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A Case of Meningeal Carcinomatosis Occurred With a 17-year Disease-free Interval After Initial Therapies for Breast Cancer

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A case of 79-year old woman diagnosed as metastatic recurrence of breast cancer in a form of meningeal carcinomatosis is reported. The relapse in this patient occurred after a 17-year disease-free period after the treatments by surgery and chemo- and endocrine therapies against the primary and metastases. Neurological symptoms included sequential bilateral hearing loss which occurred abruptly and progressed rapidly in 2-3 days, and transient but repeated facial paralysis and syncope attacks. Diagnosis of meningeal carcinomatosis was based upon the clinical symptoms including nuchal rigidity and such results of laboratory tests and examinations as elevated cerebrospinal fluid（CSF）pressure, lymphocyte-predominant high CSF cell number, positivity of tumor markers, which showed higher titers in CSF than in peripheral blood, and enhanced brain surface image by gadolinium-enhanced MRI examination, but negative for CSF cytology. Chemo-endocrine therapy with capecitabine and tamoxifen in combination with intrathecal administration of methotrexate, cytarabine and dexamethasone against acute clinical deterioration had only temporal effect, but the patient deceased after a very short course by abrupt respiratory arrest. Survival period of breast cancer patients prolonged and is expected to prolong more owing to the improvement of endocrine and chemotherapy. Meningeal carcinomatosis in breast cancer patients is a rare but possible form of metastatic recurrence, and should be taken into consideration as a possible cause of neurological symptoms.

Key words: meningeal carcinomatosis, breast cancer, intrathecal chemotherapy

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INTRODUCTION

Metastasis to meninges is a type of cancer metastasis to central nervous system, and breast cancer is a common primary disease of meningeal carcinomatosis in Europe and America［1-3］. However, it is rare in Japan with only a few case reports［4, 5］. In this report, we present a case of meningeal carcinomatosis occurred in 79-year old woman with 17-year disease free-interval after the initial therapies of breast cancer. The patient was treated with chemo-endocrine therapy including intrathecal chemotherapy, but with limited effects on the recurrence.

CASE REPORT

A 79-year-old woman was referred to our hospital because of complex neurological symptoms. At the age of 62 year-old, she had left mastectomy for her breast cancer, of which histopathological diagnosis was invasive ductal carcinoma, showing estrogen receptor(−), progesterone receptor(+), and HER2(1+). 5 months thereafter, metastases to lung and bone were found, and treated with chemotherapy and endocrine therapy, which resulted in 17-year remission till the present events.

Four months before the recent admission, she developed left hearing loss and felt dizziness. They rapidly progressed during a few days, and that made her unable to walk without a stick. Since then, transient paralysis of facial muscles and unconsciousness attacks occurred repeatedly. She was hospitalized under the diagnosis of suspicious meningitis, because of these symptoms with abnormal cerebrospinal fluid（CSF）findings. It revealed CSF pressure of 400 mmHg, cell count 30/μg（L:N=5:1）, glucose 83 mg/dl, protein 415 mg/dl, and IgG 41.5 mg/dl. Physical examination showed blood pressure of 160/82 mmHg, and pulse rate 84/min with regu-

lar rhythm. Respiratory and cardiac sounds were normal. Conjunctiva was neither anemic nor icteric. Cervical lymph nodes were not palpable. In neurological findings, her consciousness level was II-20 according to Japan Coma Scale (JCS). Left blepharoptosis, right facial palsy and nuchal rigidity were found. Pupils and light reflex were normal. Right ear was completely deaf, and left hearing was also highly disturbed. Her motor, sensory and coordinate systems could not be evaluated in detail because of consciousness disturbance. Pathologic reflexes were absent.

There were no aggravations of anemia, inflammatory reaction, liver function and renal function in the laboratory data on admission. The tumor markers, which had increased at the breast cancer surgery, showed higher titer in CSF, CA 15-3 of 262 U/ml and NCCST439 of 45 U/ml, than in blood, 177 and 30 U/ml, respectively. Cytological examination in CSF was negative. Head plain MR imagings revealed hypertrophy of both auditory nerves (Fig.1a) and right trigeminal nerve (Fig.1b). In Gd-enhanced MRI, signal intensities were increased on the surface of brainstem (Fig.2 a) and bilateral sylvius fissures (Fig.2 b), which coincided with changes in meningeal carcinomatosis.

CLINICAL COURSE

Although malignant cells were not found in the CSF cytology, we could easily suspect recurrence of breast cancer in a form of meningeal carcinomatosis. The possibility of infectious meningitis was ruled out because bacterial culture of CSF was negative. We administered glycerol, Phenobarbital, and piperacillin to prevent secondary infection. Her consciousness was gradually recovered in the first two days after admission, and she became to be able to talk and eat without any convulsions or motor pareses.

On the third day, the level of consciousness worsened to JCS II-20 again with dilation of the pupil and diminished pupillary light reflex. Although malignant cells were still absent in the second examination of CSF, we diagnosed her as having meningeal carcinomatosis due to positive Gd-enhancement around the temporal lobe and the circumference of medulla oblongata in MRI.

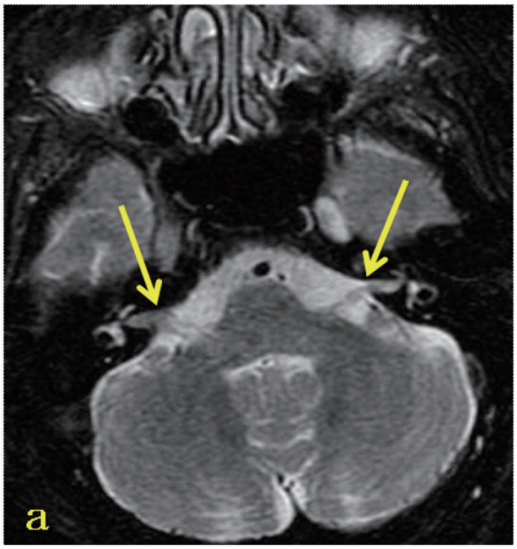
The first intrathecal chemotherapy, cytarabine 40mg, methotrexate 15 mg, and dexamethasone 4 mg, was administered on the eighth day. Her consciousness was moderately improved the following day, but she became drowsy again within two days. Intrathecal chemotherapy was repeated on the 15th and 19th day, but consciousness level was not improved and remained between JCSII-20 and JCSIII-200. However, the CSF data improved slightly with cell count 7/μg (L:N=6:1), protein 291 mg/dl and IgG 33.6 mg/dl.

Daily administration of a combination of drugs for chemo-endocrine therapy, capecitabine 2400 mg/day and tamoxifen citrate 20 mg/day, that had given her a long term remission, was begun from the 20th day of admission. One day after the fourth intrathecal chemotherapy on the 22nd day, blood oozing from oral cavity occurred, and the blood test showed a sudden decrease in the number of WBC from 3490 of 2 days before down to 360/μl. Accordingly, chemo-endocrine drugs were canceled and granulocyte-colony stimulating factor (G-CSF) and blood transfusion were administered, but she passed away by sudden respiratory arrest 2days later.

DISCUSSION

The frequency of meningeal carcinomatosis due to breast cancer is relatively high in Europe and America, and it is said that 1-3.5% of the patients with relapsed breast cancer develop meningeal carcinomatosis [6, 7], and an association between invasive lobular carcinoma and meningeal carcinomatosis is also reported. However, in Japan where invasive lobular carcinoma occurs less frequently, cases of meningeal carcinomatosis due to breast cancer are rarely discovered with only a small number of case reports [4, 5].

It should be noted that symptoms of meningeal carcinomatosis include the following: i) headache, nausea and vomiting due to increased intracranial pressure, ii) convulsions and psychosis, iii) visual impairment, diplopia and hypoacusis due to cranial nerve invasion, iv) somatic pain and sensory disturbance due to myeloradiculopathy, v) nuchal rigidity as meningeal irritation sign, and vi) dysarthria and



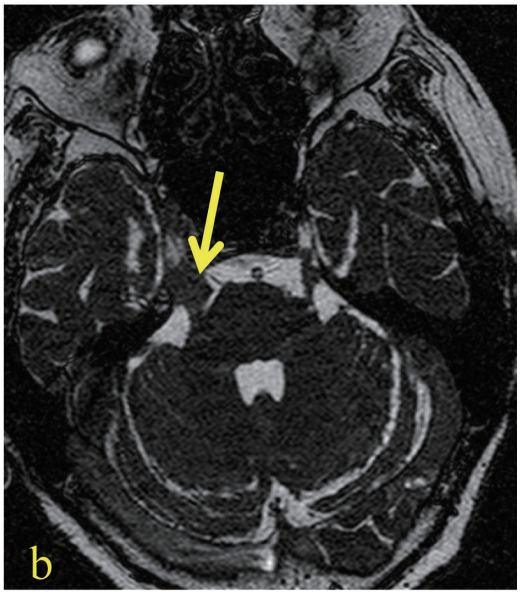
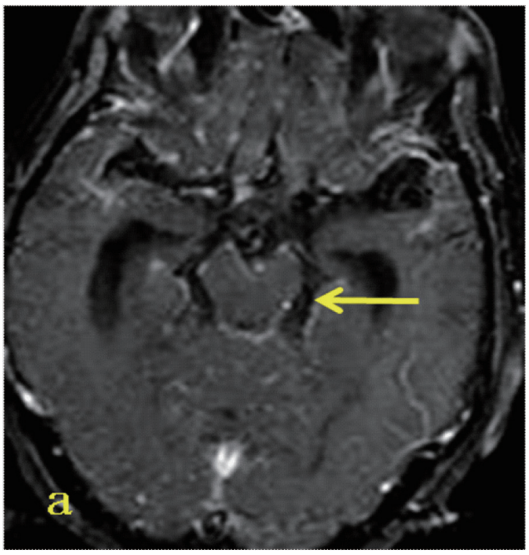


Fig. 1.
Plain MRI scan of the head
a. Swelling of bilateral auditory nerves
b. Swelling of right trigeminal nerve



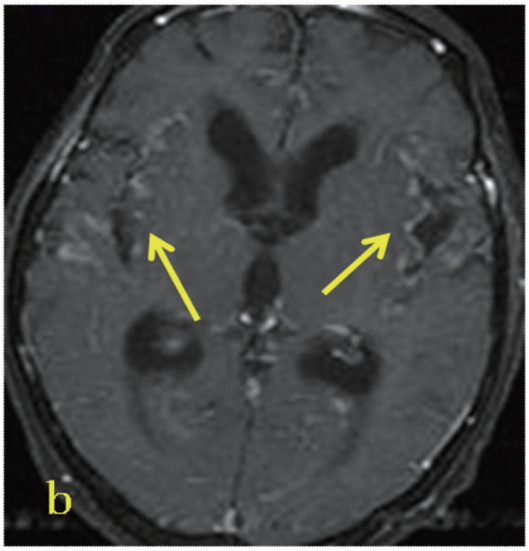


Fig. 2.
Gadolinium enhanced MRI scan of the head.
Enhanced in
a. brainstem circumference
b. bilateral surfaces of Sylvius fissures

gait disturbance. As for imaging diagnosis of meningeal carcinomatosis, Gd-enhanced MRI is useful. Although the definitive diagnosis is made by the proof of malignant cells in CSF, its precise diagnostic rate is reported to be between 50-91%[4, 8], and there are cases where we detect no malignant cells in CSF.

The prognosis of meningeal carcinomatosis is very severe. According to the case reports in Japan, mean survival duration after diagnosis was approximately 80 days [5]. There are no established treatments for meningeal carcinomatosis at present, and so generally performed now is systemic or intrathecal chemotherapy, radiotherapy, or a combination of these [9]. Although standard, systemic chemotherapy has been considered to be poorly effective for metastasis to brain and meninges, because intravenous anti-carcinogenic agents do not pass a blood-

brain barrier. However, there is a report showing its utility, in which case the blood-brain barrier was destroyed due to metastasis to brain and meninges [10]. Intrathecal dosement of methotrexate and capecitabine, which has been used to prevent leukemia spread to central nervous system, is also reported to prolong the survival period for patients with meningeal carcinomatosis of breast cancer[11].

The primary lesion in the case reported here was an invasive ductal carcinoma. Although the patient had been in remission with postoperative chemotherapy and endocrine therapy for invasive breast cancer, she developed meningeal carcinomatosis 17 years after the operation. We diagnosed her illness as meningeal carcinomatosis from neurological symptoms, elevated values of the tumor markers and positive findings in Gd-enhanced MRI, although malignant cell in CSF was negative. She showed a brief improvement of consciousness with intrathecal methotrexate and capecitabine, but the progression of the symptoms could not be stopped, and she died approximately three months after the onset of neurological symptoms.

With improvement of prognosis with chemotherapy, endocrine therapy and molecular target therapy for recurrent and advanced breast carcinoma, it is expected that cases of meningeal carcinomatosis will increase in Japan also. As early detection and treatment can prolong the survival period for patients with meningeal carcinomatosis, we should take meningeal carcinomatosis into consideration and perform further examination, including Gd-enhanced MRI, when neurologic symptoms appear in patients with a history of breast cancer.

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