

Angiosarcoma: a difficult diagnosis

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INTRODUCTION

Angiosarcoma of the breast is extremely rare. Despite modern technological advances, it still poses a diagnostic challenge. In the advent of the multidisciplinary breast team, the authors present a case of angiosarcoma of the breast in a young, previously healthy, female that presented with non-specific symptomatology, in which initial clinical and radiological assessment, including magnetic reso-

nance imaging, were non-diagnostic.

This case highlights the essential role of the pathologist in atypical and non-epithelial breast malignancies in the breast multi-disciplinary team. The authors stress the importance of sufficient tissue sampling to facilitate such a diagnosis.

DISCUSSION

Angiosarcoma of the breast, first described by Schmidt (1887), remains

a very rare and highly malignant mesenchymal neoplasm, with few long-term survivors. It accounts for 0.04% of breast malignancies, and 8% of total breast sarcomas (Lieberman et al, 1992). Clinical presentation has a female predominance, occurring at any age with a maximal prevalence in the third and fourth decades of life, when fertility tends to decrease.

Although hormonal factors have often been implicated in the pathogenesis of angiocarcinoma, hormonal receptors have been negative in almost all cases in the literature. It is frequently assumed that radiotherapy, following breast-conserving surgery for breast carcinoma, is one of the most important aetiological factors causing the initial tissue injury, often with associated lymphoedema. These angiosarcomas occur, after a latent period of several years, in the breast or the ipsilateral arm.

The most frequent clinical presentation is a painless smooth mass, ranging from 1.8 cm to 19 cm, with a varied rate of growth. Its bluish or darkened colour may be suggestive of vascular pathology and a fluctuation point sometimes occurs at the apex (Lieberman et al, 1992). The mass is usually mobile without apparent fixation to the skin or chest wall. As a result of haematogenous spread, axillary lymphadenopathy is rare (Hunter et al, 1985).

Radiological diagnosis is poorly specific and fraught with difficulties. Angiosarcomas are often ill-defined

CASE REPORT

A 28-year-old nulliparous lady was referred to the breast clinic with a 5-month history of persistent, cyclical, left-sided mastalgia. She was otherwise fit and healthy with no previous breast or nipple complaints. She was originally from Hong Kong with no family history of breast cancer. She was not prescribed any medications and was a non-smoker. On examination, tender nodularity was elicited below the left nipple. There were no other abnormalities.

Ultrasound scan (USS) of this area demonstrated an irregular area of mixed echogenicity, probably in keeping with fibroadenosis (Figure 1). Mammography performed subsequently demonstrated dense fibro-glandular tissue with no mass (Figure 2). Fine needle aspiration (FNA) of the area demonstrated fibro-fatty tissue with very scanty ductal cells. This was unsatisfactory for diagnosis (C1 cytology).

A clinical core biopsy was desired but not completed on this consultation at the patient's request. At subsequent review, a clinical core biopsy was performed in view of persistent nodularity. The core biopsy demonstrated a well-differentiated, vasoformative endothelial tumour, which appeared haemangioma-like, involving the surrounding fat and fibrous tissue, between breast ducts. In areas the lesion appeared to have an infiltrative pattern with vessels dissecting the septal fibrous tissue present. The cells showed a high degree of vascular endothelial differentiation but had enlarged hyperchromatic and mildly pleomorphic nuclei. Although mitotic figures were not identified, the appearances were suggestive of well-differentiated, grade-1 angiosarcoma (Figure 3). An expert second opinion was sought and concurred with this interpretation. There was positive immunohistochemical staining for CD34, CD31, and for factor VIII. MIB-1 proliferation was low. This is a polyclonal antibody used in paraffin embedded tissue against the Ki-67 antigen and is an indicator of cell proliferation. A magnetic resonance image (MRI) scan was recommended but was unhelpful, demonstrating no abnormality. An USS guided localisation-biopsy was performed without complication. Macroscopically the tissue was haemorrhagic. Histology confirmed the presence of a 2.2 cm, well-differentiated, invasive angiosarcoma extending to three of the resection margins.

Following counselling, she subsequently had a left mastectomy with immediate expandable implant reconstruction. This was completed without complication. Macroscopic analysis of the resected mastectomy specimen demonstrated an ill-defined residual haemorrhagic lesion measuring 4 cm x 4 cm x 2 cm. Histology confirmed the presence of residual angiosarcoma, up to intermediate-grade malignancy. Unfortunately, the inferior-superficial margin was still not clear of disease and she required re-excision to achieve a clear margin. The breast implant was not disturbed and remained *in-situ* during the re-excision. She is awaiting radiotherapy to the operative site, which has had to be delayed, as she is now seven weeks pregnant. She is otherwise well.

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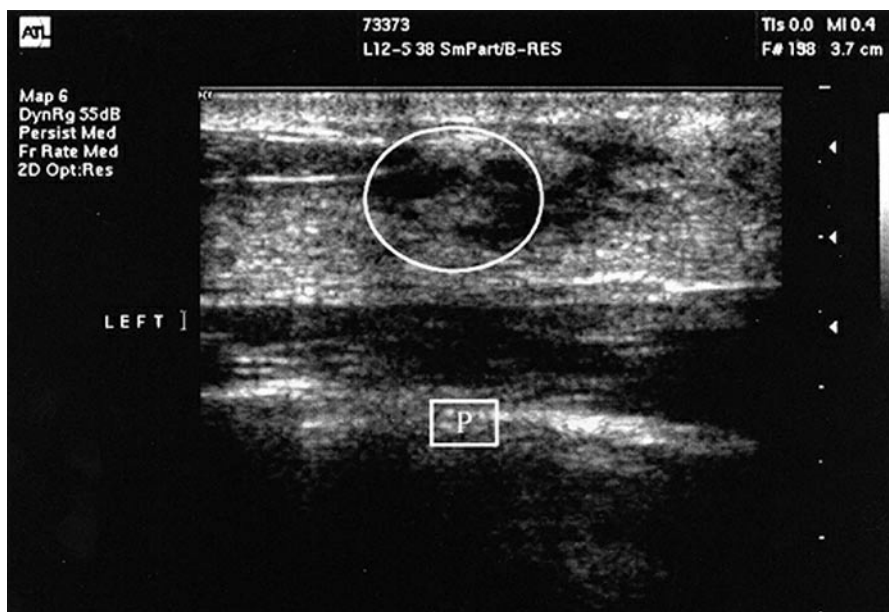


Figure 1. Ultrasound scan left breast demonstrating an irregular area of mixed echogenicity in the lower half of the breast, probably in keeping with fibroadenosis (see O). Pectoralis muscle is also labeled [P].

but tend to be somewhat larger in diameter (mean 4.6 cm), without the spiculation or calcification, which can be present in their epithelial counterparts. Whereas only 9% of epithelial

tumours are missed mammographically, Liberman et al (1992) described that 33% of angiosarcomas were missed in a mammographic review of 21 patients with proven angiosarcoma.

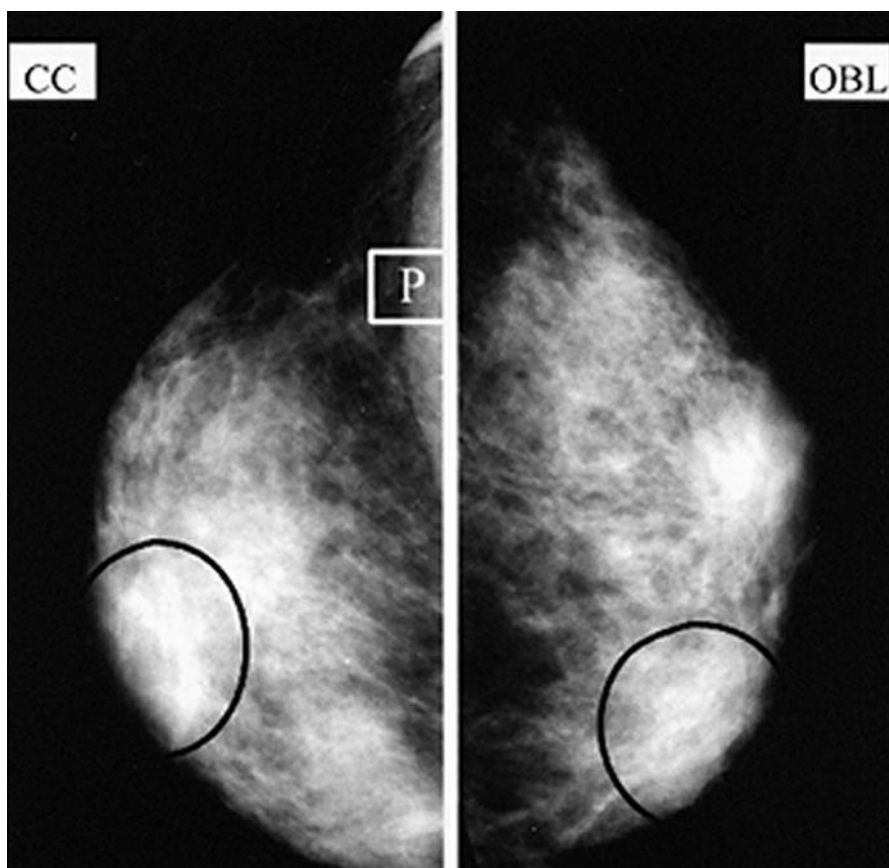


Figure 2. Mammogram of Left Breast demonstrating dense fibro-glandular tissue (O) with no discrete mass. (CC = craniocaudal view with pectoralis [P] & OBL = enhanced oblique views without pectoralis muscle).

Ultrasound can confirm the presence of a solid mass or a focal abnormality present on clinical examination or detected at mammography. Unfortunately, sonographic detection of angiosarcomatous masses has a low specificity as lesions can be solitary or multiple, well circumscribed or poorly margined, and hypo- or hyper-echoic.

The role of magnetic resonance imaging (MRI) in breast angiosarcoma has yet to be fully defined with only six cases of MRI findings associated with breast angiosarcoma reported in the literature (Yang et al, 2000; Murakami et al, 2001). MRI scans may be useful in confirming the vascular nature of the breast mass, only when a diagnosis of angiosarcoma is suspected, by detection of vascular channels containing slow moving blood on heavily T2-weighted images, particularly if gradient-echo images are obtained.

Angiosarcomas of the breast can be diagnosed by fine-needle aspiration (Vesoulis and Cunliffe, 2000; Georgiannos and Sheaff, 2003), but the usual requirement for full histopathological analysis is a needle-core or operative localisation biopsy.

Angiosarcoma of the breast can be divided histopathologically into grades 1–3, ranging from well-differentiated to poorly differentiated respectively (Liberman et al, 1992). All 3 grades have common architecture; hyperchromatic endothelial cells, interanastomosing vascular channels, and the presence of these vessels within the breast.

Grade 1 is well differentiated, with a very benign appearance, with interanastomosing channels lined by large nucleated endothelial cells, without evidence of mitoses, necrosis, or papillary projections.

Grade 2 tumours contain interanastomosing channels with endothelial tufting, focal intraluminal papillary projections, and mitoses.

Grade 3 tumours are poorly differentiated and are predominantly solid with areas of necrosis and haemorrhage called 'blood lakes'.

There is evidence of mitoses and

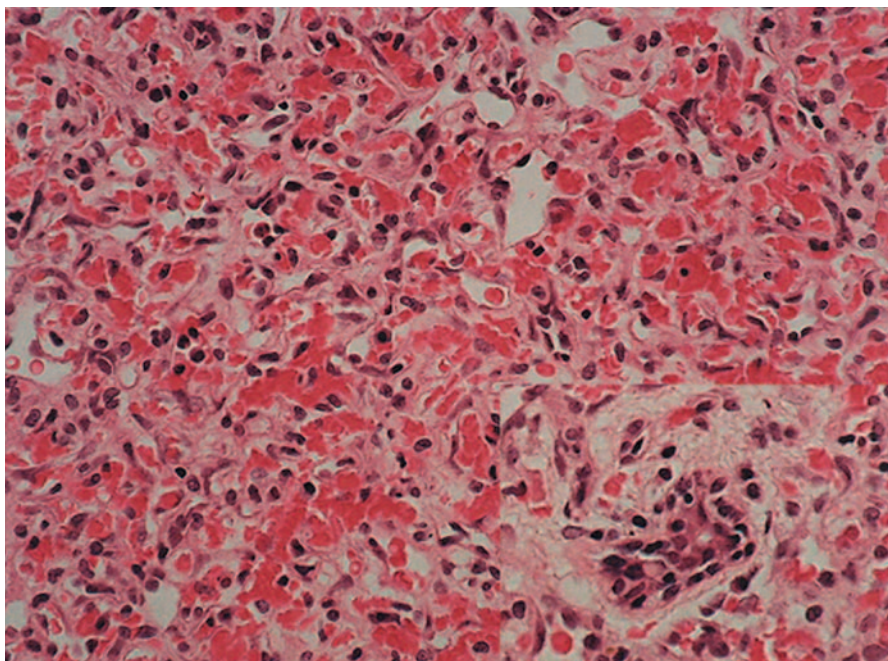


Figure 3. Breast angiosarcoma (Haematoxylin and Eosin stain x 200) demonstrating neoplastic vessels with hyperchromatic nuclei and containing red blood cells. The enhancement in the lower right hand corner (x400) shows neoplastic vessels infiltrating around a normal breast duct.

prominent endothelial tufting. Rainwater et al (1986) differentiates more significant necrosis as a grade 4 lesion. Georgiannos and Sheaff (2003) also raises the possibility of two types of angiosarcoma depending on the location of the bulk of the tumour, with radiation associated tumours arising superficially on the dermis, and non-radiation associated tumours arising deeper in the parenchymal tissue.

The presence of *in-situ* epithelial components together with immuno-histochemical studies, including cytokeratin antibodies and endothelial markers (factor VIII related antigen, CD34 and CD31), should aid with the differentiation.

Early complete excision by simple mastectomy with clear margins is the treatment of choice given the propensity of these tumours to extend microscopically beyond its gross limits. These limits of extension can be further assessed using on-table frozen section. However, this would only be appropriate for assessment of microscopic spread during the excisional surgery and not as a modality for use in the initial diagnostic process.

Although the microscopic assess-

ment of the vascular channels is possible, it can still present a significant diagnostic challenge to the histopathologist. Following mastectomy, immediate implants can still be considered provided there is no compromise of the tumour resection.

A high recurrence rate at the operative site in locally excised tumours precludes simple excision. Radical mastectomy and axillary node clearance are usually not indicated. Currently, the role of adjuvant chemotherapy and radiotherapy remains unclear. Unfortunately, some studies have reported a poor mean survival of 1–2 years for breast angiosarcomas (Lieberman et al, 1992). However, more recent studies suggest an optimistic outlook with the prognosis dependant on the histological grade. Patients with low-grade (grade 1, well differentiated) usually do well, with most living for more than 15 years and 24 years after treatment. Patients with high-grade (grade 3, poorly differentiated) were shown to have a median disease-free survival of only 15 months in one series (Georgiannos et al, 2003).

In this case the authors emphasize the clinical and radiological diagnos-

tic difficulties associated with breast angiosarcomas. It illustrates the need for full assessment of even innocuous presenting breast lumps in young women and the risk of accepting C1 cytology in such circumstances. The multidisciplinary approach identified the need for further histopathological analysis and demonstrates the importance of sufficient tissue sampling in any vascular breast lesion as an integral part of the multidisciplinary breast service.

TEACHING POINTS

Angiosarcoma of the breast remains a very rare and highly malignant mesenchymal neoplasm, with few long-term survivors. It accounts for 0.04% of breast malignancies, and 8% of total breast sarcomas.

Radiological diagnosis is poorly specific and fraught with difficulties. Early complete excision by simple mastectomy with clear margins is the treatment of choice given the propensity of these tumours to extend microscopically beyond its gross limits.

The multidisciplinary team approach is essential and demonstrates the importance of sufficient tissue sampling in any vascular breast lesion as an integral part of the breast service, even if this requires multiple biopsies. **HM**

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