CASE REPORT

A case of premenopausal breast cancer with symptomatic cerebellar metastasis successfully treated by systemic endocrine therapy alone: relationship to biological features

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Abstract We report a case of premenopausal breast cancer with symptomatic cerebellar metastasis successfully treated by systemic endocrine therapy alone. The patient developed dysarthria, headache, lightheadedness and became difficult to write gradually. The cerebellar tumor was detected by computed tomography (CT) and was suspected hemangioma or hemangioblastoma. The tumor was resected and histologically diagnosed as poorly differentiated adenocarcinoma or squamous cell carcinoma. A whole body CT scan revealed a right thyroid tumor and left breast tumor. Core needle biopsy of the breast tumor histologically diagnosed the tumor as estrogen receptor positive, progesterone receptor positive, human epidermal growth factor receptor-2 negative, and Ki-67 labeling index 5%. After these examinations, histologically, the resected cerebellar tumor showed the same subtype as the breast tumor, so the final diagnosis was metastatic breast cancer with cerebellar metastasis. The patient subsequently received radiotherapy with the CyberKnife and endocrine therapy without resection of the thyroid tumor. Her medical condition has maintained a good response and stable disease for 7.5 years after the start of treatment. Analysis of four *ESR1* mutations showed no mutations in the cerebellar metastatic lesion and breast cancer tissue. Our findings show that these tumors have high hormone responsiveness.

Keywords Breast cancer · Brain metastasis · *ESR1*

Introduction

Brain metastases in breast cancer are frequently occurred in accordance with the progress of the metastatic disease. Although the prognosis of brain metastasis in breast cancer has been improved by multimodal therapies, such as surgery, radiotherapy, endocrine therapy, chemotherapy, and molecular-targeted therapies, it is difficult to achieve long-term survival >5 years [1, 2].

Recently, a mutation of the ligand-binding domain of *ESR1*, the gene for ER α , has been detected in 20% of ER-positive metastatic breast cancer. Tumors with such *ESR1* mutations tend to be resistant to endocrine therapy. We examined *ESR1* mutation in metastatic brain tumor and breast cancer tissue by droplet digital PCR, which was already developed in our laboratory [3]. We also discuss the significance of *ESR1* mutations.

Case report

A 48-year-old premenopausal woman developed dysarthria, headache, lightheadedness and became difficult to write gradually. Karnofsky Performance Score (KPS) was 80. The cerebellar tumor was detected by computed tomography (CT) and suspected as hemangioma or hemangioblastoma. Head magnetic resonance imaging (MRI) showed a well-circumscribed mass, 41 × 46 × 31 mm, in her right cerebellar hemisphere. High signal intensity was seen on T2-weighted images and FLAIR (fluid-attenuated inversion recovery). Low signal intensity and the contrast effect of only border were seen on T2-weighted images (Fig. 1).

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Fig. 1 MRI findings of the intracranial tumor before treatment. Head MRI showed a well-circumscribed mass of $41 \times 46 \times 31$ mm in the right cerebellar hemisphere. High signal intensity was seen on T2-

weighted images and FLAIR (a, b). Low signal intensity and the contrast effect of only marginal were seen on T2-weighted images (c)

The resection of cerebellar tumor was performed by neurosurgeons. The tumor was histologically diagnosed as poorly differentiated adenocarcinoma or squamous cell carcinoma. A whole body CT scan revealed a low-absorption lesion of 10 mm in the right thyroid, an enhancement lesion of 14 mm in the left breast, and several small nodules of ≤ 5 mm in the lungs. There were no other thoracic, abdominal and pelvic abnormalities (Fig. 2). Mammography showed that the tumor had a spiculated margin in the left upper/outer region. Ultrasonography showed an irregular, indistinct, low-echoic mass of $34.8 \times 32.4 \times 20.5$ mm in the upper/outer area of the left breast. Ultrasonography showed a low-echoic tumor in the right thyroid of 12 mm but showed no lymph node metastasis. Serum tumor marker carcinoembryonic antigen and carbohydrate antigen 15–3 had normal values. The patient had no anamnesis, allergy or family history of cancer. Core needle biopsy histologically defined the breast tumor as nuclear grade 2 (atypia score 2, mitotic counts score 2); estrogen receptor (ER) positive (90% of all cancer cells); progesterone receptor (PgR) positive (90%); human

epidermal growth factor receptor-2 (HER2) negative: score 2+ (FISH-); and Ki-67 labeling index 5% (Fig. 3). After these examinations, the resected cerebellar tumor was ER positive (80%), PgR positive (70%), and HER2 negative (score 1+) (Fig. 4), so the final diagnosis was metastatic breast cancer with cerebellar metastasis, classified as T2N0M1, stage IV.

Combination of oral steroids and stereotactic radiation therapy to the resected area were performed after brain surgery without resection of the breast cancer. As systemic therapy, luteinizing hormone releasing hormone (LHRH) agonist, every 4 weeks by subcutaneous injection, and tamoxifen was started after resection of metastatic brain cancer. The left breast tumor was shrunk by around 50% and she maintained a partial response during the treatment. Although variable tumor cells were found in some of the tissues by core needle biopsy at 2 years after initiation of treatment, most of the tissues showed necrosis and hyalinization. We evaluated that the therapeutic effect was good pathologic therapeutic effect of Grade2a equivalent.

Fig. 2 CT findings of breast and thyroid cancer. Contrast-enhanced CT revealed an enhancement lesion of 14 mm in the left breast (a), and a low-absorption lesion of 10 mm in the right thyroid (b). No other thoracic, abdominal and pelvic abnormalities were recognized

Fig. 3 Pathological findings of breast cancer by core needle biopsy before treatment. Left breast cancer was defined as papillotubular carcinoma, nuclear grade 2 (atypia score 2, mitotic counts score 2) (a, b), ER positive: 90% (c), PR positive: 90% (d), HER2-negative: 2+ (FISH-) (e)

Fig. 4 Pathological findings of resected cerebellar tumor. Resected cerebellar tumor was defined as ER positive: 80% (a), PR positive: 70% (b), HER2-negative: 1+ (c)

At 4 years after initiation of treatment, we changed the endocrine therapy from combination with LHRH agonist to tamoxifen alone because of the patient's age. Furthermore, at 5 years after first diagnosis, no hot spot including thyroid tumor was detected by positron emission tomography (PET)–CT. Therefore, partial resection of the left breast was performed. The resected tumor was ER positive (100%), PgR positive (30%), and HER2 negative (score 1+) and shrunk by around 60% during the treatment. Her medical condition has been stable without recurrence for 7.5 years after the start of treatment. KPS improved from 80 to 90.

ER (6 F11, Ventana), PgR (16, Ventana), and HER2 overexpression (CB11, Ventana) were evaluated by immunohistochemistry. All of the tumor tissues from the metastatic cerebellar lesion, primary breast cancer, and breast cancer at 2 and 5 years showed high expression of

ER, negative expression of HER2, and low labeling index of Ki-67 (Table 1). Analysis of four *ESR1* mutations in the ligand-binding domain (Y537N, Y537C, Y537S and D538G) showed that they were absent in the cerebellar metastatic lesion and breast cancer tissue treated by tamoxifen (Table 1). These results showed that the cerebellar metastatic lesion and breast cancer tumors had high hormone responsiveness.

Discussion

Brain metastases are observed in 10–16% of metastatic breast cancer and breast cancer is the second most common cause of brain metastases. [4, 5]. Postoperative surveillance of brain metastases is not common in patients with breast cancer. If there are signs of neurological problems, brain

Table 1 Characteristics of breast cancer and metastatic brain tumor

	Metastatic brain tumor at diagnosis	Beast tumor at diagnosis	Breast tumor after 2 years	Breast tumor after 5 years
Material	Resected mass	Core needle biopsy	Core needle biopsy	Resected mass
ER	80%	90%	90%	100%
PgR	70%	90%	20%	30%
HER2	1+	2+ (FISH-)	1+	1+
Ki67	5%	5%	5%	5%
ESR1 mutation (Y537N, Y537C, Y537S, D538G)	No mutation	n.d.	n.d.	No mutation

n.d. not done

metastases are often discovered by CT and MRI examinations of the head. In our case, the patient consulted a neurosurgeon because of symptoms of dysarthria, headache and lightheadedness. The brain tumor was histologically diagnosed as metastatic breast cancer. The diameter of the primary breast tumor was 3 cm, but the patient did not notice the tumor.

For treatment of metastatic and recurrent breast cancer, if the tumor is thought to be non-life threatening and hormone dependent, ER positive and HER2 negative, endocrine therapy should be recommended as first-line treatment [6, 7]. After resection of the cerebellar tumor and postoperative stereotactic radiotherapy, our patient complained of mild impairment of speech and mobility of the right upper limb, but CT revealed no other distant metastatic lesion. Therefore, we recommended endocrine therapy alone with LHRH agonist and tamoxifen as first-line systemic therapy [8, 9].

The average survival time of breast cancer with brain metastases is about 8.7 months from diagnosis but the average survival time of ER-positive breast cancer is a little longer at ~9.3 months from diagnosis [10]. However, there are reports that average survival time is 1 month without treatment, 6–8 weeks with steroids, and 3–6 months with addition of whole brain irradiation [11, 12]. It is reported that tamoxifen has good transfer to brain metastatic tissue [5]. However, its efficacy has not been confirmed in clinical trials and there are only a few reports of patients responding to treatment [5]. In our case, the primary breast tumor and brain metastases were diagnosed as strongly ER positive and HER2 negative, so reduction of the primary tumor was observed by endocrine therapy with a focus on tamoxifen. At 5 years after initial treatment, PET showed no active lesions except for the original breast cancer, so we removed the primary breast cancer by partial mastectomy without radiation therapy. This resected breast cancer was ER positive (100%), PgR weakly positive (30%) and HER2 negative.

Recently, some somatic mutations in the ligand-binding domain of *ESR1* gene have been reported in around 20% of patients, which are related to resistance to hormone therapy. In our laboratory, analysis of four *ESR1* mutations (Y537 N, Y537C, Y537S and D538G) was developed using a droplet digital PCR method [3]. No mutations were detected in the metastatic cerebellar or breast tumor tissue at 5 years after administration of tamoxifen. This result is consistent with the fact that the wild type *ESR1* has maintained high hormone dependency and good outcome, as our patient condition has been stable with no recurrence and good quality of life for 7 years postoperatively.

Compliance with ethical standards

Conflict of interest Yutaka Yamamoto received lecture fees from Chugai Pharmaceutical Co., Ltd. Hirotaka Iwase received lecture fees and research funding from AstraZeneca and Takeda Co., Ltd. Other authors have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants included in the study.

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