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【 CASE REPORT 】

Multiple Myeloma Presenting with Autoimmune Autonomic Ganglionopathy

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Abstract:
Autoimmune autonomic ganglionopathy is an autonomic disorder that occurs as a symptom of paraneoplastic neurological syndrome. To date, there have been no reports on multiple myeloma with autoimmune autonomic ganglionopathy. A 37-year-old Japanese woman suffered from orthostatic hypotension was diagnosed with multiple myeloma (IgG kappa type), and a serological examination revealed the presence of anti-ganglionic nicotinic acetylcholine receptor (anti-gAChR) antibodies. She was treated for multiple myeloma, as a result, the autonomic disturbance improved and her anti-gAChR antibody titer decreased to undetectable levels, despite the fact that she only achieved a partial remission of multiple myeloma. Treatment for multiple myeloma may improve autoimmune autonomic ganglionopathy.

Key words: multiple myeloma, autonomic disturbance, autoimmune autonomic ganglionopathy

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Introduction

Multiple myeloma (MM) is a plasma cell neoplasm that mainly develops in elderly patients and which is occasionally complicated by neuropathy. The neuropathies that occur due to MM include radiculopathy and spinal cord compression (which are induced by extramedullary plasmacytoma), peripheral neuropathy (which occurs due to amyloidosis), and polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (POEMS) syndrome. However, there is only one reported case of MM with autonomic disturbance (1).

Autoimmune autonomic ganglionopathy (AAG) is an autoimmune disease that is induced by anti-ganglionic nicotinic acetylcholine receptor (anti-gAChR) antibodies, which bind to the acetylcholine receptor in the autonomic ganglia (2). The manifestations of AAG include symptoms associated with autonomic disturbance, such as orthostatic hypotension, disturbance of sweating, dysuria, and constipation. This disease occurs as a complication of paraneoplastic neurological syndrome associated with small cell lung carcinoma, thymoma, bladder carcinoma and rectal carcinoma (3-5). However, there are no reports of AAG occurring in association with MM. Moreover, MM rarely complicates autoimmune disease (6), and there are no reports of AAG with MM.

In the present report, we describe the first case of MM complicated by AAG. Treatment for MM, plasma exchange, and intravenous immunoglobulin reduced the anti-gAChR antibody titer and resulted in a recovery from autonomic disturbance, despite the fact that the patient experienced a partial remission (PR) of MM.

Case Peport

A 37-year-old Japanese woman visited our hospital on foot complaining of walking difficulty of 2 months in dura-

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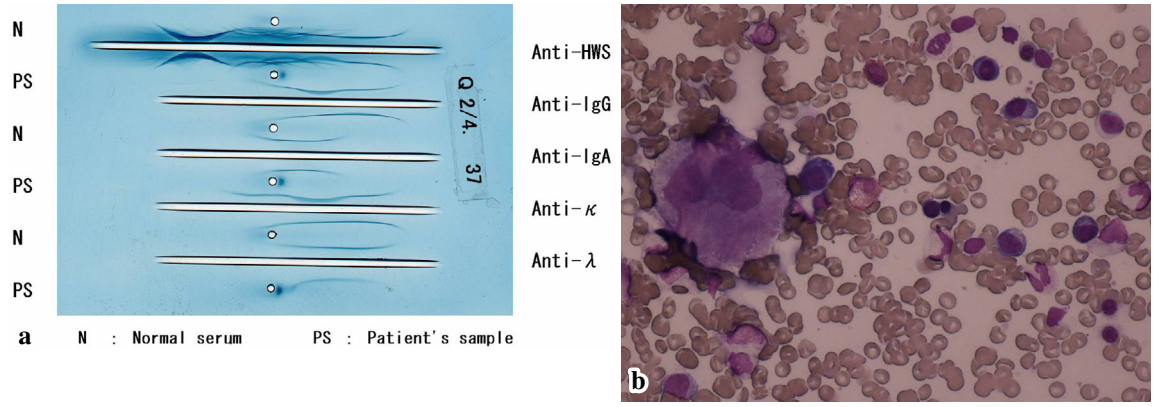

Figure 1. **a) Serum immunoelectrophoresis revealed IgG kappa type monoclonal protein. b) A bone marrow smear revealed increased plasma cells in the nucleated cells.**

tion. She suffered renal heavy-chain deposition disease and IgG kappa was detected in her serum; she had been diagnosed with monoclonal gammopathy of renal significance (MGRS) in another hospital 3 years previously. In spite of the administration of steroid pulse therapy at the diagnosis of renal heavy-chain deposition disease, she had been receiving hemodialysis for 3 years. Her rare renal disease had been the subject of a previous report (7).

On admission, her height and body weight were 166.5 cm and 57.9 kg, respectively. Her blood pressure was 118/72 mmHg, her pulse rate was 73 beats/min, and her body temperature was 36.4℃. On physical examination, bilateral numbness of the lower legs and feet, proximal lower limb muscle weakness, a waddling gate, and Gower's sign were evident. However, cerebellar symptoms, central nervous system manifestations, and changes of the deep tendon reflexes were not evident. After admission, rapid onset orthostatic hypotension appeared and on the 20th day of hospitalization she could not sit up due to orthostatic hypotension.

Laboratory tests revealed the following: white blood cell count, 5,600/μL; hemoglobin, 9.9 g/dL; platelet count, 22.1×10^4/μL; serum creatinine, 9.07 mg/dL; total protein, 4.6 g/dL; albumin, 2.4 g/dL; Ca, 8.5 mg/dL (unadjusted data); immunoglobulin (Ig) G, 1,280 mg/dL; IgA, 115 mg/dL; IgM, 25 mg/dL; free kappa chain, 9,650.0 mg/L; free lambda chain, 52.6 mg/L; kappa/lambda ratio, 183.5; C3, 28 mg/dL; C4, 2 mg/dL; CH50, undetectable; C1q, 474 μg/mL; and plasma vascular endothelial growth factor, 93 pg/mL. Her hepatobiliary function was normal. A urinalysis was not performed due to the presence of anuria.

Serum immunoelectrophoresis revealed IgG kappa type monoclonal protein (Fig. 1a). A bone marrow smear revealed that 24.8% of the nucleated cells were dysplastic plasma cells (Fig. 1b). Flow cytometry of the bone marrow revealed myeloma cells that were positive for CD38, CD56, and CD138, and negative for CD19, CD20, MPC1, CD45, and CD49a. A fluorescence *in situ* hybridization test of the bone marrow revealed myeloma cells containing an IgH-fibroblast growth factor receptor (FGFR)3 fused gene without trisomy. There was no evidence of focal bone lesion on whole body computed tomography or amyloidosis on ultrasonic cardiography and gastroscopy with biopsy. These findings were consistent with a diagnosis of IgG kappa-type MM.

The T1 window of magnetic resonance imaging (MRI) revealed that the right hamstring and gluteus maximus muscles were more atrophic than the left (Fig. 2a). MRI with short tau inversion recovery revealed areas of high intensity in the lumbar paraspinal muscles, gluteus maximus muscle and internal obturator muscle (Fig. 2b). A cerebrospinal fluid examination revealed the following: total protein, 88.9 mg/dL; albumin, 364.2 mg/L; glucose, 55 mg/dL; nucleated cells, 13 cells (12 mononucleated cells, one multinucleated cell). The coefficient of variation of R-R (CV-RR) interval on electrocardiography was revealed to be 1.55%, which showed an autonomic disturbance. An electromyogram revealed that the lumbar paraspinal muscle contraction was impaired. A nerve conduction velocity study revealed that the motor and sensory nerves of the leg had a low amplitude and a low conduction velocity. These results indicated an axonal disorder and demyelination of the peripheral nerves. Moreover, serological examinations were positive for anti-α3 subunit gAChR antibodies, and anti-β4 subunit gAChR antibodies (8). These findings were consistent with a diagnosis of "AAG with peripheral neuropathy".

On the 25th day of hospitalization, the patient was treated for symptomatic MM with BD [a 5-week cycle of bortezomib (1.3 mg/m^2, via subcutaneous injection on days 1, 8, 15 and 22) plus dexamethasone (20 mg/body, orally on days 1, 2, 8, 9, 15, 16, 22 and 23)] because AAG is reported to be one of the paraneoplastic neurological syndromes (3-5). After two courses of BD, 18 rounds of plasma exchange, and intravenous immunoglobulin, the patient's free kappa chain level decreased from 9,650.0 mg/L to 138.0 mg/L. This indicated a PR (of the patient's MM), as defined by the International Myeloma Working Group (9). Accordingly, the patient could sit down on her own, her CV-RR interval was improved, and her anti-α3 subunit gAChR antibody and anti-β4 subunit gAChR antibody titers became negative on the 72nd day of hospitalization (Fig. 3). However, borte-

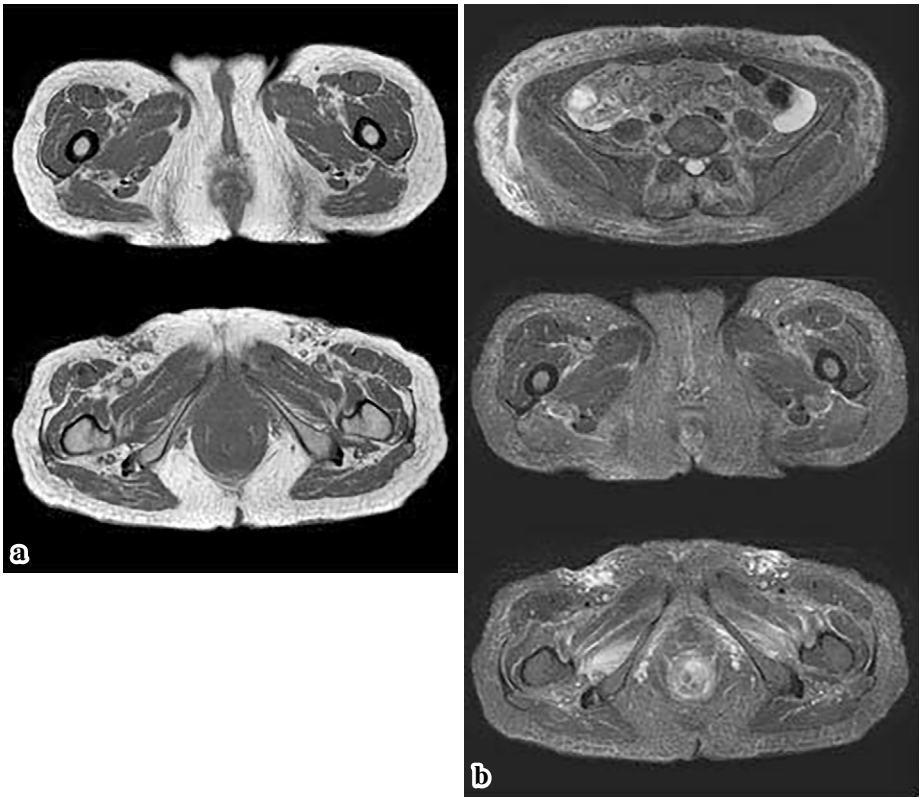

Figure 2. **a) The right hamstring and gluteus maximus muscles were more atrophic than the muscles on the left in the T1 window of MRI. The upper image shows the gluteus maximus muscle; the lower image shows the internal obturator muscle. b) The upper image shows the lumbar paraspinal muscles, the middle image shows the internal obturator muscle, and lower image shows the gluteus maximus muscle. A high intensity area is observed in the right lumbar paraspinal muscles, both internal obturator muscles and the right gluteus maximus muscle in the STIR window of MRI.**

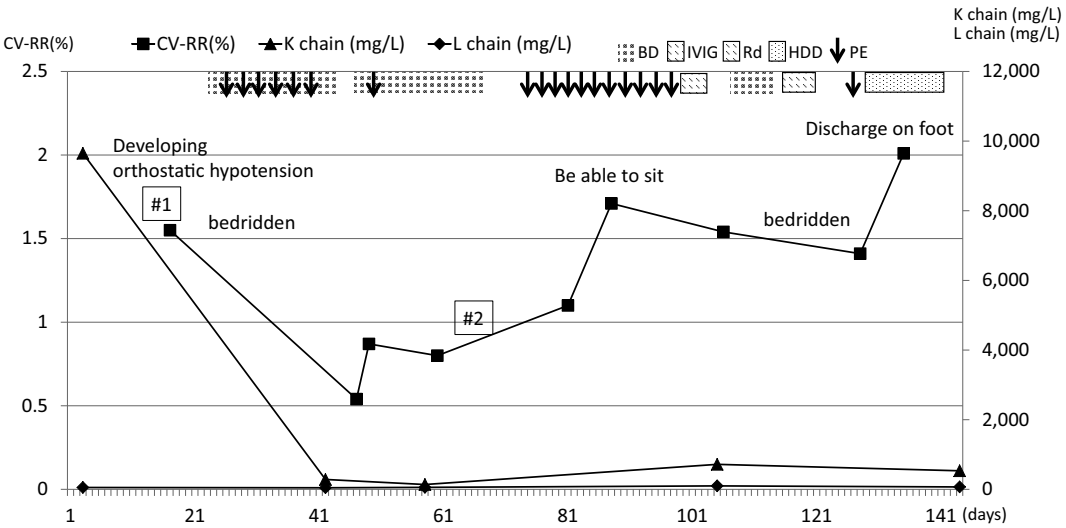

Figure 3. **The clinical course of the patient. The left vertical axis represents the percentage of CV-RR, the right vertical axis represents the kappa chain and lambda chain. The horizontal axis represents the days after admission. K chain: kappa chain, L chain: lambda chain, BD: bortezomib+dexamethasone, IVIG: intravenous immunoglobulin, Rd: lenalidomide+dexamethasone, HDD: high-dose dexamethasone, PE: plasma exchange, #1: anti-α3 subunit gAChR antibody and anti-β4 subunit gAChR antibody were positive, #2: anti-α3 subunit gAChR antibody and anti-β4 subunit gAChR antibody were negative.**

zomib worsened her peripheral sensory neuropathy (CTCAE version 4.0: grade III), and was therefore discontinued. Unfortunately, LD [a 4-week cycle of lenalidomide (5 mg/body, orally on days 1-21) plus dexamethasone (20 mg/body, orally on days 1-4 and 15-18)] also worsened her sensory peripheral neuropathy (CTCAE version 4.0: grade III). Thus, she was treated with high-dose dexamethasone [This consisted of a 4-week cycle of dexamethasone (20 mg/body, orally on days 1-4, 9-12 and 17-20)] and rehabilitation. As a result, she was discharged on foot on the 138th day of hospitalization.

Discussion

The present case was significant for two findings. First, MM and AAG were found to coexist. Second, treatment for MM, plasma exchange, and intravenous immunoglobulin induced a good remission of AAG with a reduction of the anti-gAChR antibody titer, despite the fact that only PR of MM was achieved.

This is the first report on the coexistence of MM and AAG in a patient. MM has been reported to induce peripheral neuropathy; this symptom occurs in 7.2% of MM patients (10). Moreover, treatment-related peripheral neuropathy has been reported to occur in association with bortezomib (11), thalidomide (12), lenalidomide (13), and pomalidomide (14). In the previously mentioned case of MM with autonomic disturbance (1), the cause of the autonomic disturbance was not evident. Thus, this represents the first case of MM with autonomic disturbance in which the cause was evident. Is this case extremely rare? It is possible that similar cases occur more frequently but are not reported because, in the clinical setting, many hematologists do not take the initiative to perform a neurological examination in cases in which MM is aggravated by events, such as bone fracture, or when a patient's activities of daily living are impaired by peripheral neuropathy. Autonomic disturbance may be hidden in such a case; thus, MM with autonomic disturbance may require more than hematology-specific knowledge. There may be other cases of treatable autonomic disturbance that occur in association with MM.

The second point of clinical significance is that treatment for MM, plasma exchange, and intravenous immunoglobulin induced a good remission of AAG and reduced the patient's anti-gAChR antibody titer, despite the fact that only a PR of MM was achieved. The treatments for AAG include immunosuppression therapy (such as steroids, azathioprine, rituximab (15), and mycophenolate mofetil), intravenous immunoglobulin and plasma exchange. The role of immunosuppression therapy is to suppress the production of anti-gAChR antibodies, plasma exchange performed to clear up the anti-gAChR antibodies in the serum, and intravenous immunoglobulin is administered to capture anti-gAChR antibodies in the serum. Nakane et al. reported that six of seven cases responded to immunosuppression therapy (16), and Iodice et al. also reported that all six of their cases responded to immunosuppression therapy (17). In the present case, treatment for MM played had the effect of immunosuppression therapy for AAG; thus, the patient recovered from orthostatic hypotension and her anti-gAChR antibody titer remained below the limit of detection for at least 1 year after discharge. This case was definitely diagnosed as AAG complicated with MM. We must therefore consider the possibility that an abnormal monoclonal protein secreted by myeloma cells bound directly to the ganglionic nicotinic acetylcholine receptors. If the monoclonal protein bound directly to the ganglionic nicotinic acetylcholine receptors, autonomic disturbance and anti-gACgR antibodies would have remained because the patient's MM was only in PR-meaning that the monoclonal protein obviously remained. Thus, we did not examine whether the monoclonal proteins or ganglionic nicotinic acetylcholine receptors were directly bound, the monoclonal protein might not bind to ganglionic nicotinic acetylcholine receptor. Treatment for MM may be one option for achieving immunosuppression in AAG patients who are resistant to conventional treatment.

MM is a plasma cell neoplasm that produces abnormal immunoglobulin. The purpose of treatment is to reduce the number of abnormal plasma cells. Immunosuppression occurs as an adverse event in patients undergoing MM treatment because the numbers of normal plasma cells and other immunocompetent cells are also reduced by the treatment for MM. However, this indicates the possibility that treatment for MM may be effective for treating autoimmune diseases. Bortezomib has been used in the treatment of systemic lupus erythematosus (18), lenalidomide has been used in the treatment of systemic lupus erythematosus (19-22) and Behcet's disease (22), and high-dose dexamethasone has been used in the treatment of autoimmune thrombocytopenia (23-25). These results and the present case indicate the possibility that treatment for MM might be effective in the treatment of refractory autoimmune disease.

In conclusion, MM may accompany AAG. In the present case, treatment for MM effectively improved the patient's AAG and autonomic disturbance. We must be aware of the possibility of hidden autonomic disturbance in MM patients, which may be treatable by treatment regimens that are typically used for MM, plasma exchange, and intravenous immunoglobulin. Further reports should be accumulated to determine whether the incidence of hidden autonomic disturbance in MM patients is higher than previously thought, and to determine the best treatment regimen for autonomic disturbance in patients with MM.

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

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