New onset of myasthenia gravis after intravesical Bacillus Calmette-Guerin
A case report and literature review

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Abstract
Rationale: Recently, drug-related myasthenia gravis (MG) has received attention, because the number of reported cases involving MG associated with immune checkpoint inhibitors, a new immunotherapy, is increasing. We present a case involving the new onset of MG, in which the symptoms started shortly after intravesical Bacillus Calmette-Guerin (BCG) for bladder cancer.

Patient concerns: A 69-year-old male with bladder cancer developed ptosis and diplopia 4 days after the completion of a treatment regimen with intravesical BCG weekly for 6 weeks.

Diagnoses: Ocular MG was confirmed by a positive serum anti-acetylcholine receptor antibody test.

Interventions: Treatment with high-dose methylprednisolone pulse therapy was given, after insufficient treatment with pyridostigmine bromide and 10 mg/d prednisolone.

Outcomes: Symptoms resolved completely 12 days after high-dose methylprednisolone pulse therapy.

Lessons: Intravesical BCG could be listed as a novel drug that may induce a new onset of MG along with drugs such as D-penicillamine and immune checkpoint inhibitors.

Abbreviations: BCG = Bacillus Calmette-Guerin, ICI = immune checkpoint inhibitor, MG = myasthenia gravis, TUR = transurethral resection.

Keywords: bladder cancer, drug-related, intravesical Bacillus Calmette-Guerin, myasthenia gravis

1. Introduction
Myasthenia gravis (MG) is an autoimmune disease affecting the neuromuscular junction. It is well-known that symptoms of MG can be aggravated by various types of drugs.[1] In addition, subclinical MG may become apparent after treatment for other disorders. Finally, some medications potentially induce the new onset of MG.[2-4] Recently, drug-related MG has received special attention because of immune-related autoimmune events after treatment with immune checkpoint inhibitors (ICIs).[5-7]

We reviewed 498 patients who were followed in Keio MG Clinic between January 1999 and December 2016. All clinical information was collected after receiving written informed consent from the patients, as approved by the institutional review board of Keio University Hospital (No. 20090278). Of the 498 patients, we found 3 patients (0.6%) that we believed exhibited drug-related MG. Briefly, a 68-year-old woman experienced worsening of MG after treatment with atorvastatin.[8] In addition, a 69-year-old woman experienced exacerbation of subclinical MG after treatment with pilsicainide, an anti-arrhythmia drug. The remaining patient experienced the development of new-onset MG after intravesical Bacillus Calmette-Guerin (BCG), and is presented as a case report. To our knowledge, such a case has not been previously documented in the literature.

2. Case report
A 69-year-old man with bladder cancer was treated with intravesical BCG after transurethral resection (TUR) and presented with new-onset ocular symptoms. He had no past history, nor a particular family history. Intravesical BCG was injected weekly for 6 weeks in the previous hospital. He did not have any side effects after the first dose of intravesical BCG, but experienced dizziness and urinary frequency after the second dose. Four days after the final injection of BCG, he developed ptosis and diplopia. One month after the onset, he visited an
| Author | Year | Age/sex | Type | Medication | Disease | Time to onset | Initial symptoms | Treatment | Prognosis (time to recovery) |
|--------|------|---------|------|------------|---------|--------------|-----------------|-----------|--------------------------------|
| Norris et al. | 1964 | 31/F | Anticonvulsant | Phenytoin | Epilepsy | 22 y | Ocular, generalized | Withdrawal of drug only | Recovered (6 mos) |
| Peterson | 1966 | 11/F | Anticonvulsant | Trimethadione | Epilepsy | N/I | Ocular, generalized | Pyridostigmine | Recovered (4.5 mos) |
| McQuillen et al. | 1968 | 51/M | Antibiotics (aminoglicoside) | Kanamycin | Renal infection | 2 wks | Generalized | Withdrawal of drug only | Recovered |
| Herishanu and Rosenberg | 1975 | 40/F | Beta-blocker | Propranolol | Hypertension | N/I | Ocular, generalized | Withdrawal of drug only | Recovered |
| Burke et al. | 1975 | 40/M | Antirheumatics | D-Penicillamine | Rheumatoid arthritis | 8 mos | Ocular, generalized | Pyridostigmine | Recovered (2 mos) |
| Neil et al. | 1976 | 25/M | Psychotropics | Lithium | Manic | 4 mos | Ocular, generalized | Pyridostigmine | Recovered |
| Sghirlanzoni et al. | 1988 | 18/F | Antimalarial agent | Chloroquine | SLE | 7 wks | Ocular, generalized | Pyridostigmine, steroid | Recovered (6 mos) |
| Bashuk and Krendel | 1990 | 19/F | Magnesium | Magnesium | Pneumonia | 10–15 min | Generalized | Withdrawal of drug only | Recovered (1 d) |
| Fujiyama et al. | 1991 | 30/M | Antirheumatics | Bucillamine | Rheumatoid arthritis | 14 mos | Generalized | Pyridostigmine, plasmapheresis, azathioprine, IVMP | Recovered |
| Barocchi et al. | 1995 | 61/M | Interferon | Interferon-α | Bladder cancer | 3 mos | Ocular, generalized | Pyridostigmine, steroid | Recovered |
| Krishnan et al. | 1995 | 30/M | Iron chelator | Desferrioxamine | Hemolytic anemia | 2 y | Ocular, generalized | Pyridostigmine | Recovered |
| Pipers et al. | 1996 | 28/M | Antibiotics (macrolide) | Clarithromycin | Toxoplasmosis | After first dose | Ocular, generalized | Pyridostigmine | Recovered (6 h) |
| Tarsy et al. | 2000 | 80/F | Botulinum toxin | Botulinum toxin A | Myasthenia gravis | 13 y | Generalized | Pyridostigmine, neostigmine, steroid, IVIg | Recovered (5 mos) |
| Parmar et al. | 2002 | 65/F | Statin | Atorvastatin | Hyperlipidemia | 3 mos | Ocular, generalized | Withdrawal of drug only | Recovered (6 wks) |
| Gunduz et al. | 2006 | 45/M | Antibiotics (fluoroquinolones) | Levofloxacin | Pneumonia | 3.5 d | Generalized | Pyridostigmine, steroid | Recovered (10 d) |
| Fee and Kesarwani | 2009 | 66/M | Anti-TNFα therapy | Etanercept | Rheumatoid arthritis | 6 y | Generalized | Withdrawal of drug only | Recovered (6 mos) |
| Liao et al. | 2014 | 70/F | Anti-CTLA4 inhibitor | Ipilimumab | Melanoma | 7 wks | Generalized | Plasmapheresis, IVMP, IVIg, pyridostigmine | Recovered (2 wks) |
| Shirai et al. | 2016 | 81/F | Anti-PD-1 inhibitor | Nivolumab | Melanoma | 2 wks | Generalized | Pyridostigmine | Died |
| Zimmern et al. | 2016 | 69/F | Anti-PD-1 inhibitor | Pembrolizumab | Melanoma | 9 wks | Ocular, generalized | Pyridostigmine, IVMP, steroid, PE | Died |
| Current case | 2017 | 69/M | intravesical BCG | Bladder cancer | Ocular | 6 wks | Pyridostigmine, IVMP, steroid | Recovered (2.5 mos) |

BCG = Bacillus Calmette-Guérin, CTLA-4 = cytotoxic T-lymphocyte-associated protein 4, F = female, IVIg = intravenous immunoglobulin, IVMP = intravenous methylprednisolone, M = male, N/I = no information, PD-1 = programmed cell death protein 1, SLE = systemic lupus erythematosus, TNF = tumor necrosis factor.
ophthalmologist who performed an Edrophonium chloride (Tensilon) test, which was positive. He was started on pyridostigmine bromide, but the effect was insufficient. Three months after the onset of symptoms, he visited our neurological department because his oculor symptoms were persistent.

He had asymmetrical bilateral ptosis and limitation of oculor movement. His quantitative MG score was 8 (3 each for ptosis and diplopia and 1 each for bilateral hand grips). Neurological symptoms varied within a day. Other physical examination was normal including rashes. Anti-acetylcholine receptor (ACHR) antibodies were elevated to 1.8 nmol/L (normal range below 0.2 nmol/L). Hemoglobin A1c, thyroid function, and antinuclear antibody were all negative. Brain MRI was normal, and chest CT was normal including thymus. Differential diagnosis such as brain tumor, stroke, diabetes, and thyroid-associated ophthalmopathy were all unlikely due to brain MRI and blood tests. Fluctuation of symptoms within a day suggested neuromuscular junction disease. Since the patient had ptosis and limitation of oculor movement (MG symptoms) and anti-AChR was positive, he was diagnosed with oculor MG (late onset).[1] Because pyridostigmine bromide was insufficient, daily activities were highly impaired, and the risk of immunodeficiency or diabetes was not high, prednisolone 10 mg/d was added to the treatment; however, it was not sufficient either. Then, he was treated twice with methylprednisolone 1g/d for 3 days. His oculor symptoms started to improve 5 days after the first dose of high-dose intravenous methylprednisolone therapy. The oculor manifesta-
tion disappeared completely 12 days after the first dose. He has not undergone BCG injection since this episode and has had no relapse of MG during the 1-year follow-up.

3. Discussion
Intravesical BCG is used to prevent the recurrence and progression of nonmuscle invasive bladder cancer after the TUR procedure.[2] First described by Morales et al[10] in 1976, intravesical BCG after TUR is known to provide a significant advantage over TUR alone in delaying tumor recurrence in patients with medium/high-risk Ta or T1 bladder cancer.[11] The immune response triggered by BCG to the bladder urothelium activates proinflammatory cytokines and promotes neutrophils, monocytes/macrophages, lymphocytes, natural killer cells, and dendritic cells.[12,13] Common side effects of BCG treatment are urininary frequency, cystitis, fever, and hematuria.[11] Systemic BCG infection has also been reported.[12] With regard to immunological side effects, there have been case reports of interstitial pneumonitis after intravesical BCG.[14,15] however, there has not been a reported case of MG in the past literature.

To elucidate the clinical characteristics of new-onset MG that occurs after drug administration, we searched the PubMed (MEDLINE) databases using combinations of the keywords “myasthenia gravis” and “side effect,” “medicine,” “induce,” “drug-induced,” and “trigger” for articles published on these topics. Table 1 summarizes the first case reports showing the new onset of MG triggered by medications[12–31] based on the literature and the present patient. Noxious medications included anticonvulsants,[13,16] antibiotics,[18,27,30] and various types of immunotherapies.[3,5,25,31] Among various causative drugs, the new onset of MG induced by D-penicillamine was frequently reported.[20,32,33] Similarly, ICIs including antibodies against programmed death-1 (nivolumab and pembrolizumab)[34,35] and an antibody against cytotoxic T-lymphocyte-associated antigen 4 (ipilimumab)[36] have a strong association with new-onset MG.

It is important that causative drugs of new MG onset are not only administered systemically, such as via oral medicines and intravenous agents, but are also administered locally. In fact, Khella and Kozart[31] reported that a 72-year-old man with glioma developed drug-related MG after receiving eye drops containing a beta-blocker. Additionally, Iwase and Iwase[34] described that a 78-year-old woman with plebharospasm developed new-onset MG after a botulinum toxin injection. Although intravesical BCG was administered locally to the bladder in our patient, the development of MG could occur.

A limitation of the present report is that our patient alone cannot support a clear association between intravesical BCG and the new onset of MG. There is no basis to conclude that a comorbidity exists between MG and bladder cancer. In addition, MG is not listed as a paraneoplastic syndrome in cancers. In this regard, MG was induced in patients with bladder cancer after treatment with interferon[25] or nivolumab.[35] Likewise, we hypothesize that intravesical BCG potentially caused MG by modifying the immune system rather than the bladder cancer itself.

We note that intravesical BCG is stated to be used in precaution in MG patients. Among our 498 MG patients, we have experienced 1 MG patient who underwent intravesical BCG for bladder cancer. A 68-year-old man with a history of MG crisis was treated with intravesical BCG for bladder cancer, but his MG symptoms did not worsen during the course. It is important to carefully determine whether MG symptoms appear or become aggravated after the treatment of various immunotherapies in patients with or without a history of MG.

4. Conclusions
We presented the first case of new-onset MG induced after intravesical BCG for bladder cancer. Further reports and studies are necessary to elucidate BCG’s potential effect on onset of MG.

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