Demyelinating Neuropathy and Autoimmune Hemolytic Anemia in a Patient with Pancreatic Cancer

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Abstract

We herein report the case of a patient with pancreatic cancer who manifested features of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) and autoimmune hemolytic anemia (AIHA). A 78-year-old Japanese man presented with AIHA and was treated with steroids and splenectomy. Although the AIHA improved following splenectomy, the patient suffered from sensorimotor neuropathy soon after undergoing surgery. The electrophysiological features indicated demyelinating neuropathy. The neuropathy was refractory to immunomodulatory treatment, and intensive investigations revealed pancreatic cancer. The patient’s neurological deficits improved significantly after the surgery for cancer. Although the combination of AIHA and CIDP has been reported anecdotally, this is the first case of the coexistence of these diseases as paraneoplastic syndromes.

Key words: autoimmune hemolytic anemia, chronic inflammatory demyelinating polyneuropathy, pancreatic cancer, paraneoplastic syndrome


Introduction

Paraneoplastic syndromes present as signs or symptoms caused by immune cross-reactivity between the tumor and normal host tissues or tumor secretion of functional peptides and hormones (1). These syndromes may affect diverse organ systems, including the neurological, hematological, endocrinological, dermatological and rheumatological systems (1). Among these conditions, paraneoplastic neurological syndromes exhibit a wide range of features that affect various areas of the nervous system (2). The representative forms of paraneoplastic neurological syndrome include encephalomyelitis, limbic encephalitis, subacute cerebellar degeneration and sensory neuronopathy (2-4). Although several types of paraneoplastic neurological syndromes may occur simultaneously or at different time points in a single patient (2, 4-7), the combination of involvement of the nervous system and extraneurals in a paraneoplastic setting has not been well documented.

In this report, we describe a patient with pancreatic cancer who manifested slowly progressive demyelinating neuropathy compatible with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) and autoimmune hemolytic anemia (AIHA). Although sensory neuronopathy is the most common form of paraneoplastic neuropathy (2-4, 8), features compatible with CIDP may arise as a form of paraneoplastic neurological syndrome (4). In contrast, AIHA is a well-known paraneoplastic phenomenon that occurs in patients with lymphoproliferative disorders, and there are a number of case reports of the association between AIHA and solid tumors (9).

Case Report

A 71-year-old man first noted dizziness and general fatigue two weeks before his first referral to our hospital. As these symptoms became gradually worse, he visited the hematological department of our hospital and was admitted. The patient had a history of gastric malignant lymphoma at

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Received for publication December 21, 2012; Accepted for publication March 27, 2013
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57 years of age that was treated with gastrectomy and chemotherapy, and he remained in good condition thereafter. There was no particular family history of neurological diseases. A general physical examination revealed no abnormalities, with the exception of jaundice and anemic conjunctiva. The patient’s body weight was 45 kg and his height was 156 cm. A laboratory examination revealed a reduced hemoglobin level (3.6 g/dL; normal value, 13.5-18.0 g/dL) with a slightly increased mean corpuscular volume (111.8 fl; normal value, 84.0-104.0 fl). The reticulocyte count was increased (17.9%; normal value, 0.5%-1.5%). The level of lactate dehydrogenase was elevated (540 IU/L; normal value, 431-180 IU/L). The serum haptoglobin level was less than 10 mg/dL. Both direct and indirect Coombs tests were positive. Moreover, the patient demonstrated a negative result for antiplatelet antibodies and a normal platelet count (209,000/mm³; normal value, 130,000-370,000/mm³). The levels of serum cobalamin and folate were not reduced.

Based on these results, we diagnosed the patient with AIHA. On thoracoabdominal computed tomography (CT), mild mediastinal lymphadenopathy was observed; however, the level of soluble interleukin-2 receptor was not elevated (431 U/mL; normal value 145-519 U/mL). The oral administration of prednisolone (0.5 mg/kg/day) with supplementation of red cell concentrates was initiated. Although the dose of prednisolone was increased to 1.0 mg/kg/day 14 days later, both direct and indirect Coombs tests were still positive 43 days after the initiation of treatment. The patient underwent splenectomy as an additional treatment for AIHA. The hematological abnormalities improved after surgery, and the dose of prednisolone was tapered.

At approximately the same time as the surgery, the patient noticed numbness in the distal portions of all four limbs. He became aware of weakness in the extremities and experienced difficulty climbing stairs two weeks after the surgery. He was referred to the neurological department one month after the surgery and was administered 0.2 mg/kg/day of prednisolone. Nerve conduction studies were performed as previously described (10, 11). The tests revealed a prolongation of distal latencies, an increased distal compound muscle action potential duration (12) and slowing of the sensory nerve conduction velocities in the bilateral median nerves (Table). Neither temporal dispersion nor conduction block of the compound muscle action potentials between the proximal and distal sites of stimulation was observed (13). F-waves were not elicited in the right median or bilateral tibial nerves. Thereafter, the numbness spread throughout both forearms and feet. The weakness in the extremities also became gradually worse, and the patient was unable to walk two months after the surgery. A neurological examination conducted at that time revealed no impairment of consciousness. The cranial nerves were normal. The muscle weakness was moderate in the upper limbs and proximal portions of the lower limbs and severe in the distal portions of the lower limbs. The patient’s light touch and pain sensations were preserved, whereas his vibration and position sensations were moderately impaired in the distal portions of the four extremities. No laterality of motor or sensory signs was noted. The deep tendon reflexes were generally hypoactive, with a greater reduction observed in the lower limbs. The plantar responses were flexor on both sides. Abnormalities in the nerve conduction indices became more evident on re-examination of the nerve conduction studies compared with that observed on the first examination (Table). M-proteins were negative in the serum. A cerebrospinal fluid examination revealed elevated protein levels (107 mg/dL) with a
Based on the diagnosis of CIDP (13), intravenous immunoglobulin (IVIg, 400 mg/kg for five days) was administered. Although the patient’s muscle weakness improved slightly a few days after the initiation of the treatment, the improvement continued for only a short time. High-dose intravenous methylprednisolone (IVMP, 1,000 mg/d for three days) was administered, and prednisolone (1.0 mg/kg/day) was subsequently given orally two weeks after the IVIg. However, the improvement in the patient’s weakness in the extremities was limited and continued for only a few days. The patient became bedridden. Muscle atrophy became evident, particularly in the distal portions of the lower limbs. The level of soluble interleukin-2 receptor and the results of thoracoabdominal CT were reexamined; however, no remarkable findings were revealed. Plasma exchange was initiated four weeks after the initial IVIg treatment. The patient’s weakness gradually improved after the initiation of plasma exchange. However, repetitive plasma exchange was required to maintain the effectiveness of the treatment. As the refractoriness to immunomodulatory treatment and the concomitance of AIHA led us to suspect that the patient had a paraneoplastic syndrome, whole-body fluorodeoxyglucose positron emission tomography/CT (FDG-PET/CT) was performed six weeks after the initial IVIg treatment. Accumulation of FDG was found at the site of the pancreatic body. As the serum CA19-9 level was elevated (183 U/mL; normal, <37 U/mL) at that time, endoscopic ultrasound-guided fine-needle aspiration of the lesion was performed, which revealed adenocarcinoma. Screening for onconeural antibodies, including anti-Hu, anti-Ri, ANNA-3, anti-Yo, anti-PCA-2, anti-PCA-Tr, anti-CV2, anti-amphiphysin, anti-striatal, anti-P/Q type calcium channel, anti-N-type calcium channel and anti-ganglionic acetylcholine receptor antibodies, was performed; however, the results obtained were all negative.

The dose of prednisolone was tapered and eventually discontinued three months later. During this period, plasma exchange was required every week to prevent exacerbation of the muscle weakness. Following the cessation of the prednisolone administration, distal pancreactectomy was performed. The muscle weakness was moderate in the upper limbs and severe in the lower limbs before surgery and gradually improved after surgery, despite the cessation of plasma exchange. No immunomodulatory treatment was required and the patient was able to walk without assistance five months after the surgery. However, an increase in the serum CA19-9 level was observed two months after the surgery. Tumor recurrence became evident on abdominal CT, and the patient was unable to receive oral foods five months after the surgery. Nevertheless, no deterioration of the neuropathic symptoms was observed. Improvement in the occurrence of F-waves was observed in the bilateral median nerves at that time (Table). Although parenteral nutrition was administered, the patient died seven months after the surgery due to a rapidly developing high fever and respiratory insufficiency.

**Discussion**

Previous reports suggest that both AIHA and CIDP may occur in paraneoplastic settings (2, 4, 9). Although the classical feature of paraneoplastic neuropathy is subacute sensory neuronopathy, the condition may present with characteristics of Guillain-Barré syndrome, CIDP, brachial plexopathy, vasculitic neuropathy, autoimmune autonomic ganglionopathy and chronic gastrointestinal pseudo-obstruction (4, 8). Typical CIDP is a demyelinating disorder defined as chronically progressive, stepwise or recurrent neuropathy manifesting as symmetrically proximal and distal weakness and sensory dysfunction in all extremities developing over at least two months (13). The characteristics of the electrophysiological data in our patient were prolongation of distal latencies, an increased distal compound muscle action potential duration, slowing of the sensory nerve conduction velocity and a reduction in F-wave occurrence from the early phase of neuropathy. These findings were compatible with the electrodiagnostic criteria for CIDP (13), suggesting that the demyelinating lesions were primarily located in the nerve roots and the distal portions of the nerves. Preferential involvement of the distal portions of nerve segments is a characteristic feature of anti-myelin-associated glycoprotein neuropathy (14). Although muscle weakness is often observed in the distal portion of the lower limbs in patients with anti-myelin-associated glycoprotein neuropathy, it rarely overshadows the sensory features and gait disturbance that are usually dependent on sensory ataxia (15). On the other hand, muscle weakness, rather than sensory impairment, was the primary feature in our case. Paraneoplastic neuropathy with anti-CV2/CRMP-5 antibodies can develop into demyelinating neuropathy with slow progression (16). However, findings of CIDP without anti-CV2/CRMP-5 antibodies have also been reported in association with solid tumors (17-20).

An impediment to considering the disease in this patient to be paraneoplastic syndrome was the stability of the hematological and neuropathic deficits in spite of possible tumor recurrence, as suggested by the increase in the serum CA19-9 level. Regarding paraneoplastic neurological syndrome, it has been suggested that the immune response is independent of the original tumor trigger (7).

A few reports have described patients with peripheral neuropathy concomitant with AIHA or Evan’s syndrome, which is a combination of AIHA and immune-mediated thrombocytopenia (21-26). Patients with features of CIDP have also been reported (23, 26). However, these previous reports did not describe the association between the tumor and the disease setting.

In our patient, AIHA was the initial manifestation, and the features of CIDP followed the splenectomy performed to treat the AIHA. Intensive investigations, including FDG-PET/CT, performed in parallel with the administration of immunomodulatory treatment for CIDP revealed pancreatic...
cancer. Before the patient underwent resection of the pancreatic cancer, immunomodulatory treatment for neuropathy was only partially effective, and the disease progressed shortly after the treatment was administered. After the surgery, no immunomodulatory treatment was needed and the patient’s neuropathy gradually improved. Taking these observations into account, the CIDP and AIHA observed in this patient can be considered to constitute paraneoplastic syndrome.

Inflammatory mechanisms induced after surgery to treat AIHA, which have been reported to comprise postsurgical inflammatory neuropathy, are another possible explanation for the manifestation of CIDP in our patient (27). However, in a previous large-scale study of postsurgical inflammatory neuropathy, most cases were characterized by focal or multifocal neuropathy caused by microvasculitis in the epineurium, and the patients exhibited favorable responses to immunomodulatory treatment (27). In contrast, our patient demonstrated symmetric polyneuropathy and refractoriness to immunomodulatory treatment.

It has been reported that paraneoplastic neuropathy can occur as a form of recurrence of paraneoplastic syndrome, even though the first paraneoplastic manifestation is different from neuropathy (7). In addition, various types of paraneoplastic neurological syndromes may be observed concomitantly with paraneoplastic neuropathy (4). Similarly, the details of this case suggest that paraneoplastic syndrome of various organs can be observed in a single patient, either at different time points or simultaneously.

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

Acknowledgement

This work was supported by grants from the Ministry of Health, Labour and Welfare and the Ministry of Education, Culture, Sports, Science and Technology of Japan and the Kimi Imai Memorial Foundation for research of Incurable Neuromuscular Diseases.

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