CASE REPORT – OPEN ACCESS

International Journal of Surgery Case Reports 24 (2016) 26–31

Contents lists available at ScienceDirect

International Journal of Surgery Case Reports

journal homepage: www.casereports.com

Angiosarcoma arising in the non-operated, sclerosing breast after primary irradiation, surviving 6 years post-resection: A case report and review of the Japanese literature

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ARTICLE INFO

Article history:
Received 4 February 2016
Received in revised form 1 May 2016
Accepted 1 May 2016
Available online 6 May 2016

Keywords:
Angiosarcoma
Radiation therapy
Breast surgery
Breast cancer
Occult breast cancer

ABSTRACT

INTRODUCTION: Angiosarcoma consists only 0.04% of all breast malignancies and has a poor prognosis. This is the first reported case of an angiosarcoma arising in the non-operated breast after primary irradiation for occult breast cancer. The patient underwent mastectomy, surviving disease free for 6 years.
PRESENTATION OF CASE: A 73-year-old woman with a past history of irradiation of the non-operated left breast complained of skin thickening and crust formation on the left nipple 8 years post-irradiation. Considering the clinical history and radiological studies, recurrent cancer was suspected and biopsy was performed. However, no proof of malignancy was obtained. As clinical symptoms continued to advance, informed consent was obtained and mastectomy was performed. Histological examination of the surgical specimen revealed angiosarcoma.
DISCUSSION: In this case, angiosarcoma occurred after radiation on a non-operated breast. Preoperative diagnosis was not achieved even with two cytology specimen and one biopsy. Each showed only fibrosis and inflammatory changes. The background breast tissue inflammation should have been caused by radiation. Marked fibrosis and the rather small number of sarcoma cells in the breast tumor in this case may be why bioptic diagnosis was difficult. Kaplan-Meier analysis of 60 Japanese breast angiosarcoma patients showed significantly better prognosis in patients with a tumor 2 cm or smaller.
CONCLUSION: Angiosarcoma may occur in the non-operated breast, post irradiation. The potential difficulties of diagnosing angiosarcoma against background fibrosis should be kept in mind. Initial radical surgery currently represents the only effective treatment for improving survival in these patients.

1. Introduction

Angiosarcoma represents less than 1% of soft-tissue sarcomas [1]. Angiosarcoma of the breast, which represents 0.04% of breast malignancies, can be divided into primary and secondary angiosarcoma. Factors that predispose individuals toward secondary angiosarcoma include radiotherapy, Stewart-Treves syndrome and chronic lymphedema [2]. Radiation-induced angiosarcoma is being reported with increasing frequency. Most cases occur in the setting of breast-conserving therapy and subsequent radiotherapy [1]. However, there has been no report about angiosarcoma after irradiation on a non-operated breast. Also, despite the generally poor prognosis of angiosarcoma, our case is disease free 6 years post-operation.

2. Case report

A 73-year-old woman received fine needle aspiration cytology (FNAC) for a swelling left axillary lymph node in November 2001. FNAC showed metastatic carcinoma, and axillary lymph node dissection was performed. As FNAC revealed lymph node metastasis, sentinel lymph node biopsy was unnecessary. The diagnosis was comedo carcinoma, estrogen and progesterone receptor negative, and HER2/neu positive. As the primary disease could not be identified on radiological examination, occult breast cancer was suspected. Postoperatively, she received 3 courses of cyclophosphamide, epirubicin and 5-fluorouracil, with subsequent

Abbreviation: FNAC, fine needle aspiration cytology.

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http://dx.doi.org/10.1016/j.ijscr.2016.05.001

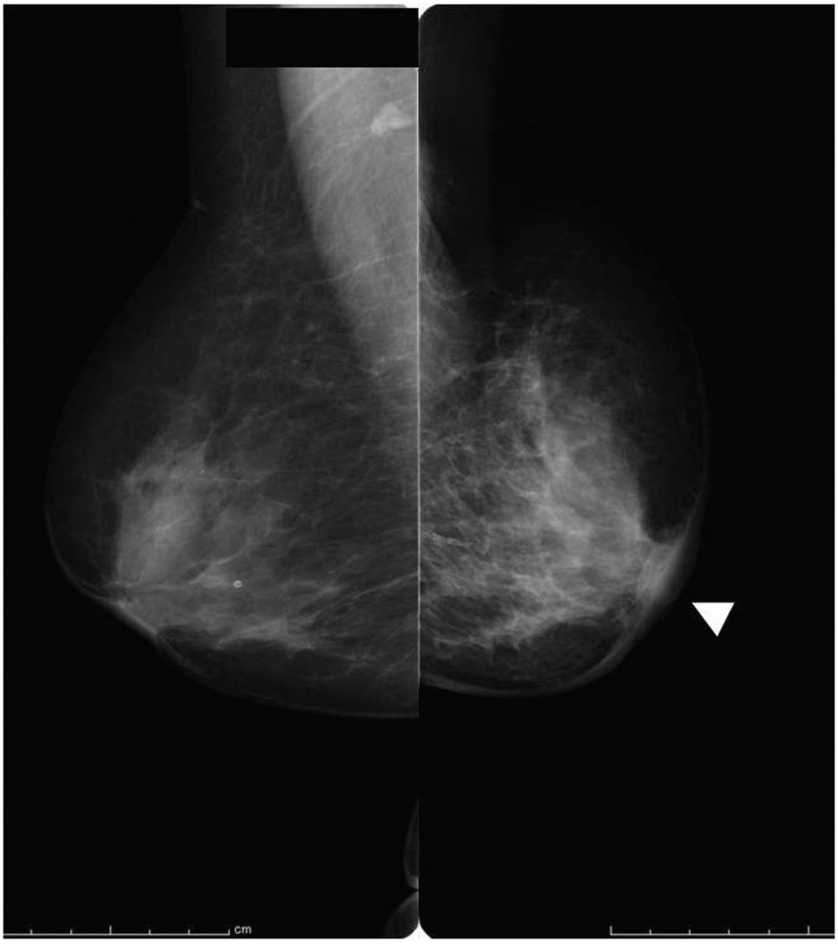

Fig. 1. Mammography. Mediolateral oblique view revealing skin thickening and distortion around the left nipple (arrow). No tumor or calcification is apparent.

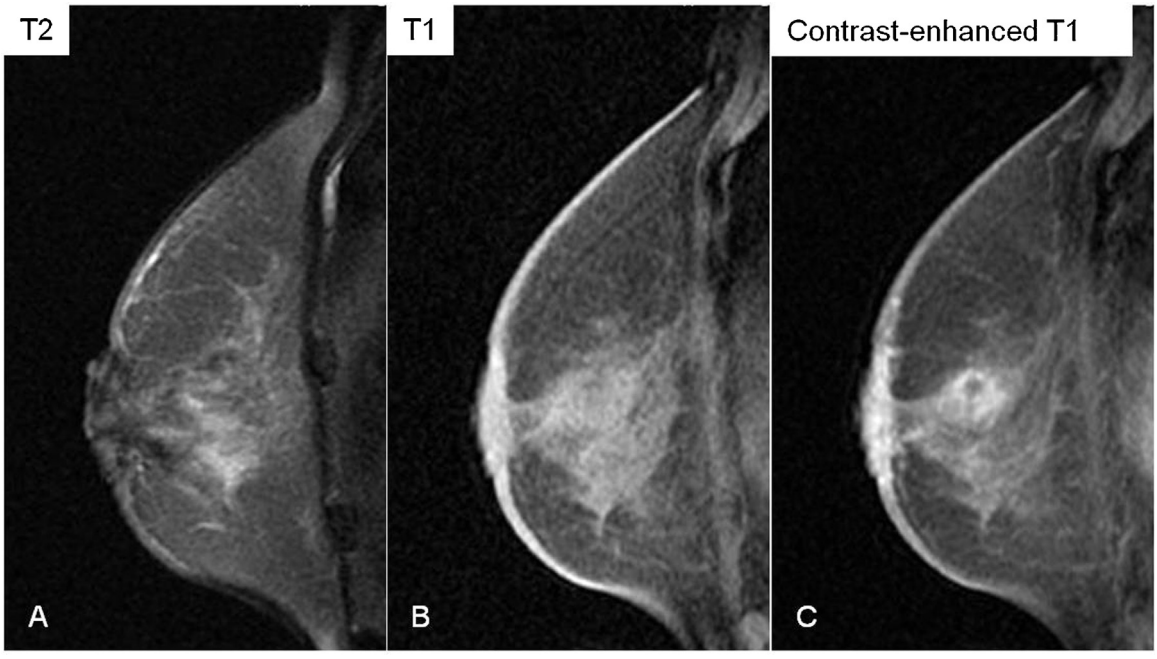

Fig. 2. Magnetic resonance imaging.
A mass with irregular margins. The mass shows heterogeneous hyperintensity on T2-weighted imaging (A), and hypointensity on T1-weighted imaging (B). Contrast-enhanced T1-weighted imaging shows enhancement of the mass (C).

Table 1
Clinicopathologic features of 60 Japanese angiosarcoma cases.

Author	Year	Age of patient at diagnosis	Tumor diameter at diagnosis	Operative method	Site of recurrence	Observation period (Months)	Outcome
Sakaguchi	1932	27	16	Mastectomy	Surgical site, Contralateral breast, Bilateral ovary	37	Dead
Ishizuka/Watanabe	1965/1974	52	12	Mastectomy + Axillary dissection	Lung, Bone	51	Dead
Tanaka/Hamazaki	1971/1978	22	13	Mastectomy + Axillary dissection	Surgical site, Lung, Liver	37	Dead
Watanabe	1973	51	3	Mastectomy	Stomach, Lung, Pharynx, Uterine Cervix, Chest wall	14	Dead
Kunii	1982	42	1	Mastectomy + Axillary dissection	None	11	Alive
Koike	1982	21	7.2	Mastectomy + Axillary dissection	Surgical site, Chest wall	24	Dead
Shikama	1986	28	18	Mastectomy	Contralateral breast, Bone, Lung, Bilateral ovary	15	Dead
Sakuma	1987	19	22	Mastectomy	Surgical site, Contralateral breast, Chest wall	30	Alive
Yamashina	1987	71	16	Mastectomy + Axillary dissection	Lung	6	Alive
Tamura	1987	24	9	Mastectomy + Axillary dissection	None	26	Alive
Kawazu	1988	42	7.3	Mastectomy + Axillary dissection	Skin	12	Alive
Matoba/Shou	1988	25	16	Mastectomy + Axillary dissection	Surgical site, Skin, Bilateral ovary	27	Alive
Iseki	1989	60	1.3	Mastectomy + Axillary dissection	None	8	Alive
Yokoyama	1990	33	9	Mastectomy + Axillary dissection	Surgical site, Skin	21	Alive
Ishikawa	1990	26	20	Mastectomy + Axillary dissection	Lung, Skin	5	Dead
Nagahara	1993	19	8	Mastectomy + Axillary dissection	Lung, Bone, Liver, Skin	10	Dead
Okanobu	1994	34	1.3	Mastectomy + Axillary dissection	None	18	Alive
Hayashi	1994	52	9	Mastectomy + Axillary dissection	Lung	2.5	Dead
Hakata	1995	43	1	Mastectomy + Axillary dissection	Skin	15	Alive
Nakano	1995	82	2	Mastectomy	Lung, Bone, Liver, Skin	3	Dead
Ishizawa	1995	38	4	Lumpectomy	Residual Breast, Liver	39	Dead
Tachibana	1996	24	10	Mastectomy + Axillary dissection	None	10	Alive
Nagasawa	1997	64	2	Mastectomy	None	10	Alive
Murakawa	1997	46	1.7	Mastectomy	None	60	Alive
Michigami	1997	24	10	Lumpectomy	Surgical site, Skin, Contralateral breast	12	Alive
Kagawa	1997	35	5.5	Lumpectomy	Surgical site, Skin, Chest wall, Lung, Mediastinum, Digestive tract, Thyroid, Kidney, Adrenal gland, Ovary, Gall bladder, Spleen, Bone	6	Dead

Takanashi	1997	32	10	Mastectomy + Axillary dissection	Head skin, Ovary, Lung, Liver	8	Dead
Takanashi	1997	25	15	Mastectomy + Axillary dissection	Ovary, Bone, Liver, Pelvis	34	Dead
Shichinohe	1998	34	0.7	Partial mastectomy + Axillary dissectionn	None	60	Alive
Kiyono T	1998	64	26	Mastectomy	None	84	Alive
Yamamoto	1998	24	6	Mastectomy	Ipsilateral breast, Lung, Liver, Bone	29	Dead
Tanaka	1999	26	8	Mastectomy + Axillary dissection	None	12	Alive
Yamada	1999	42	6	Mastectomy + Axillary dissection	Contralateral breast, Lung, Liver, Adrenal gland, Bone	15	Dead
Yoshida	2000	41	1.5	Partial mastectomy + Axillary dissectionn	None	60	Alive
Abe	2000	79	2	Mastectomy	Subcutaneous fat of ipsilateral breast	6	Alive
Ueki	2000	19	1.5	Mastectomy	None	30	Alive
Tsumagari K	2000	52	6	Mastectomy + Axillary dissection	None	9	Alive
Tsumagari K	2000	26	11	Mastectomy + Axillary dissection	None	18	Alive
Tsumagari K	2000	19	9	Mastectomy + Axillary dissection	Bone, Liver, Lung, Brain, Surgical site, Nasal cavity	27	Dead
Kitamura	2001	46	Hand fist size	Mastectomy	Skin, Liver, Lung	24	Dead
Fujisawa	2003	65	5	Mastectomy	Lung, Skin	16	Alive
Nishiyama	2003	18	14	Mastectomy	Surgical site, Lung, Liver	9	Dead
Nakayama	2004	40	3	Mastectomy	Contralateral breast	51	Alive
Nakata	2004	51	8	Mastectomy + Axillary dissection	None	16	Alive
Yoneyama	2005	32	5.5	Mastectomy + Axillary dissection	None	72	Alive
Sadashima	2007	60	2	Mastectomy	None	12	Alive
Ueda S	2008	28	7	Mastectomy	Bone	6	Alive
Yoshida C	2008	38	9	Mastectomy	None	2	Alive
Ueda S	2008	44	4	Mastectomy	Bilateral breast, Bilateral ovary, Bone, Lung, Liver	41	Dead
Sakamoto M	2009	32	8	Mastectomy	None	4	Alive
Takenaka M	2009	87	11	Mastectomy	Lung	2	Dead
Miyasaka M	2010	59	12	Mastectomy	None	17	Alive
Komatsu M	2010	54	5.5	Mastectomy	None	2	Alive
Oda T	2011	27	5	Mastectomy + Tissue expander	Ovary, Bone, Liver, Pelvis	3	Alive
Satou F	2011	61	10	Partial mastectomy + sentinel lymph node biopsy	Ovary, Bone, Liver, Pelvis	14	Alive
Hosono Y	2011	47	3.2	Mastectomy + Sentinel lymph node biopsy	Lung, Liver	29	Dead
Hoskimoto N	2012	27	7	Mastectomy	Skin	40	Alive
Okaminami Y	2013	33	5	Mastectomy	None	42	Alive
Mizumoto S	2014	78	16	Mastectomy + lymph node sampling	Rt knee, pleura	13	Dead
Our case	2015	73	3.5	Mastectomy	None	60	Alive

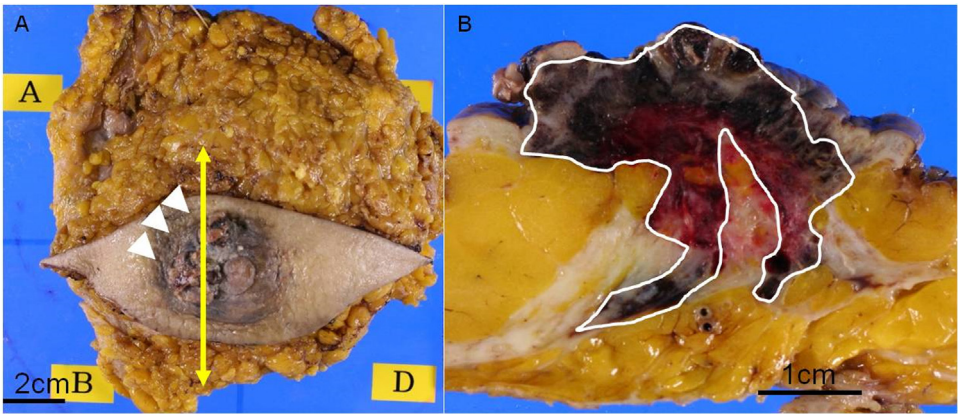

Fig. 3. Pathology (gross).
(A) The resected specimen, showing an irregular mass accompanied by crust formation and skin thickening at the areola (arrows). (B) Cross-section of the specimen (vertical arrow in A). A brownish irregular mass leading into the skin thickening is seen beneath the nipple.

irradiation (50 Gy) to the left breast. We have also proposed the choice of mastectomy, which the patient refused.

In November 2007, ultrasonographic study showed a hypoechoic area in the left breast. Core needle biopsy revealed inflammatory pseudotumor.

Then, in May 2009, she complained of skin-thickening and crust formation at the left areola. Mammography revealed skin-thickening and distortion around the left nipple (Fig. 1). Ultrasonography showed the hypoechoic area recognized in 2007, with thickening of the overlying skin on the left nipple. Magnetic resonance imaging showed a 3.5 cm mass with irregular margins. It was heterogeneous and hyperintense on T2-weighted imaging, hypointense on T1-weighted imaging, and gradually enhanced in a dynamic study (Fig. 2). Marked enhancement was suggestive of malignancy, but the gradual enhancement was inconsistent with common breast malignancies. Computed tomography showed skin thickening and an enhanced area with obscure borders beneath the left nipple.

From radiological studies, primary breast cancer, recurrence or sarcoma was suspected. Given the clinical history, recurrence was strongly suspected. Even though FNAC, Vacuum-assisted biopsy (VACORA®; Bard Biopsy Systems, Tempe, AZ) and skin biopsy specimens were performed, diagnosis of malignant tumor was not obtained.

However, as skin thickening of the peri-nipple area continued to advance, clinically malignant tumor was suspected. After careful discussion with the patient, informed consent was obtained and simple mastectomy was performed in June 2009.

Macroscopically, an irregular shaped mass with crust formation and skin-thickening was observed in the areola region of the resected specimen (Fig. 3).

Histopathological examination revealed oval-shaped neoplastic stromal cells arranged in sinusoidal pattern, accompanying mitoses and background fibrosis (Fig. 4). The tumor was negative for estrogen, progesterone and HER2/neu receptors. Immunohistochemical staining yielded positive for CD34, vimentin and factor VIII, and negative for cytokeratin. The histological diagnosis was angiosarcoma of the breast.

Paclitaxel was administered as postoperative chemotherapy. Now, 6 years post-operation (February 2016), the patient is clinically free of disease.

3. Discussion

Breast angiosarcoma is rare, and primary angiosarcoma of the breast makes up only 0.00005% of all breast malignancies [2]. The

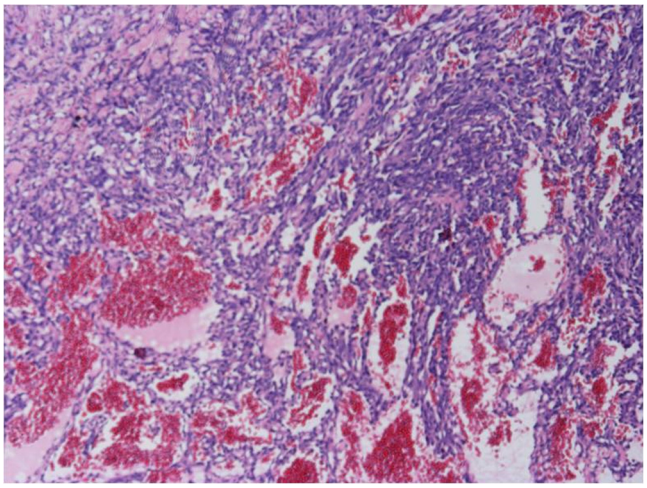

Fig. 4. Pathology (microscopy).
Microscopic examination of the surgically resected specimen, revealing oval-shaped cells arranged in the form of endovascular cells, accompanied by mitosis and background fibrosis.

frequency of angiosarcoma increases to 0.16% after radiotherapy. This represents an approximately 3200-fold increase in relative risk for patients who undergo breast-conserving surgery [3].

Angiosarcoma should thus be considered in any post-radiation patient with skin thickening or mammographic density [4].

Angiosarcoma tend to present 5–6 years, after breast-conserving therapy and subsequent radiotherapy [5].

According to the recent literature, (1) axillary lymph node detection (ALND) + radiotherapy and (2) ALND + mastectomy are both the treatment of choice in occult breast carcinoma. (1) and (2) have the same survival outcomes [6,7]. We would like to point out that one has to keep in mind the possibility of the development of angiosarcoma in the cases that received treatment choice (1).

The unique feature about this case is the cause of the angiosarcoma. In usual case reports, the patients receive both breast conservation surgery and radiotherapy. In the diagnostic imaging of angiosarcoma in these cases, it is hard to tell whether the back ground fibrosis was caused by surgery and radiotherapy, or the tumor itself. However, in our case, we had performed only radiotherapy, and it is reasonable to consider that angiosarcoma occurred from a radiation scar. This case is valuable in the respect that from its clinical course, rather intense fibrosis occurred in the breast caused by irradiation, and the development of angiosarcoma

from the sclerosing breast was confirmed by the interpretation of the resected specimen.

In the reported cases, preoperative diagnosis of angiosarcoma is usually made by needle biopsy specimen [1,8]. However, due to the variety of pathological features, some angiosarcoma cases are misdiagnosed as hemangioma [9].

In our case, preoperative diagnosis of angiosarcoma was not achieved even with two cytology specimen and one biopsy. Each showed only fibrosis and inflammatory changes.

Wijnmaalen et al. reported background breast tissue inflammation caused by radiation in 8 cases of angiosarcoma, also finding fibrosis in 7 (88%) [10].

When angiosarcoma occurs against such a background, correct diagnosis may be difficult. Marked fibrosis and the rather small number of sarcoma cells in the breast tumor in the present case may be why bioptic diagnosis was difficult. In this case, the tumor was considered to be high grade from its clinically aggressive nature, and as histology revealed abundant mitosis.

The potential difficulties of diagnosing angiosarcoma against background fibrosis should be kept in mind, particularly in tumors consisted of rather small number of angiosarcoma cells, and marked fibrosis caused by radiation.

Concerning treatment, initial radical surgery currently represents the only effective treatment for achieving long-term survival in angiosarcoma patients [8].

Other reports have indicated that hyperfractionated radiotherapy of secondary high-grade angiosarcoma has resulted in reduced cell repopulation [11].

Adjuvant chemotherapy, paclitaxel for example, may also reduce the local recurrence rate [1]. In the present case, paclitaxel was performed.

Angiosarcoma has a poor prognosis, and median overall survival is 22–37 months [3]. Vorburger et al. reported that tumors 5 cm or smaller in diameter have a better prognosis than those larger than 5 cm [12].

The clinicopathologic features of 60 reported Japanese angiosarcoma cases were reviewed. The relation between tumor diameter and prognosis was analyzed by Kaplan-Meier method (SPSS®; IBM, Armonk, NY).

The mean observation period was 22.7 months (2–84 months), the mean age was 41.5 years old (18–87). Mean tumor diameter was 7.8 cm (0.7–26 cm). The operations performed were mastectomy in 54 cases (90.0%), partial mastectomy in 6 cases (10.0%). Axillary dissection was performed in 28 cases (46.7%), but there were no lymph node metastasis. Distant metastasis was found in 32 (53.3%) cases (Table 1). Kaplan-Meier analysis showed significantly better prognosis in patients with a tumor 2 cm or smaller in diameter ($p = 0.0457$) [13].

Conflict of interest

None.

Funding

None.

Ethical approval

This study has been approved by the ethics committee (Ethics and Compliance Committee of Shizuoka Saiseikai General Hospital). Reference No. 27-17-01.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. I can provide this should the Editor ask to see it.

Author contribution

Takaaki Ito and Kenichiro Tanaka: study concept or design, writing the paper, operating surgeon.

Kiyoshi Suzumura: data analysis or interpretation, operating surgeon.

Shouji Hoshi: histological examination.

Yoshichika Okamoto, Koji Oda and Masaki Terasaki: study concept or design, critical revision.

Guarantor

Takaaki Ito, Kenichiro Tanaka.

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