, leading to unintended attacks on healthy tissues, giving rise to immune-related adverse events. One such complication is ICI-associated myocarditis, in which an excessive immune response targets cardiac tissue. Additionally, several other adverse cardiovascular effects have been observed, including myopericarditis, dilated cardiomyopathy, Takotsubo cardiomyopathy, arrhythmias, myocardial infarction, ischemic stroke, and venous thromboembolism.[2,4] The reported incidence of ICI-related myocarditis ranges from 0.04% to 1.14%. What sets it apart from other immune-related adverse events is its significantly higher associated mortality, which ranges from 25% to 50%.[2,4]

In the context of ICI-induced myocarditis, atrial and ventricular arrhythmias are well-documented adverse events, occurring either independently or in conjunction with ICI-associated myocarditis. The combination of complete AV block associated with myocarditis and sick sinus syndrome is a rare occurrence. Katsume et al. reported a case of pembrolizumab-induced sick sinus syndrome with histopathologic evidence of ICI-induced myocarditis, which improved notably after administration of a pulse of steroids. A point worth noting is that sinus node dysfunction can co-occur with ICI-associated myocarditis due to inflammation around the sinus node, or it can manifest as an independent immune-mediated adverse event.[5] In the present study, the authors speculate that the sinus node dysfunction observed in their patient likely was linked to ICI-associated myocarditis, considering the timing of its presentation.

Pembrolizumab is administered via an in-hospital dose infusion every 3 weeks, taking approximately 30 minutes. However, a crucial point to recognize is that adverse

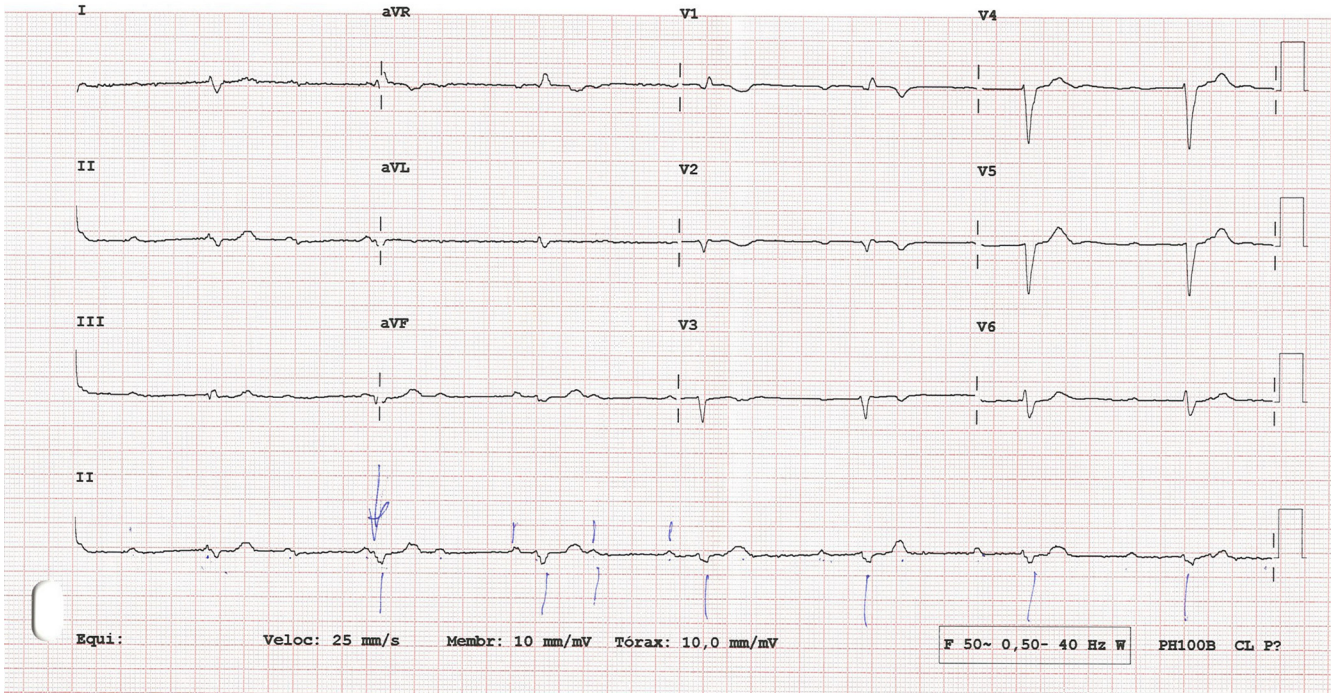

Figure 1. Electrocardiogram on admission showing complete atrioventricular block.

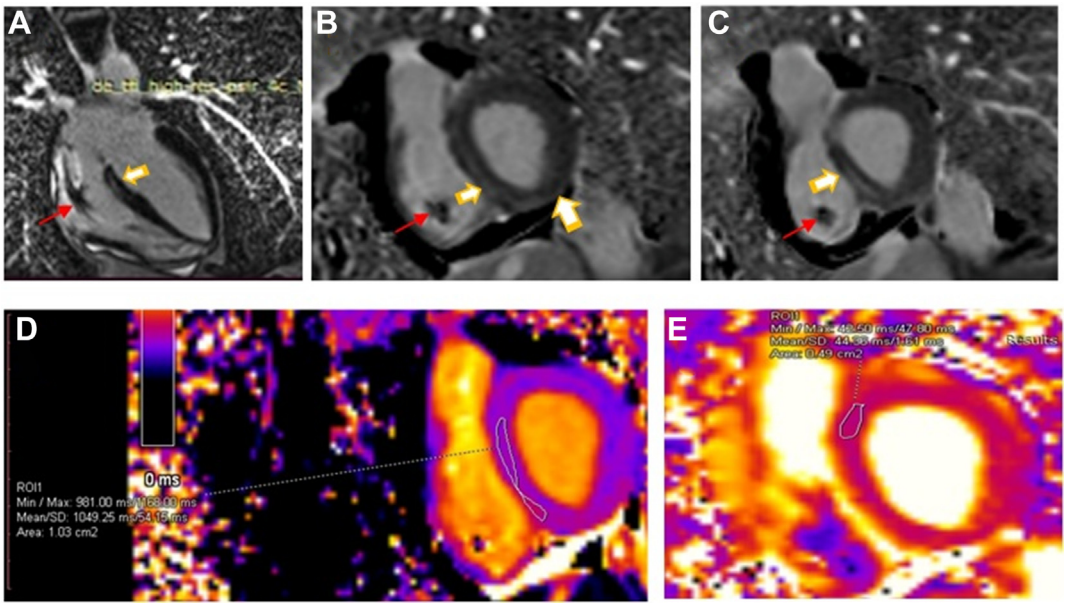

Figure 2. Initial cardiovascular magnetic resonance image of the patient. (**A-C**) Phase-sensitive inversion recovery late gadolinium enhancement imaging, (**D**) T1 mapping; (**E**) T2 mapping. Pacemaker leads are shown by **red arrows**. **Yellow arrows** point towards areas of late gadolinium enhancement.

cardiovascular events may occur during the intervals between cycles when the patient is no longer under direct clinical supervision, highlighting the critical importance of implementing systematic cardiovascular surveillance tailored to the patient's specific cardiovascular risk profile. Such surveillance should include, at the very least, an initial evaluation of serum troponin and an ECG at baseline, to ensure early detection and timely management of potential cardiac complications.

Recognizing risk factors is essential in formulating an effective management strategy for ICI-induced cardiotoxicity. Notably, the combination of 2 ICIs or simultaneous administration of other cardiotoxic drugs presents a well-supported risk factor. Patients with known autoimmune disorders, such as rheumatoid arthritis, systemic lupus erythematosus, or sarcoidosis, may face a heightened risk, particularly if they have experienced prior cardiac involvement. For patients with ICI-related skeletal myositis, a thorough cardiological evaluation (ECG, serum natriuretic peptides, cardiac troponin measurements, echocardiography) is advised to assess potential cardiac involvement and identify ICI-induced myocarditis in such cases. Interestingly, the impact of a history of previous myocardial damage (eg, myocardial infarction or myocarditis) on ICI-mediated cardiotoxicity remains unclear.[6]

According to the 2022 European Society of Cardiology Guidelines on Cardio-oncology,[2] high-risk patients receiving dual-ICI therapy or other cardiotoxic drugs, and those with a history of noncardiovascular immune adverse events or cancer therapy—related cardiac dysfunction, require comprehensive cardiovascular surveillance. For these high-risk patients, each treatment cycle should include the evaluation of serum troponin levels and ECG monitoring. Additionally, a baseline TTE evaluation is recommended.

Although routine TTE monitoring in asymptomatic patients did not show significant clinical benefits in previous trials, its consideration may be warranted for high-risk patients and those with elevated baseline cardiac troponin levels.[2]

The timing of onset for ICI-associated myocarditis varies significantly. Studies indicate that most cases occur within the first 1 to 2 months after initiating ICI treatment, with symptoms appearing at around 27 to 65 days, on average. However, late presentations at up to 454 days after starting ICI therapy have been reported.[7] Of note, late cardiovascular events, occurring beyond the 90-day mark, are not as thoroughly understood as earlier events. Nevertheless, they tend to carry a greater risk of noninflammatory heart failure, progressive atherosclerosis, hypertension, and higher mortality rates.[2]

In this particular case, the delayed presentation of AV block during the advanced treatment phase resulted in a late diagnosis and premature pacemaker implantation, without prior steroid administration, per current guidelines. However, based on a multicentre registry, a point worth noting is that most conduction abnormalities associated with ICI myocarditis are still treated with a permanent pacemaker, despite evidence suggesting the potential reversibility of immune therapy.[5]

Non-fulminant ICI-associated myocarditis was later diagnosed, considering the presence of a major criterion for ICI-myocarditis (CMR findings) and 2 other minor criteria (clinical presentation with syncope and presence of AV block), according to the European Society of Cardiology Guidelines on Cardio-oncology,[2] leading to permanent withdrawal of pembrolizumab. Furthermore, the calculated Naranjo scale score indicates a probable adverse drug reaction, thereby providing additional substantiation for our findings. This alignment is reinforced by prior investigations examining the outcomes of ICI-associated myocarditis, wherein patients exhibiting Naranjo scale scores ranging from "possible" to "definitive" were included.[3]

Holding therapy is strongly advised for all grades of ICI-associated myocarditis, and a rechallenge is rarely attempted, primarily due to limited evidence regarding the risks associated with restarting the drug.[2] In our patient's case, the clinical response was maintained during the suspension of immunotherapy. However, more research and evidence on rechallenging immunotherapy are imperative, particularly for patients who depend on its maintenance.

Conclusion

In conclusion, ICI-associated myocarditis is a rare yet emerging condition with diverse clinical presentations. Prompt diagnosis and management are crucial, involving ICI suspension, inpatient monitoring with electrocardiography, and methylprednisolone initiation. Multidisciplinary collaboration is essential, and cardio-oncology teams should be available to monitor patients on ICI treatment.

Ethics Statement

The study was conducted in accordance with the Declaration of Helsinki.

Patient Consent

The authors confirm that a patient consent form has been obtained for this article.

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Disclosures

The authors have no conflicts of interest to disclose.

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