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SHORT COMMUNICATION

Improved survival in patients with breast rhabdoid tumors with multi-agent adjuvant chemotherapy combined with irradiation

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Abstract
Purpose Malignant rhabdoid tumors (MRT) have poor prognoses. Breast MRT is extremely rare; only three cases have been documented, with a mean prognosis of 7 months. Multi-agent chemotherapy with mastectomy and irradiation, as used in this case, may extend survival in breast MRT.
Patient and methods A 68-year-old woman who underwent a standard mastectomy was diagnosed with breast MRT. Postoperatively she received six cycles of cyclophosphamide/methotrexate/5-fluorouracil followed by oral administration of doxifluridine and anastrozole, after which no metastasis was detected. About 8 months postoperative, magnetic resonance imaging revealed cervical bone metastasis, and local irradiation and nine doses of "basic chemotherapy" consisting of biweekly paclitaxel and anastrozole were administered. About 4 months later, multiple lung metastases were revealed, and four doses of "basic chemotherapy" with added pirarubicin hydrochloride were administered. Four months after that, multiple large liver metastases were discovered, and five doses of "basic chemotherapy" with added carboplatin were administered.
Results The 19-month survival period of our case was almost three times that of reported breast MRT patients.
Conclusion Multi-agent chemotherapy combined with irradiation may be associated with the relatively long survival of the present case.

Keywords Breast · Rhabdoid tumor · Chemotherapy · Irradiation

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Introduction

The first case of malignant rhabdoid tumor (MRT), which was derived from a kidney, was reported in 1978 [1]. Since then, it has been demonstrated that MRTs can be derived from various other organs, such as the lung, liver, heart, genital tract, and brain [1–11]. Breast MRT is extremely rare; only three cases have been documented in the literature since the first case was reported in 1995 [6].

The microscopic findings of MRT include a solid growth pattern of polygonal cells with eosinophilic intracytoplasmic inclusion bodies. Immunohistochemically, these cells stain positive for cytokeratin (an epithelial cell marker) and vimentin (a mesenchymal cell marker) [3, 6–8]. In addition, examinations by electron microscopy have revealed perinuclear aggregations of intermediate filaments in the cytoplasm. Reverse-transcriptase polymerase chain reaction (RT-PCR) of frozen samples and cultured cell lines of MRT has revealed mutated codons of cytokeratin 8 gene involved in the conformational change of intermediate filaments [9].

The prognosis of patients with MRT is very poor; most patients die within a year of diagnosis [6]. A standard chemotherapy regimen has not yet been established, although some regimens for MRT of liver, chest wall and ovary have been reported to be effective [7, 10, 11]. We present a patient with breast MRT in whom a multi-agent regimen of adjuvant chemotherapy appears to have extended the survival.

Case report

A 68-year-old woman was transferred to our hospital with a chief complaint of a left breast mass that had been rapidly growing over the last 2 months. Physical examination on admission revealed an elastic, firm, ill-defined mass with an irregular surface measuring 11.0 × 8.5 cm. The tumor was fixed with underlying muscles, but the adjacent axillary and supraclavicular lymph nodes were not palpable. Computed tomography (CT) demonstrated that the tumor had central necrosis and had already invaded her major pectoral muscle. There were no metastatic lesions in the lung or liver, and bone scintigraphy showed no abnormal accumulation. As the aspiration biopsy of the tumor demonstrated the presence of a solid carcinoma, we performed a standard radical mastectomy.

The resected tumor was a stiffly elastic, gray- and white-colored mass with central necrosis and accumulated blood inside. The pathologic size of the tumor was 7.0 × 7.0 × 5.5 cm and all of the ten resected lymph nodes were metastatic. The pathological examination revealed that the tumor was composed of polygonal cells with rounded vesicular nuclei, prominent nucleoli, and abundant eosinophilic cytoplasm revealed by hematoxylin and eosin staining (Fig. 1). The resected lymph nodes were histologically positive for metastasis. In terms of immunohistochemical staining, the tumor cells were positive for cytokeratin (AE1/AE3, CAM5.2) (Fig. 2), vimentin (Fig. 3), and neural cell adhesion molecules (NCAM), while they were negative for S100, desmin, chromogranin A, synaptophysin, estrogen receptors, progesterone receptors, and HER2/neu protein. In the cytoplasm, perinuclear aggregation of intermediate filaments was observed by electron microscopy (Fig. 4).

The patient's postoperative course was uneventful. She was discharged on the 14th postoperative day.

The patient received six cycles of CMF [cyclophosphamide (CPA) 500 mg/m^2, methotrexate (MTX) 40 mg/m^2, 5-fluorouracil (5-FU) 500 mg/m^2] starting 1 month after the operation. Thereafter, she received oral administration of doxifluridine (800 mg/day) and anastrozole. Six months later, CT scan and ultrasonography (US) documented no metastasis in the brain, lung, liver, or other organs.

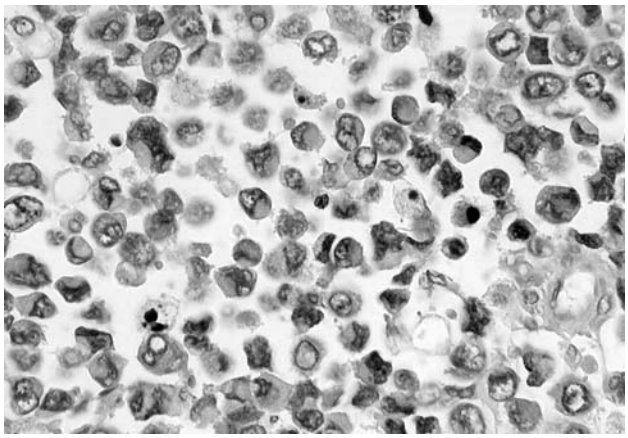

Fig. 1 The tumor was composed of polygonal cells with rounded vesicular nuclei, prominent nucleoli, and abundant eosinophilic cytoplasm revealed by hematoxylin and eosin staining

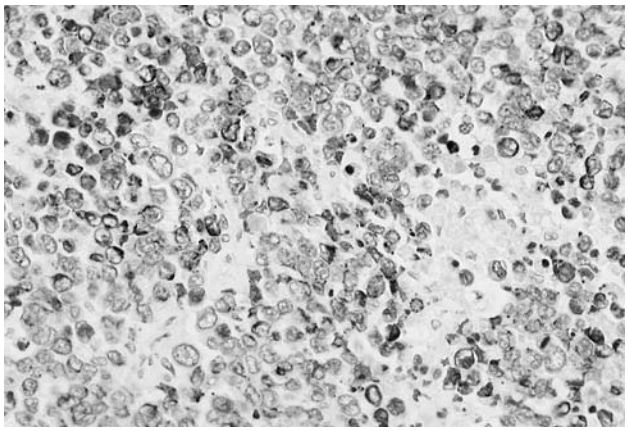

Fig. 2 Cytokeratin were expressed in the cytoplasm

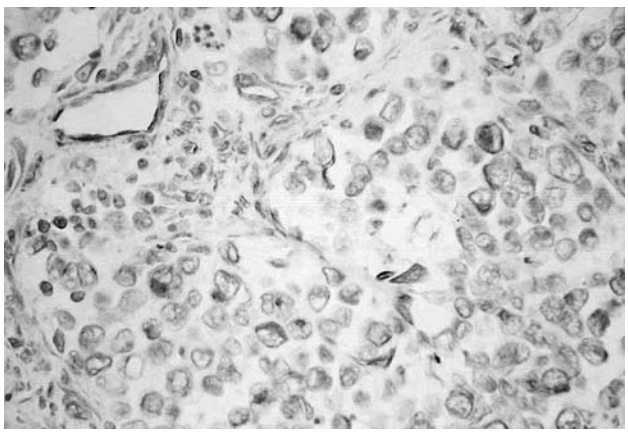

Fig. 3 Vimentin were expressed in the cytoplasm

Some 8 months after the operation, the patient suddenly began to feel right shoulder pain and notice numbness in her right arm. Cervical magnetic resonance imaging (MRI) and bone scintigraphy demonstrated bone metastasis in the fifth cervical vertebrae. Local irradiation (35 Gy) of her

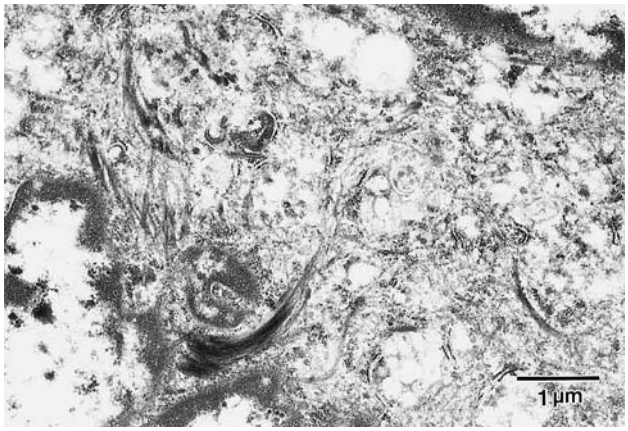

Fig. 4 In the cytoplasm, perinuclear aggregation of intermediate filaments was observed

neck and nine doses of salvage chemotherapy consisting of paclitaxel (80 mg/m^2) and anastrozole were administered every 2 weeks. This regimen was defined as "basic chemotherapy" in subsequent recurrences. About 4 months later, a CT examination during the above regimen revealed small nodules of multiple lung metastases, but no liver metastasis. On further progression of disease, as assessed by CT, every 2 weeks for a total of 4 doses of chemotherapy consisting of pirarubicin hydrochloride (20 mg/body) and paclitaxel (80 mg/m^2) with anastrozole was attempted leading to stabilization of disease. However, 4 months after that, CT imaging revealed, not only slightly increased numbers and sizes of lung metastases, but also multiple large liver metastases even though US had not detected any liver metastasis 2 months prior. Based on the rapid liver metastases, five doses of chemotherapy were conducted every 2 weeks, with each dose consisting of carboplatin (2.5 AUC) and paclitaxel (80 mg/m^2) combined with anastrozole. The patient died of respiratory failure due to carcinomatosis 19 months postoperatively.

Discussion

Rhabdoid/teratoid tumors of central nervous system are associated with a very poor prognosis; a recent study reported that the majority of patients die of the disease 3–62 months after diagnosis, with a median survival of 16.75 months [12]. In terms of breast MRT, Koibuchi and colleagues [6] reported a patient who died of respiratory failure 8 months after detection of the tumor and 5 months after surgery, regardless of neoadjuvant chemotherapy with cyclophosphamide. Mogotlane and colleagues described the two other documented patients of breast MRT [8]. In one, a mastectomy was performed with second-level axillary clearance, and the patient died of disseminated disease 9 months postoperatively after chemotherapy of tamoxifen and radiation therapy. The other patient was lost to follow-up, after a mastectomy and axillary node clearance was performed. The survival period of our case was 21 months after detection of the tumor and 19 months postoperatively, while the average of the two patients for whom data was available was only 7 months after surgery. Our patient survived almost three times as long as they did (Table 1).

The strategy for the treatment of MRTs should be based on knowledge of the biological characteristics of the sarcoma as it develops in other soft tissue [6]. However, standard evidence-based chemotherapeutic and radiotherapeutic regimens have not been established for MRTs. Moreover, MRTs may be observed in pure form, in which the rhabdoid phenotype occurs without the carcinomatous component, or in composite form, in which carcinoma are

Table 1 Summary of reported cases of malignant rhabdoid tumors of the breast

	Authors	Age	Size (cm) Stage	Chemotherapy	Radiation therapy	Immunohistochemistry (positive stain)	Metastatic sites	Survival (months)
1	Koibuchi et al. [6]	65	13 × 12 × 10 IIIA	Cyclophosphamide (NAC)	(+)	Vimentin, keratin, NSE, EMA	Chest wall, lung	8[a]/5[b]
2	Mogotlane and Chetty [8]	61	12 × 8[c]	TAM	(−)	CAM5.2, AE1/3, vimentin, pRb	Lung, disseminated disease	9[b,c]
3	Mogotlane and Chetty [8]	45	5 × 4[c]	(−)	(−)	CAM5.2, AE1/3, vimentin, P53, pRb	–[c]	–[c]
4	Our case	68	7 × 7 × 5.5 IIIB	CMF, doxifuridine, anastrozole, paclitaxel, pirarubicin, carboplatin	(+)	CAM5.2, AE1/3, vimentin, NCAM	Bone, lung, liver	21[a]/19[b]

NAC neoadjuvant chemotherapy, *TAM* tamoxifen, *CMF* cyclophosphamide/methotrexate/5-fluorouracil

[a] Survival period from detection

[b] Survival period from operation

[c] Unknown or not mentioned

mixed with tumor cells with rhabdoid differentiation [13]. Hence, treatment options seem complicated by considerations of the tissue of origin and biological characteristics.

The two reported patients who were not lost to follow-up had received adjuvant or neoadjuvant chemotherapy using only one drug. Our patient initially received six cycles of CMF postoperatively followed by oral administration of doxifluridine and anastrozole, which may have led to the relatively long recurrence-free period. Aromatase inhibitors, of which anastrozole is one, slow the proliferation of breast cancer cells [13] or estrogen receptor-negative endometrial cancer cells in vivo [14] by inducing apoptosis. Koshida et al. [15] indicated that the growth inhibition of MRT cells by 4-hydroxy-tamoxifen (4-OHT) involved apoptosis, and the apoptotic effect of 4-OHT on MRT cells was observed even in an ER-alpha-negative cell line. They also speculate that TAM has various effects that appear to be independent of steroid-related pathways, inhibits protein kinase C, binds to calmodulin, and possesses antioxidant properties. We speculate that anastrozole induces apoptosis through the steroid-unrelated pathways as well as TAM. Therefore, although estrogen and progesterone receptors were negative in our case, we continually used anastrozole for treatment in the hope of inducing apoptosis after CMF. Thereby, anastrozole might have extended the survival period of our patient with breast MRT. On the other hand, combination chemotherapy based on paclitaxel might have improved our patient's prognosis after recurrence. In conclusion, we think that the use of only one drug limits the survival time and multi-agent drug is necessary for improvement of breast MRT prognosis, although there have only been a few cases of it. Hosoi et al. [10] reported an infant with chest wall MRT who showed 7-year remission after relapse. The patient received multi-agent chemotherapy with doxorubicin, vincristine, cyclophosphamide, ifosfamide, and etoposide after the first surgery. She also received surgical resection of local recurrence, irradiation, and chemotherapy of a different regimen. Jayaram et al. [7] described a successful treatment of a patient with MRT of the liver surviving more than 3 years after liver transplantation and chemotherapy. The patient received multi-agent chemotherapy with ifosfamide, carboplatin, and etoposide (ICE) alternating with vincristine, adriamycin, and cyclophosphamide (VDC) before surgery and post transplant. Long survival periods can be expected if the chemotherapy is able to control the micro-metastasis. Banzai et al. [11] claimed that combination chemotherapy with isosfamide, epirubicin, and cisplatin (IEP) may be useful in the treatment of MRT of the ovary. Considering these reports, we are convinced that regardless of the regimen, multi-drug combination chemotherapy prolongs the survival time of MRT patients.

The effective treatment for MRT remains controversial, although many chemotherapy regimens have been attempted with/without radiation therapy. The results of previous reported cases suggested that complete surgical resection of the primary tumor might be effective regardless of the involvement of sentinel lymph nodes. New chemotherapy regimens might extend patient survival in the future. In the meantime, however, further accumulation of treatment experience according to the individual organ from which MRTs are derived is needed.

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