Asian Biomedicine Vol. 7 No. 3 June 2013; 449-454 DOI: 10.5372/1905-7415.0703.199

Clinical report

Neoadjuvant gemcitabine and docetaxel in primary breast angiosarcoma revealed complete pathological remission

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Background: Breast angiosarcoma is a rare but aggressive vascular-origin soft tissue tumor. Surgery is the main treatment. However, recent evidence has shown activity of the single agents, paclitaxel or docetaxel, in unresectable or metastasis angiosarcoma.

Objective: To report the case of a patient who received systemic chemotherapy as part of multidisciplinary approach to improve clinical outcome.

Results: We report the case of a 56-year-old female patient who presented with a locally advanced primary angiosarcoma of the left breast and received a combination gemcitabine and docetaxel as neoadjuvant chemotherapy in addition to standard multidisciplinary treatment. The patient was followed for at least 20 months without evidence of disease recurrence.

Conclusion: A perioperative combination chemotherapy consisting of docetaxel and gemcitabine can be considered as a strategy to achieve a pathological complete response and durable remission.

Keywords: Breast angiosarcoma, neoadjuvant gemcitabine and docetaxel

Breast angiosarcoma is a rare tumor that accounts for less than 1% of all breast malignancies [1, 2], and is usually rapidly proliferative and shows extensively infiltrative growth. Breast angiosarcoma could be divided into primary (de novo) and secondary (therapy-related) sarcomas depending on the etiology of involvement [3]. Primary angiosarcoma is a very rare condition and it has a worse prognosis than the secondary type. Primary angiosarcoma has a lower 5-year overall survival rate of 46% vs. 69%, respectively [4]. Surgery is its main treatment; however, the extent of surgery remains challenging issues because of the infiltrative nature of the cancer. Furthermore, because of the aggressiveness of the tumor, metastasis usually develops [5]. So far, there has not been any standard chemotherapy as a result of the rarity of the tumor, either in adjuvant or neoadjuvant approaches. Paclitaxel has been widely used in phase II studies [6, 7]. Some report activity of docetaxel, anthracycline-ifosfamide, and gemcitabine-taxane in advanced stage or recurrent disease [8, 9]. Hereby, the authors report a case of unresectable locally advanced primary angiosarcoma of the left breast in a patient who received neoadjuvant chemotherapy that resulted in a pathologically complete remission.

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Case report

A 56-year-old woman was referred to our institute because of her progressively enlarging left breast mass for 6 months. She first went to another hospital where a normal mammography was found, but two months later she developed nipple discharge and pain in her left breast. She denied previous medical illness. There was no history of chest wall radiation or breast surgery. Family history revealed breast cancer in her younger sister. The patient described in this case report has given their informed consent for this report to be published.

Physical examination revealed a swollen and dark discoloration of the overlying skin of the left breast and some part of it extended to the right chest wall; an ill-defined soft tissue lesion, 7 cm in diameter was found in her left breast. It had a reddish discharge via the nipple with thickening skin coverage; no skin retraction, but no axillary lymphadenopathy was found. Otherwise it was unremarkable.

Further mammography (Hologic Selenia Dimensions 2D, Bedford, MA, USA) was conducted to evaluate the mass lesion. Contrary to the clinical examination, the mammographic finding did not demonstrate any discrete mass, architecture distortion or cluster of microcalcifications. It showed heterogenously dense fibroglandular tissue of both breasts. The left breast was asymmetrically enlarged with increased parenchymal density, diffuse skin, and trabecular thickening. No significant enlarged left axillary nodes (**Figure 1**) were detected. However, additional ultrasonography revealed an ill-defined irregular hypoechoic mass with multiple vascular feedings at the subareolar area of the left breast (**Figure 2**). The estimated size of the mass by ultrasonography was measured about $1.9 \times 0.8 \times 0.9$ cm^3 (volume = 1.53 ml), which was much smaller than the estimated lesion size measured by the physical examination. Diffused skin thickening and subcutaneous edema were also observed by ultrasonography.

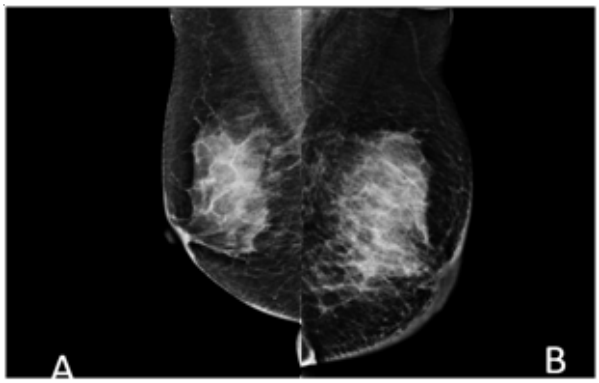

Figure 1. Preoperative mammography shows asymmetrically enlarged and diffusely increased parenchymal density, diffuse skin and trabecular thickening of the left breast (**B**) compared with the normal right breast (**A**) without discrete mass or cluster of microcalcifications. No significant enlarged left axillary node was detected.

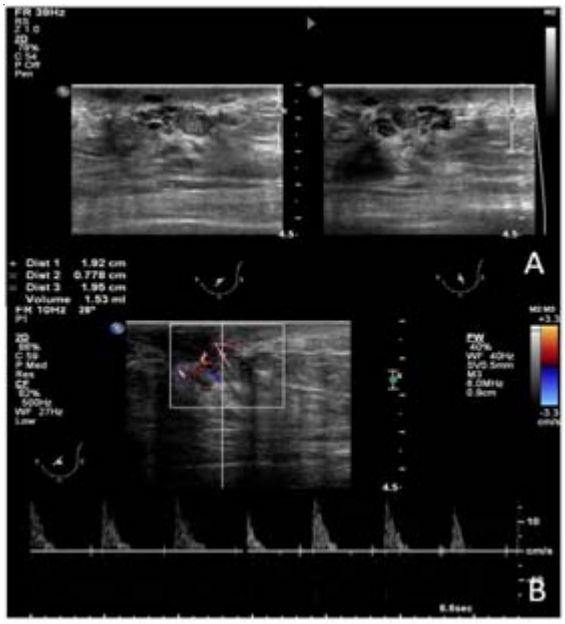

Figure 2. Ultrasonography of the left breast (**A**) shows an ill-defined irregular hypoechoic mass at the subareolar area with multiple vascular feedings when using a color Doppler technique (**B**), estimated size about $1.9 \times 0.8 \times 0.9$ cm^3 (volume = 1.53 ml). Diffuse skin thickening and subcutaneous edema of the left breast were demonstrated.

An incisional tissue biopsy was taken after an undiagnosed fine-needle aspiration. Sections of the breast tissue showed closely-packed neoplastic round-to-spindle-shaped cells with small number of vascular channels (**Figure 3A**). Mitoses and necrosis were frequently seen. Immunohistochemical study revealed diffuse and strongly positive CD31 (**Figure 3B**), and scattered positive CD34 (**Figure 3C**), but negative S100, CD45, CD43, CD30, CD3, CD138, κ, λ, HHV8, MPO, and CD68 immunohistochemistry. The final diagnosed breast angiosarcoma was documented.

MRI, the preferred diagnostic test of choice for breast angiosarcoma, was conducted to define the extent of the disease. The information from MRI can lessen the surgical planning and it has been reported as a useful screening test for contralateral breast angiosarcoma of the breast [10, 11]. MRI of the breast (1.5 T Excite HD, General Electric, Milwaukee, Wis., USA) revealed an infiltrative mass at the central part of the left breast involving subcutaneous tissues, the skin and left nipple–areolar complex. Almost all the mass showed low signal intensity (SI) on T1WI and markedly high SI on T2WI. After intravenous gadolinium administration, the mass exhibited rapidly intense arterial enhancement and prolonged enhancement in the subsequent delayed phase, representing a type II time–signal intensity curve (**Figure 4**). There were several subcentimeter nodules showing similar SI scattering in the remainder of the left breast. A small area of hemorrhage, which was possibly caused by the previous incisional biopsy, was detected. However, the presence of other hemorrhagic foci other than at biopsy site was observed, and supported the diagnosis of angiosarcoma [12]. Computed tomography (CT) of the chest revealed no discrete pulmonary nodule, pleural effusion, or significant enlarged mediastinal lymph node.

The extended and poorly demarcated area of the tumor limited the initial surgical approach, then neoadjuvant chemotherapy was planned ahead to downsize the primary tumor. The patient had a preexisting cardiac condition; frequent ventricular arrhythmia (PVC), which might limit anthracycline usage. Subsequently, a combination of chemotherapy, which aimed to attenuate the maximized response, consisting of gemcitabine and docetaxel was chosen. The schedule dosage of gemcitabine was 600mg/m^2 on days 1 and 8, while docetaxel was given at 75 mg/m^2 on day 8. No prophylactic G-CSF was given. The chemotherapy was well-tolerated by the patient. She received combination chemotherapy for 4 cycles. A follow-up clinical examination revealed regressive infiltrative lesion of the left breast mass. A follow-up MRI of the breast confirmed this and the MRI showed a decreased in size and extension of the left breast mass and multiple small enhancing nodules (**Figure 5**). A scheduled surgery was planned after the 4 cycles of the combination treatment. Modified

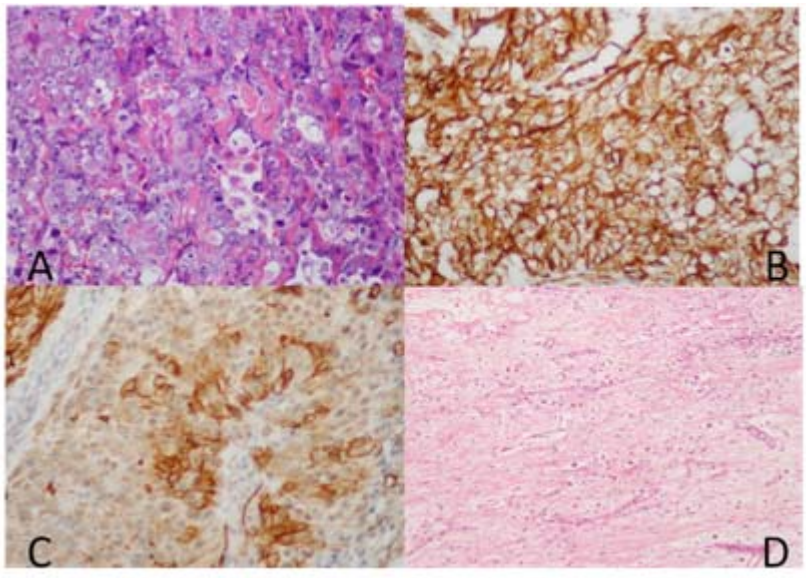

Figure 3. Histological finding of breast angiosarcoma in this case. Hematoxylin and eosin staining represents solid areas of spindle-shaped and round-shaped cells admixed with small number of blood vessels with plump and pile up endothelial lining cells (**A**). Tumor cells reveal diffuse and strongly positive staining for CD31 (**B**). Scattered positive staining for CD34 (**C**). Posttreatment shows reactive fibroblasts mixed with lymphocytes and histiocytes. No residual tumor is seen (**D**).

radical mastectomy and trans-rectus abdominis musculocutaneous were conducted. Intraoperative findings indicated neither palpable tumor nor lymphadenopathy. The patient developed postoperative seroma and a wound infection complication. Delayed wound healing was approached with split thickness skin graft. The modified radical mastectomy specimen revealed no residual tumor, which is the best surrogate endpoint (**Figure 3D**). Another two cycles of chemotherapy were given to consolidate efficacy of the treatment. No adjuvant radiation was given because of the poorly defined extend of the disease. Clinical examination, blood chemistry, and a chest X-ray were conducted along the 24-month follow-up period. The latest chest/abdomen CT and breast MRI revealed no evidence of disease recurrence. The duration from first diagnosis of angiosarcoma to the latest chest/abdomen CT and breast MRI was 20 months. The single modality, combination chemotherapy docetaxel/gemcitabine regimen was the key factor to strengthen disease-free survival of this locally advanced unresectable angiosarcoma.

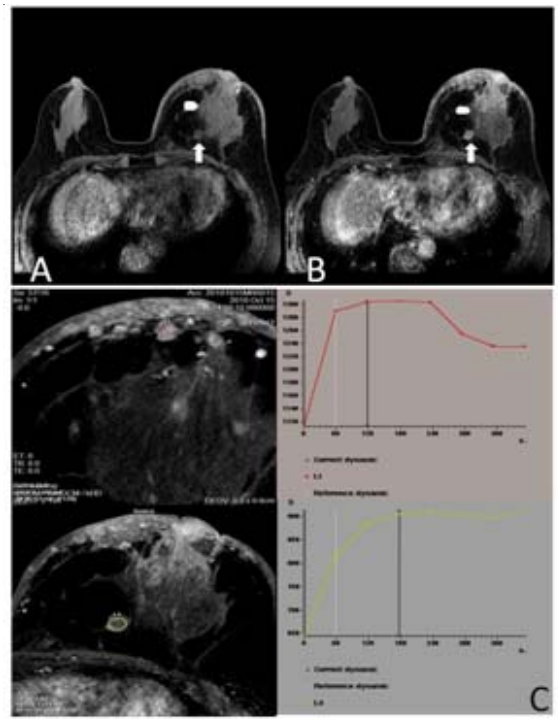

Figure 4. MRI of the breast reveals an infiltrative mass at the central part of left breast involving subcutaneous tissue, skin, and the left nipple–areolar complex. Almost all the mass shows low signal intensity (SI) on T1WI. Precontrasted MRI (**A**) compared with the arterial phase (**B**) shows a rapidly intense arterial enhancement and prolonged enhancement in subsequently delayed phase, representing a type II time–signal intensity curve (**C**). There are several subcentimeter enhancing nodules showing similar SI scattering in the left breast (arrow). A small area of hemorrhage is also detected (arrowhead).

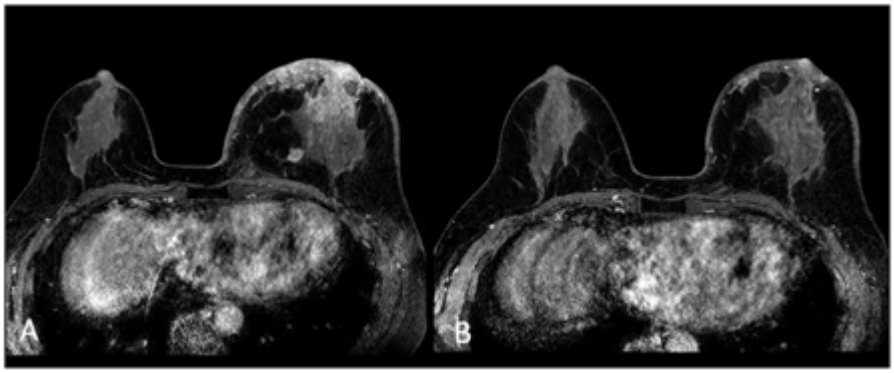

Figure 5. Post-treatment MRI (**B**) compared with the pretreatment MRI (**A**) shows decreased size and degree of enhancement of the infiltrative mass and scattered nodules.

Discussion

Primary angiosarcoma of the breast is an extremely rare histological subtype of breast cancer. There are limited numbers of reported studies. In comparison, among various types of soft tissue sarcoma of the breast and trunk wall, this tumor subtype has the worst survival outcome [1, 13]. Furthermore Scow et al. also reported there is worse overall survival outcome of primary angiosarcoma compared with secondary angiosarcoma, regardless of the histopathological characteristic findings, which reflects the distinct nature of this malignancy [4]. Early detection of small tumor size is correlated with better survival [13]. This might be the way to improve clinical outcome. To select an appropriate investigation method might be a good starting point. The commonly used methods for evaluating a general breast lesion, such as mammography, might be inappropriate for evaluation of an abnormal lesion suspected to be angiosarcoma because of its nonspecific features [4, 14-17]. The mammographic visible masses may appear as circumscribed or ill-defined margins, round, oval or lobulated shaped and may present as coarse calcifications. However, there are up to one-third of the patients diagnosed with angiosarcoma of the breast present with normal mammographic findings, which may lead to misdiagnosis and delayed treatment. Yang et al. reported 24 angiosarcomas of the breast, 19% of 16 available mammograms did not reveal any abnormality and were classified as BI-RADS 0 according to the American College of Radiology Breast Imaging Reporting and Data System (ACR BI-RADS). The remainder were classified as ACR BI-RADS 2 and 4 for 31% and 50%, respectively. Liberman et al. also reported negative mammographic findings in 7 (33%) cases [16]. Breast ultrasound and MRI are useful in the diagnosis of angiosarcoma, especially in the mammographically occult angiosarcoma. The lack of visibility by mammography, but visibility by ultrasound and MRI may be attributed to the dense breast parenchyma pattern, vague, and noncalcified features [14]. Breast ultrasonographic features may present as an ill-defined heterogenously hypoechoic mass with or without posterior enhancement. The presence of multiple vascular channels on Doppler ultrasonography supports the nature of hypervascular tumors. The MRI characteristics of breast angiosarcoma are low SI on T1WI, markedly high SI on T2WI, rapidly intense enhancement on the arterial phase and prolonged enhancement on the subsequently delayed phase. These characteristics are suspected to be the result of plenty of blood-filled vascular space and channels. The presence of multiple stages of hemorrhage within the mass is the important finding, which can distinguish angiosarcoma from other hypervascular tumors, and also can be a suggestive finding for diagnosis of angiosarcoma of the breast [12]. The presence of distant metastasis, especially pulmonary metastasis, at the time of diagnosis is also an important diagnostic clue.

Surgical resection is the primary modality for patients with angiosarcoma who have curative aim. Even though there is no consensus evidence, chemotherapy is thought as a part of multidisciplinary managements. Taxane-based chemotherapy is composed of paclitaxel and docetaxel. Both agents have shown activity in single-drug treatment in cutaneous angiosarcoma [6, 7, 9]. The single agent gemcitabine, was also shown to have activity in angiosarcoma even though it is less well-established than taxane-based chemotherapy, the overall response rate of gemcitabine was 68% in one of the retrospective studies [18]. However, in the situation of a neoadjuvant approach that aims to maximize the response of the treatment, a combination of chemotherapies might be better than a single agent. A combination of gemcitabine and docetaxel, which has previously been shown active in uterine leiomyosarcoma and other nonleiomyosarcoma histology, might be an interesting regimen [19, 20]. Superiority of combination gemcitabine and docetaxel over single agent held across the pretreatment assignment histological stratification in a randomized phase II study [20], and also in a retrospective study in various histological subtypes such as angiosarcoma, osteosarcoma, malignant peripheral nerve sheath tumor, Ewing's sarcoma [21]. The strong synergistic effect of antitumor activity of docetaxel after gemcitabine was shown an in vitro study of a sarcoma and a breast carcinoma cell line [21]. This combination regimen has also been shown responsible for a complete response in a case of cutaneous and pulmonary angiosarcoma [22, 23] as well as in our present case. The clinical tolerability of both agents has been demonstrated in many clinical trials. Combination of gemcitabine and docetaxel is an active and promising regimen in angiosarcoma, which may lead to an improved treatment response and patient outcome.

The authors have no conflict of interest to report.

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