Available online at www.sciencedirect.com

ScienceDirect

Neuromuscular Disorders 27 (2017) 914–917

www.elsevier.com/locate/nmd

Case report

Double-seropositive myasthenia gravis with acetylcholine receptor and low-density lipoprotein receptor-related protein 4 antibodies associated with invasive thymoma

Hidehiro Ishikawa [a,*], Akira Taniguchi [a], Yuichiro Ii [a], Osamu Higuchi [b], Hidenori Matsuo [c], Shunya Nakane [d], Masaru Asahi [a], Atsushi Niwa [a], Hidekazu Tomimoto [a]

[a] Department of Neurology, Mie University Graduate School of Medicine, 2-174 Edobashi, Tsu, Mie 514-8507, Japan
[b] Department of Clinical Research, Nagasaki Kawatana Medical Center, Nagasaki, Japan
[c] Department of Neurology, Nagasaki Kawatana Medical Center, Nagasaki, Japan
[d] Department of Neurology, Graduate School of Medical Sciences, Kumamoto University, Kumamoto, Japan

Received 29 June 2016; received in revised form 13 May 2017; accepted 1 June 2017

Abstract

We describe two cases of myasthenia gravis (MG) with double seropositivity for acetylcholine receptor (AChR) and low-density lipoprotein receptor-related protein 4 (LRP4) antibodies (AChR/LRP4-MG) with invasive thymoma. Both cases showed myasthenic weakness, which was restricted to the ocular muscles for >5 months from onset, and then unprovoked severe clinical deterioration supervened with predominant bulbar symptoms. The patients responded adequately to therapeutic intervention. Serum AChR antibody levels at post-intervention were markedly decreased, whereas LRP4 antibodies were almost unchanged in case 1 and slightly decreased in case 2. Although our results suggest that patients with AChR/LRP4-MG are likely to present with more severe symptoms than those with LRP4-MG, none of the previously reported cases had thymomas. Coexistence of autoantibodies may reflect breakdown of self-tolerance caused by invasive thymomas. The main cause affecting symptoms of MG in our cases was probably AChR antibodies, and anti-LRP4 antibodies might have been an exacerbating factor.

Keywords: Myasthenia gravis; Acetylcholine receptor antibody; LRP4 antibody; Thymoma; Tacrolimus; Intravenous immunoglobulin

1. Introduction

Myasthenia gravis (MG) is an autoimmune disease of the neuromuscular junction that is characterized by muscle weakness and fatigue. Autoantibodies against acetylcholine receptor (AChR) and muscle-specific kinase (MuSK) are sensitive and specific diagnostic markers, as well as pathogenic factors of MG [1]. The presence of low-density lipoprotein receptor-related protein 4 (LRP4) antibodies is associated with mild symptoms of MG, and MG with LRP4 antibodies (LRP4-MG) can manifest purely as ocular MG [2]. Thymoma-associated MG is almost always AChR antibody-positive. However, thymomas are rarely observed in association with MG with MuSK or LRP4-MG [3,4]. Our laboratory has only experienced one patient with MG and MuSK with an obvious thymoma (8.5 × 24 mm) [5].

Double-seropositive MG with AChR and LRP4 antibodies (AChR/LRP4-MG) has rarely been reported [4,6–8]. These patients frequently presented with bulbar symptoms and none of them developed a thymoma [6,7]. We report here two patients with MG who presented with double seropositivity for AChR and LRP4 antibodies associated with an invasive thymoma.

2. Case report

2.1. Patient 1

A 74-year-old woman was admitted to our hospital with fluctuating ptosis of the right eye, which had persisted for the previous year and a half. Mild weakness was restricted to the ocular muscles. However, severe deterioration occurred, which was characterized by prominent bulbar, neck, and respiratory muscle involvement (% vital capacity [VC] of 50%) over the preceding 2 months. There were no episodes of infection, a change in medication, or stress. Her past medical history included hypertension, congestive cardiac failure, and atrial fibrillation. A neurological examination showed right fatigable ptosis, limb

* Corresponding author. Department of Neurology, Mie University Graduate School of Medicine, 2-174 Edobashi, Tsu, Mie 514-8507, Japan. Fax: +81 59 231 5541.
E-mail address: hidehiro-i@clin.medic.mie-u.ac.jp (H. Ishikawa).

http://dx.doi.org/10.1016/j.nmd.2017.06.001
0960-8966/

muscle weakness, and prominent bulbar, neck, and respiratory muscle weakness. Deep tendon reflexes were normal and no autonomic dysfunction was observed. Screening for autoantibodies showed positivity for antinuclear antibodies, anti-double stranded DNA IgG, anti-Sjögren's syndrome-related antigen A, and anti-U1 ribonucleoproteins. Anti-AChR antibodies were positive (22.9 nM/L; normal range: <0.3 nM/L). Anti-LRP4 antibodies were also positive [1.45 antibody index (AI)] in this patient. A detailed description of analysis of Anti-LRP4 antibodies and AI is given in Supplementary Appendix S1. Anti-MuSK antibodies were negative. Repetitive nerve stimulation on trapezius and nasal muscles showed a >10% decrement in compound muscle action potentials. The patient was diagnosed with MG and classified as Myasthenia Gravis Foundation of America (MGFA) IIIB. Chest computed tomography (CT) showed the presence of an anterior mediastinal mass that appeared to be infiltrating the trunk of the pulmonary artery (Fig. 1A). Initial treatment with pyridostigmine was stopped because of a rash. Her condition was gradually stabilized after treatment with tacrolimus (1.5 mg daily) and intravenous immunoglobulin (IVIG) (0.4 g/kg daily for 5 days). Her MGFA-postintervention status (PIS) [9] reached the minimal manifestation (MM) level approximately 1 week after IVIG. Thymectomy was subsequently performed. A histological examination showed a thymoma ($23 \times 17 \times 25$ mm) of WHO type B (B2 with areas of B3). The Masaoka stage was IVa (Fig. 1B). The thymoma was invading the pericardium. Treatment with tacrolimus was continued, and her MGFA-PIS remained at the MM level for 10 months after thymectomy. Her serum anti-AChR antibody level was 1.3 nM/L and %VC was 76%. Her serum LRP4 antibody levels before and after intervention were 1.65 AI and 1.64 AI, respectively.

2.2. Patient 2

A 64-year-old woman was referred with a clinical diagnosis of MG. She complained of a 5-month history of mild bilateral eyelid ptosis. She reported subacute deterioration leading to generalized weakness, respiratory insufficiency (%VC of 54%), and dysphagia over the preceding 2 weeks without obvious aggravating factors. On neurological examination, the patient had severe muscle weakness in the neck and palate. Deep tendon reflexes were normal, and no autonomic dysfunction was observed. Laboratory investigations, including routine blood tests, thyroid function, and muscle enzymes, were normal. She was positive for antinuclear antibodies, anti-double stranded DNA IgG, anti-Sjögren's syndrome-related antigen A, and anti-cardiolipin antibody IgG. Anti-AChR was positive (64.5 nM/L; normal range: <0.3 nM/L) and anti-LRP4 antibodies were also positive (4.65 AI). Repetitive nerve stimulation demonstrated a low amount of compound muscle action potentials at the trapezius, nasal, and digiti minimi muscles. She was diagnosed with MG, which was classified as MGFA IIIB. Chest CT showed masses located in the anterior mediastinum

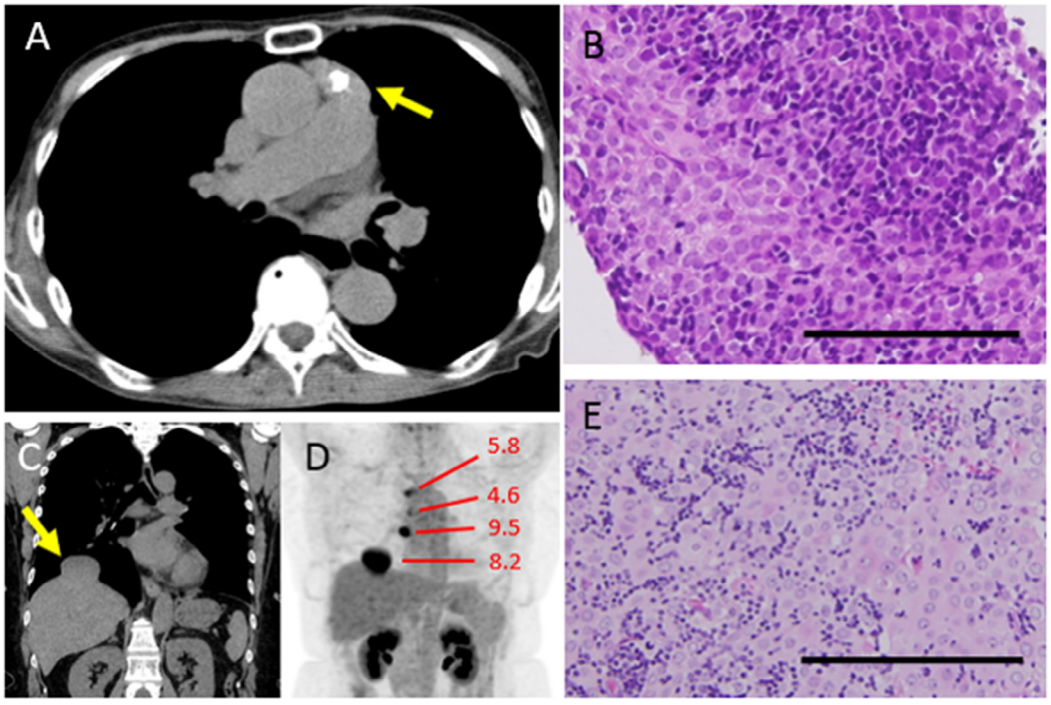

Fig. 1. Findings of thymomas. (A) Computed tomography (CT) thoracic scan (axial, Patient 1). The yellow arrow shows an anterior mediastinal mass (28 mm) with calcification that appeared to be infiltrating the trunk of the pulmonary artery. (B) Histopathology shows a neoplastic epithelial component with distinct nucleoli among a moderate population of lymphocytes. There are areas of sheet-like growth of neoplastic epithelial cells, suggesting type B2 thymoma with areas of type B3 thymoma (hematoxylin–eosin stain). Bar = 100 µm. (C) CT thoracic scan (coronal, Patient 2). The yellow arrow shows a tumor (diameter, 46 mm) located in the right pleura that appears to be a hepatocele. (D) ^{18}F-fluorodeoxyglucose-positron emission tomography shows hypermetabolism in the lesions and the standardized uptake values were 5.8, 4.6, 9.5, and 8.2. (E) Microscopically, the tumor in the right pleura includes a neoplastic epithelial component and appears as scattered plump cells with vesicular nuclei and distinct nucleoli among a moderate population of lymphocytes (hematoxylin–eosin stain). Bar = 100 µm.