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Case Report

Immune-related Giant Cell Myocarditis after Immune Checkpoint Inhibitor Therapy in a Patient with Urothelial Carcinoma and Myasthenia Gravis

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Abstract

Immune-related adverse events (irAEs) have drawn global attention after the extended use of immune checkpoint inhibitors (ICIs) in the past decade. These inflammatory side effects hinder cancer treatment and potentially have a negative impact on the prognosis. Myocarditis is an infrequent but often life-threatening irAE, and the pathogenesis remains unclear owing to its rarity and fulminant nature. We present a case of immune-related giant cell myocarditis after pembrolizumab treatment for unresectable urothelial carcinoma of the bladder in a patient with underlying invasive thymoma and myasthenia gravis. This unusual presentation highlights the complexity of immune crosstalk in patients with autoimmune diseases who receive ICI therapy. Further, investigations and individualized treatment for this population are warranted to minimize toxicity.

Keywords: Giant cell myocarditis, immune checkpoint inhibitor, myasthenia gravis

Introduction

Immune checkpoint inhibitors (ICIs) enhance cellular immunity against cancer cells and they have been approved for various cancer types within the past decade. At the same time, immune-related adverse events (irAEs), inflammatory side effects caused by activation of the immune system, have been widely observed.[1] In comparison with other irAEs, myocarditis is less frequent but has a significantly higher mortality rate. In an analysis of the Food and Drug Administration database, the incidence of ICI-related myocarditis was only 0.08%, but the mortality rate was 39.9%.[2] Histopathological analysis of the affected myocardium mostly revealed T-cell and macrophage infiltration, whereas multinuclear giant cells, sometimes observed in autoimmune myocarditis, were barely recorded. We present a case of immune-related giant cell myocarditis (GCM)

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after pembrolizumab treatment for unresectable urothelial carcinoma of the bladder in a patient with underlying invasive thymoma and myasthenia gravis (MG).

Case Report

A 71-year-old man had underlying recurrent but indolent invasive thymoma and MG, neither of which had required medical treatment for >10 years. He was diagnosed with a muscle-invasive urothelial carcinoma of the bladder and decided to receive chemoradiation for bladder preservation. However, unresectable disease recurred 4 months later. As he was ineligible for platinum-based treatment, he received salvage pembrolizumab (200 mg intravenously every 3 weeks).

Exertional dyspnea and right ptosis developed 1 week after the first dose of pembrolizumab. Pyridostigmine (180 mg daily) and low-dose prednisolone (10 mg daily) were administered according to a clinical diagnosis of MG exacerbation. However, he returned to the hospital 2 days later due to limited response and also the presence of other symptoms of heart failure, including orthopnea and peripheral edema. His MG was confirmed by an elevated titer of serum acetylcholine receptor antibody (9.47 [reference range: <0.2] nmol/L), but the probability of a severe exacerbation was low based on intact vital capacity. On the other hand, myocardial injury was recorded based on elevated serum cardiac markers (CK: 1278 [reference range: 30–223] U/L; CK-MB: 130.8 [reference range: <6.22] mg/mL; troponin-T: 2764 [reference range: <14] ng/mL) as well as a new interventricular conduction block on electrocardiography [Figure 1]. The systolic and diastolic functions of the left ventricle were intact on the echocardiogram, and coronary angiography did not reveal significant coronary arterial disease. A subsequent endomyocardial biopsy confirmed the diagnosis of GCM with CD3+, CD20+, CD68+ inflammatory cells, and the presence of multinuclear giant cells, but no pathogen was identified [Figure 2]. His clinical condition stabilized after high-dose steroids (intravenous methylprednisolone 1.5 mg/kg daily), and the cardiac markers normalized within 2 weeks.

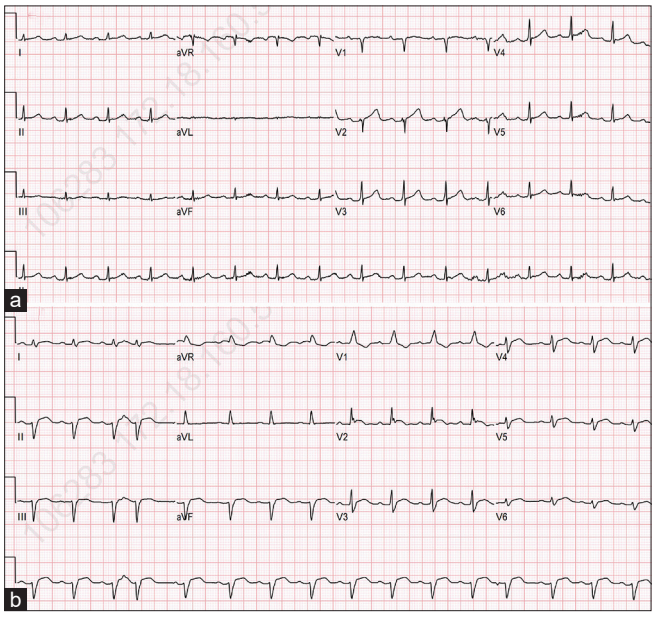

Figure 1: (a) Baseline electrocardiogram, (b) New interventricular conduction block

Discussion

ICI-related myocarditis, as with other irAEs, represents an inflammatory side effect arising from activated T-cell immunity caused by ICIs. The clinical presentation varies, from asymptomatic cardiac marker abnormalities to fulminant cardiogenic shock. In a large observational cohort study, the median onset from ICI administration was 38 days, with a wide range from 4 to 557 days.[2] The definite pathogenesis of ICI-related myocarditis was not completely understood. One histopathological report revealed infiltration of T-cells and macrophages in the affected human myocardium. Exact clones of immune cells were also observed in the tumor and skeletal muscle, suggesting that activated T-cells may target shared or homologous antigens between these organs.[3] A similar immune profile within the myocardium was also reported in an experimental animal model.[4] In addition, no infiltration of giant cells was observed in human and animal models of ICI-related myocarditis.[3,4]

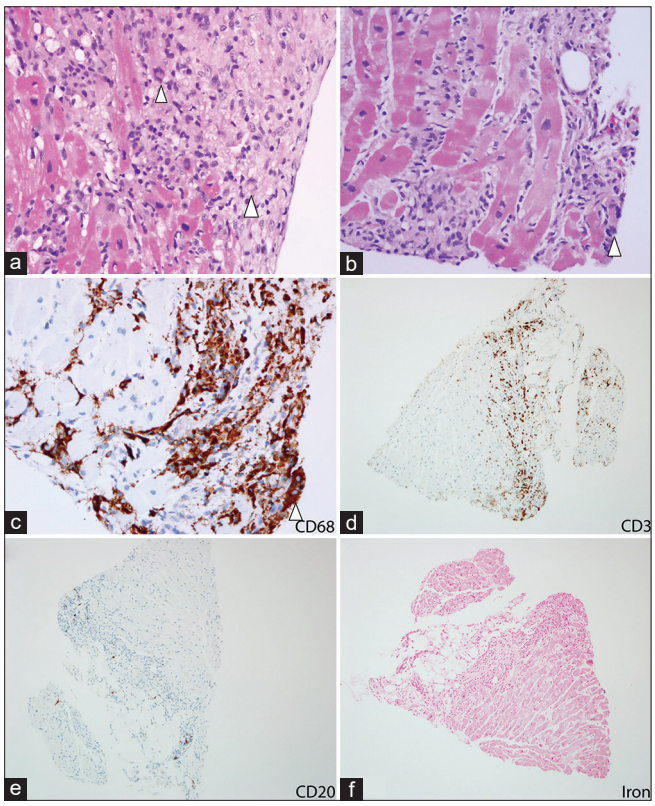

Figure 2: Pathological examination of the endomyocardial biopsy. Diffuse histiocytic infiltration with giant cell formation (white arrowhead) between cardiomyocytes is discernible (a and b). The histiocytic infiltrate is highlighted by CD68 immunohistochemical staining (c); note that the multinucleated giant cell (white arrowhead) was also positive for CD68. Scant B- and T-cell infiltration was seen (d and e). Iron stain (f) was negative, indicating no evidence of ischemic infarction

On the other hand, GCM has a much longer history before the use of ICIs. It is first described in 1905[5] and is considered to be a rare but more fatal type of myocarditis. The main histopathological feature of GCM is the infiltration of multinuclear giant cells beside Tcells and macrophages.[6] An autoimmune process has been proposed as the pathogenesis of GCM, based on a 19% rate of concomitant autoimmune diseases in previous case series.[7] The relationship between MG and GCM has also been documented.[8] However, the exact etiology of GCM remains undetermined, as most patients do not have a concomitant autoimmune disease.

In our patient, a temporal relationship between myocarditis and pembrolizumab indicated potential causation. Nevertheless, the presence of giant cell infiltration suggested that his condition was different from other cases of ICI-associated myocarditis reported in the literature. We hypothesize that pembrolizumab-induced myocardial injury through previously inactive autoimmune processes associated with his underlying MG.

Because patients with underlying autoimmune diseases have mainly been excluded from the clinical trials of ICI, data on immune-related myocarditis in such a setting are lacking. Some observational data have supported that the risk of exacerbating autoimmune diseases after ICI therapy is approximately 35%, most of which is low grade.[9] However, no previous study has focused on the details of myocarditis, including the pathological characteristics. Here, we reported a rare case of immune-related GCM after the use of an ICI in a patient with underlying MG. Further studies to investigate the safety of ICI administration in patients with indolent or well-controlled autoimmune diseases are warranted.

Ethical approval

This study was approved by the IRB of National Taiwan University Hospital (IRB approval number: 202107039W). The patient consent was waived by the IRB.

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Conflict of interest

There are no conflicts of interest.

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