Primary Breast Angiosarcoma: A case report and literature review

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Abstract

Breast angiosarcomas are a specific subgroup of sarcomas classified as primary or secondary, the latter being related with radiotherapy following breast conserving surgery and the presence of chronic lymphedema. Primary breast angiosarcomas predominantly occur in younger females usually with non-specific clinical and imaging features. Surgery is the treatment of choice. Standard guidelines are not available in the absence of consensus on the effectiveness of chemotherapy. Adjuvant radiotherapy has been used for local control. We present a case of a primary breast angiosarcoma on the grounds of a previously excised benign lesion and review the literature on these aggressive tumours.

Case report

A 55-year-old postmenopausal, otherwise fit and healthy female, presented to our breast clinic with a few months history of a developing localized soft swelling and fullness in the upper inner quadrant of her left breast. She had a family history of two second degree relatives with breast cancer. Four years earlier she had an open biopsy of a reportedly palpable mass of the upper half of the same breast. Histology of that specimen demonstrated a benign complex sclerosing lesion with negative CK 5/6 and P63 immunostaining assay.

On clinical examination a mild diffuse swelling was observed. There was no tenderness, skin discoloration, nipple discharge or retraction. The patient was referred for diagnostic work up including mammogram, ultrasound and breast MRI. Digital mammography with 3D tomosynthesis demonstrated the presence of heterogeneously dense breast tissue (ACR C) with no suspicious findings, asymmetry and discrete mass or suspicious calcification. The ultrasonographic evaluation revealed a diffuse ill-defined area of increased echotexture containing multiple hypoechoic non-vascular lesions with a maximum diameter of about 4cm. MRI demonstrated a 6cm area, exhibiting persisting and plateau enhancement kinetics and a heterogeneous signal intensity on T1 and T2 weighted sequences, reflecting the presence of glandular and adipose tissue components. A hamartoma was reported in the differential diagnosis of the MRI report. There were no clinical or imaging signs of lymphadenopathy. The lesion was assigned a BI-RADS category IV (Figure 1a and b).

A second look US scan with multiple guided core needle biopsies was performed (Figure 1c). Pathology described a highly vascular tissue sample, vascular endothelial cells with mild cellular atypia, presence of hob nail like cells, and a Ki-67 of 20-30%. Immunostaining assay for vascular endothelial marker CD31 and markers FLI1 and ERG was markedly positive. A diagnosis of

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Figure 1: Mammogram, ultrasound and breast MRI: A. Spot compression mammogram with non-specific findings. B. Determination of a diffuse area of increased echo texture by ultrasonographic imaging. C. MRI indicates the presence of a large lesion of the superior inner quadrant of the left breast exhibiting persisting and plateau enhancement kinetics.

Figure 2: Surgical procedure: A. Surgical planning and mastectomy with partial excision of the pectoralis major muscle. B. Cross section of the resected breast showing a poorly circumscribed tumour that extends to the overlying skin.
a low to intermediate grade angiosarcoma was concluded. Due to the discordance of the radiology and pathology reports, the sample was referred to a second pathologist who confirmed the diagnosis of well differentiated PBAS. Staging with abdominal, chest and head CT scans did not reveal distant metastases (Figure 2a and b).

Following a detailed discussion, the patient was submitted to a right mastectomy and sentinel lymph node biopsy. A superficial layer of pectoralis major fibers underlying the area of concern was removed en block with the breast. Gross examination of the specimen confirmed the presence of a 5.8cm tumor with irregular margins within the breast parenchyma. On cut section the mass had a dark brown to pink color and soft consistency. Microscopically, the tumor was composed of an intricate anastomotic network of vascular channels, with papillary formations, mild to moderate cellular atypia and a mitotic index of 8/mm². Necrosis was absent. The closest radial margin was > 15mm, while the posterior margin though close was negative and there was no infiltration towards the muscle fibers. The 2 sentinel lymph nodes were also negative. The final diagnosis was low/intermediate grade breast angiosarcoma (T3 N0M0) (Figure 3a, b).

The oncology board suggested adjuvant radiotherapy only which the patient received in 30 cycles. At 15 months postoperatively the patient remains disease free.

Discussion

Breast sarcomas account for less than 5% of soft tissue sarcomas and less than 1% of all breast malignancies, with angiosarcomas representing the predominant histological subtype. Breast angiosarcomas (BAS) have a vascular origin and based on etiology, are divided in two clinically distinct entities, primary and secondary(1). Primary breast angiosarcomas (PBAS) represent 0.04-0.05% of all malignant breast tumors. Approximately 20% of BAS are primary with an incidence of about 17 new cases per million women(2). PBAS have no established risk factors. Even though the pathophysiological pathway underlying angiosarcomas formation remains unclarified, recent studies have defined risk factors including UV radiation, chronic lymphoedema, occupational exposure to vinyl chloride and certain familial syndromes, with radiotherapy acknowledged as the predominant risk factor for secondary BAS (3). PBAS usually develop during the third and fourth decade of life (median age 35 years) (1,4) and are often associated with pregnancy as 6-12% of PBAS cases occur in gestating women, suggesting involvement of hormonal mechanisms. Hormonal dependency of PBAS is not supported by the fact that estrogen receptor positivity is uncommon. Moreover, cases of PBAS in post-menopausal women have been reported (5).

PBAS clinical manifestations vary. They may present with a sense of fullness of the breast, an evolving
asymmetry or a rapidly growing painless palpable mass. The subcutaneous tissue and overlying skin are rarely involved. When the tumour is superficial skin thickening and purple/bluish skin discoloration or even ulceration may be apparent (6, 7). Nipple discharge and retraction has also been described (7).

The imaging diagnosis of PBAS is challenging especially in younger patients with dense breasts and low grade tumors. Mammography may demonstrate asymmetrical density or the impression of an ill-defined mass with irregular shape and circumscribed or indistinct margins. The presence of coarse calcifications and skin thickening, have also been reported. Mammograms appear normal in one third of the cases (8,9,10). Ultrasonographic features are also non-specific and may include a hypoechoic or hyperechoic mass, diffuse ill-defined regions of mixed echo texture or even irregular anechoic cystic portions. Color Doppler may demonstrate hypervasularity (11,12). MRI is the imaging modality of choice for the characterization and diagnosis of BAS. In most cases MRI allows the assessment of the regional extent of the tumor and its vascular properties. Common findings include a heterogeneous mass with hypointensity on T1-weighted and hyperintensity on T2-weighted images, with washout kinetics being dependent on the grade of the tumor (2,13). PET -CT has been proposed for further investigation, with the lesions usually exhibiting diffuse FDG uptake(14).

Preoperative histological diagnosis by fine-needle aspiration or preferably tru-cut biopsy, can be challenging due to the highly vascular nature of these tumors and their resemblance to other breast abnormalities. A false negative rate of up to 37% has been reported for FNAC, however core biopsy specimens and full thickness incisional biopsies are considered conclusive (15,16).

Donnell et al. have stratified breast angiosarcomas into three grades: 1) Group I (low grade) comprising of anastomotic vascular channels coursing through surrounding breast tissue, 2) Group II: (intermediate grade) with increased mitotic rate, papillary formation with or without solid or spindle cell foci and 3) Group III (high grade) with prominent sarcomatous areas, solid and spindle cell foci with numerous mitosis, areas of necrosis, hemorrhage and infarction (17). Characteristics of any of the above groups can co-exist in the same tumor, while the less well-differentiated features of groups II and III tend to be located in the tumor center rather than the periphery, thus explaining the large number of false negative FNAC exams and the need for thorough histopathological evaluation (7,17).

Various immunohistochemical stains are used to differentiate BAS from other types of invasive carcinomas. The presence of endothelial markers CD31 (the most specific marker), CD34 (the most sensitive marker) and factor VIII (von Willebrand factor) confirm the diagnosis. Ki-67 rates are exhibited indicating the invasive tendency of sarcomas. However, misdiagnosis is fairly common with up to 37% of cases being initially reported as benign (18,19,20). The differential diagnosis includes hemangioma, angiolipoma, pseudoangiomatous stromal hyperplasia, fibroadenoma, benign spindle cell proliferative lesion, mastitis, invasive carcinoma, squamous cell carcinoma with sarcomatoid features, myoepithelioma, fibromatosis, sarcoma-like liposarcoma and malignant phyllodes tumor(21,22).

Staging is based on AJCC guidelines in accordance with other soft tissue sarcomas. Tumor grade and size, nodal involvement the presence or absence of distant metastasis are incorporated and evaluated (1). BAS show a propensity towards hematogenous rather than lymphogenous spread and aggressively procure metastases to the lungs, skin, liver, bones, central nervous system, spleen, ovary, lymph nodes and heart (23,24). Very rarely BAS can manifest bilaterally (7).

Surgery represents the curative modality of choice for BAS. Complete resection with optimal margins is the mainstay of treatment since positive margins are significantly associated with higher risk of local failure (8,25,26). Due to the rarity of the tumor, therapeutic recommendation between breast conserving treatment and total mastectomy is not yet definite, the former usually employed in small tumors where adequate margins can be ensured. Mastectomy is generally performed in larger or ill-defined masses.

Since BAS metastasize hematogenously axillary surgery is performed in cases of clinically positive nodes, histologically proven isolated nodal disease or enlarged palpable nodes as intra-operative findings (15,27). There is no international consensus on adjuvant chemotherapy for operable or inoperable BAS or subsequent metastatic disease. Adjuvant paclitaxel as first line treatment for unresectable BAS has been reported with promising results. Second line treatment options (pazopanib, bevacizumab, eribulin mesylate)have also been reported recently (28,29). Given the benefits of chemotherapy in metastatic and unresectable BAS it is arguable that adjuvant chemotherapy should be advocated for patients with high risk localized disease.

Radiotherapy may be beneficiary, however, the validity of the studies is questionable due to the small number of cases. Previous studies supported adjuvant radiotherapy particularly in cases of incomplete surgical resection with positive margins (30). Radiotherapy is sometimes proposed for locoregional control and reportedly has a favorable
outcome for patients with tumors larger than 5 cm who are at higher risk for local recurrence (31).

Several studies have classified BAS as an aggressive malignancy with a poor overall prognosis, compared with other breast malignancies. Grade and tumor size at diagnosis are considered to be the most consistent prognostic factors. Low grade tumors are associated with significantly higher survival rates, and according to some studies, with clinical presentation and overall prognosis (32,33). Although it is suggested that tumor size is an important prognostic factor and some studies have related larger tumors with decreased OS and increased risk of LR, however, these results are not reproduced in other studies depicting the need for a larger sample size (32,34,35). Positive margins are associated with worse prognosis (27). BAS median DFS and OS times are 2,26 years and 2,96 respectively, while the 5-year OS rate of localized PBAS is 50-60% (37). Case reports also suggest that PBAS may also rarely present as a multifocal tumor (38). A cohort study of 103 breast sarcoma cases 41% of which angiosarcomas, showed a statistically significant correlation between residual tumor and/or close margins (of less than 10mm) and poor survival rate (39). Several studies have illustrated the importance of tumor size as a prognostic factor revealing an increased risk of local recurrence and decreased overall survivor with large tumor size (40, 41). It has been reported that lymph node metastases may occur among high grade sarcomas in 3-25% of cases predominantly regional metastatic diffusion from epithelioid subtype sarcomas (42). Despite the hematogenous metastatic route attributed to angiosarcomas, lymph node metastasis has also been reported (38, 43). Therefore, sentinel node biopsy appears an acceptable choice, especially when the total mastectomy approach is preferred, potentially protecting the patient from a second surgery, in case the pathology report reveals the co-existence of synchronous invasive breast cancer. A case of concurrent breast stroma sarcoma and breast carcinoma has been reported in literature (44).

**Conclusion**

Primary breast angiosarcomas are rare and aggressive mesenchymal malignant tumors characterized by unusual clinical and radiological characteristics, rapid growth and high hematogenous metastatic potential. Our case illustrates their clinical, imaging and histopathological diagnostic challenges. Core needle biopsy is useful for initial diagnosis and Immunohistochemistry is mandatory since microscopic findings may be misinterpreted as benign. Complete resection with wide margins is the main surgical treatment goal. Axillary surgery should be tailored to clinical findings and surgery type. Chemotherapy may be beneficial in cases of high-grade and metastatic lesions. Despite the concern about the radiation related etiology of secondary breast angiosarcomas, it may reduce local recurrence rates following surgery for primary breast angiosarcomas.

**References**

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