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Development of Mixed Symptoms of Chemotherapy-Induced Peripheral Neuropathy and Meningeal Carcinomatosis in a Patient With Recurrent Breast Cancer: A Case Report

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Background: Patients with breast cancer can have a prolonged survival due to the advances in treatment; however, they are more likely to go to a pain clinic for the side effects and pain associated with treatment. The patient provided HIPAA compliant consent for the inclusion of their clinical information in this report.

Case Report: A 32-year-old woman with breast cancer had brain metastases during treatment for relapse and received multiple stereotactic radiotherapies. She visited our pain clinic on foot with a complaint of numbness in her fingertips, which was probably due to chemotherapy-induced peripheral neuropathy (CIPN). Moreover, transient neurological symptoms were observed in bilateral arms and low back. Two weeks after the initial presentation, tumors in the cauda equina and spinal cord caused lower and upper-limb pain and paralysis.

Conclusion: When patients with breast cancer undergoing relapse treatment present with neurological symptoms, the cause should be actively investigated.

Key words: Chemotherapy-induced peripheral neuropathy, recurrent breast cancer, meningeal carcinomatosis, supportive care

BACKGROUND

Advances in treatment methods have allowed for the long-term survival of patients with breast cancer, even those who experience recurrence (1,2). Therefore, detailed supportive care is required to ensure that patients' ability to perform activities of daily living as well as their quality of life does not diminish owing to adverse events caused by treatment or to symptoms that develop as a result of recurrence or metastasis. Breast cancer drug therapy frequently uses drugs that typically cause peripheral neuropathy (PN), with chemotherapy-induced PN (CIPN) being a widely known adverse reaction (3,4). In contrast, more patients with recurrent breast cancer who have been treated for a long period are presenting with central nervous system metastases (5).

CASE REPORT

The patient provided HIPAA compliant informed consent for the inclusion of their clinical information in this report.

A 32-year-old woman was found to have a mass on her left breast and was referred to the breast surgery department of our hospital by a doctor from a nearby facility in 20XX-4 year. Upon examination, we detected an invasive ductal carcinoma that was estrogen receptor-negative, progesterone receptor-negative,

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and human epidermal growth factor receptor 2 (HER2)-positive, with an MIB-1 index of 60%. We consequently diagnosed the patient with stage IIA (T3N0M0) breast cancer. She underwent partial mastectomy with sentinel lymph node biopsy after 8 cycles of trastuzumab, docetaxel, and carboplatin therapy as primary systemic chemotherapy. Irradiation (50 Gy in 25 fractions) was then performed, after which follow-up ensued.

She had a local recurrence in 20XX-2 and underwent partial mastectomy with sentinel lymph node biopsy. She received epirubicin and cyclophosphamide therapy and nab-paclitaxel therapy as post-recurrence chemotherapy.

Tunnel vision narrowing and visual field abnormalities occurred in 20XX-1 year, but they improved within a few hours. She underwent magnetic resonance imaging (MRI) on suspicion of brain metastases, and 3 metastatic brain lesions up to 1.5 cm in diameter were detected in her bilateral temporal lobes. Positron emission tomography revealed a new metastatic lesion in the left lung field. Thereafter, the patient received stereotactic radiotherapy at another hospital and started taking oral fluorouracil preparations. In Y month 20XX, stereotactic radiotherapy was performed on 9 locations because of multiple new lesions in the brain.

The patient's regimen was switched to eribulin. Approximately 3 days after eribulin therapy started, the patient developed a strong numbness in the fingers (Eastern Cooperative Oncology Group Common Terminology Criteria for Adverse Events grade 2). In the same year, multiple new lesions in the brain were confirmed again, prompting stereotactic radiotherapy on eight locations. In the following month, on the eighth cycle of eribulin administration, the patient was referred to a pain clinic for the purpose of alleviating the numbness in her fingers and toes.

On her first visit, the patient complained of numbness in her fingers and toes, occasional dysesthesia in both the upper limbs and transient low back pain. Examination revealed grade 1 numbness and hypoesthesia in the fingers and toes, normal sensation of the upper and lower limbs, and a manual muscle test (MMT) score of 5/5. Based on these findings, it was determined that the symptoms had a typical glove-and-stocking pattern and that the patient's finger numbness was due to CIPN. In addition, the possibility that her previous treatment for multiple brain metastatic lesions caused the transient spontaneous pain in her upper limbs and low back was considered.

Two weeks after the patient's first visit to our department, she exhibited a gradual increase in significant right lower limb weakness and numbness in both lower limbs. X-ray examinations did not show deformities in the cervical and lumbar vertebrae, and plain brain computed tomography was not able to identify any factors that could have caused the symptoms. As for neurological findings, lower limb sensation was dull on the right, the MMT score was 4/5 for both sides, and bilateral tendon reflexes were decreased. On the day after her admission, the pain that she had in both lower limbs suddenly worsened. Loxoprofen (180 mg/day) was administered for lower limb pain, and tramadol (100 mg/day) was further added because the pain was not relieved. When the pain became severe, acetaminophen (400 mg/dose) was administered. MRI confirmed a tumor of approximately 2 cm in the cauda equina at the L2–3 level (Fig. 1). The tumor was presumed to be a metastatic tumor based on her medical history.

The patient's MMT score for the lower extremities on both sides worsened to 2/5, and she developed bladder and rectal disorders as well. Radiotherapy on the same site was immediately started; however, pain in both shoulders and movement disorder in the upper limbs simultaneously occurred. MRI of the cervical cord revealed an intramedullary cervical cord tumor from C7 through T2 (Fig. 2).

Steroid administration (8 mg/d) was started on the fifth day after irradiation to the cauda equina began, and radiotherapy to the cervical spinal cord (20 Gy in 5 fractions) was continued. Regarding the patient's movement disorder in the upper limbs, her MMT score increased to ~4, but she had difficulty recovering her lower limb muscle strength. Thereafter, her general condition was stable without any problems with her level of consciousness, and she was discharged home. However, approximately 1 month later, she was readmitted with severe neck pain and headache, and MRI detected a cervical cord tumor at another site and numerous brain metastatic lesions (Fig. 3).

Additional irradiation to the cervical cord (20 Gy in 5 fractions) and whole brain irradiation (30 Gy in 10 fractions) were performed. The patient was scheduled to be discharged from the hospital, but her consciousness became suddenly impaired, probably due to the exacerbation of brain metastasis. She died 5 months after the onset of her limb symptoms.

DISCUSSION

The expected long-term survival of patients with breast cancer has increased owing to advances in mul-

tidisciplinary treatment methods, such as drug therapy, surgery, and radiotherapy (1,2). Therefore, symptom control for adverse events is the key to continued treatment. On the other hand, this very long-term survival of patients, even those with recurrent or metastatic breast cancer, accounts for the increasing prevalence of meningeal carcinomatosis, which was not previously seen often (6,7).

Breast cancer drug therapy is selected on the basis of the cancer subtype, depending on the therapeutic effect predictors and prognostic factors. One of the adverse events of drug therapy is CIPN. In recent years, there has been an increase in the number of patients visiting pain clinics.

Chemotherapy for breast cancer frequently uses anthracyclines and taxanes, which easily induce PN (3,4). Taxanes, in particular, cause PN by damaging nerve axons in a dose-dependent manner. The glove-and-stocking sensation is a typical distribution pattern of impaired sensory modalities. Axonal disorders often improve over time with discontinuation, but neuropathy can have long-term effects (8); the incidence of CIPN in breast cancer treatment is reported to range substantially from 19% to 85% (9). Eribulin, which is recently used, also leads to CIPN but less frequently. In the case, the patient continued to use a drug that easily induces PN for 4 years, and the numbness she described at the time of examination was a grade 1 glove-and-stocking type of sensory disorder. For this reason, her symptoms were typical of CIPN.

On the other hand, her hyperesthesia in the upper limbs and low back pain had already disappeared by the time she first visited our department. Therefore, we judged her symptoms as transient and secondary to multiple treatments for brain metastasis. Studies have reported that bone metastases are the most common lesions in breast cancer recurrence and the most common type of metastasis that affects the prognosis of the disease, followed by lung and brain metastases in the range of 2.6% to 16%. The frequency of brain metastasis is low (10,11); however, brain metastatic lesions have been reported to occur in 10% to 16% of all patients with breast cancer during the course of treatment (12), and the prognosis is poor (13-15). In addition, 43% of patients with brain metastasis may develop secondary meningeal carcinomatosis (16), for which cranial nerve symptoms are widely known to be the most frequently occurring initial symptoms (17). Therefore, the possibility that meningeal carcinomatosis had already developed at the time her visual field abnormalities occurred could not be ruled out.

Fig. 1. Sagittal T2-weighted magnetic resonance image of the patient's cervical cord showing an intradural extramedullary mass at the L2–3 level (arrow).

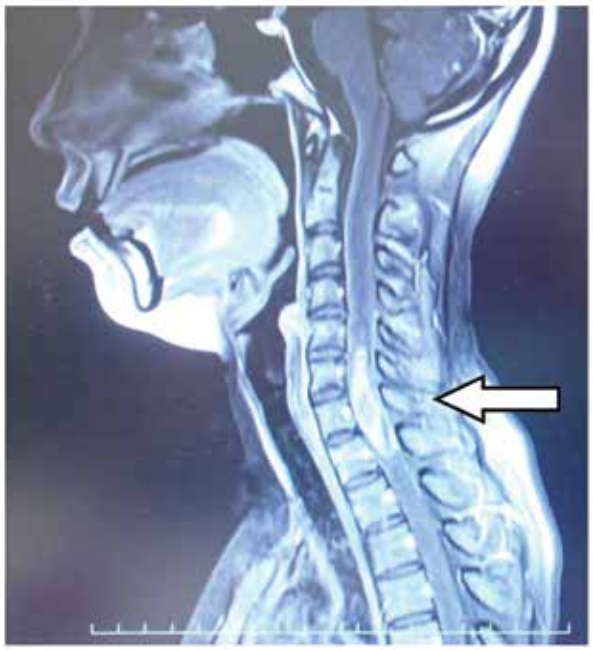

Fig. 2. Sagittal T1-weighted magnetic resonance image of the patient's cervical cord showing an intramedullary mass at the C6–T1 level (arrow).

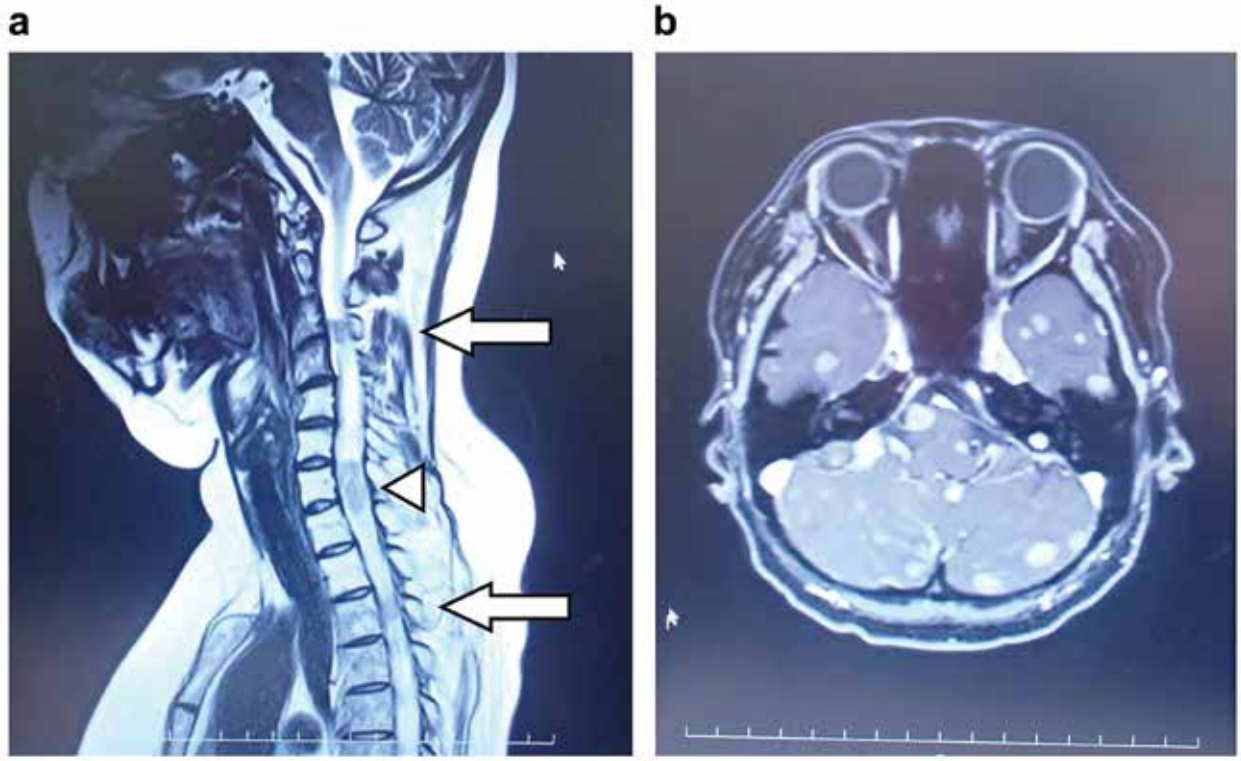

Fig. 3. Sagittal T2-weighted magnetic resonance image of the patient's cervical cord showing an intramedullary mass (arrowhead) and new metastatic lesions (arrows) after radiotherapy (left) and axial T2-weighted magnetic resonance image showing multiple brain metastatic lesions (right).

Meningeal carcinomatosis is defined as intrathecal metastasis of cancer cells and presents with various symptoms, depending on the locus. If it is intracranial, it presents with cranial nerve symptoms, such as intracranial hypertension and hearing or visual impairment; if a mass forms in the spinal cord cavity, nerve compression may occur. According to Mirimanoff and Choi (18), meningeal carcinomatosis, or drop metastasis (19), occurs in 10% of patients with metastasis under the cerebellar tentorium regardless of their cancer type, and it rapidly manifests as lower limb symptoms, such as pain and motor paralysis due to nerve compression of the tumor (20,21). In this case, transient upper limb and lower back pain are likely to indicate the manifestation of meningeal carcinomatosis. Diverse cancer metastasis to the central nervous system is believed to be a result of the inability of most therapeutic agents to easily cross the blood-brain barrier (5). Recent research into breast cancer brain metastasis has shown that the incidence of meningeal carcinomatosis after stereotactic radiotherapy is higher than that of other cancer types (22). Meningeal carcinomatosis is diagnosed by cytological examination with cerebrospinal fluid or gadolinium-based MRI (23). Its treatment requires a multidisciplinary approach, but its prognosis is extremely poor once it develops; furthermore, a standard definitive treatment method has not been established to date. Therefore, careful follow-up for early detection of neurological symptoms as well as further research into new therapies, such as immunotherapy, are needed.

When a patient with breast cancer is referred to a pain clinic, the type of breast cancer and treatment strategy should be carefully checked. Because recurrent breast cancer is a progressive disease, it is necessary to consider the possibility of recurrence at new sites and investigate symptoms other than those already known. In this case, an imaging test should have been performed, even if the initial test did not reveal any abnormalities. Particularly, if metastasis is observed under the cerebellum, the possibility of the symptoms being derived not only from the brain but also from the spinal cord should be considered. If metastases to the

spinal cord were detected early in this case, prophylactic steroids and radiation therapy could have suppressed or delayed the onset of symptoms.

As a pain clinician, the possibility of recurrence at new sites should always be considered when diagnosing new neurological symptoms in patients with recurrent breast cancer with brain metastases.

CONCLUSION

Supportive therapy concurrent with drug therapy for recurrent breast cancer with brain metastasis requires more careful observation of neurological symptoms, taking into account the possibility of meningeal carcinomatosis as well as CIPN.

Author Contributions

KK described and designed this article. Collection of data and drafting of the manuscript were performed by KK, HS, and TS; the manuscript was revised by KK, HS, and TS; and supervision and final approval were given by TS. All authors have read and approved the final manuscript.

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