中文題目：免疫檢查點抑制劑所引發的心肌炎，一個少見但致命的疾病
英文題目：Immune checkpoint inhibitor-related myocarditis: A rare but fatal disease

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Introduction

Immune checkpoint inhibitor is a novel category of anti-cancer agent that wildly used by oncology doctors nowadays. When the T cell binding to the tumor cell, immune checkpoint proteins on the tumor cell engage and send “off” signal to the T cell inhibiting the immune system and destroying function. By blocking this pathway, T cells are allowed to recognize and kill cancer cells. However, the amplified immune system might also misrecognize and attack the normal cell of the recipient. This uncontrolled immune response is called “Immune-related adverse event (IRAE)”. Herein, we introduced a patient diagnosed with an immune checkpoint inhibitor (ICI)-related myocarditis after receiving two doses of Nivolumab (Anti-PD1 inhibitor) as a treatment for hepatic cell carcinoma (HCC).

Case presentation

A 67-year-old male with HCC, T2N0M0 stage II, BCLC B received 2 doses of Nivolumab 200mg as part of anti-cancer therapy. He began to complain of intermittent chest tightness and dyspnea on exertion after the second dose. 28 days after 2nd dose of Nivolumab treatment, the patient visited the emergency department because of severe chest pain. Lab examination showed elevated high sensitivity troponin-I with a value of 5.604 ng/mL. Electrocardiography (EKG) (**Figure 1**) showed V1-5 ST elevation with T wave inversion and QTc prolongation. Coronary angiography revealed patent coronary arteries without stenosis. Initial echocardiography showed preserved left ventricular ejection fraction (64.2%) without regional wall motion hypokinesia. But the patient visited the emergency department again because of worsen chest pain and dyspnea 36 days after 2nd dose of treatment. Higher troponin I level elevated up to 16.0996 ng/mL and EKG (**Figure 1**) showed worse ST elevation at lead II, III, aVF, V1-V6. Repeat echocardiography revealed left ventricular global hypokinesia and reduced systolic function(LVEF:34.3%). Sustained pulse ventricular tachycardia(VT) developed and the patient accepted electric cardioversion twice in the intensive care unit(ICU).

Under the impression of ICI-related myocarditis, pulse therapy with methylprednisolone 1g per day for 3 days and then tapered methylprednisolone 80 mg

per day for a maintenance dose. As pulse therapy went through, ST elevation on EKG gradually remitted, and cardiac enzyme gradually decreased (**Figure 1**). After steroid treatment, an electrophysiology study (EPS) reveals the non-inducibility of sustained VT with programmed stimulation. Hematoxylin and eosin stain(H&E stain) of the myocardial biopsy showed inflammatory infiltration with myocyte destruction (**Figure 2A**). Immunohistochemical stain(IHC stain) showed CD8+ T-cell predominant infiltration (**Figure 2B**) and programmed cell death 1 ligand 1(PD-L1) expression on injured myocytes (**Figure 2C**). Those finding were compactable to ICI-related myocarditis. We gradually tapped down his steroid dose and followed his condition for three months. Subsequent echocardiography showed recovery of LV systolic function but still right heart dilatation with reduced right ventricular systolic function.

Discussion

ICI-related myocarditis is a rare but fatal disease. The exact mechanism of ICI-related myocarditis is still unclear now. Hypothesis stand for ICI myocarditis include the same antigen between myocyte and tumor cell, T-cell targeted a myocyte antigen that is different but similar to the tumor cell, or the blockage of immune checkpoint over activate T-cell to target dissimilar antigen of the normal myocyte.[1]

Although ICI-related myocarditis carries a high mortality rate, it usually is misdiagnosed, or delayed diagnosed. The cardinal symptoms of ICI-related myocarditis including chest pain, fatigue, dyspnea, orthopnea, fatal arrhythmias, and heart failure are usually nonspecific. Differential diagnosis includes coronary artery disease (CAD), viral myocarditis, and new-onset heart failure. Besides, the clinical presentation of ICI-related myocarditis can vary from asymptomatic elevation of cardiac biomarkers to severe cardiogenic decompensation. The history of using ICI is thus important for clinicians to put ICI-related myocarditis into consideration. Specific presentation of ICI-related myocarditis might be co-expression of other IRAEs. ICI-related myasthenia gravis and ICI-related myositis are more commonly associated with ICI-related myocarditis. [1] When the recipient of ICI spontaneously presents with chest pain, myositis, and proximal weakness, clinicians should always be aware of ICI-related myocarditis.

Endomyocardial biopsy is considered the golden standard test of ICI-related myocarditis. The histologic diagnosis of myocarditis is based on Dallas criteria and is made up of two components: inflammatory infiltrate and myocardial necrosis.[2]
Histopathologic analysis of ICI-related myocarditis might show lymphocyte, histocyte and macrophage infiltrate within the endocardium and conduction system. Destruction of myocytes is also a common histologic finding.[3] In addition, immunohistochemical

(IHC) staining typically showed positive T-cell marker CD3 and macrophage marker CD63.[3] The infiltrate cell contained abundant CD4+ and CD8+ T-cell. [1, 3, 4] Neither CD20+ (a surface marker of B-cell) positive cell nor antibody deposits wound be found.[3, 4] The H&E stain and IHC stain of our patient show all the feature above but are not enough to support the diagnosis of ICI-related myocarditis. We checked the expression of PD-L1 on myocytes and were impressed with the positive finding. Increased PD-L1 expression in the injured myocardium is a specific characteristic finding of IHC-related myocarditis. It is hypothesized that cytokine-induced cardioprotective mechanism up-regulates PD-L1 on myocytes to avoid the self-targeting immune response. Blockade of this pathway by ICI provoked ICI-related myocarditis.[3, 4]

Treatment of ICI-related myocarditis is mainly initiated with steroids. Mahmood et al suggested that a higher dose of steroid therapy is related to a lower risk of a major adverse cardiac event.[5] We administrated pulse therapy as initial therapy and then gradually tapped down the dose. Although we delayed in starting steroid treatment, a good response was reported in no meter cardiac enzyme, sequential telemetry waveform, and surveillance of LV function. Whether the time when steroid therapy start relates to treatment efficacy and the outcome of ICI-related myocarditis is questionable. Further research is, therefore, necessary to establish a standard treatment strategy and protocol for ICI-related myocarditis.

Conclusion

Diagnosis of ICI-related myocarditis is mainly based on the history of ICI use and the increased expression of PD-L1 on the IHC stain of the myocyte. Pulse therapy is well established and wild used to treat ICI-related myocarditis. Although often delayed diagnosis, ICI-related myocarditis shows a good response to steroid therapy.

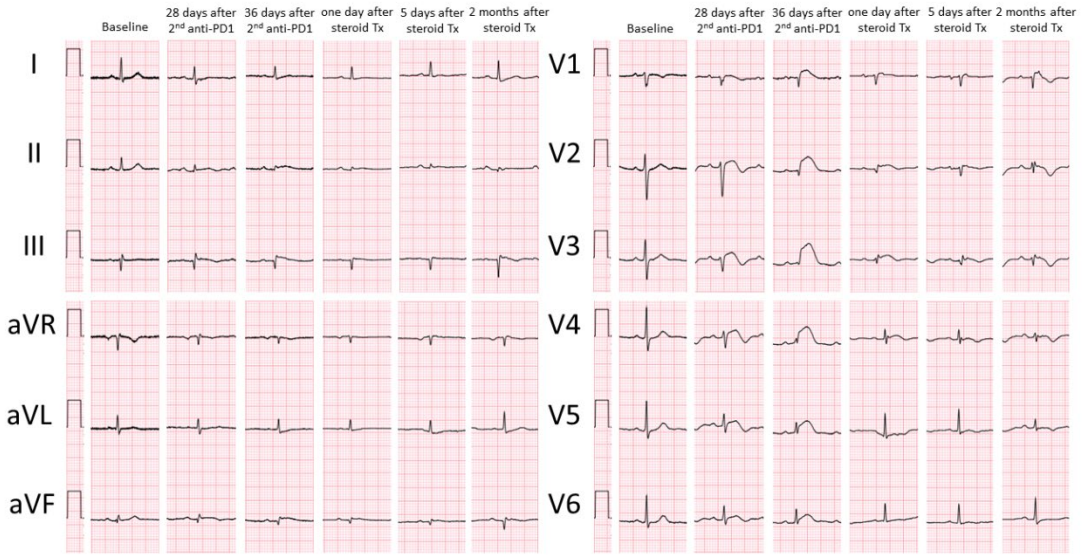

Figure 1

Series ECG change of immune checkpoint inhibitor-related myocarditis and recovery from steroid treatment. Progressive ST elevation in precordial leads(V1-V6) and inferior leads(II, III, aVF) after two doses of Nivolumab (Anti-PD1 inhibitor) infusion. ST elevation remitted after steroid treatment. Residual T wave inversion in V1-V5 and ICRBBB after recovery from myocarditis.

PD1:programmed death-1; ICRBBB: incomplete right bundle branch block

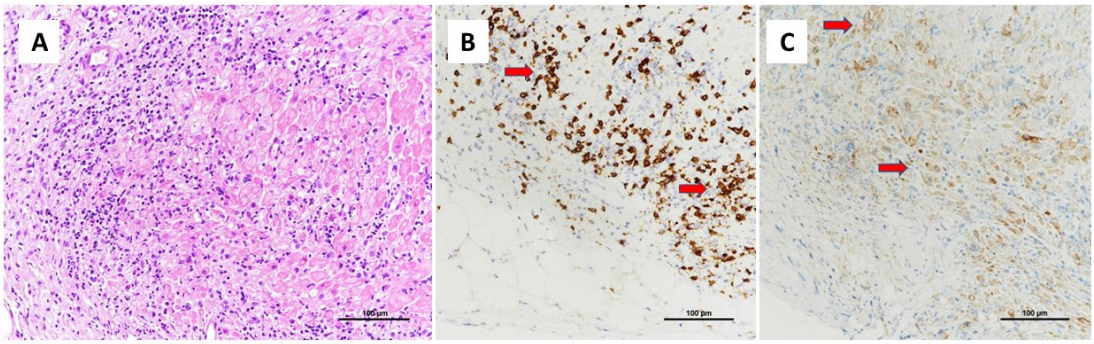

Figure 2

(A) H&E stain shows inflammatory infiltrate with myocyte destruction. (B) IHC stain shows CD8+ T-cell predominant infiltration (Red arrow). (C) Specific IHC stain shows PD-L1 expression on injured myocyte (Red arrow).

H&E stain: hematoxylin and eosin stain; IHC stain: immunohistochemical stain; Programmed cell death 1 ligand 1:PD-L1

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