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【 EDITORIAL 】

A Diverse Range of Cardiac Adverse Events Associated with Immune Checkpoint Inhibitor Therapy

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Immune checkpoint inhibitors (ICIs) have shown significant clinical benefit in the treatment of a variety of cancers. However, by enhancing immune responses in non-target organs, such as the cardiovascular system, these agents may cause a wide range of immune-related adverse events (irAEs) (1, 2). In this issue of *Internal Medicine*, Nishikawa et al. (3) reported a rare case of sinus node dysfunction that co-occurred with ICI-associated myocarditis. They reported that high-dose methylprednisolone pulse therapy under the support of a temporary pacemaker resulted in the resolution of sinus node dysfunction within a few days. This is the first report of sick sinus syndrome with histopathological evidence for ICI-induced myocarditis.

Myocarditis is the most well-known and biologically plausible cardiac irAE of ICI therapy associated with immune-related pathophysiology. However, in recent years, a wide-range of cardiovascular complications encountered during ICI therapy have been reported in many journals. Atherosclerotic cardiovascular diseases, such as myocardial infarction and ischemic stroke, were not commonly recognized as a part of irAE spectrum and thus were not generally considered as a potential ICI toxicity. However, a recent study by Drobni et al. provided evidence that ICI therapy was associated with an increased risk of atherosclerosis-related cardiovascular (CV) events (4). They conducted a matched cohort study that included 2,842 cancer patients treated with ICIs and 2,842 controls matched by age, the history of CV events, and type of cancer. In this large cohort study, ICI therapy was associated with a 3-fold increase in atherosclerotic CV events [hazard ratio (HR) 3.3, 95% confidence interval (CI) 2.0-5.5] in a multivariable model that included known CV risk factors. Venous thromboembolism (VTE) is a common complication of cancer that contributes significantly to the excess mortality of patients with cancer. Nonetheless, until recently, no comprehensive research on ICI treatment or VTE development had been conducted. Moik et al. (5) recently reported that in a cohort of 672 patients treated with ICI with a median follow-up of 8 months, the cumulative incidence of VTE was 12.9% (95% CI, 8.2-18.5), and the occurrence of VTE was associated with increased mortality (transition HR, 3.09; 95% CI, 2.1-4.6). More recently, Gong et al. (6) studied 2,854 patients treated with ICIs and found that the rate of VTE was >4-fold higher after starting an ICI (HR 4.98, 95% CI 3.7-8.6). Other than atherosclerotic diseases and VTE, various CV complications associated with ICI therapy have been reported, including congestive heart failure, pericardial disease, coronary artery spasm, and Takotsubo cardiomyopathy. Oncologists and cardiologists must keep in mind that ICI treatment can result in a variety of heart diseases, as systemic and local inflammation can either directly affect the myocardium or make the heart more vulnerable to traditional risk factors.

Cardiac adverse events (AEs) not clarified in clinical trials of antitumor drugs have been steadily reported after marketing, as in this case report. The factors associated with the above-mentioned situation are as follows: patients with complications are usually excluded from clinical trials, the observation period of clinical trials is limited, and rare complications cannot be detected when the sample size in clinical trials is small (7). Nishikawa et al. (3) detailed the clinical course of ICI-induced sinus node dysfunction, including its onset, diagnosis, treatment, and prognosis, allowing readers to share their experiences with AEs. This narrative information is extremely beneficial to healthcare providers, who must manage AEs, particularly in cases of serious and novel AEs (7).

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