Double primary recurrent human epidermal growth factor receptor 2-positive breast cancer and esophageal cancer that responded well to chemotherapy

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Abstract

Double primary breast and esophageal cancer have been no reported cases in which treatment methods other than surgery were selected because of multiple metastasis or advanced cancer. The patient was a 52-year-old woman who had received left pectoral muscle-preserving mastectomy and axillary lymph node dissection (level 2) 7 years prior, following the diagnosis of left breast cancer. The postoperative diagnosis was pT2 N3a M0 stage IIIC and luminal human epidermal growth factor receptor 2 (HER2) phenotype. After the surgery, six courses of triple chemotherapy with 5-fluorouracil (5-FU), epirubicin, and cyclophosphamide and four courses of docetaxel (DTX) were administered, and letrozole was administered for 5 years. Seven years after the surgery, swelling of her left axillary, supra-, and subclavicular lymph nodes, and sternum osteolysis were observed on computed tomography (CT). Radioisotope uptake was observed in the esophagus on positron emission tomography. An esophageal cancer was observed in the upper thoracic esophagus on esophagogastrosocopy. The patient was administered a local treatment for esophageal cancer and systemic chemotherapy for both cancers. As a primary therapy, double chemotherapy with 5-FU and cisplatin (FP) (two courses) + radiotherapy on the esophagus and left supraclavicular lymph nodes (total target dose of radiotherapy was 60 Gy /30 fractions) was performed with the concomitant use of trastuzumab and zoledronate. Marked shrinkage [complete response (CR)] of the esophageal cancer was observed on esophagogastrosocopy and shrinkage (partial response) of the left axillary and supra- and subclavicular lymph nodes were observed on CT. The secondary treatment included pertuzumab + trastuzumab + DTX. Bilateral pleural effusions were observed in the eighth course; therefore, DTX was withdrawn and the treatment was continued with only the molecularly targeted drugs. Two years have passed since the initiation of treatment. The individual lymph node metastatic foci have disappeared or markedly shrunk (CR) on CT scans and the sternal metastases have remained hard without change. In addition, CR for esophageal cancer has been maintained. We report a case of double primary recurrent HER2-positive breast cancer and esophageal cancer that responded well to radiotherapy and chemotherapy.

Keywords HER2-positive breast cancer · Esophageal cancer · Double primary cancer · Chemoradiation therapy (CRT) · Triple chemotherapy with pertuzumab, trastuzumab, and docetaxel

Introduction

Breast cancer and esophageal cancer often occur in association with cancers of other organs [1–3]. However, there are few cases of double primary breast and esophageal cancers. The Pathological Autopsy Cases in Japan published annually from 2004 to 2013 indicated only nine cases of double primary cancer among 1872 and 3283 autopsy cases of breast and esophageal cancers, respectively. Double primary cancer is observed in 0.27–0.38% of esophageal cancer cases and 0.17–0.48% of breast cancer cases. Thus, double primary cancer of the breast and esophagus is very rare. In addition,

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most cases of double primary cancer are metachronous, and there are few cases in which both cancers were treated simultaneously. Surgery was chosen for all of these cases [4, 5], and there were no cases in which treatment other than surgery was chosen because of multiple metastases or advanced cancer.

The present patient had a double primary luminal-HER2-type breast cancer, which recurred 7 years after surgery, and esophageal cancer. The recurrent breast cancer had non-cur-able factors. We chose chemotherapy for this patient, who

showed a very good treatment effect; therefore, we report this case.

Case report

The patient was a 52-year-old woman who had been diagnosed with left breast cancer and received left mastectomy and axillary lymph node dissection in 2007. She did not have any family history of breast or ovarian cancer. She had breastfed all two of her children and had been premenopausal. There was also no history of oral contraceptive pills or hormone replacement therapy. She did not smoke or drink except for social drinking. The final histopathological diagnosis was a $28 \times 25 \times 16$ mm scirrhous carcinoma of the lymph nodes [level 1, 14/27; level 2, 6/9 (positive/total)], which was f, ly positive, v negative, mild intraductal component, Nuclear Atypia 3, Mitotic Counts 2, Nuclear Grade 3, estrogen receptor (ER)-positive (80%), progesterone receptor (PgR)-positive (60%), human epidermal growth factor receptor 2 (HER2)-positive (3+), and with a MIB-1 index of 32%. The phenotype was luminal-HER2 and the pathological tumor-node-metastasis (pTNM) stage was T2N3aM0 stage IIIC [6] (Figs. 1, 2a–d). A submucosal tumor of the esophagus was indicated by an esophagogastros-cope, and diagnosed as leiomyoma by biopsy. Because administration of trastuzumab was not the first-line treatment for HER2 positive breast cancer in 2007, we selected

Fig. 1 Pathological diagnosis of the primary breast cancer. Cancer cells showing a tubular or cord-like structure, which are invasively growing associated with the fibrous stroma. Papillotubular carcinoma–scirrhous carcinoma **a** HE stain $\times 40$, **b** $\times 100$

Fig. 2 Phenotype of the invasive luminal-HER2 ductal carcinoma. Immunopathologically, this carcinoma was **a** ER-positive (80%), **b** PgR-positive (60%), and **c** HER2-positive (score 3). **d** MIB-1 index: 32%

six courses of 5-FU 500 mg/m², epirubicin 75 mg/m² and cyclophosphamide 500 mg/m² (FEC75) and four courses of docetaxel (DTX, 75 mg/m²) for the postoperative chemotherapy. Postoperative radiotherapy was not administered for unknown reasons. Subsequently, administration of leuporelin acetate was started as an endocrine therapy. Since an ovarian cyst had been pointed out in preoperative CT, the usage of tamoxifen was not selected considering the possibility of exacerbation. However, bilateral ovarian cystomas

increased over the course of 1 year; therefore, bilateral ovariectomy was performed. After this surgery, the leuporelin acetate was switched to letrozole, and the administration of this drug was continued for 5 years. In blood tests performed in 2014, her CA15-3 level rose to 48.5 U/mL (Fig. 3); therefore, a detailed examination was performed. Swellings of the left subclavicular and left cervical paraesophageal lymph nodes as well as sternum osteolysis were detected on computed tomography (CT) (Fig. 4a). Furthermore, fluorine-18 (18F) fluorodeoxyglucose (FDG) positron emission tomography–computed tomography (PET–CT) revealed 18F uptake in the upper thoracic esophagus, sternum, and right femur, as well as in the swollen left axillary and mediastinal lymph nodes (Fig. 4b, c). Subsequent esophagogastroscope revealed an elevated + flat type tumor in the upper thoracic esophagus (Fig. 5a). The submucosal tumor was located closer to the caudal side of the current lesion, and a Lugor non-staining zone was observed on the surface layer, which looked like a flat mucosal type. A high, elevated lesion was found on the mouth side of the submucosal tumor with a broad base, and it was thought that the submucosal tumor was not involved in the diagnosis of the depth of the tumor, and was diagnosed as muscle propria invasion. This case was diagnosed as squamous cell carcinoma by biopsy (histopathological examination) (Fig. 5c). It was HER2-negative (Fig. 5d). The mediastinal lymph nodes were observed near the esophageal cancer; therefore, we considered metastasis

Fig. 3 Trends of tumor markers in CEA, CA15-3. In blood tests performed in 2014, the recurrence was found with elevation of her CA15-3 level. As radiation chemotherapy progressed, CA15-3 gradually normalized and is still maintained

Fig. 4 Pretreatment image findings of the recurrent cancer. Left supra- and subclavicular lymph node metastases, left axillary lymph node metastasis, sternal metastasis, and right femur metastasis are visible. Uptake of 18F is observed in the esophagus by FDG-PET (arrow). **a** Contrast CT showing the left supra- and subclavicular lymph node metastases; **b** FDG-PET–CT showing the sternal metastasis; **c** FDG-PET–CT in which pink indicates the lymph node metastasis; yellow, bone metastasis; and green, suspected esophageal lesion

Fig. 5 Upper thoracic esophageal cancer and lymph node metastasis, biopsy results: well differentiated squamous cancer, HER2-negative. **a** Esophagogastroscope: Lugol staining; **b** Contrast CT; **c** biopsy: HE stain $\times 100$; **d** HER2 stain negative (score 0)

from the esophageal cancer and diagnosed the condition as TNM stage T2N1M0 stage II [7] (Fig. 5b).

In view of the prognosis and quality of life, 5-FU 400 mg/m²/day $\times$ 10 days and cisplatin 40 mg/m² $\times$ 2 (FP) and chemoradiotherapy (CRT) treatment were performed to control the esophageal cancer; in addition, trastuzumab was concomitantly used for its efficacy in HER2-positive breast cancer. The radiotherapy on the esophagus and left supraclavicular lymph nodes (total target dose of radiotherapy was 60 Gy/30 fractions) was performed for local control of the esophageal cancer. The details of the radiotherapy were initial external irradiation to the esophagus and left supraclavicular fossa (40.0 Gy/20 fractions/28 days, 2.0 Gy/day, anterior–posterior opposing portal irradiation) (Fig. 6a) and additional 20 Gy irradiation divided into the esophageal tumor (Fig. 6b) and the left supraclavicular lymph nodes (20.0 Gy/10 fractions/14 days, 2.0 Gy/day, grazing incidence opposing portal irradiation) (Fig. 6c). Since side effects of bone marrow suppression strongly appeared in the anterior–posterior opposing portal irradiation, it was changed to grazing incidence opposing portal irradiation. After the treatment, the lesions were evaluated. Although an elevation was observed by esophagogastroscope, it was a submucosal tumor diagnosed as leiomyoma by biopsy in 2007 and its size and morphology had not changed since 2007. The irregular mucosal lesion in the esophagus had disappeared and malignant findings were not observed in biopsy of the Lugol-voiding lesions. In accordance with the Response Evaluation Criteria in Solid Tumours version 1.1 (RECIST

1.1), this response was considered a complete response (CR). CT revealed that the total of the shorter diameters of three lymph nodes, i.e., one lymph node anterior to the pectoralis minor and two left axillary subclavicular lymph nodes, were decreased by approximately 31.2% from 73.4 (18.3 + 34.3 + 20.8) to 22.9 (7.5 + 15.4 + 0) mm; this response was considered a partial response (PR). Subsequently, a triple combination chemotherapy with pertuzumab 840 mg (after the second time, 420 mg), trastuzumab 8 mg/kg (after the second time, 6 mg/kg), and DTX 75 mg/m² was administered, expecting that this treatment to be effective against HER2-positive breast cancer and that DTX would also be effective for esophageal cancer. At the end of the eighth course, respiratory discomfort appeared, and bilateral pleural effusions (Grade 2 on Common Terminology Criteria for Adverse Event (CTC-AE) ver. 4.0) and atelectasis were observed. The pleural effusion was collected and subjected to cytology, which showed a no malignancy result. When DTX was withdrawn and the treatment was continued with only pertuzumab and trastuzumab, the pleural effusions completely disappeared. Subsequently, CT revealed that the lymph nodes had further shrunk from 22.9 (7.5 + 15.4 + 0) to 5.0 (5.0 + 0.0 + 0.0) mm, achieving a CR. No relapse of the esophageal lesion was observed by esophagogastroscope (Fig. 7a, b).

Zoledronate (a bisphosphonate) has been concomitantly administered to limit bone metastasis since the start of the CRT and the bone conditions have been managed without increase in bone changes or fractures.

Fig. 6 Radiotherapy on the esophagus and left supraclavicular lymph nodes was performed. The radiotherapy total 60 Gy was done in three ways: **a** initial 40 Gy with anterior–posterior opposing portal irradiation to a wide area; additional 20 Gy with grazing incidence opposing portal irradiation divided into **b** the esophageal tumor and **c** the left supraclavicular lymph nodes

Since then, for 14 months until now (2017), no relapses of disease or adverse reactions have been observed and good activities of daily living (ADL) have been maintained.

Discussion

Borst et al. reported that esophageal metastasis of breast cancer was observed in 2 of 2605 cases (0.077%) [8] and a search of Igaku Chuo Zasshi (ICHUSHI) from 1986 to 2016 revealed only 48 cases of such metastasis; thus, esophageal metastasis of breast cancer is relatively rare. In general, studies have reported that esophageal metastasis of breast cancer may be lymphatic metastasis and the swellings of the surrounding mediastinal lymph nodes and lymphatic vessels in the submucosa through the muscularis propria are pathologically filled with metastatic cancer cells [9]. In the present case, swelling was observed from axillary to the cervical paraesophageal lymph nodes; therefore, there was a possibility that this condition was a recurrent esophageal metastasis of breast cancer. However, biopsy of the tumor indicated squamous cell carcinoma; therefore, the condition was not

metastasis but was rather diagnosed as a double primary cancer. There was a possibility that the swellings of axillary and supra- and subclavicular lymph nodes were lymph node metastases from the esophageal cancer. However, metastases to Rotter's and axillary lymph nodes are observed in only 1.1% of esophageal cancer cases [10]; therefore, it was difficult to explain the appearance of this condition by esophageal cancer alone. Considering the original stage of the breast cancer and re-elevation of CA15-3 level, the left supra- and subclavicular and axillary lymph node metastases were considered to be recurrent breast cancer.

Individual cancers of a double primary cancer are generally independently involved in prognosis [11]. When multiple cancers exist simultaneously, the malignant disease that most affects the prognosis is prioritized in the treatment strategy [12]. The 5-year survival rate of stage II esophageal cancer is 49.5% [13], and that of stage IV breast cancer is 30–50%. Thus, there was not much difference between the survival rates of both cancers; therefore, response rates to treatment, expected future symptoms, and treatment duration should be taken into consideration. In the Guidelines for Diagnosis and Treatment of Carcinoma

Fig. 7 Image evaluation 8 months after the treatment initiation. The esophageal cancer achieved a CR and the elevation was determined to be an esophageal submucosal mass. The metastatic lymph nodes have shrunk and disappeared (arrows). **a** Esophagogastroscopy: Lugol staining; **b** enhanced CT

of the Esophagus, surgery with preoperative chemotherapy, CRT, and CRT + surgery are the recommended treatment methods for stage II esophageal cancer [13]. Among these, surgery with preoperative chemotherapy is often selected. However, the present patient had a recurrent multiple bone metastasis of the breast cancer, which was a non-curable resection factor. Considering the periods of total esophagectomy, invasive three-field dissection, and the perioperative period are a treatment-free period of breast cancer, the breast cancer progression was considered to be a possible prognostic factor. Iizuka et al. suggested selecting drugs that are commonly effective for both cancers when selecting chemotherapeutic drugs for double primary cancer if similar efficacies for both cancers were desired [14]. 5-FU, which is

used in CRT, is also used in chemotherapy for breast cancer in various regimens, including triple chemotherapy with cyclophosphamide, adriamycin, and 5-FU (CAF) and FEC. 5-FU alone may also be effective for breast cancer. We determined that a CRT that should also be effective for breast cancer would be better suited for this patient. The median overall survival of patients with stage II and III esophageal cancer with CRT (5-FU + CDDP + radiation 60 Gy) is 29.1 months (JCOG0966) [15]. In addition, with regard to first-line therapy for recurrent advanced HER2-positive breast cancer, pertuzumab + trastuzumab + DTX therapy is the standard therapy in the Clinical Practice Guideline for Systemic Treatment of Breast Cancer, with a median overall survival rate of 56.5 months (CLEOPATRA) [16, 17]. The expected symptoms due to the progression of esophageal cancer include impaired oral ingestion, carcinomatous lymphangitis, tumor hemorrhage, and infiltration into mediastinal organs; in comparison, the expected symptoms due to the progression of recurrent breast cancer metastasis (lymph nodes and bones) include pathological fractures, bone marrow carcinomatosis, and lymphedema in the extremities. In the present case, due to impaired oral ingestion due to esophageal cancer, which appeared relatively early and decreased the patient's ADL, in addition to the esophageal cancer prognosis, we determined that the esophageal cancer should be controlled first.

In performing CRT first, considering that the breast cancer was HER2-positive, it was possible that the breast cancer could progress during the treatment period, despite the administration of 5-FU. However, considering the invasive potency of CRT, the addition of anthracycline- or taxane-type anticancer drugs would be difficult. Takahashi et al., concomitantly administered 5-FU + CDDP (FP) and trastuzumab for a double primary hepatocellular carcinoma and breast cancer, reporting few adverse events even though the molecularly targeted drug trastuzumab was concomitantly administered and the inhibitory effect against HER2-positive breast cancer was high [18]. Although cancers of the double primary cancer were different, efficacy could be expected without much physical burden to this patient; therefore, we decided to concomitantly administer trastuzumab with CRT. The treatment of this patient was completed as planned without adverse events during the treatment period and the treatment was effective for both cancers.

Radiotherapy treatment plays an important role and it seems that this case also benefits greatly. External irradiation on the esophagus and left supraclavicular fossa were performed with FP. There was a possibility that the swellings of supra- and subclavicular lymph nodes were metastases from the esophageal cancer, and the supraclavicular cavity was included in the irradiation range. The axillary node and bone metastasis were not included. However, there are reports that drug therapy and radiotherapy are effective for regional

lymph node recurrence [19]. Therefore, radiotherapy should be considered if chemotherapy becomes ineffective.

Subsequently, treatment with pertuzumab + trastuzumab + DTX was performed, which provided a good treatment result. Because DTX is used for the treatment of esophageal cancer, it was also treated during the treatment for breast cancer. This may have also contributed to the good result in the current case. Some studies have reported HER2-positive cases among esophageal squamous cell cancer cases and that the treatment effect of trastuzumab can be expected [20, 21]. We also performed histological immunostaining of the esophageal cancer in this patient; however, the result was negative. Therefore, the anti-HER2 drug was considered to be effective only for breast cancer.

In conclusion, we report a case of a double primary HER2-positive breast cancer and esophageal cancer, for which a primary treatment with CRT (FP with radiotherapy on the esophagus and supraclavicular lymph nodes: 60 Gy) and a secondary treatment with pertuzumab + trastuzumab + DTX were performed. A good treatment effect on both cancers has been observed for approximately 2 years.

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