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【 EDITORIAL 】

Sick Sinus Syndrome: More Than a Needle-in-a-haystack Manifestation of Immune Checkpoint Inhibitor-associated Myocarditis

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Immune checkpoint inhibitors (ICIs) are anticancer drugs that remove the brakes from T cells targeting tumors by inhibiting cytotoxic T-lymphocyte antigen-4 (CTLA-4) or programmed cell death 1 (PD-1)/programmed cell death ligand 1 (PD-L1) and have dramatically improved the outcomes of patients with advanced or refractory cancers (1). However, ICIs adversely allow T cells to infiltrate non-target organs and damage non-cancer cells that share a common antigen with cancer cells, leading to immune-related adverse events (irAEs) (1). A growing body of registry-based studies has clarified the spectrum of cardiac irAEs, including myocarditis, rhythm and conduction disturbances, and pericardial diseases (1). Takotsubo-like cardiomyopathy can manifest as a cardiac irAE, but the pathophysiological relevance is unclear (1). Among cardiac irAEs, myocarditis is the most serious concern, as it is often fulminant with a high mortality rate of 30% to 50% according to pharmacovigilance studies (2, 3). Since the incidence is relatively low [0.06% in patients treated with nivolumab alone and 0.27% in patients treated with nivolumab plus ipilimumab, according to a corporate safety database (4)], it is particularly important to make an accurate diagnosis promptly for the earlier initiation of intensive corticosteroid therapy.

In this issue of *Internal Medicine*, Nishikawa et al. reported a woman with lung cancer who presented sick sinus syndrome (SSS) as a manifestation of ICI-induced myocarditis (5). While she was admitted to the hospital for a fever and worsening renal function after the second course of pembrolizumab monotherapy, sinus pauses during the sinus rhythm and on termination of atrial fibrillation (tachycardia-bradycardia syndrome) were observed on electrocardiogram (ECG) monitoring. Although echocardiography revealed a normal ejection fraction of the left ventricle, modest elevation of cardiac troponin suggested worsening myocarditis. According to a single-center registry, a high proportion of patients with ICI myocarditis showed an abnormal ECG (89%) and elevation of cardiac troponin (94%) at the time of presentation (6). In the present patient, the early diagnosis and initiation of corticosteroid therapy prevented the development of fatal myocarditis, and in due course, the SSS improved under temporary pacing support. Arrhythmias were observed in 19% of patients with ICI myocarditis according to a pharmacovigilance study (2), and many of the fatal cases developed complete heart block and ventricular tachycardia (4). The arrhythmogenicity associated with ICI myocarditis is likely a sequela of inflammation by T cells and macrophages infiltrating the conduction system. In the present case, an endomyocardial biopsy of the right ventricular septum revealed focal infiltration of T cells and macrophages. Although direct histopathological evidence was lacking, SSS might develop as a manifestation of inflammation extending to the sinus node.

This is the first article reporting the occurrence of SSS in patients with ICI myocarditis (5). Whether the incidence of SSS is extremely low or SSS is diagnosed less often than it is actually present is unclear. A systematic review and meta-analysis of 48 randomized controlled trials revealed that ICI treatment was not associated with an increased risk of supraventricular or ventricular arrhythmias and conduction disturbance (7), but the rates of adverse cardiovascular events in cancer randomized controlled trials are markedly lower than those observed in the real world. The accumulation of similar cases and real-world data concerning cardiac irAEs will be required to clarify the clinical impact of SSS in ICIs-treated patients. Several algorithms have been proposed concerning the surveillance of patients treated with ICIs (1, 6, 8, 9), and periodic screening with a 12-lead ECG as well as cardiac troponin is commonly recommended by

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these algorithms. Given the life-threatening nature of ICI myocarditis, we should cautiously suspect the onset of myocarditis when any ECG changes, especially tachy- or bradyarrhythmias, including SSS, are observed.

Author's disclosure of potential Conflicts of Interest (COI).
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