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Clinicopathological features of breast angiosarcoma: A 16-years single-institution experience



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ABSTRACT

BACKGROUND: Breast Angiosarcoma is a rare type of malignancy arising from endothelial cells lining blood vessels, accounting for 1% of all soft tissue breast tumors. This retrospective study describes the clinical pathological features and clinical management and outcomes of a series of 5 patients with primary and secondary Angiosarcoma of the breast present to King Faisal Specialty Hospital and Research Center during the last 16 years.

METHODS: A retrospective review of our institution's pathology database was conducted and all patients who had a pathologically confirmed breast angiosarcoma were included in this study. The patient's data, including demographic characteristics, pathological features, clinical management history and clinical outcomes were collected.

RESULTS: Five patients were diagnosed with Breast Angiosarcoma (one secondary and four primary cases). The median age of patients with primary angiosarcoma was 22 years (range 13–25 years). All primary cases were presented late as post-excisional biopsy at local hospitals. Median tumor size was 6 cm (range 4.0–17.0 cm). All primary angiosarcoma patients had total mastectomy. Three-year disease-free survival (DFS) of patients with primary angiosarcoma was 25%. 5-year surviving rate of primary angiosarcoma was 50%. Recurrence was observed in three of the patients with primary Angiosarcoma and in the case of post irradiation Angiosarcoma.

CONCLUSIONS: Our study demonstrates that Breast Angiosarcoma exhibits high recurrence and mortality rates. Early detection, small tumor size, and clear surgical margins seem to be crucial factors for survival. Mastectomy with adequate tumor margin is recommended and close long-term follow-up is of utmost importance. Surgery for local recurrence may be potentially curative.

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1. Introduction

Breast angiosarcoma is a rare malignancy arising from endothelial cells lining blood vessels and accounting for 1% of all soft tissue breast tumors. Breast Angiosarcoma can be primary (of unknown cause) or secondary (following adjuvant radiation therapy for breast cancer). The prognosis for primary Breast Angiosarcoma is directly related to the tumor grade at time of diagnosis, while that for the secondary type is usually poor [1–3]. The lesion typically exhibits an aggressive pattern with metastatic potential. Radical surgical mastectomy remains the gold-standard treatment [3].

While this type of breast malignancy is extremely uncommon, data in the literature does include a number of case reports and case series. The objective of this report was to describe the clinical pathological features, clinical management and outcomes of a series of patients with primary and secondary breast angiosarcoma who presented to our institution during the last 16 years. The work has been reported in line with the SCARE [4] and PROCESS criteria [5].

2. Patients and methods

The study is a case series, retrospective in design, single institution and all cases are consecutive. All patients with breast soft tissue sarcoma listed in the department of pathology database at King Faisal Specialist Hospital and Research Center (KFSH&RC, Riyadh, Saudi Arabia) from 2000 to 2015 were identified for this study. Patients who had a pathologically confirmed Breast Angiosarcoma

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were included, whereas those who presented with benign lesions or adenocarcinoma were excluded.

Patients data were retrospectively reviewed for all available history including age, gender, menopausal status, history of radiation and/or adjuvant therapy, tumor size and grade, surgical procedures, local recurrence, and systemic metastases.

The time of diagnosis was defined as the date of histologic confirmation of Angiosarcoma. Tumor size was defined as the maximum dimension of the tumor as determined by final histopathological assessment. For patients referred after an excisional biopsy, tumor size was defined as the maximum dimension of the resected tumor described in the pathologic report. Histological tumor grade was classified as low, intermediate or high, based on pathology reports.

Disease free survival (DFS) was defined as the time from the date of pathologic diagnosis to the date of first progression (local-regional or distant) or death. Patients were censored if they had not experienced recurrence or death at the last follow-up. Patients with synchronous metastases at diagnosis were excluded from the DFS analysis.

Overall survival (OS) was defined as the time from the date of the pathologic confirmation of Angiosarcoma to the date of death from any cause. Patients were censored if they were still alive at their last follow-up.

3. Results

Four primary cases and one secondary case of breast angiosarcoma were identified between 2000 and 2015. All our cases were women; four were young (13–25 years old) and one was post-menopausal of 56 years of age; mean age was 27.6 years. A presentation of summary of all cases is exhibited in Table 1.

3.1. Case 1

A 56-year-old post-menopausal Saudi Arabian woman (gravidia 10, para 0) with a 6-year history of oral contraceptives use underwent conservative surgery (BCT) and axillary dissection (AXD) (24 lymph nodes, of which one node was positive with metastasis) for left-breast grade 2 invasive ductal carcinoma on Dec 16, 2003. The tumor was 0.8 cm in size, lobular carcinoma in situ (LCIS) and ductal carcinoma in situ (DCIS), with free margins (1 mm from deep margin), ER and PR positive, and HER2 negative. After surgery, the patient received four cycles of cyclophosphamide/doxorubicin, followed by external beam radiation for 6 weeks, then by Tamoxifen for 5 years, and she was continued on Letrozole (Femara®).

On Sep 27, 2010, skin nodules and discoloration appeared around the left mastectomy scar; punch skin nodule biopsy confirmed Angiosarcoma. Small nodules developed with ulceration in the right breast and Angiosarcoma was suspected bilaterally. The patient underwent right simple mastectomy as well as excision of the skin and subcutaneous tissue of the left chest wall, subsequently covered with skin graft. Final pathology confirmed left breast multi-centric intermediate grade Angiosarcoma: the largest focus measured 9 cm, there was no residual ductal cell carcinoma (ducts showed radiation effect), and margins were free. The right breast had no evidence of malignancy but a focus of chronic inflammation with surface ulceration was noted.

Two months later, nodules recurred on the skin of the left grafted chest wall as confirmed by fine needle aspiration (FNA).

The patient refused to undergo a second surgery and she travelled to the US where she received 4 cycles of chemotherapy successively followed by radical chest wall surgical resection (including skin, muscles, and ribs), a TRAM flap to cover the chest wall defect, and 18 cycles of chemotherapy. The patient is currently disease free and doing well.

Table 1 Summary of patients with breast Angiosarcomas presented 2000–2015.

Case #	Age	menopause	Stage	side	Prior radiation	Operative Treatment	Tumor size(cm)	Grade	Margin	ADJRx	Recurrence	DFS (m)	Treatment of recurrence	OS (m)	status
Case 1	56	post	T4N0M0	L	yes	Chest wall excision/skin graft	9	2	free	no	yes	5	Chest wall excision	Disease free	Alive
Case 2	13	pre	TxNxM0	R	no	Mastectomy/AXD	4 × 3	3	free	no	yes	2	Chest wall excision	36	Died
Case 3	25	pre	TxN0M0	L	no	Mastectomy	9 × 9	3	free	no	no	96	No recurrence	Disease free	Alive
Case 4	22	pre	TxN0M0	R	no	Mastectomy (SSM)	10 × 6 × 5	2	medial	no	yes	14	S. Mastectomy with implant removal	Disease free	Alive
Case 5	22	pre	TxN0M1	R	no	Mastectomy	17	3	free	no	-	6	-	6	Died

L Left, R Right, AXD Axillary lymph node dissection, SSM Skin sparing mastectomy, ADJRx Adjuvant Radiation therapy, DFS disease free survival, OS overall survival, m month, T tumor size, N lymph node, M metastases.

3.2. Case 2

A 13-year-old Palestinian girl (premenopausal), born in eastern province of Saudi Arabia, developed a lump in her right breast which was noticed by her mother on Jan 7, 2004. The lump was painless and rapidly growing, no known history of oral contraceptive use, nor personal or family history of breast or ovarian cancer. She visited a local hospital within 2 weeks from symptoms appearance and was diagnosed with fibroadenoma. A lumpectomy was performed and the tumor was reported as grade 3 invasive ductal carcinoma of 4 × 3 × 1 cm size.

On Jan 18, 2004, she underwent right modified radical mastectomy (MRM) with axillary dissection which confirmed residual 0/8 lymph nodes.

The patient referred to our institution in May 2004 where the examination of outside slides confirmed the diagnosis of high-grade Angiosarcoma. Resection margins were negative; tumor cells were strongly and diffusely positive for CD31 vascular marker and focally positive for CD34. The tumor cells are negative for desmin, smooth muscle actin (SMA), muscle specific actin (MSA), vimentin and S100.; CT scan and bone scan were negative for metastases.

Three years later, the Angiosarcoma recurred at the axillary tail; chest wall excision was performed and pathology revealed recurrent high-grade Angiosarcoma (tumor size 2.5 × 2.5 × 2 cm with lymph vascular invasion and positive deep margin). The patient visited another local hospital where she underwent resection and chemotherapy without any signs of improvement and she eventually died in Sep 2008 at the age of 16.

3.3. Case 3

A 25-year-old premenopausal divorced woman (G0) from the central province of Saudi Arabia developed a growing left breast mass with skin ulceration 6 months before she presented to the local hospital where inoculation of the mass was performed and revealed pleomorphic liposarcoma with incomplete excision. (17 × 13 × 8 cm). Two months later, recurrence occurred at the site of surgery.

The patient had no prior history of radiation or hormonal replacement therapy, nor personal or family history of breast or ovarian cancer. She had chronic iron deficiency anemia (diagnosed at age of 24) that improved with iron supplementation.

She presented to our institution on Oct 20, 2007, with a blue discolored lump in the left breast at the site of her previous surgery with a radial scar at 3 o'clock with indurations, no defiant mass was detected, retracted nipple, and multiple enlarged left axillary lymph nodes.

Mammography showed a left breast high-density nodule (2 × 3 cm) at the upper outer quadrant and another nodule (1.6 × 0.9 cm) at the lower inner quadrant suggestive of residual tumor with skin thickening but with no suspicious micro-calcifications. Ultrasound revealed multiple nodules in all quadrants of the left breast with post-operative distortions, and CT-scan and bone scan showed no distant metastases.

Outside pathology slide was examined at our institution and high-grade Breast Angiosarcoma was confirmed (17 × 13 × 8 cm).

On Nov 27, 2007, simple mastectomy was performed and pathology showed high grade, poorly differentiated Angiosarcoma (9 × 9 × 3 cm) with free margins, one reactive lymph node, and no metastases. The tumor cells were positive for CD34 and weakly positive for S100 and negative for CD31, desmin, muscle-specific actin, EMA, cytokeratin, and low molecular weight cytokeratin.

The patient was regularly followed-up without any further treatment; she underwent a reconstructive surgery for her left

breast in Oct 2009, and is still on annual follow-up (median follow-up: 8 years) with no signs of recurrence.

3.4. Case 4

A 22-year-old Jordanian, single premenopausal woman developed right breast lump at the retro-areolar region one month before she presented to a local hospital, where she underwent an excisional biopsy and diagnosed with a 6-cm intermediate grade angiosarcoma.

On May 2003, months after biopsy, she presented to our institution after she developed another painless and progressively expanding lump at the site of surgery.

She had no previous history of radiation or hormonal replacement, nor personal or family history of breast or ovarian cancer.

Mammography was inconclusive because of high density of the breast; ultrasound showed a large ill-defined heterogeneous mass of 6 × 7 cm in the upper inner quadrant of the right breast with high and low echogenic areas of increased vascularity. Bone and CT- scans were negative for distant metastases.

On June 25, 2003, the patient underwent a right skin-sparing mastectomy with immediate reconstruction at our institution and histopathology showed an intermediate grade angiosarcoma, of 10.5 × 6 × 5 cm tumor size, with anterior and medial margins positive for the tumor (positive CD34, CD31, and factor VIII). Re-excision was done and showed skin and deep margin invasion; the second pathology ruled out residual Angiosarcoma.

Nine months later, the patient developed small nodules at the scar of previous surgery. Recurrence was confirmed by FNA showing spindle cells with multinucleated giant cells and histocytes. Re-excision with implant removal was performed and final pathology confirmed the recurrence of angiosarcoma (multifocal, free margins). The patient was afterwards on regular follow-up for 2 years with no signs of recurrence.

On Dec 12, 2006, the patient underwent TRAM reconstructive surgery of the right breast. Eleven months later, she developed small nodules in the right reconstructed breast. FNA confirmed recurrence of Angiosarcoma; TRAM of right breast was excised and showed a 6-cm angiosarcoma mass invading the skin, subcutaneous tissue, and skeletal muscles with deep margins and 0.1 cm from inferior margin. Re-excision was performed and showed no residual tumor with negative margins. The patient has been on regular follow-up since then (median follow-up: 12 years) without any signs of recurrence.

3.5. Case 5

A 23-year old single premenopausal female college student from the eastern province of Saudi Arabia presented with a primary Breast Angiosarcoma and lung metastasis.

She first noticed a mass in the right breast, increasing in size over 2 years, but not associated with pain, nipple discharge, or skin changes. She underwent lumpectomy at a local hospital and was diagnosed with cystic benign phyllodes tumor. One week later, a bluish discolored mass developed at the site of excised mass; hematoma was suspected but the mass grew to 9 cm. She presented to our institution on Sept 24th 2013 with a painless lump in the upper inner quadrant of her right breast 6 months after lumpectomy.

She had no previous history of radiation or hormonal replacement therapy, nor personal or family history of breast or ovarian cancer.

On examination, the periareolar scar was extending from 10 to 3 o'clock. A blue discolored mass was seen at the upper inner quadrant of the right breast, of 9 × 9 cm, soft, with areas of skin necrosis and small multiple blue discolored lumps around the main mass



Fig. 1. Right breast of Case 5 showing A blue discolored mass was seen at the upper inner quadrant of the right breast, of 9 × 9 cm, soft, with areas of skin necrosis and small multiple blue discolored lumps around the main mass.

without skin necrosis, a big painless and underlying mass occupying the right breast, with nipple retraction but without discharge. There was no axillary lymph node involvement and the left breast was normal (Figs. 1 and 2).

review of pathology slides at our institution showed a low-grade angiosarcoma of unknown tumor size and margins.

Ultrasound of the right breast showed a large ill-defined heterogeneous hyper-vascular mass extending from the immediate retro-areolar region, with extensive vascular channels, of arterial and venous component, and with low resistive index on power Doppler assessment.

IV-contrast CT-scan of the chest, abdomen, and pelvis showed a huge soft tissue mass occupying the right breast, of about 17 cm with coarse calcification, no axillary nor mediastinal lymphadenopathy, and multiple lung nodules suggestive of metastasis. Bone scan was negative.

The patient underwent right simple mastectomy on Sept 30, 2013, and pathology showed high-grade angiosarcoma, 0.1 cm from deep margin. The patient was planned to receive external beam radiation, but the second chest CT done on Feb 16, 2014, confirmed the progression of lung metastases. The patient died 7 months after presentation to our institution.

Three out of the five patients are currently alive; case 2 died three years after diagnosis and case 5 died seven months after diagnosis.

In primary Angiosarcoma patients, 3-year DFS rate was 25% and 5-year OS rate was 50%. Recurrence was observed in three patients with primary angiosarcoma, and in post irradiation angiosarcoma.

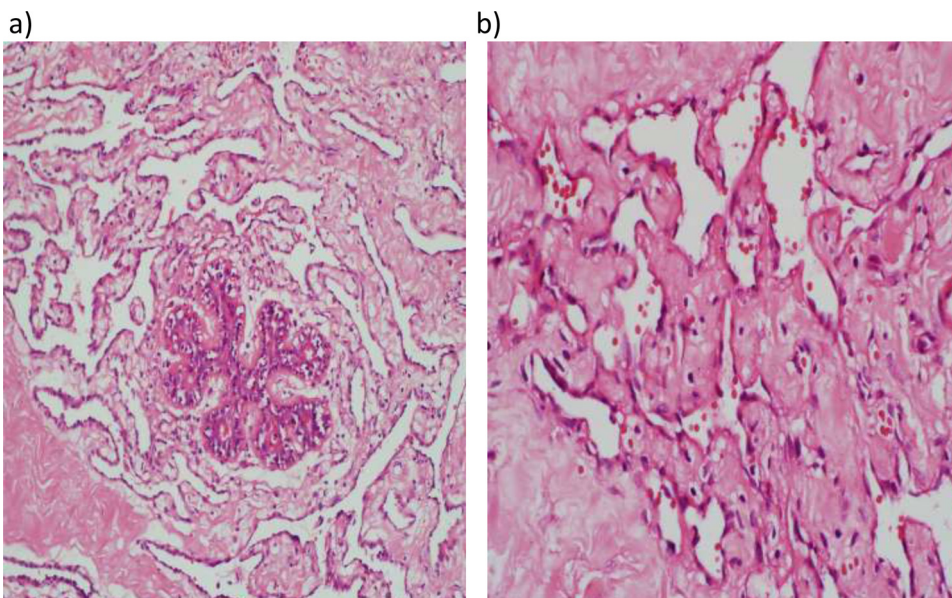


Fig. 2. Microscopic photograph of the breast lesion of case 5 stained by H&E shows a) vascular spaces infiltrating breast stroma around duct and b) Anastomosing vascular channels dissecting lobular stroma.

4. Discussion and conclusion

This case series describes the five cases with Breast Angiosarcoma treated at KFSH&RC from 2000 until 2015. The rarity of this type of malignancy, whether primary or secondary, impedes the initiation of large studies investigating the exact risk factors for developing Breast Angiosarcoma or comparing different treatment modalities' outcomes. Consequently, to date, most information available on the subject was derived from sporadic case reports that lack unified criteria in terms of diagnosis, staging, and treatment, which makes them highly subjective. Most reports describe cases of secondary Breast Angiosarcoma, while very few series of primary Angiosarcomas are published.

Primary cases in our study were very young, which is coherent with the literature stating that primary Angiosarcoma is more common in younger premenopausal females with no previous cancer history [6].

The common clinical finding in primary cases was the presence of bluish discolored rapidly growing lumps at the site of excisional biopsy, while skin nodules were noticed at the site of radiation in the secondary case. These findings represent the typical clinical presentation cited in the literature for both types [3,6].

Four patients had localized disease at presentation, while one patient had distant metastasis. This type of sarcoma is known for its metastatic potential: although it is unlikely to invade adjacent lymph nodes, frequent metastatic sites include the bones, the lungs, the liver, and the contralateral breast [2].

Recurrences developed in three patients: two presenting with primary disease and one with post radiation disease. Local and distant recurrences are usually frequent in Angiosarcomas and are considered as a poor prognostic indicator [1,7].

While mammography and ultrasound are the most commonly used diagnostic tools prior to biopsy, they might miss certain tumors especially in younger patients with denser breast tissues. MRIs seem to be better able to detect typical signs of malignancy [3].

In the absence of evidence-based guidelines on the treatment of Breast Angiosarcoma, different studies have reported several modalities. Total mastectomy with wide surgical resection seems to be the gold standard, but it is controversial whether or not it should be followed by chemotherapy; some studies propose the use of breast conservative surgeries followed by radiotherapy for primary smaller lesions [2,3,7]. Axillary dissection does not seem to improve the clinical outcome and is unnecessary in the majority of cases [7].

In conclusion, our report demonstrates that Breast Angiosarcoma exhibit high recurrence and mortality rates. Early detection, small tumor size, and clear surgical margins seem to be essential for better prognosis. Mastectomy with adequate tumor margin is recommended and close long-term follow-up is of utmost importance.

Conflicts of interest

The authors declare that there are no potential conflicts of interest to declare.

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Ethical approval

Project # 2151 136 Final Report. Clinicopathological Features & Outcome of Breast Angiosarcoma; A Study of Sixteen Years'. Experience of Clinical Practice in Single Institution. The Final Report (email received on 05 May 2016) on the above-referenced project was reviewed by the Research Ethics Committee (REC) on 11 May 2016. The REC has accepted the revised Final Report.

Consent

Consent from the patient was secured for this case series and is available upon request.

Author contribution

Badria Aljohani, Taher altwajeri, Ihab Anwar, Asma Tulba, Osama Al malik: Study concept and design.

Badria Aljohani, Ahmed alameer, Turki alzaydi, Saad Alawwad, Osama Al malik: Acquisition of data.

Badria Aljohani, Taher altwajeri, Osama Al malik: Drafting of the manuscript and edition.

Badria Aljohani, Taher altwajeri, Ihab Anwar, Asma Tulba, Osama Al malik: Critical Revision of the manuscript for important intellectual content.

Guarantor

The guarantor for this manuscript is Badria Aljohani and Osama Almalik.

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