Case report

Paraneoplastic neurological syndrome in a patient with gastric cancer

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Abstract

Paraneoplastic neurological syndromes (PNSs) are a heterogeneous group of neurological disorders caused by immune-mediated mechanisms. The incidence of PNS is much less than 1% for solid tumors, except for small-cell lung cancer and thymoma. We report a rare case of gastric cancer that presented with primary clinical findings of PNS. The patient was a 63-year-old woman who was admitted for worsening neuropathy. Laboratory and neurological tests excluded a nutritional deficit, diabetes mellitus, and connective tissue disease as causes of her neuropathy. Computed tomography (CT) of the abdomen, positron emission tomography (PET)-CT, and endoscopy of the stomach revealed gastric cancer with lymph node swelling. Distal gastrectomy was performed and pathological and immunohistochemical examinations indicated endocrine cell carcinoma. The gastrectomy stopped the exacerbation of her symptoms and recurrence was not observed, but the neurological disorders were irreversible. This case suggests that early diagnosis of the primary tumor is required to improve the outcome in patients with PNS.

Key words Paraneoplastic neurological syndrome · Gastric cancer · Sensory disturbance · Endocrine cell carcinoma

Introduction

The development of peripheral nervous system dysfunction in patients with cancer usually reflects the side effects of therapy, infiltration of nerves or spinal roots by the tumor, or nutritional deficits. Paraneoplastic neurological syndromes (PNSs) are defined as a heterogeneous group of neurological disorders with mechanisms other than these causes [1]. The cause may be immune-mediated, but the pathogenesis is incompletely understood. The more common syndromes are Lambert-Eaton

myasthenic syndrome, which affects approximately 3% of patients with small-cell lung cancer, and myasthenia gravis, which affects 15% of patients with thymoma. For other solid tumors, the incidence of PNS is much less than 1% [2]. Here, we report a rare case of a patient with gastric cancer presenting with primary clinical findings of PNS.

Case report

The patient was a 63-year-old woman with well-controlled diabetes and hypertension who presented with sensory disturbance and a feeling of “pins and needles” in her lower distal extremities in May 2007. She was treated with oral medicine and a nerve block injection at a neighborhood clinic, but her condition did not improve. Her neurological disorder became more severe, such that she was unable to walk, and the symptoms spread to the upper extremities. Therefore, she was admitted to our hospital for examination and treatment in September 2007.

A neurological examination showed asymmetrical apalesthesia in the lower legs. Severe pain, warmth, and tactile sensations were present below the knees, and her Rankin score was 4 on admission. Sensory nerve conduction study (SCS) showed absent sensory potentials in the bilateral sural nerves and right ulnar nerve when a motor nerve conduction study (MCS) was within normal limits in the bilateral median, ulnar, and tibial nerves (Fig. 1).

Laboratory tests showed normal levels of vitamins B1, B2, B6, B12, and E, and folic acid, and no disturbance of electrolyte balance. An elevated titer of antinuclear antibody, of 640 units, was present, but elevated titers of antibodies specific for connective tissue disease were not detected. Lumbar puncture showed negative cytology and no inflammatory changes (such as pleocytosis, intrathecal synthesis of IgG, and oligoclo-

Fig. 1. Neurophysiological studies showed reduced or absent sensory potential with normal results on motor nerve conduction study (MCS). SCS, Sensory nerve conduction study

nal bands). These results excluded a nutritional deficit, diabetes mellitus, and connective tissue disease as underlying causes.

Computed tomography (CT) of the abdomen revealed bulky lymph node swelling close to the celiac artery (Fig. 2A). On positron emission tomography-CT (PET-CT), tumor-specific uptake (standard uptake value [SUV]_{max} 6.1) was observed in the same region (Fig. 2B). Endoscopy of the stomach and upper gastrointestinal tract revealed a type 3 tumor located in the lesser curvature of the gastric angle (Fig. 3A, B). Histological examination of biopsied specimens indicated that the tumor was poorly differentiated adenocarcinoma. Based on these results, the patient was diagnosed with sensory neuropathy due to the remote effect of gastric cancer. After the administration of one course of intravenous immunoglobulin (IVIG) treatment, curative distal gastrectomy with lymphadenectomy was performed. Macroscopically, the tumor was of type 5 and located in the lesser curvature (Fig. 4). Microscopically, there were two tumors with different pathology in a background of atrophic-metaplastic multifocal gastritis. One tumor was moderately differentiated adenocarcinoma (Fig. 4A)

that had invaded to the subserosa. Bizarre nuclei that were human chorionic gonadotropin (hCG)-positive were scattered in some parts of the tumor. The other tumor had arisen from the submucosa with a background of highly lymphatic infiltration. Rosette-like formations were recognized (Fig. 4B), suggesting endocrine differentiation. There was no continuity between the two tumors (Fig. 4A, B). The latter tumor was found to be an endocrine cell carcinoma, based on immunohistochemical findings (Fig. 5). All metastatic lymph nodes were also positive for endocrine cell carcinoma. The TNM stage of the tumor was T2N1M0.

The patient's short-term postoperative course was good, with oral intake restarted on the 4th postoperative day. IVIG treatment was initiated on the 14th postoperative day, but led to little alleviation of the disability, with the Rankin score remaining at 4. The patient was discharged on the 28th postoperative day. TS-1, an oral fluoropyrimidine, was administered on an outpatient basis as adjuvant chemotherapy, but was discontinued because of severe neutropenia, thrombocytopenia, and stomatitis. We are continuing to follow the patient closely without any treatment. After the gastrectomy,

Fig. 2. **A** Computed tomography (CT) showing lymph node swelling close to the celiac artery (*arrow*). **B** Positron emission tomography (PET) showing tumor-specific uptake [standard uptake value (SUV)_{max} 6.1] in the same region (*arrows*)

Fig. 3. **A** Upper gastrointestinal image and **B** gastrointestinal fiberscopy indicating a type 3 tumor in the gastric angle

we obtained the patient's informed consent and examined the serum sample kept before the gastrectomy. We could identify Anti-Hu antibody as "well-characterized" paraneoplastic antibodies. To date, her neurological status is stable and no evidence of recurrence has been observed as of April 2010.

Discussion

Paraneoplastic neurological syndromes (PNS) are a heterogeneous group of neurological disorders in patients with cancer that are caused by mechanisms other than the side effects of cancer therapy, tumor infiltration of

Fig. 4. Top, left and right; macroscopically, a type 5 tumor was found in the gastric angle. **A, B** The tumor was microscopically heterogeneous, with regions of moderately differentiated adenocarcinoma (**A**) and undifferentiated carcinoma with rosette-like formation (**B**). H&E, $\times 100$

Fig. 5. **A** H & E staining and **B–D** immunohistochemistry showing strong staining for synaptophysin (**B**), chromogranin A (**C**), and CD56 (**D**). $\times 40$

nerves or spinal roots, or nutritional deficits [1]. The incidence of PNS is far less than 1% for solid tumors, except for small-cell lung cancer and thymoma [2]. In our patient, the main clinical symptom was asymmetrical sensory disturbance with sensory ataxia of the extremities. The asymmetry, subacute progression, and results of laboratory tests indicated that these symp-

toms were not due to a nutritional deficit or diabetic neuropathy, and specific antibodies for connective tissue disease were not observed. We were unable to detect “well-characterized” paraneoplastic antibodies before we operated, but, based on the presence of subacute sensory neuropathy as a classical syndrome and the presence of gastric cancer, we diagnosed “definite” PNS

based on the diagnostic criteria for PNS established by an international panel of neurologists [1], and performed a gastrectomy. After the gastrectomy, we confirmed the diagnosis by detecting Anti-Hu antibody in the serum sample that was kept before the gastrectomy. The lack of exacerbation of the patient's neurological disturbance after the gastrectomy, without any treatment, supported this diagnosis. This diagnosis is also consistent with the pathological findings of endocrine cell carcinoma for the patient's gastric tumor and lymph node metastases, because this carcinoma is pathologically similar to small-cell lung cancer, with which the incidence of PNS is higher.

Endocrine cell carcinoma in the stomach has a worse oncological prognosis than other histological types of gastric cancer. Fortunately, despite the failure of adjuvant chemotherapy, the present patient has shown no evidence of recurrence, and exacerbation of her neurological status has stopped. Several reports have suggested more limited metastasis and a better outcome for patients with small-cell lung cancer who develop immunity to paraneoplastic antigens [3–5]. That is, the immune-mediated reaction that causes the neurological disorder may also simultaneously suppress metastasis.

PNS often precedes diagnosis of the tumor by weeks or months [6–8]. In our patient, the neurological impairments were apparent 5 months before the detection of gastric cancer. Removal of antigens by resection of the tumor and suppression of the immune response by IVIG were performed after diagnosis, but the PNS was not resolved. In this context, it has been reported that PNS is unresponsive to treatment when the deficits are fully established and irreversible neurological damage has occurred [9–11]. In most instances, the tumor is revealed by computed tomography (CT) of the chest, abdomen, and pelvis, and whole-body fluorodeoxyglucose positron emission tomography (PET) may also be useful for detecting the primary lesion [12, 13]. However, if the primary lesion is in the gastrointestinal tract, the tumor may be missed using these approaches. In such cases, methods such as endoscopy are needed to detect the primary lesions. As was apparent in the rare case of gastric cancer with PNS described here, early detection

is the key for improved oncological and neurological outcomes. Therefore, careful and rapid examinations are needed when such neurological disorders are observed.

References

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