**Case Report:**
Post-radiation Angiosarcoma and Bilateral Mastectomy

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Abstract. We report the occurrence of bilateral angiosarcoma after radiation therapy for breast carcinoma in a 64 yr-old woman. The first angiosarcoma developed 17 yr after radiation therapy to the right breast; the second angiosarcoma developed 1.5 yr after radiation therapy to the left breast. Recognizing angiosarcoma in radiated breast tissue is essential to appropriate therapy. The role of irradiation after surgery as adjuvant therapy is to be reviewed. (received 8 April 2002; accepted 20 May 2002)

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Introduction

Angiosarcoma of breast is a rare malignant tumor first described by Schmidt in 1887 [1]. Breast carcinomas are usually treated by surgery followed by radiation and/or chemotherapy [2]. Primary benign and malignant vascular tumors of the breast, though not common, have been reported in the literature [3]. Angiosarcoma is known to develop after radiation therapy or mastectomy for breast carcinoma [4-9]. It usually occurs after 3-11 yr [10, 11]. Post-radiation changes in the breast make the diagnosis of angiosarcoma challenging. Here we report a patient with bilateral breast carcinoma treated by surgery and radiation, who developed angiosarcoma in both breasts. No previously reported case of bilateral post-radiation angiosarcoma was found in the English literature.

Case Report

A 43-yr-old woman developed a tumor in the right breast in 1983. The family history was positive for breast cancer in her mother, multiple maternal aunts, and a maternal cousin. She was otherwise healthy, and was married with two children. She was a non-smoker and she drank alcoholic beverages only on social occasions.

After a biopsy diagnosis of carcinoma, the patient underwent partial mastectomy with axillary lymph node dissection. The pathological examination revealed infiltrating ductal carcinoma (diameter 1 cm) with negative margins and 19 negative axillary lymph nodes. The cancer was positive for estrogen receptor and progesterone receptors. Surgery was followed by 6600 rads of radiation to the affected right side over a period of 50 days. No chemotherapy was administered at this time. The post-radiation period was unremarkable. She had annual follow-up examinations and appeared in good health.

Seventeen years later, on routine mammography, an area of density was noted in the left breast. The tumor was surgically excised. Histological examination revealed an intraductal and infiltrating duct carcinoma (diameter 1 cm), which was positive for estrogen receptor and negative for progesterone receptor and Her-2 neu receptor. The carcinoma extended to the inked resection margins. The excision was followed by left partial mastectomy with extended axillary dissection. The axillary dissection showed 8 negative lymph nodes.

The patient received partial 4 cycles of chemotherapy with adriamycin and cyclophosph-
amide, followed by tamoxifen. In addition, she received radiation (6100 rads) to the affected left side over a period of 2 mo.

One mo after completion of radiation therapy to the left side, purple bruising discoloration developed on the skin over the right breast in 2 areas, which each measured approximately 1 cm. A true-cut needle biopsy revealed nonspecific intravascular thrombosis with perivascular mononuclear histiocyte-like infiltration. After the true-cut needle biopsy, significant expansion of the skin changes was noted in the superior and inferior lateral aspect of the right breast. The skin was thickened and had a purple edge. Biopsy at this time showed chronic inflammatory changes with intravascular thrombi and occasional entrapped histiocyte-like giant cells and sparse Kaposi’s sarcoma-like hemorrhagic nests in the dermis. In view of these findings, supported by positive factor VIII and CD 34 reactions, a diagnosis of low-grade angiosarcoma was rendered.

A right simple mastectomy was performed. The specimen consisted of a breast that showed scarring of the skin with a poorly defined geographic tan-pink to violaceous discoloration over the infero-lateral quadrant and the medial half. The cut section showed similar violaceous discoloration in the dermis, with hemorrhagic congestion and thrombotic vessels. Under the scar, a biopsy cavity was noted (diameter 8 cm), surrounded by hemorrhagic soft tissue. Histological examination of this area demonstrated proliferating capillary vessels (Fig. 1) with atypical endothelial cells in hemorrhagic and thrombotic background. In some areas, the endothelial cells showed large and globoid cells protruding into the lumen of RBC-containing clefts and capillaries. Some tumor cells were spindle shaped and loosely arranged in a desmoplastic background. Many of these cells had prominent nuclei with lacy or dense chromatin. Occasionally, prominent cells were visible with enlarged hobnail-like nuclei. The neoplastic cells showed positive reactions for CD 34 and factor VIII. Despite Masson tumor-like and Kaposi’s sarcoma-like areas, the histological appearance was diagnostic of low-grade angiosarcoma. At the resection margins, pectoralis muscles were negative for sarcoma, but at one point the superficial pectoralis fascia was infiltrated by sarcoma (Fig. 1). The post-surgical period was complicated by delayed wound healing.

Twelve mo after the right mastectomy and the diagnosis of angiosarcoma in the right breast, the skin over the left breast showed a bruise-like lesion, similar to that previously observed on the skin of the right breast. Pathological examination of a biopsy specimen revealed perivascular lympho-histiocytic infiltrate and capillary thrombi. The purple violaceous area of the skin was removed by wide excision 4 mo later. The histological examination revealed atypical Kaposi sarcoma-like endothelial proliferation with hemorrhagic thrombotic areas similar to that of the right side more than a year earlier. The endothelial cells showed enlarged nuclei, hobnail, with prominent nucleoli, and projections into interconnected vascular spaces. The stromal changes varied from hemorrhagic Kaposi-like to desmoplastic scar-like tissue. Low grade angiosarcoma with unusual features was diagnosed. Results of immunohistochemical reactions supported this diagnosis.

A simple left mastectomy was performed shortly after the biopsy. Besides the scar, the mastectomy specimen showed purplish discoloration of the skin and a cavity measuring 4 x 3 cm, surrounded by tan-red indurated tissue. The histological examination showed minute nests of proliferating capillary vessels lined by atypical Kaposi sarcoma-like endothelial cells consistent with low-grade angiosarcoma (Fig. 2) in a background of congested thrombosed vessels with a mononuclear histiocyte-like infiltrate resembling Masson’s tumor. The sarcoma was limited to the skin and subcutis. Breast parenchyma showed a desmoplastic reaction without any evidence of tumor.

Discussion

Angiosarcoma of breast is extremely rare. Less than 0.05% of malignant tumors of breast are angiosarcomas [12]. Chen et al [13] reported that 21% of mammary angiosarcomas were bilateral in a series of 87 patients. The mean age of these patients are 35 yr. In another study, only 1 bilateral angiosarcoma was observed in a series of 40 cases [3]. Rosen at al [14] found no bilateral angiosarcoma in
Fig. 1. Post radiation angiosarcoma of the right breast (Panel A. Top left.) Histological section shows Kaposi-like areas showing a hemorrhagic area with extravasated red blood cells and fine capillary proliferation. Also shown is a solitary group of atypical endothelial cells lying in desmoplastic stroma. (H&E, 200 X magnification).
(Panel B. Top right.) Multiple distended and partly thrombosed capillary vessels give a Masson’s tumor-like appearance. Some neoplastic vessels are interconnected and lined by atypical cells ranging from pyknotic spindle to plump hobnail cells. (H&E, 200 X magnification).
(Panel C. Left.) Multiple neoplastic vessels with large atypical endothelial cells in a background of fibrillar connective tissue. The large lining cells look like hobnails with prominent nuclei and nucleoli. Note the desmoplastic background and the proximity of the angiosarcoma to the fascia in the left lower corner. (H&E, 200 X magnification).
Fig. 2. Post-radiation angiosarcoma of the left breast.
(Panel A. Top left.) Hemorrhagic areas with cleft formation and sinusoidal capillaries lined by atypical endothelial cells with prominent nuclei and nucleoli. The background of the cells is collagenous matrix with a few inflammatory cells and an area with thrombosis. (H&E, 200 X magnification)
(Panel B. Top right.) Histopathological section shows collagenous scar-like changes at the bottom; above it capillary vessels lie in a desmoplastic background lined by hobnail-like cells that protrude in clefts and slit-like capillaries. (H&E, 200 X magnification)
(Panel C. Right.) Two adjacent interconnected and distended vessels are seen in a background of desmoplastic connective tissue. The lining cells are large endothelial cells with prominent nuclei that contain lacy chromatin and prominent nucleoli. (H&E, 200 X magnification)
a series of 63 patients [14]. However, there are 3 reported cases of bilateral angiosarcoma [6,15,16]. None of these 3 patients had received irradiation. The first case, reported by Kumar et al [15], was a 29-yr-old woman who developed primary angiosarcoma in one breast followed by an additional tumor in the contralateral breast one year later. The second case, described by Khoshim et al [16], was a 42-yr-old woman who developed angiosarcoma in both breasts, which were diagnosed almost simultaneously. Marchant et al [6] reported a 28-yr-old woman with bilateral densities on mammogram, which on excisional biopsy showed angiosarcomas on both sides.

In general, most angiosarcomas present with purplish thickened localized discoloration of the skin. Assessment of the prognosis is difficult [17], but it is influenced by the histologic grade [13]. The average interval between irradiation and the diagnosis of angiosarcoma is 7 yr, with a range from 3 to 20 yr [7]. The first angiosarcoma in our case developed 17 years after radiation to the right breast. It is interesting that the subsequent angiosarcoma, in the left breast, developed 1.5 yr following radiation therapy to that breast. The short time to develop angiosarcoma in the left breast is intriguing. A possibility of incidental exposure of the left breast to radiation at the time of the radiation to the right breast (17 yr earlier) cannot be excluded with certainty. On the other hand, it is possible that the radiation given to the first breast (i.e., the right breast) hypersensitized the second breast (i.e., the left breast) by creating an immunologically privileged site for additional radiation.

Differentiating an angiosarcoma from benign skin lesions, such as a hemorrhagic, Masson’s tumor-like thrombosis with endothelial cell proliferation, can occasionally be very difficult [18,19] and has to be reviewed with a knowledge of the history of radiation therapy. Similarly, even minute Kaposi sarcoma-like nests should be taken seriously and used as a diagnostic clue in the diagnosis of low-grade post-radiation sarcoma. Angiosarcomas have a tendency to develop in areas with chronic lymphedema [5] and at sites of long standing congestion and inflammation. All of these phenomena may have played a role in the development of angiosarcomas in our case, but they do not explain the markedly different intervals (17 yr and 1.5 yr) between radiation and the appearance of primary angiosarcomas in the right and left breasts.

Disruption of the BRCA-2 gene is responsible for mutations that cause various types of cancer and such changes can be synergized by irradiation, as demonstrated in a mouse model [20]. In our patient, the initial radiation may have induced genetic changes; the second irradiation to an already mutated gene may have induced the second malignancy within an exceptionally brief period.

In conclusion, radiation as a carcinogen has been known for nearly one hundred years and several cases of radiation-induced angiosarcoma have been reported. What makes our case interesting is the bilateralness of the angiosarcomas and the striking differences in the time post-irradiation that elapsed before their development.

References


