Letter

DOI: 10.5582/irdr.2024.01022

A patient treated with ofatumumab for myasthenia gravis in conjunction with systemic lupus erythematosus and thyroid carcinoma

Xi Rong[1], Meijie Qu[1], Liwei Jiang[2], Min Liu[1,*]

[1] Department of Neurology, The Affiliated Hospital of Qingdao University, Qingdao, China;
[2] Department of Otolaryngology-Head and Neck Surgery, The Affiliated Hospital of Qingdao University, Qingdao, China.

SUMMARY Myasthenia gravis (MG) is an autoimmune disease mediated by B cells and is associated with acetylcholine receptor (AChR) and muscle-specific receptor tyrosine kinase (MuSK) antibodies in the postsynaptic membrane at the neuromuscular junction. Anti-CD20 monoclonal antibodies, such as ofatumumab demonstrated promising disease control in MG patients. We presented the rare case of a 34-year-old female with acetylcholine receptor-positive myasthenia gravis (AChR-MG), concomitant with systemic lupus erythematosus (SLE) and metastatic thyroid carcinoma, who was treated with ofatumumab and exhibited improvements during follow-up.

Keywords myasthenia gravis, ofatumumab, anti-CD20 monoclonal antibody

Myasthenia gravis (MG) — an antibody-mediated disorder — is characterized by muscle weakness and fatigue, where auto-antibodies target the nicotinic acetylcholine receptor (nACHR), the muscle-specific tyrosine kinase (MuSK), lipoprotein receptor-related protein 4 (LRP4), or agrin in the postsynaptic membrane at the neuromuscular junction (*1*). MG is commonly seen in younger females (< 40 years) with symptoms such as ocular symptoms (ptosis and fluctuating diplopia), dysarthria, hoarseness, dysphagia, facial weakness, limb weakness, and shortness of breath (*2*). Similar to other autoimmune diseases (ADs), MG patients have a higher risk of being affected by a second autoimmune disease, including autoimmune thyroid disease, followed by systemic lupus erythematosus (SLE) and rheumatoid arthritis (*3,4*). SLE is a systemic autoimmune disease characterized by antibodies to nuclear and cytoplasmic antigens with variable clinical features, disease course, and prognosis (*5*). Several studies have addressed the potentially increased risk of cancers in MG. Cancer development has been linked to a mutual immunological deficit and a simultaneous increased risk of autoimmune disease (*6,7*).

Several autoimmune conditions, including MG, multiple sclerosis, and B-cell proliferative disorders, exhibit promising responses to monoclonal antibodies that target CD20 and deplete B-cells. The first of these agents developed was rituximab, a murine-human chimeric anti-CD20 monoclonal antibody, which has been used successfully in MG patients refractory to conventional immunosuppressive therapy (*8*). Ofatumumab is a fully human anti-CD20 monoclonal antibody that binds to a distinct CD20 epitope from that of rituximab and increases cellular-dependent cytotoxicity and apoptosis. The off-label use of ofatumumab demonstrated excellent disease control in MG patients refractory to conventional therapy (*9*).

Here, we presented the rare case of a 34-year-old female with acetylcholine receptor-positive myasthenia gravis (AChR-MG), concomitant with SLE and metastatic thyroid carcinoma, who was treated with ofatumumab and exhibited improvements during follow-up.

A 34-year-old female was admitted to our hospital with manifestations of double vision, dysphagia, and limb weakness for 3 years. Her medical history was notable for Still's disease manifested as fever, arthritis for 5 years, and hypertension. She was diagnosed with papillary thyroid carcinoma with lymph node metastasis and underwent surgery twice (9 years and 3 years ago).

After her second thymectomy, the patient developed fluctuating double vision, slurred speech, and dysphagia. A year ago, her symptoms worsened significantly with limb fatigue, choking cough when drinking water, occasional chest tightness, and multiple falls. Four months ago, she was referred

Table 1. Laboratory and immunoserological analysis of the patient

Analysis	Finding	Normal values
Leukocytes , × 10^9/L	5.3	3.5-10
Hemoglobin (g/L)	125	122-157
Platelet (× 10^9/L)	115	100-300
Creatinine (μmol/L)	52	58-96
Alanine aminotransferase (U/L)	6	0-31
Albumin (g/L)	40	35-53
Lactate dehydrogenase (U/L)	174	0-247
TSH (μIU/mL)	0.722	0.27-0.42
FT4 (pmol/L)	17.4	12-22
TGAb (IU/mL)	13.8	0-115
TPOAb (IU/mL)	11.3	0-34
ANA Hep2 – IIF	1:3,200 homogenous type of staining	-
Anti-ds-DNA	negative	-
Anticardiolipin Ab IgG (ELISA) (GPL- U/mL)	51	0-10
Anticardiolipin Ab IgM (ELISA) (MPL- U/mL)	4.95	0-10
Anti-SSA	++	-
p-ANCA	+	-
Complement C3 (g/L)	0.87	0.9-1.8
Complement C4 (g/L)	0.171	0.1-0.4
IgG (g/L)	15.5	7-16
IgM (g/L)	1.36	0.4-2.3
IgE (IU/mL)	292.7	0-100
Coombs test (anti-IgG)	+	-

TSH thyroid-stimulating hormone, FT4 free thyroxin, TGAb antithyroglobulin antibody, TPOAb antithyroid peroxidase antibody.

to the Neurology Clinic, and her antibody tests for neuromuscular junction (NMJ) diseases were positive for acetylcholine receptor antibody (AChR; 14.7 nmol/L) and negative for VGCC, Musk, Titin, and Raynodine antibodies. She was diagnosed with AChR-antibody-positive, generalized MG and began taking 60 mg of pyridostigmine thrice daily. Her symptoms were not effectively controlled, so she was admitted to the Neurology department.

The physical examination revealed no hives, lymphadenopathy, synovitis, or edema. The cardiopulmonary and abdominal examinations were normal. The cranial nerves examination revealed limitations of abduction on both sides. The functional tests of trunk and extremity muscle groups exhibited mild muscle weakness and fatigue. Her QMG score was 15/39. The laboratory tests for blood, urine, liver enzymes, creatinine level, and thyroid function were normal. The immunoserological analysis revealed positive ANA on a substrate of HEp2 cells (indirect immunofluorescence) in a dilution higher than 1:3200 homogeneous type of staining, positive anti-cardiolipin antibodies (both IgG and IgM type), anti-SSA, and p-ANCA, with signs of complement activation. Her serum immunoglobulin levels were extremely high. The direct Coombs test was positive, but there were no other laboratory or clinical signs of active hemolysis (Table 1).

The thyroid ultrasonography exhibited postoperative changes. The chest CT demonstrated multiple pulmonary nodules, which radiologists interpreted as thyroid cancer metastases (Figure 1). The abdominal sonography and echocardiography were both normal.

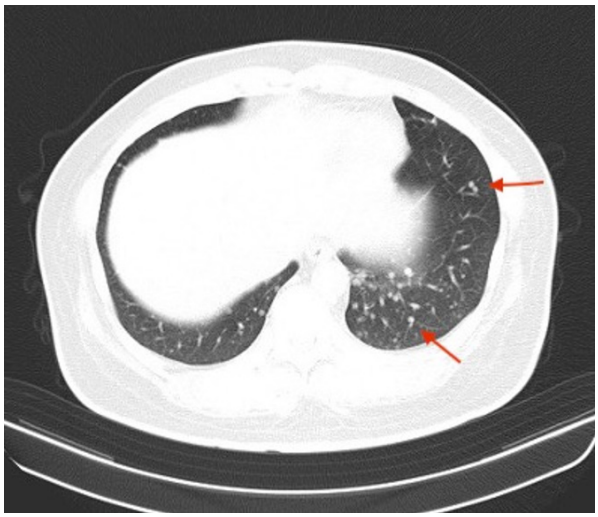

Figure 1. Chest CT. Multiple pulmonary nodules are shown by red arrows.ing intensity of HMW-MAA-positive cells in primary ALM lesions.

Five years ago, the patient was diagnosed with Still's disease, manifested as fever and arthritis. During this time, the rheumatologist diagnosed SLE based on the following criteria of the American College of Rheumatology: fever, autoimmune hemolysis, joint involvement, anti-cardiolipin antibodies, and low C3 (*10*). Following a multidisciplinary team consultation by Oncology, Radiology, Rheumatology, and Neurology departments, glucocorticoid and immunotherapy, such as anti-CD20 monoclonal antibodies, were considered reasonable treatments. Immunosuppressants, including

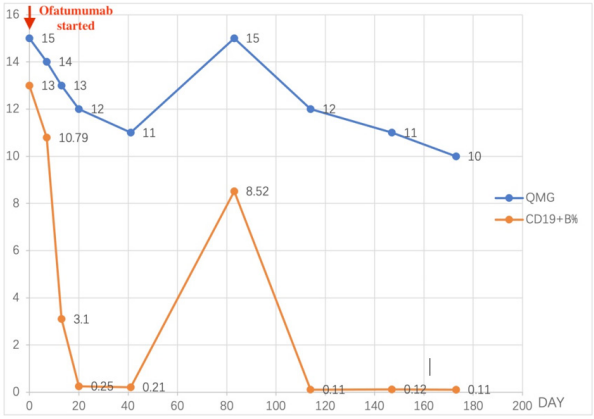

Figure 2. Curves of QMG score and CD19+ B Lymphocyte subsets versus time. The patient was started with ofatumumab on Day 0, then her QMG score (blue curve) and CD19+ B Lymphocyte subsets(orange curve, %) were recorded to Day 180.

Azathioprine, Mycophenolate mofetil (MMF), or Tacrolimus, were not recommended concerning metastasis of thyroid cancer. The young lady patient refused to take glucocorticoid, concerning its side effects as obesity and skin changes. We thus applied for off-label use of ofatumumab within our institution. She received three infusions of ofatumumab (20 mg) at weeks 0, 1, and 2, then 20 mg every month as a maintenance dose from week 4. During the six-month follow-up period, clinical signs of MG, including diplopia, dysphagia, and extremity weakness, improved substantially. Her QMG score and CD19+ B Lymphocyte subsets were recorded and are shown in Figure 2.

Rheumatic diseases, such as SLE, can affect the definitive diagnosis and treatment of MG patients and should be sought out. These diseases share a higher prevalence in young women, a relapsing-remitting course, and a positive autoimmune antibody (*5*). The majority of reported cases (61.5%) demonstrated that MG preceded SLE, but there have been cases where SLE preceded MG (*11*). This patient had fever and arthritis, which were suggestive of SLE, several years before the onset of MG symptoms, but SLE was not diagnosed until after the onset of MG. CXCL13, a chemokine that activates B and T lymphocytes, can further contribute to the pathogenesis of SLE and MG (*12*).

MG and SLE are both chronic autoimmune diseases requiring prolonged use of corticosteroids and immunosuppressants. For this patient with metastatic thyroid cancer, corticosteroid-sparing immunosuppressants (CSIS) was not a preferred choice, as studies have found a clear correlation between CSIS exposure and cancer risk in MG patients (*7,13*). Anti-CD20 monoclonal antibodies, such as ofatumumab, can reduce the concentration of serum auto-antibodies by eliminating CD20+ B cells, which has been demonstrated to be effective in some rituximab-intolerant SLE patients. It may be considered an organ-threatening, refractory autoimmune disease, including SLE and MG (*14*). Future controlled studies must evaluate the efficacy, doses, and appropriate re-treatment regimens for ofatumumab.

In this patient, we observed a parallel correlation between CD19+ B cell proportion and the QMG score, a scale of disease severity. CD19+ B cell proportion decreased from 13% to 0.25% within 20 days after ofatumumab injections, consistent with the improvement of her clinical symptoms. However, a transient increased QMG score (*15*) and CD19+ B lymphocyte subsets (8.52%) were observed at 80 days, probably due to her upper respiratory tract infection which was resolved after antibiotics treatment.

CD19 — a main surface antigen of plasma cells— plays an important role in secreting pathogenic antibodies, such as AChR-Ab. CD19+ B cell proportion strongly correlates with the severity of MG in a prediction model (*15*), which was consistent with the curve of this patient.

This case study demonstrated the effectiveness of ofatumumab in treating a patient with AChR-MG concomitant with SLE and metastatic thyroid carcinoma. Ofatumumab may be a future therapeutic option for MG, especially in those who cannot tolerate conventional immunosuppressants.

Funding: None.

Conflict of Interest: The authors have no conflicts of interest to disclose.

References

1. Gilhus NE, Verschuuren JJ. Myasthenia gravis: Sbgroup classification and therapeutic strategies. Lancet Neurol. 2015; 141:1023-1036.
2. Punga AR, Maddison P, Heckmann JM, Guptill JT, Evoli A. Epidemiology, diagnostics, and biomarkers of autoimmune neuromuscular junction disorders. Lancet Neurol. 2022; 21:176-188.
3. Mao ZF, Yang LX, Mo XA, Qin C, Lai YR, He NY, Li T, Hackett ML. Frequency of autoimmune diseases in myasthenia gravis: A systematic review. Int J Neurosci. 2011. 121:121-129.
4. Shi J, Huan X, Zhou L, Xi J, Song J, Wang Y, Luo S, Zhao C. Comorbid autoimmune diseases in patients with myasthenia gravis: A retrospective cross-sectional study of a Chinese cohort. Front Neurol. 2021; 12:790941.
5. Raut S, Reddy I, Sahi FM, Masood A, Malik BH. Association between systemic lupus erythematosus and myasthenia gravis: Coincidence or sequelae? Cureus. 2020; 12:e8422.
6. Gilhus NE, Nacu A, Andersen JB, Owe JF. Myasthenia gravis and risks for comorbidity. Eur J Neurol. 2015; 22:17-23.
7. Verwijst J, Westerberg E, Punga AR. Cancer in myasthenia gravis subtypes in relation to immunosuppressive treatment and acetylcholine receptor antibodies: A Swedish nationwide register study. Eur J Neurol. 2021; 28:1706-1715.

8. Lindberg C, Bokarewa M. Rituximab for severe myasthenia gravis--experience from five patients. Acta Neurol Scand. 2010; 122:225-228.
9. Waters MJ, Field D, Ravindran J. Refractory myasthenia gravis successfully treated with ofatumumab. Muscle Nerve. 2019; 60:E45-E47.
10. Aringer M, Costenbader K, Daikh D, *et al*. 2019 European League Against Rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus. Ann Rheum Dis. 2019; 78:1151-1159.
11. Jallouli M, Saadoun D, Eymard B, Leroux G, Haroche J, Le Thi Huong D, De Gennes C, Chapelon C, Benveniste O, Wechsler B, Cacoub P, Amoura Z, Piette JC, Costedoat-Chalumeau N. The association of systemic lupus erythematosus and myasthenia gravis: a series of 17 cases, with a special focus on hydroxychloroquine use and a review of the literature. J Neurol. 2012; 259:1290-1297.
12. Bekircan-Kurt CE, Tuncer Kurne A, Erdem-Ozdamar S, Kalyoncu U, Karabudak R, Tan E. The course of myasthenia gravis with systemic lupus erythematosus. Eur Neurol. 2014; 72:326-329.
13. Citterio A, Beghi E, Millul A, Evoli A, Mantegazza R, Antozzi C, Baggi F, Cornelio F, Durelli L, Clerico M, Piccolo G, Cosi V. Risk factors for tumor occurrence in patients with myasthenia gravis. J Neurol. 2009; 256:1221-1227.
14. Masoud S, McAdoo SP, Bedi R, Cairns TD, Lightstone L. Ofatumumab for B cell depletion in patients with systemic lupus erythematosus who are allergic to rituximab. Rheumatology (Oxford). 2018. 57:1156-1161.
15. Chen J, Li S, Feng L, Wang H, Huang X, Feng H. Nomogram for the acute exacerbation of acetylcholine receptor antibody-positive generalized myasthenia gravis. Neurol Sci. 2023; 44:1049-1057.

Received May 14, 2024; Revised June 20, 2024; Accepted July 9, 2024.

**Address correspondence to:*
Min Liu, Department of Neurology, The Affiliated Hospital of Qingdao University, 16 Jiangsu Road, Qingdao266000, China.
Email: liumin1968@qdu.edu.cn

Released online in J-STAGE as advance publication July 18, 2024.