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, Yuko Kawahara, Koh Tadokoro, Kota Sato, Ryo Sasaki, Yoshiaki Takahashi, Mami Takemoto, Nozomi Hishikawa, Toru Yamashita, Takeru Asano, Tomoko Inomata and Koji Abe

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 18F-2-deoxy-2-fluoro-D-glucose positron 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

(Intern Med 58: 283-286, 2019)
(DOI: 10.2169/internalmedicine.1269-18)

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-
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 0-40 IU/L), alanine aminotransferase 58 IU/L (normal 0-40 IU/L), alkaline phosphatase 1,238 IU/L (normal 106-322 IU/L), gamma-glutamyl transpeptidase 213 IU/L (normal 0-64 IU/L), retinal 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 Alc [7.4% (normal 4.9-6.0%)]. Serum protein electrophoresis showed M protein, 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 mmH2O), watery clear CSF, an elevated cell number 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 abnormalities in the median, tibial and sural nerves. Gadolinium (Gd)-enhanced T1-weighted brain magnetic resonance imaging (MRI) revealed abnormalities of the 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 (Figure i).

| Reference | 5 | 2 | 3 | 6 | 4 | Present case 2018 |
|-----------|---|---|---|---|---|-------------------|
| Age       |   |   |   |   |   | 49                |
| Sex       |   | Female |   | 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 | none | Lt | Lt | Lt | Lt |
| Other neurological findings | 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 | normal | motor axonal neuropathy of median and ulnar N | 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 glucouronyl paragloboside, U/L: upper limb.
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 antibod-
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).

Financial Support
This work was partly supported by a Grant-in-Aid for Scientific Research (B) 17H0419619, (C) 15K0931607, 17H0419619 and 17K1082709, and Grants-in-Aid from the Research Committees (Kaji R, Toba K, and Tsuji S) from the Japan Agency for Medical Research and Development (AMED) 7211700176, 7211700180 and 7211700095.

Acknowledgement
We are grateful to Dr. Yohei Noda (Department of Otolaryngology-Head and Neck Surgery, Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama University) for his help in a left tonsil biopsy, and Dr. Susumu Kusunoki (Department of Neurology, Kindai University Faculty of Medicine) for his help in the serological analyses of anti-ganglioside antibodies.

References
1. Shihashi G, Yagi T, Suzuki S, et al. Immune-mediated neuropathy with anti-disialosyl IgM antibodies in diffuse large B-cell lymphoma: a case report and literature review. Intern Med 54: 1647-1651, 2015.
2. Capone F, Sauchelli D, De Vitis I, et al. Hypoglossal palsy and coeliac disease: an uncommon presentation for a common disease? Clin Neurol Neurosurg 113: 426-429, 2011.
3. Chi MS, Ng SH, Chan LY. Asymmetric acute motor axonal neuropathy with unilateral tongue swelling mimicking stroke. Neurologist 21: 106-108, 2016.
4. Han TH, Kim DY, Park DW, Moon JH. Transient isolated lower bulbar palsy with elevated serum anti-GM1 and anti-GD1b antibodies during aripiprazole treatment. Pediatr Neurol 66: 96-99, 2017.
5. Sakakibara Y, Morii M, Kusunoki S, et al. Unilateral cranial and phrenic nerve involvement in axonal Guillain-Barré syndrome. Muscle Nerve 25: 297-299, 2002.
6. Yamagami M, Sakurai Y, Hamada K, et al. Unilateral hypoglossal nerve palsy with asymmetric facial and limb paresis in axonal Guillain-Barré syndrome. Neurology and Clinical Neuroscience 4: 25-27, 2016.
7. Nores GA, Lardone RD, Comin R, Alaniz ME, Moyano AL, Irazoqui FJ. Anti-GM1 antibodies as a model of the immune response to self-glycans. Biochim Biophys Acta 1780: 538-545, 2008.
8. Stork AC, van der Pol WL, Franssen H, Jacobs BC, Notermans NC. Clinical phenotype of patients with neuropathy associated with monoclonal gammopathy: a comparative study and a review of the literature. J Neurol 261: 1398-1404, 2014.
9. Tagawa Y, Yuki N, Hirata K. Anti-SGPG antibody in CIDP: nosological position of IgM anti-MAG/SGPG antibody associated neuropathy. Muscle Nerve 23: 895-899, 2000.
10. Yoshida T, Yazaki M, Gono T, et al. Severe cranial nerve involvement in a patient with monoclonal anti-MAG/SGPG IgM antibody and localized hard palate amyloidosis. J Neurol Sci 244: 167-171, 2006.

The Internal Medicine is an Open Access journal distributed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License. To view the details of this license, please visit (https://creativecommons.org/licenses/by-nc-nd/4.0/).