Journal of Cancer Research and Practice

journal homepage: www.ejcrp.org

Case Report

Triad of Myasthenia Gravis, Myositis, and Myocarditis after Nivolumab Administration in a Patient with Cholangiocarcinoma

Wen-Chi Wu[1,2,3], **Ming-Huang Chen**[1,2,4*]

[1]Division of Medical Oncology, Department of Oncology, Taipei Veterans General Hospital, Taipei, Taiwan
[2]Center of Immuno-Oncology, Department of Oncology, Taipei Veterans General Hospital, Taipei City, Taiwan
[3]Division of Hematology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan
[4]Department of Medicine, School of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan

Abstract

Immune checkpoint inhibitors, including anti-programmed death receptor-1/ligand-1 drugs and anticytotoxic T lymphocyte-associated antigens, are novel drugs for the treatment of many cancers. However, they may rarely cause neurological immune-related adverse effects, including immune-related myasthenia gravis (MG). This condition leads to poorer clinical outcomes, especially when coexisting with myositis or myocarditis. We report a case of a patient with advanced cholangiocarcinoma along with a history of thymoma in whom a triad of MG, myositis, and myocarditis developed after nivolumab administration. Early recognition of neuromuscular symptoms remains critical to successful management.

Keywords: Acetylcholine receptor, immune checkpoint inhibitor, immune-related myasthenia gravis, nivolumab, programmed death receptor-1, thymoma

Introduction

Immunotherapy has become a major treatment in patients with relapsed or refractory solid and hematologic malignancies.[1] Programmed death receptor-1 inhibitors are crucial for treating unresectable biliary tract cancer with DNA mismatch repair or high microsatellite instability.[2] As the use of immune checkpoint inhibitors (ICIs) increases, so does the incidence of diversified adverse effects (AEs). Neuromuscular complications account for only 1% of all immune-related AEs (irAEs)[1,3] but are much more fatal. Myasthenia gravis (MG) was reported to be the most common neurological AE,[1] but the evidence remains limited. MG can progress into myasthenic crisis, which may lead to respiratory failure and death, with an estimated mortality of 25%–30%.[4,5] The complications and complexities are even higher when combined with myositis and myocarditis.[4,6] Here, we report

Submitted: 30-Mar-2022 **Revised:** 12-Jun-2022
Accepted: 03-Jul-2022 **Published:** 06-Dec-2022

Access this article online

Quick Response Code:

Website: www.ejcrp.org

DOI: 10.4103/2311-3006.362636

Address for correspondence: Dr. Ming-Huang Chen, Division of Medical Oncology, Department of Oncology, Taipei Veterans General Hospital, No. 201, Section 2, Shih-Pai Road, Taipei 11217, Taiwan. School of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan.
E-mail: mhchen9@vghtpe.gov.tw

How to cite this article: Wu WC, Chen MH. Triad of myasthenia gravis, myositis, and myocarditis after nivolumab administration in a patient with cholangiocarcinoma. J Cancer Res Pract 2022;9:153-5.

a case of immune-related MG (irMG) and probable myositis and myocarditis.

Case Report

A 48-year-old man presented with left ptosis and diplopia and was eventually diagnosed as having invasive thymoma with pericardium invasion and MG. His initial serum acetylcholine receptor (AChR) antibody titer was 16.44 nmol/L (reference: <0.5 nmol/L). The patient underwent thymectomy, anterior mediastinal tumor resection, and partial pericardiotomy in March 2016, followed by radiotherapy. The symptoms, as mentioned earlier, completely recovered 1 week after the radiotherapy started. He did not need anticholinergic agents or steroids since then.

In July 2016, a 4.7-cm liver tumor was noticed during a regular check-up. A needle biopsy confirmed poorly differentiated cholangiocarcinoma. S1–4 segmentectomy was performed, and the staging was T2N0. In 2018, the disease recurred and gradually progressed with liver and lung metastasis as well as peritoneal seeding, even after concurrent chemoradiotherapy with tegafur/gimeracil/oteracil (TS-1), chemotherapy with a regimen gemcitabine plus cisplatin, video-assisted thoracic surgery of wedge resection and segmentectomy, and gemcitabine plus TS-1. He has also had regular neurologic outpatient clinic visits since 2016. In consideration of the patient's rapidly deteriorated disease, a combination of nivolumab, gemcitabine, and cisplatin was administered on September 3, 2021. He did not report any discomfort during or after the first cycle.

However, on October 3, sudden onset of fever and shortness of breath developed 1 h after the infusion of the second cycle of nivolumab. Binocular diplopia, bilateral drooping of the upper eyelids, and general malaise were also reported. Because the patient received neurologic examinations every 3 months, and there was no evidence of recurrence of MG even during the cancer progression, we considered irAE first. His serum AChR antibody titer was 10.9 nmol/L; creatine kinase (CK), 5404 U/L (reference: 39–308); creatine kinase-MB (CK-MB), 207 U/L (reference: 25), and troponin-I, 1.675 ng/mL (reference: <0.16). A 3-Hz repetitive nerve stimulation test demonstrated a decremental response [Figure 1]. Subsequently, 12-lead electrocardiogram revealed the presence of a right branch bundle block and tachycardia. The diagnosis of Grade 2 irMG, as per the National Comprehensive Cancer Network (NCCN) guidelines, was established. Myositis and myocarditis were highly suspected. Pyridostigmine, intravenous methylprednisolone (1 mg/kg/day), and normal saline hydration were administered for 5 days. The dose of methylprednisolone was tapered every 3 days. The patient's symptoms gradually improved. At the time of discharge, his CK concentration was 248 U/L [Figure 2]. At the 1-month outpatient follow-up, neurologic examination indicated normal movement of both eyes and improvement of diplopia. Pyridostigmine 60 mg 1 tablet/day and dexamethasone 4 mg

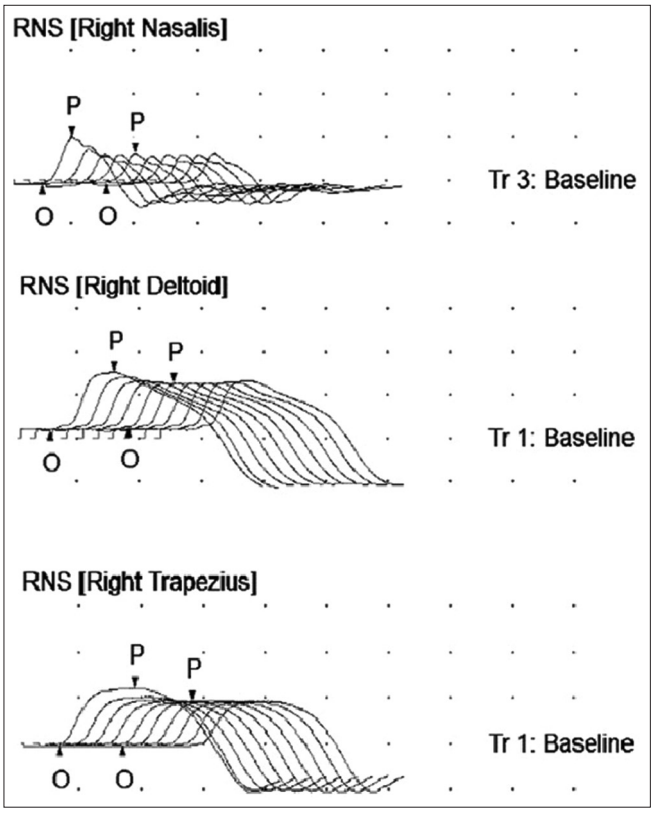

Figure 1: Repetitive 3-Hz stimulation treatment for the diagnosis of myasthenia gravis in our patient

2 tablet per day were kept. We then treated the patient's cholangiocarcinoma with fluorouracil, oxaliplatin, and leucovorin.

Discussion

Clinically, irMG is often associated with myositis and myocarditis, resulting in prolonged hospitalization and higher mortality.[4,6] The symptoms can range from being limited to the eyes – diplopia and ptosis – to life-threatening conditions, such as dysphagia, respiratory failure, or myasthenic crisis.[4,6] CK >1000 U/L is found in over 45% of patients with irMG.[7] MG is characterized by positive serum AChR binding or modulating antibodies or anti-muscle-specific kinase antibodies and neuromuscular transmission dysfunction on electrodiagnostic study.[7]

Suzuki *et al*. retrospectively analyzed 10,277 Japanese patients with cancer who received ipilimumab or nivolumab, and only 12 of the patients receiving nivolumab developed irMG; three and two of them had concomitant myositis and myocarditis, respectively, and one patient had both. The mean CK level of the 12 patients was 4799 U/L.[8] Safa *et al*. reviewed the MD Anderson Database and observed that 63 of 5898 patients with cancer developed MG in the immunotherapy setting; of them, 24 had myositis, 5 had myocarditis, and 2 had both.[9] The authors also found that 13 of the 63 patients had a preexisting history of MG and 10 developed severe MG.[9]

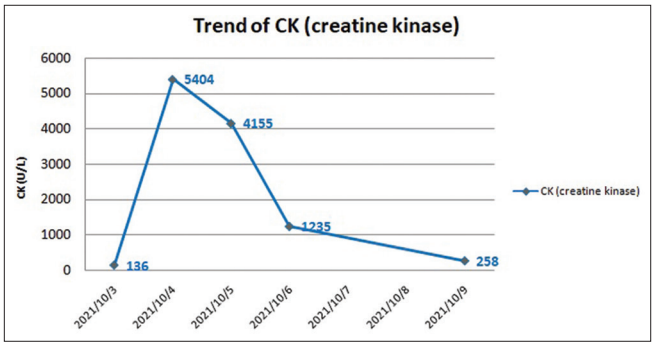

Figure 2: Trends in serum creatinine kinase

Corticosteroids (methylprednisolone 1–2 mg/kg/day or equivalent) are recommended for the treatment of irMG.[7] In case of severe and rapidly progressive disease, intravenous immunoglobulin, rituximab, and immune suppressants such as azathioprine, mycophenolate mofetil, and even plasmapheresis can be administered.[3,6] AChR antibody titer is not related to irMG severity, nor is it the surrogate marker of treatment response.[4,9] History of autoimmune and neuromuscular diseases should be screened before prescribing ICIs.[7] Any sign or symptom indicating irMG, myositis, or myocarditis should prompt a survey of the other two conditions. A multidisciplinary team, including oncologists, cardiologists, and neurologists, may thus be required.

Whether ICIs can be reused after recovery from irMG, regardless of the coexistence of myositis and myocarditis, remains unclear. The NCCN guidelines recommend permanent cessation of ICIs in patients with Grade 3 or 4 irMG.[3,7] However, recent research has demonstrated a positive correlation between irAEs and anticancer efficacy.[10] Moreover, Safa *et al*.[9] reported that no symptoms recurred in the six patients who received ICIs after irMG resolution.

Severe irMG can be fatal, especially when it coexists with myositis and myocarditis, necessitating knowledge of the risk factors and early recognition of the related symptoms. Here, we described the case of a patient with advanced cholangiocarcinoma with a history of thymoma who developed the triad of irMG, myositis, and myocarditis 30 days after first nivolumab infusion. This case adds to the evidence on neurological irAEs. Clinicians should be aware of and monitor for these potentially life-threatening symptoms. Before administering ICIs, especially in patients with autoimmune diseases, the benefits and potential complications of the treatment should be discussed for shared clinical decision-making.

Declaration of patient consent

The authors certify that they have obtained appropriate patient consent form. In the form, the patient has given his consent for the images and other clinical information to be reported in the journal. The patient understands that his name and initial will not be published and due efforts will be made to conceal the identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

The Taiwan Cancer Clinic Foundation and Melissa Lee Cancer Foundation supported the study.

Conflicts of interest

Dr. Ming-Huang Chen, an editorial board member at *Journal of Cancer Research and Practice*, had no role in the peer review process of or decision to publish this article. The other author declared no conflicts of interest in writing this paper.

References

1. Fan S, Ren H, Zhao L, Yin J, Feng G, Wang J, *et al.* Neurological immune-related adverse events associated with immune checkpoint inhibitors: A review of the literature. Asia Pac J Clin Oncol 2020;16:291-8.
2. Jakubowski CD, Azad NS. Immune checkpoint inhibitor therapy in biliary tract cancer (cholangiocarcinoma). Chin Clin Oncol 2020;9:2.
3. Jeyakumar N, Etchegaray M, Henry J, Lelenwa L, Zhao B, Segura A, *et al*. The terrible triad of checkpoint inhibition: A case report of myasthenia gravis, myocarditis, and myositis induced by cemiplimab in a patient with metastatic cutaneous squamous cell carcinoma. Case Rep Immunol 2020;2020:5126717.
4. Huang YT, Chen YP, Lin WC, Su WC, Sun YT. Immune checkpoint inhibitor-induced myasthenia gravis. Front Neurol 2020;11:634.
5. Rodolico C, Nicocia G, Damato V, Antonini G, Liguori R, Evoli A. Benefit and danger from immunotherapy in myasthenia gravis. Neurol Sci 2021;42:1367-75.
6. Lipe DN, Galvis-Carvajal E, Rajha E, Wechsler AH, Gaeta S. Immune checkpoint inhibitor-associated myasthenia gravis, myositis, and myocarditis overlap syndrome. Am J Emerg Med 2021;46:51-5.
7. Guidon AC, Burton LB, Chwalisz BK, Hillis J, Schaller TH, Amato AA, *et al.* Consensus disease definitions for neurologic immune-related adverse events of immune checkpoint inhibitors. J Immunother Cancer 2021;9:e002890.
8. Suzuki S, Ishikawa N, Konoeda F, Seki N, Fukushima S, Takahashi K, *et al.* Nivolumab-related myasthenia gravis with myositis and myocarditis in Japan. Neurology 2017;89:1127-34.
9. Safa H, Johnson DH, Trinh VA, Rodgers TE, Lin H, Suarez-Almazor ME, *et al.* Immune checkpoint inhibitor related myasthenia gravis: Single center experience and systematic review of the literature. J Immunother Cancer 2019;7:319.
10. Shen Y, Chen Y, Wang D, Zhu Z. Treatment-related adverse events as surrogate to response rate to immune checkpoint blockade. Medicine (Baltimore) 2020;99:e22153.