—Case Reports—

A Case of Paraneoplastic Neurological Syndrome Associated with Breast Cancer Detected while Searching for the Cause of Involuntary Movement

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Our case involved a 66-year-old woman who noticed progressive asymmetric involuntary movement, difficulty speaking, and difficulty swallowing. The patient fractured her femur due to a lower extremity involuntary movement while walking. During the course of her treatment for the fracture, her neurological symptoms worsened. Approximately 2 months after becoming aware of her symptoms, she visited our clinic for evaluation of difficulty with unassisted walking and weight loss due to dysphagia. To identify the cause of her neurological symptoms, hematological examination, brain magnetic resonance imaging, single-photon emission computed tomography for cerebral blood flow, electroencephalography, and a somatosensory evoked potential test were conducted. Although the cause of her neurological symptoms could not be determined, computed tomography revealed the presence of breast cancer, which led us to suspect paraneoplastic neurological syndrome (PNS). After breast cancer treatment, her neurological symptoms improved simultaneously. Therefore, the patient was retrospectively diagnosed with PNS. We report a case of PNS whose neurological symptoms followed a subacute course and were relieved after breast cancer treatment. (J Nippon Med Sch 2023; 90: 470–473)

Key words: breast cancer, paraneoplastic neurological syndrome, malignant tumor

Introduction

Paraneoplastic neurological syndrome (PNS), first proposed by Brouwer in 1919, involves various neurological disorders caused by an immunological mechanism associated with malignant tumors[1–3]. PNS has generally been considered to have a subacute progression of neurological symptoms, responds poorly to immunotherapy, and has a poor prognosis[4]. However, the establishment of early diagnosis methods and advances in the treatment of malignant tumors has opened up the possibility for improved outcomes[5].

We herein report a case of PNS in a patient with subacute progression of involuntary movements.

(In this report, "involuntary movements" is used to refer to involuntary movements as a general term, and "involuntary movement" is used to refer to involuntary movements as a symptom.)

Case Report

A 66-year-old woman who noticed trembling in her left hand, difficulty speaking, and difficulty swallowing, which had begun several months before presentation. Brain magnetic resonance imaging revealed no specific findings, and otolaryngological examination showed no abnormalities. Later, involuntary movement in her left upper limb worsened along with the appearance of involuntary movement in her left lower limb, which led to femur fracture; therefore, surgical treatment was performed. After discharge, she visited a local medical facility with the complaint of worsening neurological symp-

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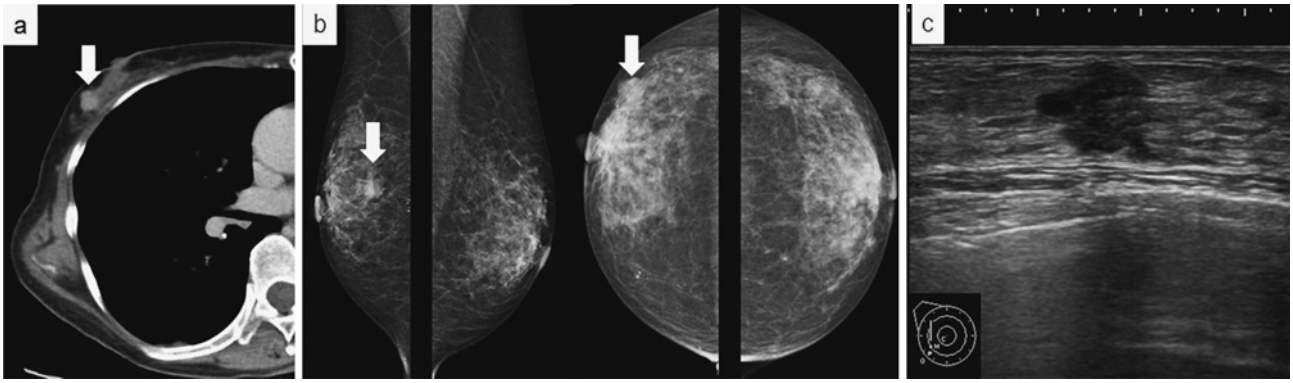

Fig. 1
a. Contrast-enhanced chest computed tomography showing an enhanced mass in the right breast.
b. Mammography showing a high-density mass with rough edges in the right breast.
c. Breast ultrasonography showing a hypoechoic mass with a rough margin.

toms and weight loss.

Rhythmic and jerky uncontrollable movement over 10 Hz were observed in her left upper and lower limbs during movement, which disappeared after approximately 1 min. During intentional movement, involuntary movement appeared rhythmic and coarse approximately 3-5 Hz in frequency, and continued as previously described. She had no medical history, no drinking habits, and never smoked.

Based on the results of her neurological examinations, the 1st-8th and 11th cranial nerves were normal. Dysarthria and dysphagia were observed due to abnormalities in the 9th and 10th nerves. Her speech was slurred, and she had mild dysphagia but normal swallowing reflex. Tongue protrusion examination revealed displacement of her tongue to the right due to the 12th nerve abnormality. Examination of motor and sensory nerves showed no abnormalities. The Babinski reflex of her left foot was weak. Her left biceps, left triceps, left radial muscles of the forearm, and left patellar tendons showed enhancement.

Intentional involuntary movement was observed during the left finger-to-nose test, and poor results were obtained for the left heel-to-shin test. No signs of meningeal irritation were detected. Autonomic nerve function also appeared normal.

Electroencephalogram examination confirmed no abnormalities. An enormous cortical potential of the left upper limb component was observed on the somatosensory evoked potential examination. Single-photon emission computed tomography showed no specific disease. However, systemic computed tomography detected a lump in her right breast (**Fig. 1a**). The tumor with a diameter of 2 cm was palpable in the upper outer quadrant of the right breast. There was no swelling of the bilateral axilla lymph nodes. Mammography indicated a high-density mass with rough edges in the upper outer quadrant of the right breast (**Fig. 1b**). Ultrasonography showed that the breast tumor was a hypoechoic mass, 14 mm in size with a rough margin (**Fig. 1c**). Core needle biopsy was performed for pathological examination, which revealed invasive ductal carcinoma cells.

Given that no significant findings were obtained during the examinations performed to determine the cause of the involuntary movement, PNS associated with breast cancer was suspected. However, laboratory antibody test results for PNS were negative (AMPH, CV2, PNMA2.Ri, Yo, Hu, recoverin, SOX1, titin, zic4, GAD65, and Tr). Moreover, malignant cells were not detected in cerebrospinal fluid. Hence, we could not determine whether these neurological abnormalities were caused by PNS. Other hematological examinations also revealed insignificant abnormalities.

Contrast-enhanced chest computed tomography showed an enhanced mass in the right breast without metastasis.

The patient was thereafter diagnosed with stage I (T1N0M0) breast cancer, for which she underwent right breast mastectomy and sentinel lymph node biopsy. At postoperative day 5, her dysarthria had improved markedly, whereas the involuntary movement of her left upper limb became mild, although still present. No change was observed in the ataxia of the left lower limb.

Postoperatively, the patient was pathologically diagnosed with stage I (T1bN0M0) invasive ductal carcinoma, 10 × 9 mm in size, positive for fat invasion, nuclear grade II, negative for lymphatic vessels infiltration, negative for vessel infiltration, negative for lymph node me-

tastasis, positive for estrogen receptor (90%), weakly positive for progesterone receptors (8%-10%), negative for human epidermal growth factor receptor type 2, and 10%-15% (normal) Ki-67 labeling index (i.e., a cell proliferation marker). Tamoxifen 20 mg/day was prescribed as adjuvant endocrine therapy.

At 3 months after surgery, ataxia had greatly improved in the left upper limb and mildly improved in the left lower limb. Improvement in her neurological symptoms was consistent with a diagnosis of PNS caused by breast cancer. At 6 months after surgery, dysarthria and ataxia of the upper and lower left limb had further ameliorated. Therefore, we diagnosed her with PNS retrospectively. Most symptoms improved after surgery, and neurological symptoms and breast cancer have not recurred as of this writing, 2 years postoperatively.

Discussion

PNS involves various neurological disorders caused by immunological mechanisms associated with malignant tumors[1]. PNS associated with cerebellar ataxia is called paraneoplastic cerebellar degeneration (PCD)[2]. The most common tumor associated with PCD is small cell lung cancer, followed by breast cancer, uterine cancer, ovarian cancer, and malignant lymphoma[6,7]. In line with this, Graus proposed typical diagnostic criteria[4] that define PNS and possible PNS according to symptoms, antineutral antibodies, and presence of tumors.

Despite the absence of precise statistical data, PNS has been estimated to account for 0.01%-1% of malignant tumor cases[9]. Symptoms often progress subacutely, and neurological symptoms often precede discovery of a tumor. PCD is characterized pathologically by widespread loss of cerebellar Purkinje cells[10,11]. One study reported the appearance of antibodies reactive to cerebellar Purkinje cells in sera of patients with PCD associated with ovarian cancer[12].

Anti-Yo antibodies and anti-Ri antibodies are associated with PNS, with anti-Yo antibodies appearing most frequently in approximately 38% of PCD cases associated with breast and ovarian cancers. According to an autopsy case, CD8-positive T cells were reported[13] to infiltrate the dentate nucleus of the cerebellum early during disease progression, suggesting the involvement of cellular immunity targeting the cerebellum, in addition to fluid factors.

In general, PNS, including PCD, responds poorly to treatment. Given the infrequency of PNS, no treatment guidelines have yet been established. Early treatment (surgery and chemotherapy) of the primary malignancy is important for the stabilization and improvement of symptoms[14]. Although studies have reported on additional therapies, such as steroid pulse therapy, high-dose immunoglobulin therapy[15,16], rituximab (an anti-CD20 antibody)[17], plasma exchange therapy[17], and immunosorbent therapy[18], their therapeutic efficacy has been inconsistent.

In our patient, breast cancer was identified while searching for the cause of subacute progression of ataxic symptoms. Enlarged cortical components of somatosensory evoked potentials (giant SEPs) recorded in her left upper limb identified her involuntary movement as myoclonus. The focus of this was suspected to be cerebral cortical loop circuits originating in the cerebellar dentate nucleus or pyramidal tract in consideration of following cerebellar ataxia, dysarthria and hyperflexia in her extremities. Previous studies reported that PNS was mostly bilateral; however, cerebellar ataxia was asymmetric in our patient. We found no other reports of asymmetric symptoms in a search of the literature. Symptoms were predominantly left-sided, her symptoms were bilateral, although there were left-right differences, and imaging findings showed no left-right differences, possibly due to a left-right difference in the degree of damage to the dentate nucleus of the cerebellum. We therefore assumed that some paraneoplastic antibodies damaged a limited area of the cerebellar dentate nucleus.

Although no examination findings suggested PNS and only findings suggesting breast cancer were obtained, a clinical diagnosis was made based on the marked improvement of neurological symptoms after cancer treatment.

In general, anti-Yo antibody-positive PNS has a poor progress[4]. In this case, she has cerebella ataxia but was negative for anti-Yo antibodies. In addition, we were able to detect and treat breast cancer at an early stage and her neurological symptoms have not recurred. Thus, her PNS prognosis may be better than general PNS patients.

Conclusion

We herein report a case of PNS diagnosed retrospectively after treatment of breast cancer that was detected while searching for the cause of the patient's involuntary movement. In patients with progressive neurological symptoms of unknown cause, searching for malignancies is highly recommended.

Conflict of Interest: None declared.

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