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Primary Breast Angiosarcoma: A Rare and Challenging Case Report

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Abstract

Primary angiosarcoma of the breast is a life-threatening and rare disease (0.04% of all breast cancers -BCs-). It has a variable and non-specific clinical, radiological and histological presentation; therefore its diagnosis is usually challenging. It predominantly affects young patients and there is often an excessive diagnostic delay, due to errors in the evaluation of imaging techniques and histological study. We report the case of a 56-year-old woman, with a history of bilateral breast reduction 10 years ago but with no personal history of BC or breast irradiation, who consulted for a rapidly growing breast mass. Initially, it was interpreted preoperatively as benign (haemorrhagic cyst); but its complete surgical removal confirmed the diagnosis of primary breast angiosarcoma. The tumor had a very aggressive behaviour, causing death 5 months after diagnosis.

Keywords: *Breast angiosarcoma; Primary angiosarcoma; Breast cancer.*

Introduction

Sarcomas of the breast are histologically heterogeneous non-epithelial malignancies arising from the connective tissue of the breast. They are rare, accounting for less than 1% of all breast cancers (BCs) [1]. The subtype of sarcoma strongly linked to the breast is the angiosarcoma.

Breast angiosarcoma (malignant hemangioendothelioma) is an aggressive subtype, with rapid proliferation and infiltration of surrounding tissues; generally associated with poor prognosis. Based on their etiology, it can be classified as primary (de novo) and secondary (related to BC treatment: after radiotherapy, or due to lymphedema in the arm or breast/chest wall after surgical treatment) [2,3].

Primary angiosarcomas are non-epithelial malignant tumors that arise from vascular endothelial cells, originate in the breast parenchyma, and occasionally affect the skin. It is a rare disease with an incidence of less than 0.04% of all BCs [4] and usually with an unfavourable prognosis. Its diagnosis is often delayed due to its rarity, unusual clinical presentation, and non-specific findings from imaging tests and histology [5]. Primary angiosarcomas are diagnosed in younger women and are more likely to have distant metastases at diagnosis than secondary angiosarcomas [6].

We present the case of a primary angiosarcoma in a 56-year-old woman with no personal history of BC, which was initially interpreted as benign and evolved with very aggressive behaviour.

Case Report

Our patient is a 56-year-old caucasian woman with a

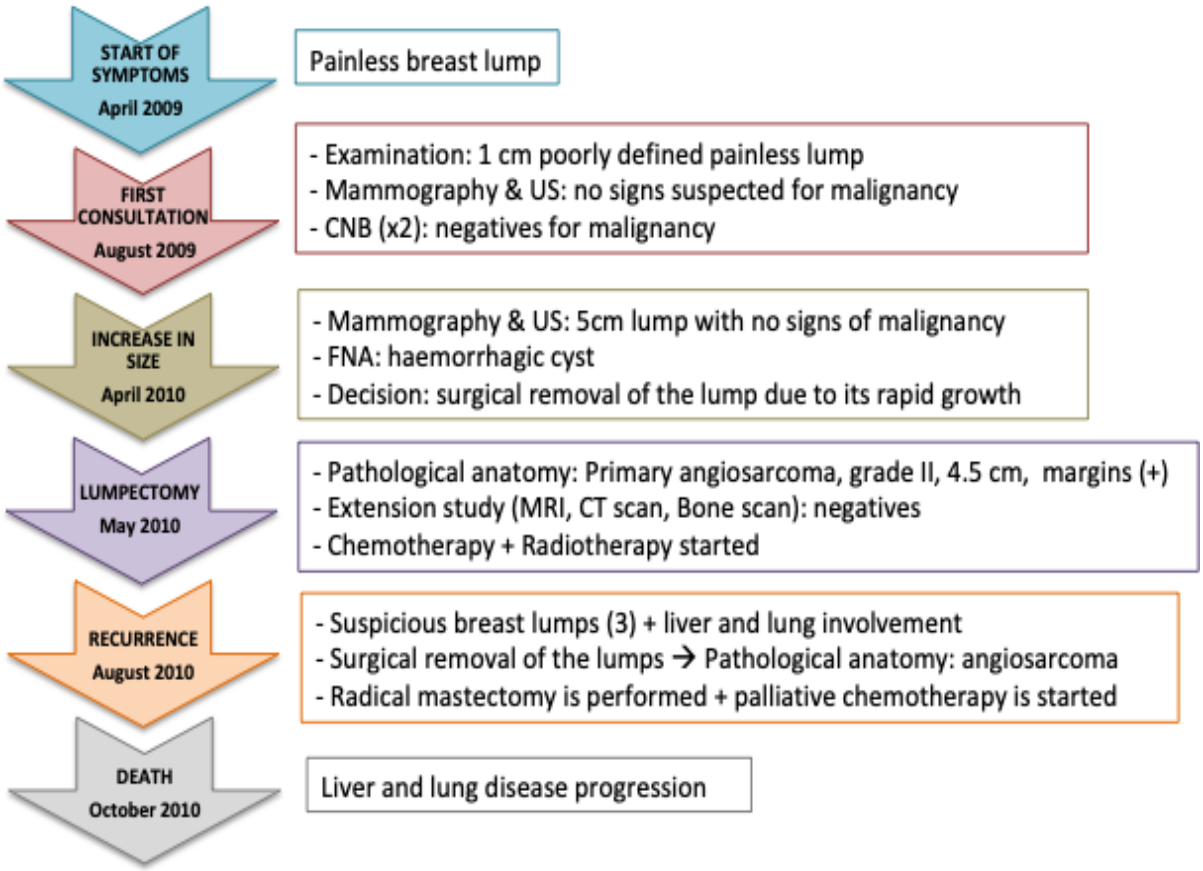
bilateral breast reduction 10 years ago, with no other personal history of interest or family history of cancer. She attended our Breast Pathology Unit of the Hospital Complex of Vigo (Spain) because of the appearance of a progressive growth lump in the lower internal quadrant of the left breast (Figure 1). Follow-up was carried out for the next 8 months without suspecting malignancy: imaging tests without malignancy criteria and biopsies negatives for malignancy (last biopsy reported as haemorrhagic cyst) (Figure 2).

Likewise, a surgical removal of the lump was performed due to its rapid growth (increase in size from 1 to 5 cm in 8 months). The pathological anatomy of the surgical specimen was reported as: moderately-differentiated (grade II) primary breast angiosarcoma of 5.5 cm in maximum diameter, with positive surgical margins. The immunohistochemical study showed positivity for CD31, CD34 and factor VIII and negativity for all epithelial markers. The post-surgical extension study was negative.

A left subcutaneous mastectomy was subsequently performed. The pathological anatomy of the surgical specimen reported the presence of focal points of residual angiosarcoma, with free surgical margins. It was decided to start adjuvant chemotherapy with EC (Epirubicin + Cyclophosphamide) for 4 cycles, associated with complementary radiotherapy.

However, after the second cycle of EC (3 months after mastectomy), breast lumps suspected of recurrence appeared as well as lung and liver involvement. The suspicious lumps were surgically removed (reported as grade II angiosarcoma, with positive surgical margins) and the surgery was completed with a left radical mastectomy (reported as grade II angiosarcoma in the central area of the breast, with negative surgical margins).

She received palliative chemotherapy with a rapid progression of liver and lung involvement, dying 5 months after diagnosis.



* US: Ultrasound; CNB: Core needle biopsy; FNA: Fine-needle aspiration; MRI: Magnetic resonance imaging (of the breast); CT scan: Computed tomography scan (cranial, thoracic and abdomino-pelvic).

Figure1. *Case report timeline*

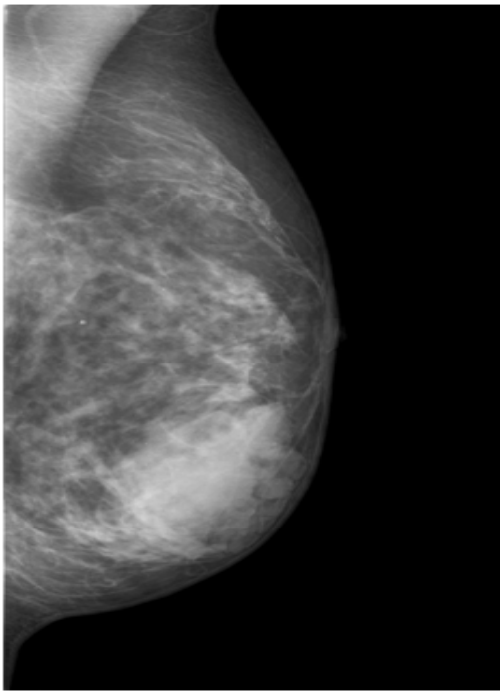


Figure2. *Mammography (April 2010): Circumscribed mass of about 5 cm in the lower internal quadrant of the left breast with polylobated contour and high density, without calcifications or architectural distorsion. During follow-up, an increase in the size and density of the mass was observed.*

Discussion

Primary breast angiosarcomas tend to occur at younger ages and with no personal history of BC, the average age at diagnosis is less than 40 years in most series (between 20 and 40 years) [2, 6, 7]. The age at diagnosis of our patient was higher than reported in the literature (56 years) and similar to that reported by Kunkiel et al. (53.5 years) in their series of 11 primary breast angiosarcomas [5]. In contrast, the average age of secondary breast angiosarcomas is older (generally over 60 years, age range between 40 and 90 years) [7-10] and they develop in patients who have received treatment for BC.

Primary breast angiosarcoma usually presents as a painless, poorly defined, palpable mass that grows rapidly [11]. Approximately 2% may have diffuse enlargement of the breast. In up to one-third of the patients, bluish skin discoloration is common possibly due to the vascular nature of the tumor [12]. Nipple retraction, discharge, or axillary node involvement are generally absent. In most reported cases, the tumor size is greater than 4 cm [6, 12].

Imaging tests are generally non-specific [13]. Primary angiosarcoma may go unnoticed on mammography due to the increased breast density of young women. Mammography usually shows a large, dense and homogeneous mass, with sharp and sometimes polylobated contours; but without calcifications or spiculations suspected of malignancy [13-15]. On ultrasound, angiosarcoma appears as a heterogeneous lesion with marked hypervascularity [13]. Magnetic resonance imaging shows a mass with low signal intensity on T1-weighted images, but high signal intensity on T2-weighted images (suggesting the presence of vascular channels containing slow-flowing blood) [13, 16].

Preoperative diagnosis, using fine-needle aspiration cytology and core needle biopsy, can be difficult due to its similarity to other breast abnormalities and its vascular nature, making it difficult to provide large samples. Chen et al. reported a false negative rate of percutaneous biopsy of 37% [17]. In our case, the preliminary pathological diagnoses were negative for malignancy; but due to the rapid increase in size we decided to perform a wide surgical excision. Surgical resection and microscopic examination of sufficient sampling of the tumour are often necessary to render a final diagnosis.

On macroscopic examination, angiosarcomas have a spongy hemorrhagic appearance, although

some present as a thickened and indurated area of the breast. Some tumors have a honeycomb-like appearance, dilated vascular channels or hemorrhagic lakes. Histologically, angiosarcoma is characterized by anastomosis of vascular channels lined by atypical endothelial cells. Generally, it has a heterogeneous architecture that encompasses a morphological spectrum with solid areas highly undifferentiated with others with a complex vascular pattern and others that are better differentiated. Primary angiosarcomas of the breast tend to have a well-differentiated architecture on their peripheral margin with flat, slightly hyperchromatic and slightly disorganized endothelial cells. If we carry out a small biopsy, we can underestimate the degree; since the poorly differentiated areas usually have a central location. Occasionally, the tumor may have an epithelioid appearance [18].

Histologically, angiosarcomas of the breast are classified according to the classification proposed by Donnell et al. [19]: grade I (well-differentiated: characterized by vascular channels invading the breast tissue with little endothelial proliferation), grade II (intermediately-differentiated: with scattered papillary endothelial formations and solid cellular foci) or grade III (poorly-differentiated: solid areas of spindle cells and papillary formations are prominent, additionally presents necrosis and hemorrhage).

Many immunohistochemical markers have been used to confirm endothelial differentiation, including Factor VIII-related antigen, Ulex europaeus agglutinin I lectin (UEAI), PAL-E485, CD31 and CD34 [12, 20, 21] that allow confirming the diagnosis. The CD31 marker is considered the most sensitive and specific endothelial marker.

The differential diagnosis of angiosarcoma should include metaplastic carcinoma, acantholytic variant of squamous cell carcinoma, hemangioma, cellular angiolipoma and pseudoangiomatous stromal hyperplasia. Immunostaining for Ki-67 and other cell cycle regulatory proteins (S-phase kinase-associated protein 2 [Skp2], p27, and cyclin D1) are useful for differential diagnosis of vascular mammary lesions, with the expectation that angiosarcomas would show a significantly higher marking index than hemangiomas [22]. Other less likely entities include: phyllodes tumor, stromal sarcoma, fibrosarcoma, liposarcoma, and reactive spindle cell nodules.

Primary angiosarcoma of the breast tends to metastasize hematogenously to the lungs, liver, bones, skin, and the contralateral breast.

There are no treatment standards for breast angiosarcomas because of their rarity. However, surgical treatment is the basis of treatment. Mastectomy with negative surgical margins is the recommended treatment, without axillary dissection (unless there are clinically positive nodes). Positive margins are associated with an increased risk of locoregional recurrence [21]. Complementary radiotherapy is necessary in the case of lumpectomy [22]. According to Johnstone et al. adjuvant radiotherapy after surgery allows better local control [23], but without effect on overall survival, as Pandey et al. [24]. Radiation and adjuvant chemotherapy do appear to improve survival when tumor size is greater than 5 cm [25, 26]. Chemotherapy is beneficial in high-grade lesions and in the metastatic setting [12, 27, 28].

The prognosis of the breast angiosarcoma is related to the tumor size, the tumor grade and the resection margin status. Positive margins are associated with a worse prognosis: an incomplete exeresis is connected with both locoregional recurrence and worst survival [29-31]. Literature presents different opinions on the correlation between tumor size and grade with prognosis.

Authors like Rosen et al., Bousquet et al. and Luini et al. demonstrated that grade I and II tumors were associated with longer disease-free survival [30-32]. Rosen et al. (1988) reported that 5-year survival for low, intermediate and high-grade tumors was 76%, 70%, and 15%, respectively [32]. Other authors, like Blanchard et al. and Nascimento et al. concluded that there was no correlation between tumor grade and the rate of local recurrence, metastasis, and survival [33, 4]. However, the largest study involving 226 women (2015) agrees with the findings of Rosen et al.: median survival was significantly lower for high-grade tumors (24 months in high-grade vs. 172 months in low-grade) [34].

Most of the authors, like Rosen et al., Bousquet et al., Blanchard et al. and Sher et al. found no correlation between tumor size and risk of recurrence or death [32, 30, 33, 28]. On the contrary, other authors, like Adem et al. and Zelek et al., demonstrated an association between tumor size and disease-free survival [35, 26]. Thus, for example, Adem et al. reported an overall

5-year survival of 50% for tumors > 5 cm and 91% for ≤ 5 cm [35].

Conclusion

Breast angiosarcoma is a rare and aggressive disease that can develop without prior exposure to surgical or radiation treatment for BC. It can often be misdiagnosed radiologically and histologically. A high degree of suspicion and careful attention to radiology-histology concordance is essential to avoid a diagnostic delay. Primary angiosarcomas must be considered in evaluation of breast masses in patients with a history of breast reduction surgery, apparently unresolved breast infection, and with negative radiological imaging. They represent a challenging clinical situation due to the unfavorable prognosis, diagnostic difficulty and non-existence of therapeutic standards.

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