Neurological Sciences (2019) 40:1481–1483
https://doi.org/10.1007/s10072-019-3731-0

LETTER TO THE EDITOR

Autoimmune autonomic ganglionopathy associated with monoclonal gammopathy of undetermined significance: a case report

Tatsuya Ueno[1] · Takashi Nakamura[1] · Akira Arai[1] · Chieko Suzuki[1] · Masahiko Tomiyama[1]

Received: 21 September 2018 / Accepted: 17 January 2019 / Published online: 26 January 2019
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Dear Editor:

Autoimmune autonomic ganglionopathy (AAG) is an acquired immune-mediated disorder characterized by severe autonomic failure [1]. Anti-ganglionic nicotinic acetylcholine receptor (gAchR) antibody is detected in approximately 50% of cases of acute or subacute AAG [1]. About 15% of AAG cases are also complicated by cancer, e.g., small cell lung carcinoma [1]. Previous reports suggested an association of multiple myeloma (MM) with AAG [2, 3]; however, no reports suggest an association between AAG and monoclonal gammopathy of undetermined significance (MGUS). The overproduction of monoclonal light chains causes amyloid light chain (AL) amyloidosis leading to autonomic failure; therefore, it is important to distinguish AAG from AL amyloidosis. We, herein, report a patient who had AAG and MGUS without deposition.

A 70-year-old Japanese man who suffered from syncope due to orthostatic hypotension was admitted to our department. He had constipation at 65 years old, dysuria at 66 years old, dry mouth at 68 years old, and photophobia at 69 years old. He reported a worsening of his dysuria and orthostatic hypotension 3 months before admission. His medical history included a transurethral resection of the prostate for benign prostatic hyperplasia at 66 years old. Family history was unremarkable. Physical examination showed decreased bowel sounds and mild abdominal distension. Neurological examination revealed that the bilateral pupil was 6 mm in diameter, and the pupils were sluggish in pupillary light reflex and convergence reflex tests. Deep tendon reflexes, superficial sensations, and deep sensations were normal, and cerebellar ataxia and parkinsonism were not shown. His blood pressure and heart rate in supine position was 138/91 mmHg and 88/min. On standing, his blood pressure decreased to 62/43 mmHg, his heart rate was 84/min, and faintness was induced. The dilated pupil changed to a miotic pupil by the administration of 0.125% pilocarpine, indicating the denervation supersensitivity as a result of damage to the ciliary ganglion, so-called Adie's tonic pupil (Fig. 1a).

Laboratory studies revealed no diabetes mellitus, anemia, hypercalcemia, HIV infection, or renal insufficiency. Serum noradrenaline level was decreased (30 pg/mL; reference range 100–450). Total IgG levels were 1100 mg/dL (reference range 870–1700 mg/dL), IgA levels were 83 mg/dL (normal range 110–410 mg/dL), and IgM levels were 62 mg/dL (normal range 35–220 mg/dL). The Schirmer test and the Rose Bengal test were negative. Lip biopsy showed chronic sialadenitis that did not satisfy the criteria for Sjögren's syndrome. The coefficient of variation of RR interval was decreased (0.54%). A nerve conduction study and intraepidermal nerve fiber density of the distal leg were normal. Brain magnetic resonance imaging and a dopamine transporter scan (^{123}I-ioflupane) were normal. ^{123}I-metaiodobenzylguanidine myocardial scintigraphy showed normal early (2.58) and delayed (2.35) heart/mediastinum (H/M) ratio, but the washout ratio was increased (42.2%). Although the anti-SS-A/Ro and anti-SS-B/La antibody and paraneoplastic autoantibody panel were all negative, an anti-gAchR antibody test (anti-α3 AchR) was positive. Furthermore, no immunoglobulin heavy chain expression on serum immunofixation was detected, but urine immunoelectrophoresis showed Bence Jones proteinuria (kappa type) (Fig. 1b). A free light chain assay of the serum showed elevated free kappa chain levels (35.8 mg/L; reference range 3.3–19.4 mg/L), normal free lambda chain levels (15.9 mg/L; reference range 5.7–26.3 mg/L), and an elevated free light chain ratio (2.25; reference range 0.26–1.65). A bone marrow smear demonstrated a 1.5% clonal expansion of the plasma cells, indicating MGUS. The pathology of the minor salivary gland, duodenum, colon, and rectum for amyloidosis was negative.

✉ Tatsuya Ueno
lacote19thg@gmail.com; tatsuya_ueno@med.pref.aomori.jp

[1] Department of Neurology, Aomori Prefectural Central Hospital, 2-1-1 Higashi-Tsukurimichi, Aomori 030-8551, Japan

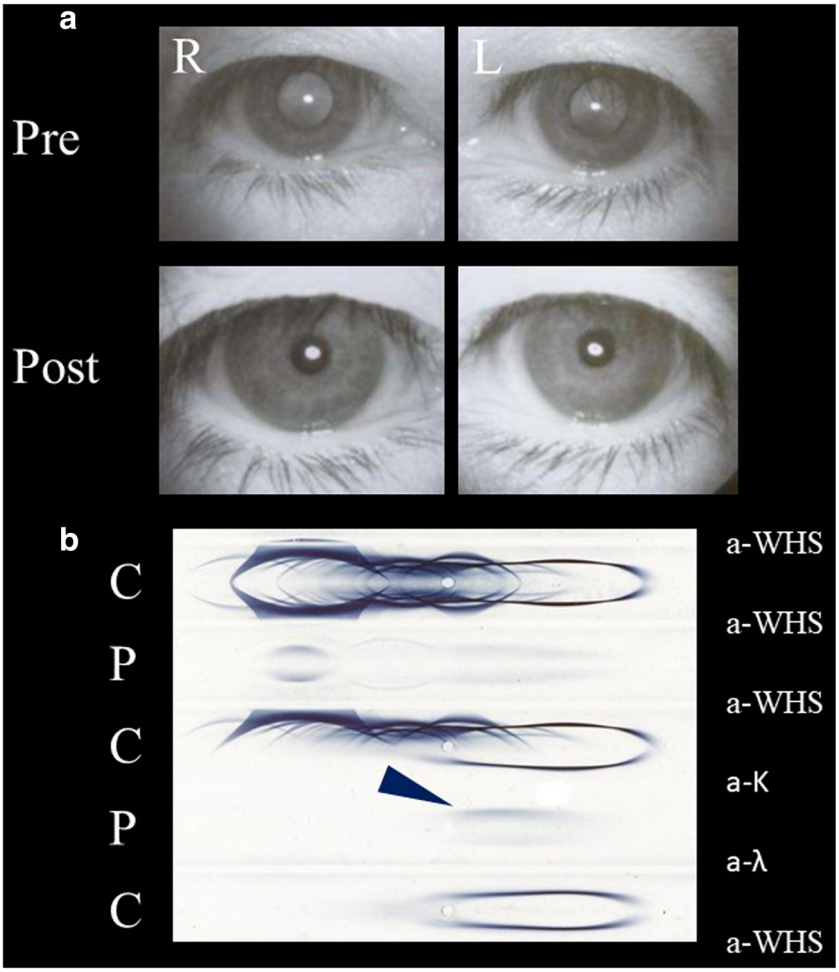

Fig. 1 (A) 0.125% pilocarpine test. The dilated pupil changed to a miotic pupil by the administration of 0.125% pilocarpine, indicating Adie's tonic pupil. (B) Urine immunoelectrophoresis. Bence Jones proteinuria (kappa type) is detected (arrow). R, right; L, left; C, control; P, patient; a-WHS, anti-whole human serum; a-κ, anti-1ight chain kappa-type; a-λ, anti-1ight chain lambda-type

[^{18}F]-fluorodeoxyglucose positron emission tomography-computed tomography was negative. Based on these results, we diagnosed the patient with AAG with MGUS.

We used midodrine (8 mg/day), amezinium (20 mg/day) to control OH, and senna (24 mg/day) for constipation. Immunotherapy was also started by the administration of intravenous immunoglobulin at 400 mg/kg body weight daily for 5 days because the patient was unable to accept side effects of steroids. One month after immunotherapy, his blood pressure and heart rate in supine position was 121/79 mmHg. Although his blood pressure was decreased to 99/42 mmHg on standing, faintness was not triggered. Dry mouth and dysuria also improved subjectively, but Adie's tonic pupil and constipation did not improve. As the impact on his daily life was reduced, the patient is under observation without additional immunotherapy.

We have presented a case of AAG with MGUS. This case suggests that MGUS may be associated with AAG. Differentiating AL amyloidosis complicated by MGUS and AAG is important because treatment options are different.

MGUS precedes MM characterized by clonal proliferation of plasma cells, and conversions to MM or related disorders are at an annual risk of 1%. The associations between immune-related conditions and MM/MGUS have been investigated because these disorders involve plasma cell dyscrasia associated with the immune system. A large population-based study revealed that several immune-related diseases elevated the risk of MM and/or MGUS [4]. With regard to the association of anti-α3 AchR antibody and MM, one patient had myeloma from a total of 78 patients positive for anti-α3 AchR antibody [2]. Nakae et al. also reported a case of AAG with MM [3]. However, there is no report of AAG with MGUS. About 15% of patients with AAG have paraneoplastic AAG usually associated with small cell lung carcinoma or thymoma [1]. Malignant tumors were not detected by imaging studies in this case. Although it is not known whether the onset of MGUS occurred before or after the onset of AAG in this case, MGUS might be associated with AAG. To the best of our knowledge, this is the first reported case of AAG with MGUS.

AL amyloidosis characterized by deposition of amyloid proteins is caused by chronic hematological plasma cell dyscrasia and affects peripheral nerves in 15–20% of patients with AL amyloidosis [5]. We should consider AL amyloid

neuropathy in patients with autonomic failure if patients have elevated monoclonal (M) protein because uncommon forms of AL amyloid neuropathy rarely cause isolated autonomic failure [5]. To differentiate AL amyloid neuropathy, a physician needs to confirm the amyloid deposition from various tissues, such as the gastrointestinal tract. Our patient had Bence Jones proteinuria with autonomic failure but had no evidence of amyloid deposition. We, therefore, believe that the autonomic failure, in this case, was caused by AAG, but not AL amyloid neuropathy.

In conclusion, we described a patient with AAG complicated by MGUS. Differentiating AL amyloidosis and AAG is important if patients with M protein have only autonomic symptoms.

Acknowledgements The authors would like to thank Dr. Tomoaki Akagi, Department of Hematology, Aomori Prefectural Central Hospital, Aomori, Japan, for performing the hematological evaluation. We thank S. Win, PhD, from Edanz Group (www.edanzediting.com/ac) for editing a draft of this manuscript.

Compliance with ethical standards

Consent for publication Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

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