RECURRENT PRIMARY BILATERAL BREAST ANGIOSARCOMA - CASE REPORT AND LITERATURE REVIEW

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Abstract

Primary angiosarcoma of the breast is a rare entity. They arise in the vascular endothelium and represent only 0.04% of all malignant breast tumours. This paper reports a case of previous primary bilateral breast angiosarcoma, with a unilateral recurrence in a 48 years old female

Introduction

Angiosarcomas are highly aggressive malignant endothelial cell tumours. In 1887, Schmidt described breast angiosarcoma (BAS) for the first time. BAS may be primary, or secondary due to radiation [1]. Primary breast angiosarcomas are extremely rare [2], and account for 0.04% of all malignant breast neoplasm [3][4][5]. They generally have a poor prognosis due to a high rate of local recurrence and early metastasis. They are more common in young women, and patients mainly present with a palpable mass [1]. Secondary breast angiosarcoma arises in older patients, and evidence suggests that, it is correlated to radiotherapy, with a latency period of 5 years or more [1][6]. In this case report we present a 48 years old lady with recurrent primary BAS and discuss the management used in her case.

Case presentation

A 48 years old woman presented with a recent history of a palpable right breast lump. Fifteen years earlier she was diagnosed with low grade angiosarcoma in the upper portion of the right breast, this was treated with wide local excision and radiotherapy. Five years later she then developed a similar lesion in the left side, which was also excised in addition to postoperative radiotherapy. The patient had no family history of breast or ovarian carcinoma.

At recent presentation, there was a 4cm discrete palpable mass in the right upper inner quadrant of the breast, which was related to the previous surgical scar. Mammogram showed a radio-opaque indeterminate well defined 4cm oval heterogeneous lesion in the right breast’s upper inner quadrant. The tumour contained small foci of calcification (Figure 1). Breast ultrasound revealed a suspicious 40mm lesion with absence of posterior acoustic shadowing, which was characteristic for breast adenocarcinoma (Figure 2). This raised a suspicion of fat necrosis due to previous surgery or BAS recurrence. Findings were graded as M4/5 and U4/5 according to BIRDS (Breast Imaging Reporting and Data System). A Computed Tomography (CT) scan revealed no tumour extension to the subcutaneous tissue or underlying pectoralis major muscle, and no definite distant metastatic disease, furthermore, a whole body bone scan demonstrated no bony lesions (Figure 3). An ultrasound guided core biopsy was taken from the lesion, which showed low grade angiosarcoma.

The recurrent right BAS was surgically removed with a breast conservation technique. Histological analysis, demonstrated that the lesion was a poorly circumscribed vascular tumour featuring severely atypical cells lining
pseudo-vascular spaces and forming solid sheets in places. The tumour cells showed both spindle and epithelioid morphology and dissected breast parenchyma. Areas of tumour necrosis were present and mitoses, including atypical forms. These features are consistent with high grade angiosarcoma (Figure 4a and 4b). The tumour measured 40mm in maximum diameter with a very close deep margin. Immuno-staining was negative for MNF116 (Epithelial marker). This marker is usually positive for BAS. As a result, this case was referred to a specialist sarcoma centre for confirmation and further immuno-staining with Erythroblast transformation specific related gene (ERG), which is an Endothelial marker. This was reported as positive and consistent with our diagnosis of angiosarcoma (Figure 5). After further discussion of the case at our Breast Multidisciplinary Team, as well as at the Soft Tissue Sarcoma Tertiary Centre, further surgery was advised. The patient was involved in the treatment decision process and following this, a bilateral completion mastectomy with ADM and breast implant based immediate reconstruction was offered and performed (Figure 6). Currently, the patient is under three monthly surveillance with chest X-ray, and progressing very well.

Radio-opaque indeterminate 4 cm oval well defined heterogeneous lesion in the right breast upper inner quadrant.
Figure 2: Right breast US: Fair well defined lesion with a heterogeneous texture 40x16x26 mm.

Figure 3: CT scan showing the right breast hypodense mass without chest wall invasion.
Figure 4 (a&b): Poorly circumscribed vascular tumour with severely atypical cells lining pseudo-vascular spaces and forming solid sheets. There are spindle and epithelioid morphology cells seen dissecting breast parenchyma. Areas of tumour necrosis are present. Mitoses including atypical forms are seen.
Figure 5: Erythroblast transformation specific related gene (ERG) [Endothelial marker] was reported positive and consistent with diagnosis of angiosarcoma.

Figure 6: Surgical outcome after bilateral mastectomy with ADM and implant based immediate reconstruction.

Discussion
Angiosarcomas are aggressive malignant neoplasms of vascular origin, also called hemangiosarcoma or hémangioendothéliosarcome. It arises in the endothelium lining the blood vessels, and usually develops on the head and neck, but can develop in other sites such as the liver and lung, but this is less frequent [7]. Angiosarcoma is an aggressive neoplasm that predominantly affects elderly patients. Most cases appear on the scalp and face de novo, however, trauma, longstanding lymphedema, and irradiation are predisposing factors [8][9]. In 1907, Borman wrote about BAS for the first time. BAS represents 1% of all soft tissue breast tumours [10], and is classified into two major groups depending on the origin and the cause; they are the primary BAS and the secondary, post-radiation therapy BAS, which is also known as a cutaneous angiosarcoma [2][10]. Primary BAS, arises within breast parenchyma and occurs sporadically in young women usually during the third and forth decades of life. Bilateral disease involvement is common, whereas nodal metastases are exceptional [11]. They form approximately 3-9% of
angiosarcomas of the breast, and up to 12% of primary BAS are diagnosed during pregnancy or shortly after, suggesting hormones involvement. Secondary BAS most frequently occurs in older patients who have previously had breast cancer treated with breast conservative surgery and radiotherapy [5][12]. The median latency period to presentation after radiotherapy from the literature was 6.13 years (range 4 to 13 years) [13]. Secondary BAS is also noticed in chronically lymphoedematous arms after axillary treatment for carcinoma. The terminology, (Stewart–Treves) syndrome, is predominantly applied to any angiosarcoma that arises in any area of chronic lymphoedema related to any cause, this may include; congenital lymphoedema, trauma and any other causes of secondary lymphoedema not associated with mastectomy [14]. The association of radiation with angiosarcoma is a well established iatrogenic phenomena, this disease category mainly involves the skin, which is why it is called as cutaneous angiosarcoma [2]. Some authors also related angiosarcoma to previous breast trauma or surgery [15]. Primary angiosarcoma usually presents as an area of tissue thickening, skin discolouration, bruising or rashes. A palpable painless mass with blue-reddish skin discolouration is a common presentation of secondary BAS [1]. The growth pattern may be rapid, and the mass usually greater than 4cm [16].

There are three histological grades of angiosarcoma described, (see Table1). Low grade variety, which consists of anastomosing vascular channels invading the breast tissue. These channels are lined by neoplastic and proliferative endothelial cells. Also, there is mild degree of atypia and minimal mitotic activity. The intermediate grade, has a more solid neoplastic vascular growth, in addition to increased mitotic rate. There is also additional cellular foci of papillary formations and spindle cell proliferation, in addition to more mitotic activity. The third grade, is the high grade lesions, where there is endothelial tufting and papillary formation. There are gross sarcomatous areas, associated with areas of tumour infarction, haemorrhage and necrosis seen [1][12][17][18].

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<th>Table 1: Histological classification of Breast Angiosarcoma, from Halls 2000 [17] and Rouse 2005 [18].</th>
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<td>Grade</td>
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<tr>
<td>40%</td>
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<tr>
<td>Papillary growth</td>
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<tr>
<td>Endothelial tufting</td>
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<tr>
<td>Cytologic atypia</td>
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<tr>
<td>Mitotic figures</td>
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<tr>
<td>Solid areas</td>
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<td>Necrosis</td>
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<td>Blood lakes</td>
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Immuno-histochemistry remains crucial in the diagnosis of angiosarcoma. The endothelial marker, CD31 (cluster of differentiation 31), also known as Platelet endothelial cell adhesion molecule (PECAM-1) makes up a large portion of intercellular junctions of endothelial cell. It is the most sensitive and specific indicator of angiogenic proliferation [19]. These tumours also show weak positivity for the CD34 protein. This marker shows expression in early haematopoietic and vascular-associated tissue. BAS also stains positive for the vascular markers; factor VIII, Fli1 and ERG. The ETS-related gene (ERG) is a transcription factor that has been linked to angiogenesis and is a marker, which could be positive in BAS [13][20][21].

Regional metastasis to the axillary lymph nodes is rare, however distant metastasis occurs most frequently to bones, lung, contralateral breast and liver [1]. Radiological findings may vary from ill-defined masses without calcifications, to well-circumscribed lesions [14]. The mammographic features do not show significant characteristics, but ill-defined masses without calcifications or speculations have been reported. This is explained by fast lesion growth, leaving no time for calcareous salt deposits to form [11]. The ultrasonic features may reveal well-circumscribed, lobulated or ill-defined margin masses, with homogeneous echogenicity. Angiosarcoma margins are
often not angular in shape and do not show posterior acoustic shadowing, which is characteristic of BAS. The colour Doppler Ultrasound scan may show the hyper-vascularty of the lesion [4]. Zahir et al, mentioned that magnetic resonance imaging (MRI) results suggest better characteristic findings for breast angiosarcoma. Low grade angiosarcoma may be seen as a large lobulated lesion with indistinct borders that show hypointensity on T1-weighted images and hyperintensity on T2-weighted images. High grade angiosarcoma however, may demonstrate hyperintensity on both T1WI and T2WI, with mixed intensity foci due to haemorrhage or venous spaces inside the mass. The highly aggressive tumours show rapid enhancement and washout pattern (type 3 curve) on contrast MRI studies [14][22][23].


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<th>Grade</th>
<th>5 Years Survival</th>
<th>Lifetime Survival</th>
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<tr>
<td>Low grade</td>
<td>76%</td>
<td>15 Years</td>
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<tr>
<td>Intermediate grade</td>
<td>70%</td>
<td>12 Years</td>
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<tr>
<td>High grade</td>
<td>15%</td>
<td>15 Months</td>
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There is no established standardised treatment for BAS that is evidence based. Radical surgery is currently the key element in the treatment. More authors are advising mastectomy as the procedure of choice. However, some authors recommend wide local excision if the tumor is smaller than 5 cm [24][25].

In our case the final decision was to perform bilateral mastectomy because the grade of the tumour had been changed from a low, to a high grade one, also there was a close margin in the lumpectomy specimen. The other fact was the disease recurrence, hence we advised for risk reducing mastectomy for the contralateral left breast, to minimise the recurrence risk in the left breast.

Generally, BAS has a poor prognosis. The factors affecting the prognosis are; tumor grade (most significant factor), tumor size at diagnosis, and margin status at surgery [26]. The 5 years survival rate of all grades of BAS at initial diagnosis is 33% [11][17][27], see table 2.

Chemotherapy is known to have a minimal effect and is used in patients with disseminated disease. Agents used are cyclophosphamide, anthracycline, or an alkylating agent combined to a pyrimidine analogue [26]. Anti-angiogenesis used against angiogenesis, such as bevacizumab, may also be useful [28]. Little is known about the use of radiotherapy, as primary BAS are small in number. Some authors advocate use of radiotherapy if resection margins are positive or less than 2 cm [29][30][31].

Conclusion
Angiosarcomas of the breast are rare. A clear cut histological diagnosis of angiosarcoma, in particular distinction from primary breast cancer, is the key principle for ideal therapy with mastectomy as the preferred option. Complete surgical excision of the lesion is crucial in BAS management. Contralateral risk reducing mastectomy may be considered in disease recurrence. Close follow up after surgery is essential to detect disease recurrence at an early stage.
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