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CASE REPORT

Coexisting of myasthenia gravis and fulminant myocarditis induced by nivolumab in a patient with ureteral epithelial cancer

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Abstract

The adverse events of immune checkpoint inhibitors (ICIs) are mostly immune mediated reactions. In this study, we presented a patient who developed coexisting of myasthenia gravis, myocarditis and anemia after treatment with nivolumab only 1 cycle for ureteral epithelial cancer. A 66-year-old woman was admitted to our department with the complaint of recurrent hematuria and backache for 2 months. This patient was diagnosed with stage IV, T4N3M1, urothelial carcinoma of the right kidney. She received immune checkpoint therapy consisting of nivolumab. Then, the physical and neurological examination found the ptosis of eyes especially the right eye and weakness of proximal limb muscles. Patient presented with sub-sternal chest discomfort, shortness of breath, electrocardiograms suggested atrial fibrillation and possible acute myocardial ischemic. One week later, this patient died of ventricular arrhythmia. This patient has increased clinical awareness by indicating that the immune-related adverse events (irAEs) could simultaneously involve multiple systems and progress quickly. Early recognition of aberrant immune activation and complete evaluation upon the occurrence of irAEs are critical.

Abbreviations:

ICIs	- immune checkpoint inhibitors
irAEs	- immune-related adverse events
NSCLC	- non-small cell lung cancer
CK	- creatine phosphokinase
CK-MB	- creatine phosphokinase-MB
BNP	- brain natriuretic peptide
Hb	- hemoglobin
AchR	- acetylcholine receptor
EMG	- electromyography
irAE	- immune-related adverse event
IVIG	- intravenous immunoglobulin

INTRODUCTION

Since William Coley found that cancer patients with post-surgical infection tend to have unfavorable prognosis in 1890s, utilizing patients own immune system to fight cancer has emerged one after another (Burdick & Coley, 1926). Owing to deepening understanding of immune escape, immune checkpoint inhibitors (ICIs) represent an exciting class of drugs that trigger the patients' immune system to recognize and combat cancer cells (Postow *et al.* 2018; Boussiotis 2016).

Nivolumab is an IgG4 antibody which targets PD-1 on the surface of T cells. Nivolumab blocks the interaction between PD-1 and its ligands, and it allows T cells to recognize tumor cells and destroy them. Nivolumab has been approved by US FDA for the treatment of advanced malignancies such as melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma, urothelial cancer, squamous cell carcinoma of head and neck, and Hodgkin's disease (Bayless & Schneider, 2015; Leventakos & Mansfield, 2016).

Since ICIs activate T cells, their adverse effects are mostly immune mediated reactions such as colitis, hepatitis, thyroiditis, hypophysitis, pneumonitis, pericarditis, skin rash, etc. It was reported that immune related AEs are generally low grade and manageable if recognized early, although severe and some fatal complications induced by ICIs have been reported (Boussiotis 2016; Bayless & Schneider, 2015; Leventakos & Mansfield, 2016). Cardiac immune-related adverse events (irAEs) appear to occur less frequently than irAEs in other organ systems, but they can be particularly complex to be diagnosed and treated (Boussiotis 2016; Bayless & Schneider, 2015; Leventakos & Mansfield, 2016). In this study, we presented a patient who developed coexisting of myasthenia gravis, myocarditis and anemia after treatment with nivolumab only 1 cycle for ureteral epithelial cancer.

CASE PRESENTATION

A 66-year-old woman was admitted to our department with the complaint of recurrent hematuria and backache for 2 months. She had no history of autoimmune disease, hypertension, diabetes or infectious diseases. This patient had renal calculus 10 years ago and received laser lithotripsy. A whole-body PET/CT scan was performed and found hypermetabolism mass in the right kidney, right lung and general multiple lymph nodes. Biopsy of right kidney was then preformed and proved to be urothelial carcinoma. Therefore, this patient was diagnosed with stage IV, T4N3M1, urothelial carcinoma of the right kidney. She received immune checkpoint therapy consisting of nivolumab (3mg/kg, as 140mg, d1). The process was going well, but two

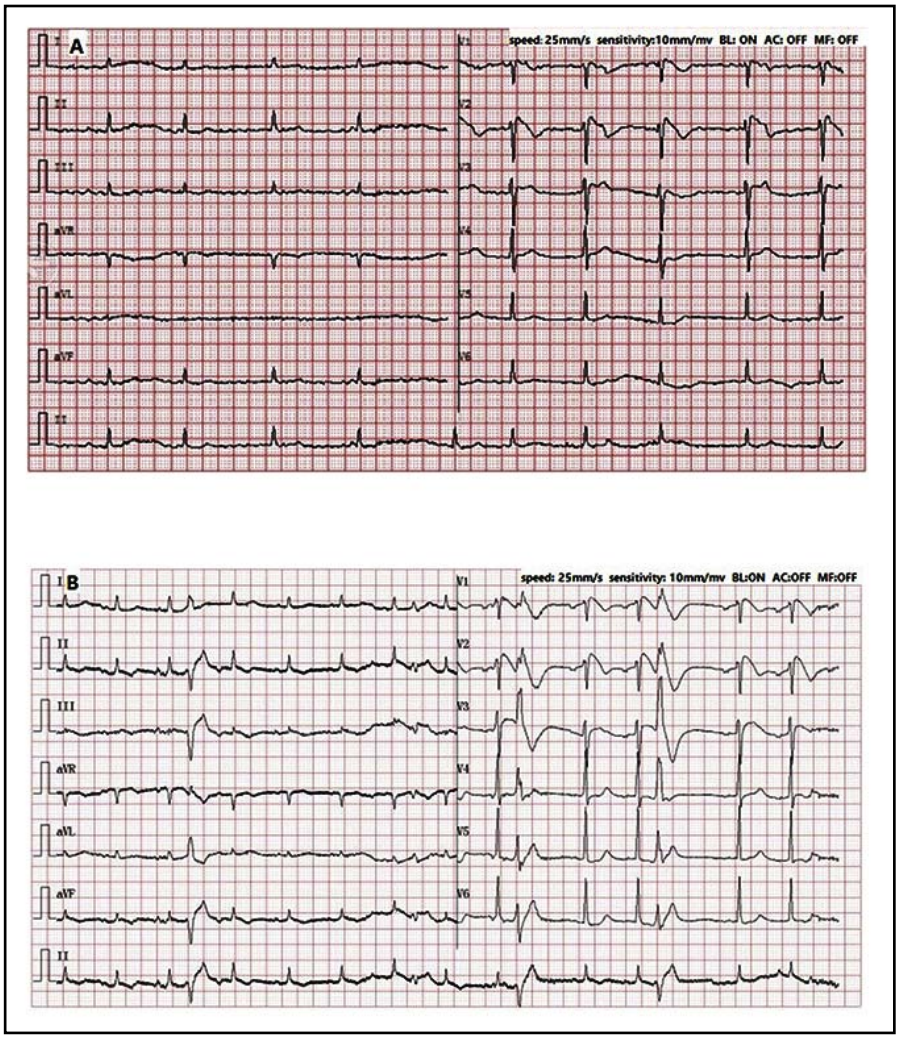

Fig. 1. Bedside electrocardiograms. **A.** It suggested atrial fibrillation and possible acute myocardial ischemic; **B.** It turned into ventricular arrhythmia 1 week later.

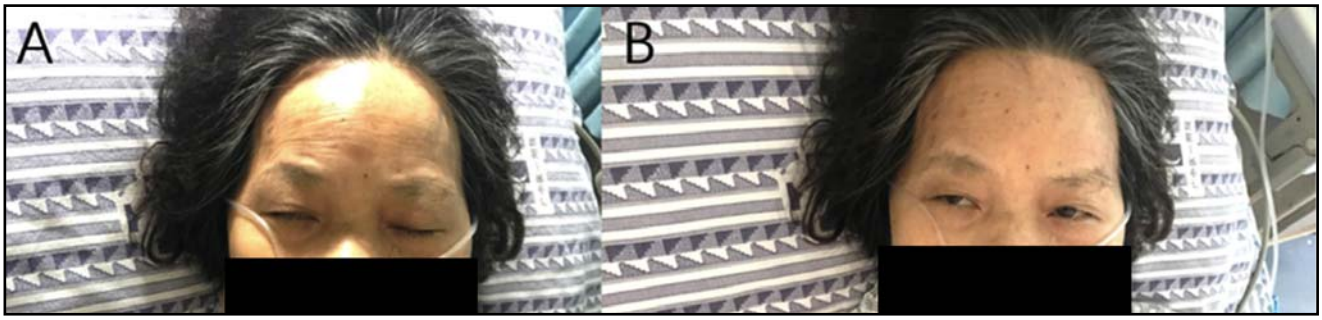

Fig. 2. Ocular myasthenia gravis. A. The ptosis of eyes especially the right eye; B. Her drooping eyelids and blurred vision was somewhat alleviated.

weeks later, she gradually developed symptoms such as anemia, drooping of eyelids, decreased vision and limbs weakness. Physical and neurological examination found the ptosis of eyes especially the right eye, and weakness of proximal limb muscles with 4 points of Medical Research Council scale for muscle strength.

Serum biochemistry examination showed elevated levels of creatine phosphokinase (CK) 536 U/L, creatine phosphokinase-MB (CK-MB) 426 U/L and brain natriuretic peptide (BNP) 399.0 pg/mL, decreased hemoglobin (Hb) 65 g/L and normal acetylcholine receptor (AchR) antibody (0.4 nmol/L). No evidence for autoimmune hemolytic anaemia was found. Head MRI showed scattered degeneration foci in the white matter of bilateral frontal subcortex, ethmoid sinus, and sphenoidal sinus inflammation. Then, the disease progressed rapidly in 2 days. Hemoglobin dropped to 49g/L, platelet decreased to 20×109 / L, while CK increased to 585 U/L, CK-MB was 452 U/L, hypersensitive troponin I was 0.003ng/mL, myoglobin was 73.6 ng/mL and BNP was 1534.3 pg/mL. Patient presented with sub-sternal chest discomfort, shortness of breath, moreover, she was too weak to finish nerve conduction study and electromyography (EMG). Bedsides, electrocardiograms suggested atrial fibrillation and possible acute myocardial ischemic (Figure 1), while bedside ultrasonic cardiogram was normal.

Given unclear etiology of her myocarditis, immune-related adverse event (irAE) of nivolumab was suspected. The patient was administrated with intravenous prednisolone (2 mg/kg/d for 7 days followed by 1g/d for 5 days) and oral pyridostigmine (60mg, 3 times a day). At the same time, she underwent blood transfusion and anti-infection therapy. Her drooping eyelids and blurred vision were partly alleviated (Figure 2), but her other blood parameters were kept growing and she had developed type II respiratory failure. One week later, this patient died of ventricular arrhythmia. Informed consent was not given since the patient had died, but informed consent of the patient's family members was obtained for the publication of this case report. Institutional Review Board of The first affiliated hospital of Guangzhou university of traditional Chinese medicine (GZTCM) hospital had approved this case report.

DISCUSSION

A broad spectrum of adverse events of immune checkpoint blockade has been reported for almost every organ. In addition to common side effects such as fatigue, they have distinct irAE (Brahmer *et al.* 2012; Michot *et al.* 2016). These irAE include autoimmune colitis, hypophysitis, hypothyroidism, hepatitis, nephritis, pericarditis and pneumonitis (Villadolid & Amin, 2015). About 40% patients had experienced grade 1 or grade 2 toxicity where grade 3 or 4 were reported in only 10% patients. Although most of these adverse events are slight and tolerable, some complications were difficult to be recognized and might lead to fatal outcomes.

Myasthenia gravis is an autoimmune disorder in which an antibody-mediated, T-cell-dependent immunological attack is directed at proteins in the post-synaptic membrane of the neuromuscular junction (Lindstrom *et al.* 1998). In severe cases, myasthenia gravis may cause respiratory failure or even death. Several case reports of myasthenia gravis caused by immunotherapy with either ipilimumab, nivolumab, or both have been reported (Montes *et al.* 2018; Shirai *et al.* 2016; Kimura *et al.* 2016; Sciacca *et al.* 2016; Polat & Donofrio, 2016; Chang *et al.* 2017). The frequency of myasthenia gravis has suggested that there might be a higher incidence of PD-1 inhibitor-associated myasthenia gravis in Asia compared with Western countries (Tan *et al.* 2017). All these patients developed symptoms after 1 to 3 doses of immunotherapy, and some of them had an elevated AchR antibody level. The treatment was mostly based on clinical experience, immunotherapy was stopped for patients, and treated with pyridostigmine, steroid, plasma exchange, or intravenous immunoglobulin (IVIG), and the symptoms of most patients could be resolved after adequate management (Chang *et al.* 2017). In our case, oral pyridostigmine (60mg, 3 times a day) also took certain effect.

The incidence of myocarditis has been considered uncommon in patients administered with immunotherapy. The possible reason is that a shared epitope between the tumor and the heart cause the same T-cell infiltration, but models for immunotherapy induced

myocarditis specifically are needed to understand the pathogenesis and test potential treatments (Norwood *et al.* 2017). IrAE is the most common etiology, while elevated CK, chest pains, and abnormal electrocardiograms strongly indicated an irAE of myositis. It also could cause acute arrhythmias, conduction disorders, heart failure, and even sudden death. If possible, muscle biopsy from patients with elevated CK levels would be helpful, while a lymphocytic T-cell infiltration in muscle tissue specimens could be found (Mahmood *et al.* 2018). Due to the low incidence of irAE induced myocarditis, data on presentation, diagnosis, treatment, and outcomes were limited (Escudier *et al.* 2017). Consultation with a cardiologist, discontinuation of immunotherapy, and administration of high-dose corticosteroids (e.g., 1 mg/kg methylprednisolone) in cases of confirmed or suspected myocarditis were recommended. TNF-α-antagonists or mycophenolate mofetil was found to be helpful. Unfortunately, an international retrospective study on fatal ICI toxic events reported that cardiac and neurologic events were especially prominent (43%) (Wang *et al.* 2018). This patient died of ventricular arrhythmia in 2 months after administrated with nivolumab.

To our best knowledge, this is the first case report of severe multiple system adverse effects involving muscles, nerves and blood related to the therapy of checkpoint inhibitors. Although immune checkpoint blockade is typically described as being well tolerated, it has long been incriminated for the severity of complications ranging from mild to fatal. These are distinct from conventional cytotoxic chemotherapy and can be life-threatening if left unrecognized. This case has increased the clinical awareness by showing that the checkpoint inhibitors related neurological irAEs could be complicated and simultaneously involve multiple neurological systems.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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