

[ CASE REPORT ]

## Asymmetrical and Isolated Hypoglossal Nerve Palsy Accompanied by a New Subset of Anti-ganglioside Antibodies in a Patient with Diffuse Large B Cell Lymphoma

Yasuyuki Ohta<sup>1</sup>, Yuko Kawahara<sup>1</sup>, Koh Tadokoro<sup>1</sup>, Kota Sato<sup>1</sup>, Ryo Sasaki<sup>1</sup>,  
Yoshiaki Takahashi<sup>1</sup>, Mami Takemoto<sup>1</sup>, Nozomi Hishikawa<sup>1</sup>, Toru Yamashita<sup>1</sup>,  
Takeru Asano<sup>2</sup>, Tomoko Inomata<sup>2</sup> and Koji Abe<sup>1</sup>

### Abstract:

Malignant lymphoma sometimes involves peripheral nerves due to paraneoplastic syndrome associated with anti-ganglioside antibodies. We report a very rare case of malignant lymphoma accompanied by an asymmetrical and isolated hypoglossal nerve palsy associated with a new subset of anti-ganglioside antibodies. Magnetic resonance imaging and <sup>18</sup>F-2-deoxy-2-fluoro-D-glucose position emission tomography showed no abnormalities of the hypoglossal nerve nucleus; however, the patient's serum was positive for anti-sulfated glucuronyl paragloboside IgM antibodies as well as anti-GM1 IgM and anti-GQ1b IgM antibodies. The present case might suggest a paraneoplastic asymmetrical and isolated hypoglossal nerve palsy associated with a new subset of anti-ganglioside antibodies.

**Key words:** anti-ganglioside antibody, hypoglossal nerve palsy, malignant lymphoma, paraneoplastic syndrome

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### Introduction

Malignant lymphoma mainly involves the peripheral nerves due to the direct invasion of malignant cells, and sometimes due to paraneoplastic syndrome associated with anti-ganglioside antibodies (1). However, to the best of our knowledge there have been no reported cases of lymphoma presenting with hypoglossal nerve palsy with anti-ganglioside antibodies. Among the five previously reported cases of asymmetrical hypoglossal nerve palsy with positive anti-ganglioside antibodies, including anti-GM1 and anti-GD1b antibodies, only one case involved an asymmetrical and isolated hypoglossal nerve palsy (Table) (2-6). We herein report a very rare case of malignant lymphoma presenting with an asymmetrical and isolated hypoglossal nerve

palsy due to paraneoplastic syndrome associated with a new subset of anti-ganglioside antibodies.

### Case Report

A 75-year-old man consulted a nearby clinic due to mild dysarthria without advanced infections (i.e., diarrhea); however, a subsequent brain MRI revealed no abnormalities. In the 3 months that followed he developed a persistent fever of 38°C, night sweats, and body weight loss (4 kg). Subsequently he showed severe dysarthria and his tongue deviated to the right on protrusion. He was admitted to our hospital for further examination at 4 months after the onset of symptoms.

On admission to our hospital, neurological examinations showed severe dysarthria, right-dominant atrophy and weak-

<sup>1</sup>Department of Neurology, Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama University, Japan and <sup>2</sup>Department of Hematology and Oncology, Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama University, Japan

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Correspondence to Dr. Koji Abe, yasuyuki@okayama-u.ac.jp

**Table. Previous and the Present Case Reports of Hypoglossal Nerve Palsy with Anti-ganglioside Antibodies.**

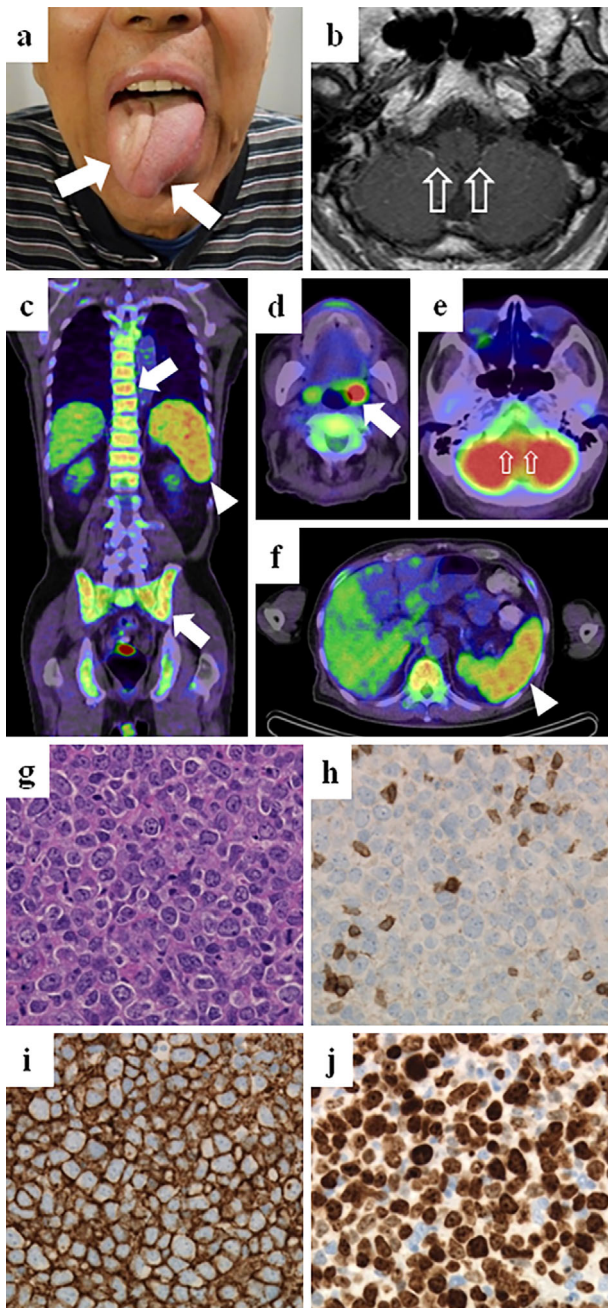
Reference	5	2	3	6	4	Present case 2018
Age	49	64	60	45	12	75
Sex	Female	Male	Male	Male	Male	Male
anti-ganglioside antibodies	GM1-IgG	GM1-IgG	GD1b-IgG	GD1a, GD1b, GQ1b, GD1b/GD1a, GD1b/GT1b-IgG	GM1, GD1b-IgG	GM1, GQ1b, SGPG-IgM
Dominant side of hypoglossal N palsy	Lt	Lt	Lt	Rt	Lt	Rt
Other cranial nerve palsy	Lt. facial N palsy, dysarthria, dysphagia	none	none	Lt. facial N palsy	Lt. glossopharyngeal and vagus N palsy	none
Other neurological findings	neck and U/L motor palsy	none	Lt. U/L and L/L palsy	Lt. U/L and L/L palsy	none	none
CSF	normal	high elevated protein (albumin 292 mg/L)	high elevated protein	normal	n.e.	elevated cell number and protein
NCS	motor axonal neuropathy of median and ulnar N	normal	motor axonal neuropathy with sensory sparing	motor axonal neuropathy of facial, ulnar and tibial N	n.e.	normal
Complications	none	Coeliac disease	none	none	ADHD, tic	DLBCL, DM

ADHD: attention deficit hyperactivity disorder, CSF: cerebrospinal fluid, DLBCL: defining diffuse large B cell lymphoma, DM: diabetes mellitus; L/L: lower limb, Lt: left, N: nerve, NCS: nerve conduction study, n.e.: not examined, Rt: right, SGPG: sulfated glucuronyl paragloboside, U/L: upper limb

ness of both sides of the tongue, and his tongue deviated to the right on protrusion (Figure a, arrows). There were no abnormal neurological findings with regard to the motor, sensory, cerebellar and autonomic systems. He had a past history of diphtheritic infection, diabetes mellitus (DM), dyslipidemia, prostate hypertrophy, and chronic renal failure.

Laboratory examinations revealed mild normocytic normochromic anemia [hemoglobin 10.6 g/dL (normal 13.7-16.8 g/dL), mean corpuscular volume 83.7 fL (normal 83.6-98.2 fL), mean corpuscular hemoglobin 27.7 pg (normal 27.5-33.2 pg)] with a high level of ferritin [1,944.0 ng/mL (normal 39.9-465.0 ng/mL)], mild liver dysfunction [aspartate aminotransferase 57 IU/L (normal 13-30 U/L), alanine aminotransferase 58 IU/L (normal 10-42 U/L), alkaline phosphatase 1,238 IU/L (normal 106-322 U/L), gamma-glutamyl transpeptidase 213 IU/L (normal 13-64 U/L)], renal dysfunction [blood urea nitrogen 21.2 mg/dL (normal 8.0-20.0 mg/dL), creatinine 1.28 mg/dL (normal 0.65-1.07 mg/dL)], elevated inflammation reactions [erythrocyte sedimentation rate >140 mm/h (normal 2-10 mm/h), C-reactive protein 10.3 mg/dL (normal <0.15 mg/dL)], high levels of lactate dehydrogenase [260 IU/L (normal 124-222 IU/L)] and soluble interleukin 2 receptor [6,630 U/mL (normal 122-496 U/mL)], and elevated blood sugar [213 mg/dL (normal 73-109 mg/dL)] and hemoglobin A1c [7.4% (normal 4.9-6.0%)]. Serum protein electrophoresis showed M pro-

tein, which was identified as immunoglobulin M kappa and lambda type Bence-Jones protein by immunoelectrophoresis. A cerebrospinal fluid (CSF) study showed a normal initial pressure (130 mmH<sub>2</sub>O), watery clear CSF, an elevated cell count [6/μL, monocyte dominant (normal ≤ 3/μL)] and protein level [57 mg/dL (normal 8-40 mg/dL)], and a normal glucose level (64 mg/dL). The CSF cytology was class III. A nerve conduction study (NCS) revealed no abnormal findings in the median, tibial and sural nerves. Gadolinium (Gd)-enhanced T1-weighted brain magnetic resonance imaging (MRI) revealed abnormalities of the hypoglossal nerve or hypoglossal nerve nucleus in the medulla oblongata (Figure b, arrows). Whole body computed tomography (CT) showed only mild splenomegaly. 18F-2-deoxy-2-fluoro-D-glucose (FDG)-positron emission tomography (PET)-CT revealed hot spots on the left side of the oropharynx (Figure d, arrow), spleen (Figure c, f, arrowheads), and generalized bone marrow (Figure c, arrows), but no abnormalities of the hypoglossal nerve nucleus in the medulla oblongata (Figure e). A bone marrow biopsy showed only hypercellular bone marrow with aggregated CD20-positive B-cells without immunoglobulin light chain restriction, and with no evidence of malignancy. In contrast, a left tonsil biopsy specimen showed the proliferation of large round atypical lymphocytes (Figure g) that were negative for CD3 (Figure h) and positive for CD20 (Figure i) and Ki-67 (Fig-



**Figure.** (a) Right-dominant atrophy of both sides of the tongue (arrows), and deviation of the tongue to the right on protrusion. (b) A representative Gd-enhanced T1-weighted brain MRI scan showing no abnormalities of the hypoglossal nerve or hypoglossal nerve nucleus in the medulla oblongata (blank arrows). (c-f) A representative whole body FDG-PET image showing hot spots in the bone marrow (c: arrows), spleen (c, f: arrowheads) and left oropharynx (d: arrow), but not in the hypoglossal nerve nucleus of the medulla oblongata (e: blank arrows). (g-j) The pathological examination of a left tonsil biopsy specimen revealed the proliferation of large round atypical lymphocytes (g) that were negative for CD3 (h) and positive for CD20 (i) and Ki-67 (j).

ure j), which led to a diagnosis of diffuse large B cell lymphoma (DLBCL). A test of the patient's serum for anti-ganglioside antibodies was strongly positive (3+) for anti-

GM1 IgM, and mildly positive (1+) for anti-GQ1b IgM and anti-sulfated glucuronyl paragloboside (SGPG) IgM antibodies.

Based on the above findings, we suspected that the bilateral hypoglossal nerve palsy was caused by a paraneoplastic syndrome related to malignant lymphoma, but with no direct invasion of the malignancy. Thus the patient was treated with cyclophosphamide (900 mg), doxorubicin (60 mg), vincristine (1.6 mg), and prednisolone (70 mg for 5 days). However, his tongue symptom did not improve, and he died of *Pneumocystis pneumonia* after 2 weeks of chemotherapy.

## Discussion

The present case showed an isolated hypoglossal nerve palsy (R>>L, Figure a) without other neurological findings, accompanied by DLBCL. Gd-enhanced brain MRI and FDG-PET-CT showed no abnormalities of the hypoglossal nerve nucleus (Figure b and e), but a test of his serum for anti-ganglioside antibodies was positive for anti-GM1 IgM, anti-GQ1b IgM and anti-SGPG IgM antibodies. He had DM, but the neurological findings and NCS revealed no abnormal findings in relation to the motor, sensory or autonomic systems. To the best of our knowledge there have been no reported cases of DM presenting with an isolated hypoglossal nerve palsy. Thus, a paraneoplastic syndrome related to malignant lymphoma, but without the direct invasion of the malignancy, was suspected in the present case.

The peripheral neuropathy observed in lymphoma is mainly due to the direct invasion of malignant cells, and sometimes due to a paraneoplastic syndrome associated with anti-ganglioside antibodies (1). Previous reports have shown five cases of asymmetrical hypoglossal nerve palsy in patients without malignancy who were positive for anti-ganglioside antibodies (Table) (2-6). Four of these cases were combined with other cranial nerves and peripheral motor palsies, while only one case involved an asymmetrical and isolated hypoglossal nerve palsy. Anti-GM1 and anti-GD1b IgG antibodies were detected in three of the five abovementioned cases, suggesting the major anti-ganglioside antibodies for hypoglossal nerve palsy. Anti-GD1a, anti-GQ1b, anti-GD1b/GD1a and anti-GD1b/GT1b IgG antibodies were reported only in one case by Yamagami et al., but were still combined with anti-GD1b IgG antibodies.

The present patient with DLBCL showed a rare asymmetrical and isolated hypoglossal nerve palsy, and his serum was positive for anti-SPGM IgM antibodies as well as anti-GM1 and anti-GQ1b IgM antibodies. In patients with autoimmune neuropathy, anti-ganglioside IgM antibodies are associated with chronic disease, including malignant lymphoma, through the mechanism of 'binding site drift', while anti-ganglioside IgG antibodies are associated with acute diseases, including Guillain-Barré syndrome, through the mechanism of 'molecular mimicry' (7). Some previously reported cases of autoimmune neuropathy in malignant lymphoma were associated with anti-ganglioside IgM antibodies.

ies, including anti-GM1, anti-GD1b, and anti-GQ1b IgM antibodies (1), while cases with M protein were accompanied by anti-SGPG IgM antibodies (8, 9). Anti-GM1 IgM antibodies are related to an asymmetrical neuropathy, while anti-GQ1b and anti-SGPG IgM antibodies are usually associated with polyneuropathy (8, 9); one exception exists in a reported case of asymmetrical facial nerve palsy in a patient who was positive for anti-SGPG IgM antibodies (10). Based on previous reports, the anti-GM1 and anti-SGPG IgM antibody positivity might have been associated with the asymmetrical and isolated hypoglossal nerve palsy in the present case. However, the anti-ganglioside IgM antibody activities were not analyzed at different clinical time points in the present case. Furthermore, the pathological mechanism through which anti-ganglioside IgM antibodies are associated with peripheral neuropathy in lymphoma has not been fully elucidated. Thus, an association between anti-ganglioside IgM antibodies and the isolated hypoglossal nerve palsy was suspected in the present case, but was not clearly confirmed.

In summary, we reported a very rare case of an asymmetrical and isolated hypoglossal nerve palsy that was accompanied by a new subset of anti-ganglioside antibodies associated with DLBCL. The present case might suggest that paraneoplastic syndrome with anti-ganglioside antibodies should be suspected in cases involving asymmetrical and isolated hypoglossal nerve palsy.

**The authors state that they have no Conflict of Interest (COI).**

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