



## Case report

# Antiganglioside antibodies and paraneoplastic neuromuscular junction disorder?



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## ABSTRACT

Based on the instructions in “Guide for authors”, our manuscript is a case reports and was submitted under “Letters to the Editor”, which should not include an abstract.

## 1. Introduction

Antiganglioside antibodies (Abs) are wide range of autoantibodies that target glycosphingolipids, enriched in the peripheral nerves. These Abs are implicated as primary immune effectors in acute motor axonal neuropathy (AMAN) and *Miller-Fisher* syndrome (MFS) variants of Guillain-Barré syndrome (GBS) [1,2]. Besides affecting peripheral nerve axons, antiganglioside Abs may also target distal portions of motor axons including neuromuscular junction (NMJ). It has been reported that antiganglioside Abs can bind to NMJs at presynaptic motor nerve terminal and thereby can exert a variety of pathophysiological effects in animal models. However, it is still unknown whether antiganglioside Abs can cause clinical NMJ disease in human or contribute to pathogenesis. We are reporting a rare case of NMJ-mediated weakness as a clinical manifestation of antiganglioside Abs (Anti GD1a and Anti GM1) in a patient, later diagnosed with a squamous cell carcinoma of the lung.

## 2. Case presentation

A 39-year-old Caucasian male with no known past medical history except for tobacco smoking (20 pack-years), presented to our emergency department with gradually progressive proximal muscle weakness, as well as bulbar symptoms, including dysphagia and dyspnea, over three months. His physical exam was remarkable for decreased muscle strength in head flexion, head extension, as well as the proximal extremities weakness with prominent fatigability. There was no ocular involvement. His respiratory mechanics including forced vital capacity (FVC) and negative inspiratory force (NIF) were significantly reduced.

Entire neuroaxis Magnetic Resonance Imaging (MRI) did not show any abnormality. Cerebrospinal fluid (CSF) studies were unremarkable (protein: 47, glucose: 67, white blood cell: 4, red blood cell: 0), with negative viral and bacterial panels. Other laboratory work ups including acetylcholine receptor Abs (ACh-R binding, blocking and modulating), anti-MusK Ab, anti-LRP4 Ab, Abs to presynaptic voltage-gated calcium channels (VGCC), and serum paraneoplastic panel were negative. Serum Antiganglioside Abs (GD1a/ GM1 Abs), checked in two separated hospitalization (each prior to IVIG therapy), were significantly increased by 3–4 folds (Table 1). 3 Hz slow repetitive nerve stimulation (RNS) study recording from ulnar nerve (abductor digiti minimi) motor units was captured at baseline, after 1 min of exercise, then every 1 min up to 5 times. RNS showed pathological decrement of more than 10%, suggesting of NMJ disorder. Rapid RNS and brief voluntary exercise test was not tolerated by patient. He was initially treated with Intravenous Immunoglobulin (IVIG) and Pyridostigmine for possible myasthenia gravis, to which, he responded well. One month later, CT chest showed lung mass and subsequent biopsy revealed squamous cell carcinoma and excluded the presence of thymoma. This patient has been treated for underlying cancer with both chemotherapy and immunosuppressant. His neurological condition remained stable on monthly IVIG, in his 9-month follow up.

## 3. Discussion

We report a rare case of paraneoplastic NMJ disorder with positive antiganglioside Abs (anti GD1a, GD1b, GM1), who was later diagnosed with squamous cell carcinoma of lung. To the date, there are only two previous cases of combined features of myasthenia gravis and Eaton-

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**Table 1**  
Serum antiganglioside antibodies panel, checked at presentation and repeated after one month.

Ganglioside antibodies	6/6/2018	7/8/2018
GM1 Antibodies IgM/IgG	18 IV	76 IV (H)
GM2 Antibodies IgM/IgG	33 IV	38 IV
GD1a Antibodies IgM/IgG	80 IV (H)	112 IV (H)
GD1b Antibodies IgM/IgG	28 IV	102 IV (H)
GQ1b Antibodies IgM/IgG	13 IV	–

Lambert syndrome with increased serum antiganglioside antibodies (GD1a, GT1b and sialylparagloboside). However, there were no association with cancer in those two cases, and one was found to have thymoma [3].

Our case is unique as it illustrates the first presentation of paraneoplastic lung cancer manifested with neuromuscular junction related weakness and elevated antiganglioside Abs (GD1a, GD1b, GM1). Even though NMJ involvement in this case was confirmed through electrodiagnostic studies, we were limited to localize that to presynaptic versus postsynaptic pathology. Our case emphasizes on neuromuscular transmission defect, as a paraneoplastic manifestation of newly diagnosed lung cancer, and in the presence of antiganglioside antibodies. The results of electrodiagnostic studies in our case were limited to demonstrate the presynaptic versus postsynaptic NMJ pathology.

Previous studies reported the role of gangliosides, particularly anti-GT3 in NMJ pathogenesis [4]. The pathophysiological actions of neuropathy-related antiganglioside Abs at the NMJ were studied by Plomp et al. It was demonstrated that antiganglioside Abs are capable of binding to NMJs and therefore, can be involved in neuromuscular synaptopathy, as the presynaptic motor nerve membrane enriched in gangliosides and lies outside the blood–nerve barrier [5]. Bullens et al. showed that complex gangliosides can form membrane receptors at NMJs for botulinum neurotoxin type-A and neuropathy-associated Abs. However, under physiological condition and when GM3 and GD3 are abundantly present, the complex gangliosides are commonly redundant for neurotransmitter release at NMJ [6]. It was previously reported that MFS patients with positive anti-GQ1b Ab have shown electrophysiological evidence of neuromuscular transmission defect, which persisted up to 3 months from initial presentation. However, it is undetermined if neuromuscular transmission defect is present in the related conditions of GBS and Bickerstaff's brainstem encephalitis [7,8]. Our case is unique in presentation. To our knowledge, no similar case of antiganglioside positive paraneoplastic neuromuscular junction disorder was previously reported. That warrants further studies to investigate the role of these Abs in the pathogenesis of NMJ disorders in human.

#### 4. Conclusion

We speculate that, in addition to AMAN, MFS and other GBS variants, antiganglioside Abs might be also associated with NMJ dysfunction. The antiganglioside Abs mediated NMJ disorder might be a new paraneoplastic association in patients with underlying lung cancer, and therefore antiganglioside Abs testing can be considered, particularly in those with negative biomarkers for NMJ disorders. However, the role of antiganglioside Abs in the pathogenesis of NMJ disorders is still undetermined, and further studies are needed to confirm this association. This case also underscores the necessity of malignancy and paraneoplastic work up in the seronegative new onset neuromuscular junction disorders. Additionally, the early diagnosis and optimal treatment with immunotherapy could potentially improve the paraneoplastic neurological symptoms and quality of life, even in advance of treatment of underlying malignancy.

#### Declaration of Competing Interest

The authors have no potential conflicts of interest to disclose.

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