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CLINICAL CASE REPORT

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Myasthenia Crisis Induced by Pegylated-Interferon in Patient With Chronic Hepatitis C

A Case Report

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Abstract: Myasthenia gravis is occasionally associated with thymoma that needs surgical resection and may progress to severe respiratory failure. We experienced a rare case of myasthenia crisis during antiviral therapy for chronic hepatitis C, in whom mediastinal thymoma was discovered and successfully managed with surgical thymectomy and meticulous medical care.

A 47-year-old-male patient complained of sudden diplopia 1 week after stopping 11-week administration of pegylated-interferon and ribavirin for chronic hepatitis C. Ophthalmologic examinations revealed ptosis on the right eyelid and restricted right eye movement. Myasthenia gravis was confirmed by positive repetitive nerve stimulation test and positive serum antiacetylcholine receptor antibody test, and mediastinal thymoma was found on chest CT scan. The ocular myasthenia gravis progressed to respiratory failure even after discontinuing antiviral treatment but eventually recovered with thymectomy, anticholinesterase administration, steroid pulse therapy, and prolonged ventilator care. We describe the clinical features of this life-threatening complication of interferon treatment along with previous myasthenia crisis cases by interferon for chronic hepatitis C.

In patients with chronic hepatitis C who is going to receive interferon-based antiviral treatment, physicians need to keep in mind the potential life-threatening manifestations of myasthenia gravis before and during antiviral treatment especially when patients complain of muscular weakness and easy fatigability.

(*Medicine* 95(21):e3782)

Abbreviations: anti-AChR antibody = anti-acetylcholine receptor antibody, CHC = chronic hepatitis C, CHC = chronic hepatitis C, DAA = direct acting antiviral agents, HCV = hepatitis C virus, IFN = interferon, MG = myasthenia gravis, Peg-INFα = pegylated interferon-alpha.

Editor: Agustin Castiella.
Received: January 26, 2016; revised: April 24, 2016; accepted: May 1, 2016.
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The authors have no conflicts of interest to disclose.

ISSN: 0025-7974
DOI: 10.1097/MD.0000000000003782

INTRODUCTION

Standard care for chronic hepatitis C (CHC) has been a combination of pegylated interferon-alpha (Peg-INFα) and ribavirin, although this treatment has suboptimal antiviral efficacy and significant adverse events.[1] Even in the latest treatment recommendation using novel direct acting antiviral agents, interferon (IFN)-based treatments are still optional.[2] The main drawbacks of interferon-based treatment are unsatisfactory response rate and various adverse effects, which often lead to premature termination of treatment followed by treatment failure. Myasthenia Gravis (MG) is an autoimmune neuromuscular junction disorder characterized by muscular weakness and fatigability.[3] MG is occasionally associated with invasive thymoma that needs surgical resection and may progress to severe respiratory failure.[4] Development of MG in patients with CHC has been rarely reported before or during antiviral treatment with interferon.[5–18] A total of 12 cases of MG[7–18] were reported in association with interferon treatment for CHC and 6 of them went through myasthenia crisis that require respiratory support.[8,9,11,13,16,18] We experienced a rare case of myasthenia crisis during antiviral therapy for CHC, in whom mediastinal thymoma was discovered and successfully managed with surgical thymectomy and meticulous medical care. We reviewed the clinical course of this life-threatening complication of IFN treatment along with the already reported myasthenia crisis cases in CHC patients.

CASE PRESENTATION

A 47-year-old male patient presented with a complaining of sudden diplopia that developed one week after 11-week of antiviral combination treatment for chronic hepatitis C (Figure 1A). Ophthalmologic examinations revealed ptosis and restricted eye movement on the right eyelid. He had been on antiviral combination treatment with Peg-IFN-α2a (180 μg/wk) (Pegasys®; Roche, Basel, Switzerland) and ribavirin (1000 mg/d) (LG Ribavirin; LG Life Sciences, Seoul, Korea) for the genotype 1b hepatitis C virus (HCV) infection. The pretreatment serum HCV RNA level was 2.32×10^7 IU/mL and AST/ALT levels were 255/323 U/L. At 6-week of treatment, WBC count decreased to 2500/mm^3 and absolute neutrophil count was 725/mm^3. The dosage of Peg-IFN-α2a was reduced to 90 μg/wk, but WBC count continued decreasing to 2000/mm^3. Five weeks later, the absolute neutrophil count was 500/mm^3 and the serum HCV RNA level was below the limit of detection (<15 IU/mL). Consequently, the antiviral treatment was promptly discontinued and the neutropenia improved on serial blood tests. One week after discontinuation of antiviral treatment, the patient complained of sudden diplopia and right eye ptosis was observed. One week later, right eye ptosis and upper extremities weakness (Grade III) were noted. He was immediately hospitalized and

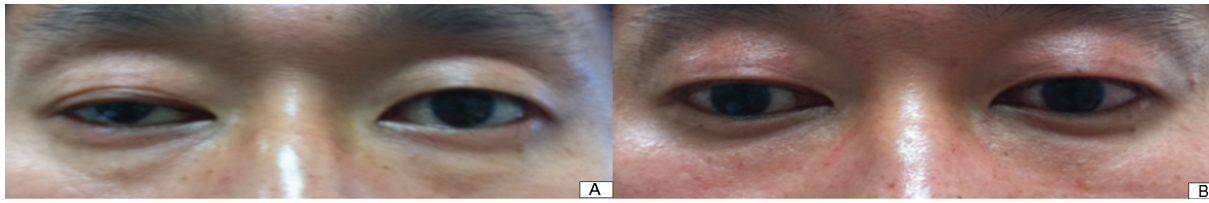

FIGURE 1. Ophthalmologic examination. Limited movement of right eye and eyelid. There was limitation at upper gaze in the right eye (A). Ptosis and restricted movement on the right upper lid was improved after treatment (B).

initial physical examination was normal except facial palsy with the right ptosis, mild dyspnea, and upper extremities weakness. Upon admission, he denied any other oral medications and had no history of vascular or thyroid diseases.

On further evaluation, the low rate repetitive nerve stimulation test (Jolly test) and Neostigmine test were positive findings for myasthenia gravis (Table 1) and serum antiacetylcholine receptor (anti-AChR) antibody level of 14.95 nmol/L (normal range: below 0.2 nmol/L). Initial symptoms of ocular MG progressed to difficulties in chewing and swallowing, followed by respiratory failure in 3 days. Administration of pyridostigmine (Mestinon®) 180 mg/day was started and chest CT scan was performed which revealed anterior mediastinal mass measuring 7 cm in its greatest dimension, whereas brain imaging study was normal (Figure 2). The patient received a surgical thymectomy and a high-grade thymoma invading pericardium and pleura (Figure 3) was observed on the pathological examination of the surgical specimen, which confirmed invasive thymoma (Type B3, WHO classification). The patient's respiratory failure aggravated after surgery, leading to an increased ventilator dependency. In response to the worsening respiratory condition, pyridostigmine dose was increased up to 600 mg/d and intravenous immunoglobulin and high-dose steroid pulse therapy were started. Timeline for hospital course and treatment was presented (Figure 4). After 40 days of intensive care, the patient has his ocular symptoms back to normal (Figure 1B) and was successfully weaned from the mechanical ventilator. He was able to walk on discharge with maintenance medications of steroid and pyridostigmine. However, his serum HCV RNA became detectable again.

DISCUSSION

Treatment for CHC with combination of peg-INF and ribavirin eradicates HCV RNA in 40% to 50% of treatment-naive patients infected with HCV genotype 1.[2] In early clinical trials, ~10% to 14% of treated patients discontinue combination treatment prematurely due to various adverse events and IFN was the major concern in most of them.[19] Unsatisfactory response rate and high rate of unbearable side effects have been the major issues of conventional combination therapy.[20]

Recently, direct acting antiviral agents (DAA) against HCV were developed and showed markedly improved clinical efficacy than the conventional combination treatment in terms of both potency and safety aspects.[2] New standards of treatments using direct acting antivirals are being established and rapidly replacing the conventional combination therapy. However, the conventional combination treatment is still widely prescribed for CHC and IFN is not completely excluded from some of the DAA-based new regimens yet. Therefore, for the treatment of CHC it is still major concern of clinicians to cope with the various side effects of IFN.

MG in patients with CHC were mostly associated with IFN treatment, but it may develop without IFN administration. Two case reports [5,6] described development of MG in CHC patients who did not receive antiviral treatment. A 35-year-old male patients with established CHC for several years without any treatment developed MG[5] and a 59-year-old male with liver cirrhosis as a result of long-standing HCV infection developed typical MG symptoms and died due to myasthenia crisis.[6] The authors suggested the cross-reactivity between HCV epitopes and the acetylcholine receptor as the underlying mechanism. The etiologic roles of various viral infections including HCV were suggested for the development of MG, but the exact significance of HCV infection per se is not clear.[21]

Though MG was not reported in large-scale analyses of CHC patients who received IFN treatment,[22] literatures suggesting the association between MG and IFN administration have been published in the form of case reports.[7–18] There were 12 cases of MG by IFN for CHC including 6 myasthenia crisis

TABLE 1. Results of Low Rate Repetitive Nerve Stimulation Test (RNST) and Stigmine Test

RNST Decrement Amplitude	Abductor Digiti quinti Muscle	Nasalis Muscle	Orbicularis Oculi Muscle	Trapezius Muscle
2Hz	−4.5%	−50.0%	−18.5%	−51.8%
3Hz	−6.0%	−41.7%	−18.8%	−48.1%
5Hz	−6.7%	−42.6%	−16.2%	−50.7%
Stigmine Test	**Before Injection**	**20 min**	**40 min**	**60 min**
Phonation	6 s	9 s	13 s	14 s
Upward gaze	33 s	38 s	30 s	32 s
Neck flexion	10 s	15 s	18 s	18 s
Arm extension	20 s	50 s	130 s	110 s
Leg elevation	15 s	19 s	26 s	27 s

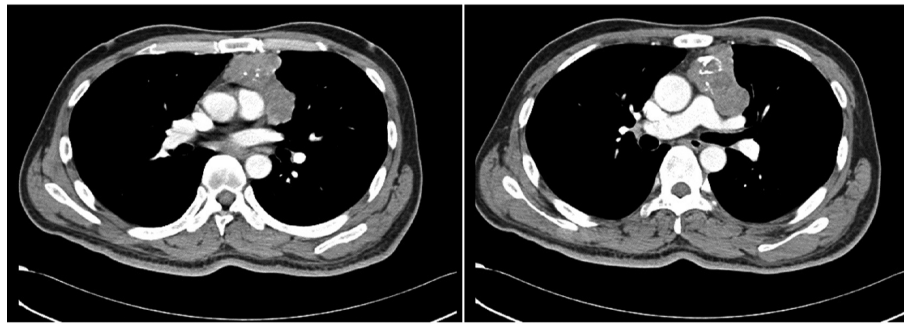

FIGURE 2. Chest CT findings. There was 7-cm sized lobulated solid mass with internal low density and calcified portion at anterior mediastinum. CT = computed tomography.

cases (Table 2). In case reports of myasthenia crisis that developed during IFN-based antiviral treatment for CHC, male patients >44 were most commonly affected and the mean age of patients was 57 years and mean interval between starting IFN administration and diagnosis of MG was 4.57 months (6 weeks to 15 months). The mean duration of IFN treatment was 4.96 months (6 weeks to 15 months). The mean level of anti-AchR antibody was high as 16.3 nmol/L. The ocular symptom was the most common presenting symptom. In most patients, respiratory distress followed advanced progression of MG symptoms and a case of severe respiratory failure was reported at 6 months after IFN discontinuation.[11] The clinical courses of MG cases by IFN for CHC were either mild or severe enough to suffer myasthenia crisis, but most of the patients were recovered eventually with medical care after discontinuing IFN treatment.

To our knowledge, this is the second case of thymoma-associated MG during IFN treatment for CHC. A case of MG that progressed to myasthenic crisis was reported at 1996 in Japanese patient who had thymomectomy for known thymoma-associated MG, 19 years before starting antiviral treatment.[9] Thymomas are responsible for 21% of MG cases and ~30% of patients with thymoma have symptoms of MG.[23,24] Myasthenic crisis is the most serious complication of MG and thymoma is one of the risk factors attributed to it.[24]

The mechanism of MG development by IFN therapy is not completely understood, but some of the complex immunological actions of IFN such as enhanced lymphocyte cytotoxicity, production of pro-inflammatory cytokines, inhibition of T suppressor cell function, activation of T helper lymphocytes by autoantigens, and differentiation of antigen-presenting cell might contribute to the development of IFN-induced autoimmune diseases.[25] The thymus plays a primary role in early-onset MG mediated by anti-AChR antibodies.[26] IFN-beta could play a central role in thymic events leading to MG by triggering the overexpression of a-AChR probably leading to thymic dendritic cells autosensitization, the abnormal recruitment of peripheral cells, and germinal center formation.[26] The epithelial neoplastic cells of thymoma are capable of presenting epitopes, which cross-reacts with different neuromuscular antigens. In addition to AChR antibodies, antibodies against striated muscle titin and RyR antigens are found in most of MG thymoma patients.[27]

On the other, it has also been suggested that some infectious viruses and HCV itself may lead to MG via mechanism of cross-reactivity between viral epitopes and the acetylcholine receptor.[28]

It is not known whether the patients who experienced MG during IFN treatment for CHC had subclinical MG before initiating treatment because pretreatment screening for MG is not routinely recommended. In some patients, pre-existing subclinical MG that might be associated with HCV infection itself, progress to overt MG during IFN treatment, whereas, in others, de novo MG might be induced by IFN administration.[29] In our patient, relatively large thymoma was diagnosed in the advanced stage after a short period of IFN administration. So it seems that thymoma-associated subclinical MG were unrecognized before treatment, which was provoked by IFN administration to progress to life-threatening

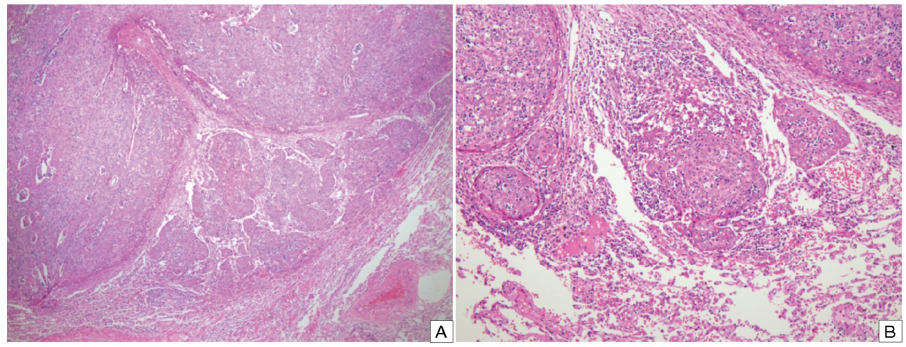

FIGURE 3. Pathologic findings. (A) H&E stain (×40) shows a multilobular growth pattern and infiltration into lung parenchyma. (B) H&E stain (×100) shows thymoma B3 findings: sheet-like growth of medium-size round or polygonal cells with slight atypia (sheet-like growth pattern); epithelial cells are mixed with a minor component of intraepithelial lymphocytes. H&E stain = hematoxylin and eosin stain.

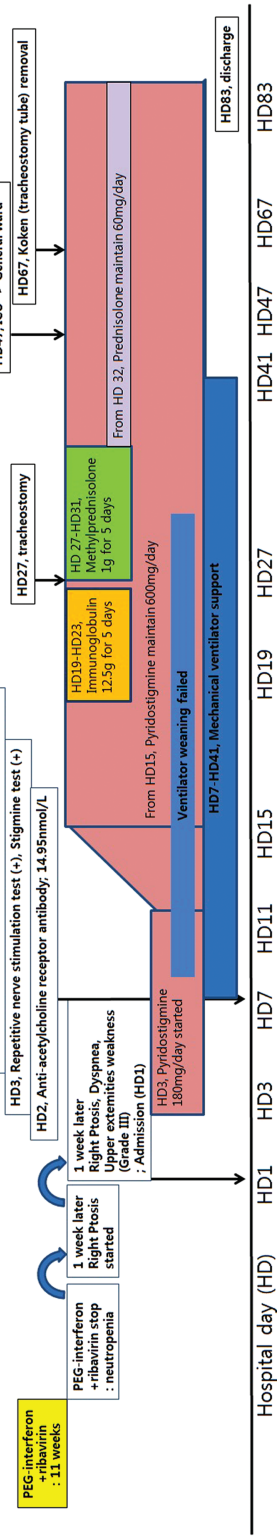

FIGURE 4. Hospital course and treatment for the presented case.

TABLE 2. List of Cases of Myasthenia Crisis by Interferon Treatment for Chronic Hepatitis C

Author	year	Age	Sex	Antiviral Therapy	Antiviral Therapy Duration	Latency	Anti-AchR Ab (Normal Range)	Previous MG History	Thymoma	Respiratory Crisis	Treatment
Mase et al[8]	1996	64	M	Peg-INF-α2a	6 wk	6 wk	12 pmol/mL (0)	Family history of MG (brother)	Negative	Respiratory crisis	Pyridostigmine Plasmapheresis corticosteroid
Konishi [9]	1996	49	M	IFN	3 mo	3 mo	Increased	Yes	Previous thymectomy	Artificial ventilation (2 weeks)	Azathioprine, prednisolone methylprednisolone
Gurtubay et al[11]	1999	66	M	INF-α-nl	6 wk	6 wk	46.1 nmol/L (<0.2)	Negative	Negative	Artificial ventilation * (3 weeks)	Pyridostigmine, immunoglobulin prednisone
Weegink et al[13]	2001	44	M	Peg-IFN- α2b/ ribavirin	15 mo	15 mo	0.89 nmol (<0.3)	–	Negative	Artificial ventilation	Pyridostigmine prednisolone
Reffet et al[16]	2007	68	M	(12 years ago, IFN α) Peg-IFN- α2a/ ribavirin	5 mo	5 mo	Low positive	Negative	Negative	Respiratory crisis	Pyridostigmine immunoglobulin prednisone Mycophenolate mofetil
Congeni and Kirkpatrick[18]	2013	61	M	(1 year ago, PEGIFN/ribavirin) Triple therapy (IFN/ ribavirin/telaprevir)	6 mo	3 mo†	19.6 nmol/L	–		BiPAP support	Pyridostigmine immunoglobulin Solumedrol
Baik	2016	47	M	Peg-IFN- α2a/ ribavirin	11 wk	3 mo	14.9 nmol/L (0.2)	Negative	Invasive thymoma	Artificial ventilation (39 days)	Pyridostigmine steroid pulse therapy immunoglobulin thymectomy

Anti-AchR Ab = antiacetylcholine receptor antibody, BiPAP = bilevel positive airway pressure, Latency = duration between myasthenia gravis symptom started and IFN therapy started, MG = myasthenia gravis

*6 months after MG was diagnosed.

†Triple therapy (interferon, ribavirin, telaprevir) started in June 2011. Ptosis was noted in September 2011. IFN and ribavirin were discontinued in December 2011.

myasthenic crisis. For the better understanding of clinical implication of IFN-induced MG in CHC treatment, screening for MG in CHC patient might be considered before starting treatment or at least, during treatment when the patient complained of fatigue, muscle weakness.

Screening for MG with serum anti-AChR antibody test is simple and helpful in many patients, but it needs further investigation in this clinical condition because some of MG patients have serum anti-AChR antibody levels within normal range.

CONCLUSION

In patients with CHC who is going to receive IFN-based antiviral treatment, whether screening for thymoma or subclinical MG should be included in basal evaluation is not clear but physicians need to keep in mind the potential life-threatening manifestations of MG before and during antiviral treatment especially when patients complain of muscular weakness and easy fatigability.

REFERENCES

1. Lee HW, Jung KS, Ahn SH. Treatment of chronic hepatitis C using newly developed oral antiviral agents. *Korean J Med.* 2015;88: 635–642.
2. European Association for the Study of the Liver. EASL Recommendations on Treatment of Hepatitis C 2015. *J Hepatol.* 2015;63: 199–236.
3. Matthew NM, Donald BS. Autoimmune myasthenia gravis: emerging clinical and biological heterogeneity. *Lancet Neurol.* 2009;8: 475–490.
4. Beydoun SR, Gong H, Ashikian N, et al. Myasthenia gravis associated with invasive malignant thymoma: two case reports and a review of the literature. *J Med Case Rep.* 2014;8:340.
5. Readig PJ, Newman PK. Untreated hepatitis C may provoke myasthenia gravis. *J Neurol Neurosurg Psychiatry.* 1998;64:820.
6. Eddy S, Wim R, Peter VE, et al. Myasthenia gravis: another autoimmune disease associated with hepatitis C virus infection. *Dig Dis Sci.* 1999;44:186–189.
7. Piccolo G, Franciotta D, Versino M, et al. Myasthenia gravis in a patient with chronic active hepatitis C during interferon-alpha treatment. *J Neurol Neurosurg Psychiatry.* 1996;60:348.
8. Mase G, Zorzon M, Biasutti E, et al. Development of myasthenia gravis during interferon-alpha treatment for anti-HCV positive chronic hepatitis. *J Neurol Neurosurg Psychiatry.* 1996;60:348–349.
9. Konishi T. A case of myasthenia gravis which developed myasthenic crisis after alpha-interferon therapy for chronic hepatitis C. *Rinsho Shinkeigaku.* 1996;36:980–985.
10. Uyama E, Fujiki N, Uchino M. Exacerbation of myasthenia gravis during interferon-alpha treatment. *J Neurol Sci.* 1996;144: 221–222.
11. Gurtubay IG, Morales G, Aréchaga O, et al. Development of myasthenia gravis after interferon alpha therapy. *Electromyogr Clin Neurophysiol.* 1999;39:75–78.
12. Harada H, Tamaoka A, Kohno Y, et al. Exacerbation of myasthenia gravis in a patient after interferon-beta treatment for chronic active hepatitis C. *J Neurol Sci.* 1999;165:182–183.
13. Weegink CJ, Chamuleau RA, Reesink HW, et al. Development of myasthenia gravis during treatment of chronic hepatitis C with interferon-alpha and ribavirin. *J Gastroenterol.* 2001;36:723–724.
14. Borgia G, Reynaud L, Gentile I, et al. Myasthenia gravis during low-dose IFN-alpha therapy for chronic hepatitis C. *J Interferon Cytokine Res.* 2001;21:469–470.
15. Bektas M, Bektas H, Gören D, et al. Development of Myasthenia gravis due to treatment of chronic hepatitis C with a combination of interferon-alpha and ribavirin. *Digestion.* 2007;75:208–209.
16. Reffet A, Oddes B, Terrier F, et al. Development of a myasthenia crisis during interferon treatment for chronic C hepatitis. *Gastroenterol Clin Biol.* 2007;31:1085–1087.
17. Kang HM, Park MJ, Hwang JM, et al. Development of ocular myasthenia during pegylated interferon and ribavirin treatment for chronic hepatitis C. *Korean J Hepatol.* 2009;15:209–215.
18. Congeni JP, Kirkpatrick RB. Pegylated interferon induced myasthenia crisis-a case report. *J Clin Neuromuscul Dis.* 2013;14:123–125.
19. Fried MW. Side effects of therapy of hepatitis C and their management. *Hepatology.* 2002;36(Suppl 1):S237–S244.
20. Dusheiko G. Side effects of alpha interferon in chronic hepatitis C. *Hepatology.* 1997;26(Supple 1):S112–S121.
21. Séne D, Limal N, Cacoub P. Hepatitis C virus-associated extrahepatic manifestations: a review. *Metab Brain Dis.* 2004;19:357–381.
22. Fattovich G, Giustina G, Favarato S, et al. A survey of adverse events in 11,241 patients with chronic viral hepatitis treated with alpha interferon. *J Hepatol.* 1996;24:24–38.
23. Mao ZF, Mo XA, Qin C, et al. Incidence of thymoma in myasthenia gravis: a systematic review. *J Clin Neurol.* 2012;8:161–169.
24. Vachlas K, Zisis C, Rontogianni D, et al. Thymoma and myasthenia gravis: clinical aspects and prognosis. *Asian Cardiovasc Thorac Ann.* 2012;20:48–52.
25. Cufi P, Dragin N, Weiss JM, et al. Implication of dsRNA signaling in the etiology of autoimmune myasthenia gravis. *Ann Neurol.* 2013;73:281–293.
26. Cufi P, Dragin N, Ruhlmann N, et al. Central role of interferon-beta in thymic events leading to myasthenia Gravis. *J Autoimmun.* 2014;52:44–52.
27. Romi F. Thymoma in myasthenia gravis: from diagnosis to treatment. *Autoimmune Dis.* 2011;2011:474–512.
28. Berrih-Aknin S, Le Panse R. Myasthenia gravis: a comprehensive review of immune dysregulation and etiological mechanisms. *J Autoimmun.* 2014;52:90–100.
29. Stübgen JP. Interferon alpha and neuromuscular disorders. *J Neuroimmunol.* 2009;207:3–17.