Case Report

Primary Angiosarcoma of the Breast: A Case Report and Review of the Literature

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Primary angiosarcoma of the breast is rare. Therefore, no randomized trial can be used as guideline for diagnosis and treatment. To achieve optimal outcome, previous reports of case series are the sources for management with expected long-term survival. The objective of the present case report is to demonstrate complete pathologic response to neoadjuvant taxanes without recurrence after two years of follow-up.

Keywords: *Primary angiosarcoma, Breast cancer, Neoadjuvant therapy*

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Soft tissue sarcomas of the breast are rare tumors. The incidence is less than 1% of all breast malignancies[1]. There are different histologic subtypes such as fibrosarcoma, angiosarcoma, malignant fibrous histiocytoma, liposarcoma, and malignant phyllodes tumor. Angiosarcoma is classified into primary and secondary. The etiology of primary angiosarcoma (PAS) has not been clearly identified; however, secondary angiosarcoma (SAS) of the breast is associated with the use of external beam radiation to the breast and with long standing lymphedema as a consequence of surgery[2,3]. It has been reported that among patients with breast carcinoma who received radiotherapy, the chance to develop angiosarcoma increased with relative risk of 11-15.9[3,4]. There is an incidence of 5-13.5 per 10,000 patients treated with breast conserve therapy[5,6]. The incidence of PAS of the breast is <0.05% of all breast malignant neoplasms[5,6]. Because of the rarity of the disease, there has been no randomized trials that can give practice guidelines for treatment. In fact, there are many interesting issues regarding angiosarcoma deserved to be discussed in order to improve the outcome. These issues include method of diagnosis, the appropriate surgical management, and the role of chemotherapy and radiation therapy.

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In this report, the authors present a patient with locally advanced primary angiosarcoma who received taxanes and gemcitabines as neoadjuvant therapy with pathologic complete response. The patient underwent mastectomy, wide resection of skin and subcutaneous tissue of entire left chest and TRAM flap reconstruction. After 2 years of follow-up, the patient is still free of disease.

Case Report

A 56-year-old female patient presented with thickening of her left breast for six months. She went to a hospital and underwent mammography with a negative result. During that period of time, she felt that the area of thickening involved all her left breast with redness of skin and bloody nipple discharge. Fine needle aspiration (FNA) was subsequently performed and ductal carcinoma was diagnosed. She was then transferred to King Chulalongkorn Memorial Hospital for further management. Initial physical examination at the authors' surgical unit revealed redness and thickening of the skin involving almost the whole left breast with extension to the left chest wall, medial and inferior aspects of the breast. There was ill-defined lesion about 6 cm in size at the central area of left breast with nipple retraction. Axillary lymph node was not palpable (Fig. 1).

Mammography demonstrated enlarged left breast, diffuse thickening of the fibroglandular tissue, skin and subareolar area without a mass lesion.

On ultrasonography examination, there were diffuse of skin thickening, subcutaneous edema and

irregular hypoechoic nodule at left outer subareolar area with highly vascularity about 1.9x0.8x0.9 cm in size. Mammography and ultrasonography classified BIRADS 6 as there was a previous FNA result from the other hospital.

Due to discordant clinical findings and absence of slides of cytology from a previous hospital, the patient underwent core biopsy, which was undiagnostic. Therefore, incisional biopsy was performed. Regarding rarity of the disease, several immunohistochemistry studies were performed to differentiate angiosarcoma from other subtypes of sarcoma. There were positive results of CD31, CD34, P53 and Ki67 (60%+) and negative results of S100, CD3, CD20, CD138, ER, PR and HFR2. With the results of microscopic findings and immunohistochemistry, incisional biopsy diagnosed high-grade angiosarcoma.

Owing to extensive lesion involving almost the whole left breast and the skin of the left chest, mastectomy with wide excision of the skin of the left chest was not recommended as an appropriate first line of treatment. The negative margin cannot be definitely obtained if mastectomy was performed. Operation with positive margin or R_1, R_2 resection usually results in high local recurrence and distant metastasis. After careful preoperative evaluation and consultation with our oncologists, patient initially received neoadjuvant chemotherapy, which consisted of gemcitabine and docetaxel to down stage the tumor.

MRI of the breast was performed before neoadjuvant chemotherapy. There was diffuse skin thickening with infiltrative mass and multiple small nodules in the left breast. No axillary lymph node enlargement was detected.

Clinical evaluation post 1-cycle of neoadjuvant chemotherapy revealed 40% reduce in size of tumor involvement. After 3-cycle of neoadjuvant chemotherapy, MRI of the breast demonstrated decreased in size, extension, enhancement of infiltrative lesion and enhancing nodules in the left breast. The response to neoadjuvant chemotherapy was dramatic. After 4-cycle of neoadjuvant chemotherapy, the bruise discoloration reduced in size to involve only at the central part of the left breast and the skin thickening and infiltrative lesions almost completely disappeared (Fig. 2). The patient subsequently underwent mastectomy, axillary lymph node dissection, and wide excision of the skin of the chest wall, which initially infiltrated by the tumors. Immediate TRAM flap reconstruction was also performed. Postoperatively,

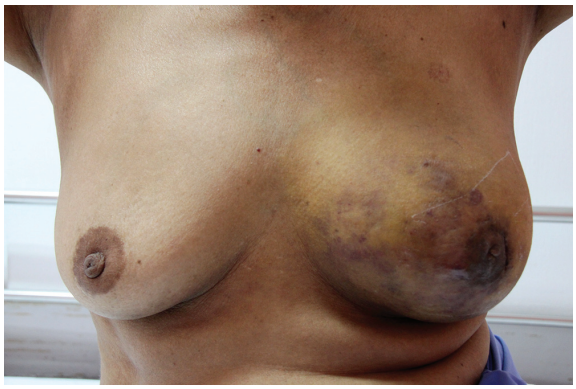

Fig. 1 A 56 year-old female patient presented with thickening of her left breast for six months.

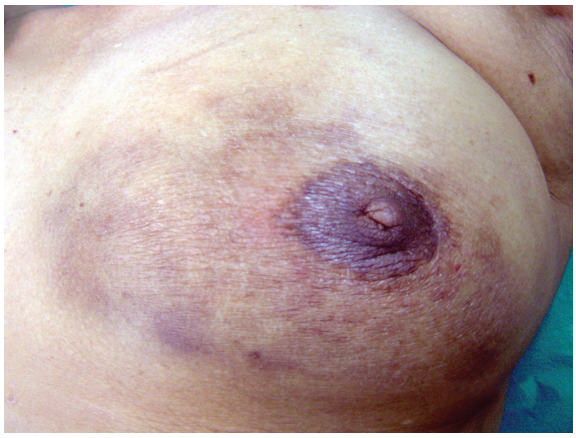

Fig. 2 After 4-cycle of neoadjuvant chemotherapy, the bruise discoloration and infiltrative lesions reduced in size.

small superficial skin flap necrosis without other serious complication was observed (Fig. 3).

Pathological examination revealed complete response to chemotherapy without viable tumor cells. There was no axillary lymph node metastasis. The patient received two additional cycles of gemcitabine and docetaxel postoperatively without serious side effects of chemotherapy. There was no evidence of distant metastasis diagnosed by CT scan of the chest and the abdomen 1 month after surgery. The patient is still free of disease at 2 years of follow-up.

Discussion

Unlike breast carcinoma, patients with angiosarcoma are usually diagnosed with advanced disease. The median age of the patients with PAS at diagnosis was 40 to 50 years[7,10]. In comparison to PAS, SAS patients are older with the peak incidence

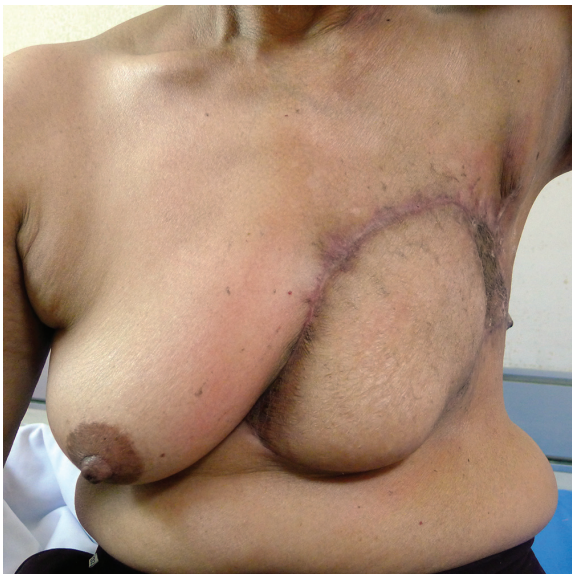

Fig. 3 The patient underwent mastectomy, wide excision of chest wall and immediate TRAM flap reconstruction.

at 60 to 70 years[6,7,9,10]. Median time between diagnosis of breast carcinoma and secondary angiosarcoma was two to eight years[5,8,10-12]. The most common presentation in PAS is a breast mass that can be detected in 50 to 75% of patients[8,9,13,14]. Less common presentations are skin thickening or swelling, bruise or rash. In contrast to PAS, SAS usually present with rash, skin color change, ill-defined patches, edema of skin, ulceration, and macules, which are detected in 70% of patients[5,8]. However, some SAS patients may be presented with a breast mass. Early diagnosis of SAS needs high index of suspicion. The changes of color at the skin or scar and the presence of rash or macule at the radiated area should alert the attending surgeon of SAS and tissue diagnosis should be urgently obtained.

In addition to different presentations from breast carcinoma, imaging study such as mammography is less accurate in angiosarcoma, there is negative result in 19 to 33%[13,14]. The finding on mammography are isodensity mass without calcifications, skin thickening, and suspicious density. High-grade tumor trends to have positive finding than low-grade tumor (100% vs. 50%)[13].

Ultrasonography can diagnose most of the patients. The most common findings are masses (62%) and diffuse lesions (38%)[14]. The majority of masses are circumscribed, hyperechoic or mixed hyperechoic and hypoechoic (>50%). There is posterior enhancement in 23% of mass lesions[14]. MRI is useful in diagnosis of angiosarcoma. All patients had positive findings such as intensely and heterogeneously enhancing masses with rapid enhancement and wash out kinetic pattern. In patients with negative mammography, ultrasonography and MRI are the reliable diagnostic imagings[14].

Tissue diagnosis should be undertaken when diagnosis of angiosarcoma is suspected even in cases of negative imaging study. FNA or core biopsy may give undiagnostic result. Multiple skin biopsies or incisional biopsies are usually required for definite diagnosis[5,8]. Due to difficulty in diagnosis and aggressiveness of the disease, both PAS and SAS are usually presented with large lesion, i.e. >5 cm[7-9,12]. This results in positive margin in nearly one third of patients who underwent mastectomy[8]. In addition, distant metastasis at first presentation occurs as high as 30%[12]. Although there is no randomized trial to compare between breast conserving therapy and mastectomy in patients with angiosarcoma, most reported patients (70-100%) undergo mastectomy[5-9,11,12]. Breast conserving therapy is not recommended because of the large size of lesion and aggressiveness of the disease. Angiosarcoma of the breast rarely metastasizes to the lymph nodes; consequently, axillary lymph node dissection is performed in less than 50% of patients with detectable metastasis in approximately 4 to 6.5%[7,8]. Several studies have been made to identify factors associated with disease free survival and overall survival such as age, prior radiation, tumor size, grade, and recurrent disease[13,14,16]. Tumor size (>5 cm) tends to decrease disease free survival and overall survival[7,16]. Tumor recurrence is also related to decrease overall survival (HR 7.89)[12]. Prior radiation has been reported to increase recurrence and risk of death[7].

Although most of the reported patients underwent mastectomy, there was positive margin as high as 30%, which resulted in high local recurrence[5,8,15]. The locoregional recurrence of 25 to 70% with median recurrent free survival of 12 to 36 months have been published[7,9,12,15]. Evidence of metastases are found in 30 to 60% of patients with recurrent disease. The common sites of metastases are bone, lung and liver[7-9,12,18].

The role of chemotherapy and radiation

Due to rarity of the disease, there is no randomized trial to establish criteria for adjuvant, neoadjuvant chemotherapy, and radiation. As mentioned above, mastectomy resulted in a significant number of

patients with positive margin; consequently, high local recurrent rate is expected. Patients with a large lesion that a mastectomy cannot give negative margin should receive neoadjuvant chemotherapy[7,9]. Adjuvant chemotherapy have been used in 20 to 70% of patients without definite criteria. Despite the limited data, angiosarcoma seems to respond to anthracycline, ifosfamide regimen that are used as first line drugs or gemcitabine, taxane as second line drugs with overall response rate of nearly 50%[7,18,19]. In addition, adjuvant radiation therapy have been used in many studies to approximately 20 to 70% of patients with variable outcome.

Chemoradiation are used more frequently in patients with inoperable than operable disease (70% vs. 20%). To date, there is no predictive factor definitely used for choosing the appropriate adjuvant therapy. Several recent studies have shown that high-grade tumor was found in the majority of patients (50-75%)[7,8,10-12]. Furthermore, estrogen and progesterone receptors were reported to be performed in less than one third of patients and most of them had negative results (>90%)[7]. According to these findings, there is no role of hormonal therapy in patients with angiosarcoma. Other immunohistochemistry for vascular marker such as CD31, CD34, factor VIII, D2-40, Ki67 are useful for diagnosis of angiosarcoma without predictive value for adjuvant therapy[17].

Prognosis in patients with recurrent disease

Although it seems to be an aggressive disease, approximately 50% of patients with recurrent disease have been reported to undergo R_0 resection. Studies in the past revealed that in the resectable group, 70% of patients received adjuvant chemotherapy and 40% received adjuvant radiation. In unresectable group, all patients received chemotherapy and 50% of these received radiation. However, the outcome was poor. After R_1, R_2 resection there was local recurrence in 30 to 100% of patients and metastases in 30 to 70% of patients[5,18]. Time to recurrence was shorter (15 months) than the first presentation. Median disease specific survival was 50 months in patients with local recurrence compared with 10 months in patients with metastasis after resection. Most of advanced disease received doxorubicin and ifosfamide or paclitaxel and gemcitabine with response rate of 20%[20,21]. The factor that associated with decreased survival was tumor size >5 cm (HR 3.26)[18].

In conclusion, angiosarcoma of the breast is an aggressive disease. The majority of patients presented with a large tumor. Surgery is the mainstay of treatment. However, nearly half of patients have had local recurrence. There are evidences that it is quite chemosensitive disease with response rate up to 50%. Most common regimens are doxorubicin plus ifosfamide or paclitaxel plus gemcitabine as second line drugs. In patients with large tumors that may result in R_1, R_2 resection, neoadjuvant chemotherapy should be considered for the purpose of negative margin. Radiation may decrease local recurrence but no statistically significant has been reported. Because of poor outcome in those with recurrence and limited data on effect of chemotherapy and radiation therapy to decrease recurrence, adequate surgery with R_0 resection is the principal part of treatment.

Potential conflicts of interest

None.

References

1. Adem C, Reynolds C, Ingle JN, Nascimento AG. Primary breast sarcoma: clinicopathologic series from the Mayo Clinic and review of the literature. Br J Cancer 2004; 91: 237-41.
2. Stewart FW, Treves N. Lymphangiosarcoma in postmastectomy lymphedema; a report of six cases in elephantiasis chirurgica. Cancer 1948; 1: 64-81.
3. Cozen W, Bernstein L, Wang F, Press MF, Mack TM. The risk of angiosarcoma following primary breast cancer. Br J Cancer 1999; 81: 532-6.
4. Huang J, Mackillop WJ. Increased risk of soft tissue sarcoma after radiotherapy in women with breast carcinoma. Cancer 2001; 92: 172-80.
5. Strobbe LJ, Peterse HL, van Tinteren H, Wijnmaalen A, Rutgers EJ. Angiosarcoma of the breast after conservation therapy for invasive cancer, the incidence and outcome. An unforseen sequela. Breast Cancer Res Treat 1998; 47: 101-9.
6. Marchal C, Weber B, de Lafontan B, Resbeut M, Mignotte H, du Chatelard PP, et al. Nine breast angiosarcomas after conservative treatment for breast carcinoma: a survey from French comprehensive Cancer Centers. Int J Radiat Oncol Biol Phys 1999; 44: 113-9.
7. Sher T, Hennessy BT, Valero V, Broglio K, Woodward WA, Trent J, et al. Primary angiosarcomas of the breast. Cancer 2007; 110: 173-8.
8. Scow JS, Reynolds CA, Degnim AC, Petersen IA, Jakub JW, Boughey JC. Primary and secondary angiosarcoma of the breast: the Mayo Clinic

experience. J Surg Oncol 2010; 101: 401-7.
9. Nascimento AF, Raut CP, Fletcher CD. Primary angiosarcoma of the breast: clinicopathologic analysis of 49 cases, suggesting that grade is not prognostic. Am J Surg Pathol 2008; 32: 1896-904.
10. Hodgson NC, Bowen-Wells C, Moffat F, Franceschi D, Avisar E. Angiosarcomas of the breast: a review of 70 cases. Am J Clin Oncol 2007; 30: 570-3.
11. Luini A, Gatti G, Diaz J, Botteri E, Oliveira E, Cecilio Sahium dA, et al. Angiosarcoma of the breast: the experience of the European Institute of Oncology and a review of the literature. Breast Cancer Res Treat 2007; 105: 81-5.
12. Vorburger SA, Xing Y, Hunt KK, Lakin GE, Benjamin RS, Feig BW, et al. Angiosarcoma of the breast. Cancer 2005; 104: 2682-8.
13. Liberman L, Dershaw DD, Kaufman RJ, Rosen PP. Angiosarcoma of the breast. Radiology 1992; 183: 649-54.
14. Yang WT, Hennessy BT, Dryden MJ, Valero V, Hunt KK, Krishnamurthy S. Mammary angiosarcomas: imaging findings in 24 patients. Radiology 2007; 242: 725-34.
15. Monroe AT, Feigenberg SJ, Mendenhall NP. Angiosarcoma after breast-conserving therapy. Cancer 2003; 97: 1832-40.
16. Zelek L, Llombart-Cussac A, Terrier P, Pivot X, Guinebretiere JM, Le Pechoux C, et al. Prognostic factors in primary breast sarcomas: a series of patients with long-term follow-up. J Clin Oncol 2003; 21: 2583-8.
17. Shin SJ, Lesser M, Rosen PP. Hemangiomas and angiosarcomas of the breast: diagnostic utility of cell cycle markers with emphasis on Ki-67. Arch Pathol Lab Med 2007; 131: 538-44.
18. Lahat G, Dhuka AR, Lahat S, Smith KD, Pollock RE, Hunt KK, et al. Outcome of locally recurrent and metastatic angiosarcoma. Ann Surg Oncol 2009; 16: 2502-9.
19. Nagano T, Yamada Y, Ikeda T, Kanki H, Kamo T, Nishigori C. Docetaxel: a therapeutic option in the treatment of cutaneous angiosarcoma: report of 9 patients. Cancer 2007; 110: 648-51.
20. Penel N, Lansiaux A, Adenis A. Angiosarcomas and taxanes. Curr Treat Options Oncol 2007; 8: 428-34.
21. Penel N, Bui BN, Bay JO, Cupissol D, Ray-Coquard I, Piperno-Neumann S, et al. Phase II trial of weekly paclitaxel for unresectable angiosarcoma: the ANGIOTAX Study. J Clin Oncol 2008; 26: 5269-74.

แองกิโอซาร์โคมาชนิดปฐมภูมิของเต้านม: รายงานผู้ป่วยและทบทวนวรรณกรรม

สุกัญญา ศรีอัษฎาพร, อภิชัย อังสพัทธ์

แองกิโอซาร์โคมาชนิดปฐมภูมิของเต้านมเป็นโรคที่พบได้น้อยมากจนไม่มีจำนวนผู้ป่วยเพียงพอที่จะทำการศึกษา เปรียบเทียบแบบไปข้างหน้าที่มีคุณภาพและความถูกต้องมากพอจะใช้เป็นแนวทางการรักษาแบบมาตรฐานได้ แนวทางการรักษาในปัจจุบันมักจะได้มาจากการศึกษารายงานผู้ป่วยที่ได้มีการตีพิมพ์ในวารสารทางการแพทย์มาแล้ว โดยมีเป้าหมายเพื่อให้ผู้ป่วยมีชีวิตยืนยาวที่สุด วัตถุประสงค์ของบทนิพนธ์นี้เพื่อเผยแพร่วิธีรักษาผู้ป่วยแองกิโอซาร์โคมาชนิดปฐมภูมิของเต้านม จำนวน 1 ราย ที่ได้รับการรักษาโดยการให้เคมีบำบัดแทกเซนส์ก่อนการผ่าตัด และตามด้วยการตัดเต้านมออกทั้งหมด ซึ่งผลการรักษาพบว่าผู้ป่วยตอบสนองต่อการรักษาเป็นอย่างดี และไม่พบการเกิดใหม่ของมะเร็งเมื่อเวลาผ่านไป 2 ปี