

Recurrent Primary Angiosarcoma of the Breast: Challenges and Pitfalls in a Case Report

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AIM: Primary breast angiosarcoma (PBA) is an exceptionally rare and highly aggressive vascular malignancy with poor prognosis, high recurrence rates, and limited evidence guiding management. We report a case of low- to intermediate-grade PBA characterized by multiple local recurrences and systemic progression but unusually prolonged survival, contributing valuable long-term follow-up data to the literature.

CASE PRESENTATION: The patient presented with a breast lesion and cutaneous involvement. Diagnosis was confirmed by histopathological and immunohistochemical findings. The patient underwent skin-reducing mastectomy, followed by radiotherapy and multiple lines of chemotherapy after early recurrence.

RESULTS: Despite progressive disease, overall survival reached 102 months from diagnosis, exceeding survival outcomes commonly reported for PBA.

CONCLUSIONS: This case highlights the aggressive and refractory behavior of PBA, the importance of accurate histopathological diagnosis and multidisciplinary management, and the need for prolonged surveillance because of the high risk of recurrence. Furthermore, the unusually long survival observed in this patient highlights the complexity of disease biology and the potential value of individualized multimodal management strategies, while the contribution of specific treatments to survival remains uncertain.

Keywords: primary breast angiosarcoma; recurrent breast angiosarcoma; breast sarcoma; rare breast tumor; case report

Introduction

Primary breast angiosarcoma (PBA) is a rare malignant tumor arising from the endothelial cells of blood vessels, accounting for less than 0.05% of all breast malignancies [1,2,3,4]. Despite its rarity, PBA is characterized by aggressive biological behavior, high likelihood of local recurrence (LR), and potential for distant metastasis with poor long-term survival outcomes [5].

Diagnosis is challenging because clinical and radiological features are often nonspecific and may overlap with those of benign vascular lesions or other breast malignancies, resulting in delayed diagnosis and underestimation of disease extent [6,7,8]. Histopathological examination with immunohistochemical confirmation is essential for definitive diagnosis [9]. Due to its low incidence, evidence regarding

optimal management remains limited and is primarily derived from small retrospective series and case reports. Although complete surgical excision with negative margins is considered the mainstay of treatment, the role of adjuvant chemotherapy and radiotherapy remains controversial, and no standardized treatment guidelines are currently available.

This report describes a case of multiply recurrent PBA in a 70-year-old woman, highlighting the diagnostic and therapeutic challenges associated with this rare neoplasm and its complex clinical course despite multimodal treatment.

Case Presentation

Patient Information

A 70-year-old caucasian female without significant comorbidities and personal or family history of neoplastic diseases presented to our Multidisciplinary Breast Center in April 2015 after self-detection of a palpable lesion in the right breast.

Breast mammography revealed a heterogeneous radiopacity of 20 × 15 mm; concurrent breast ultrasound showed a mixed hyper- and hypoechoic lesion with ill-defined margins (shown in Fig. 1). No lymphadenopathies were detected.

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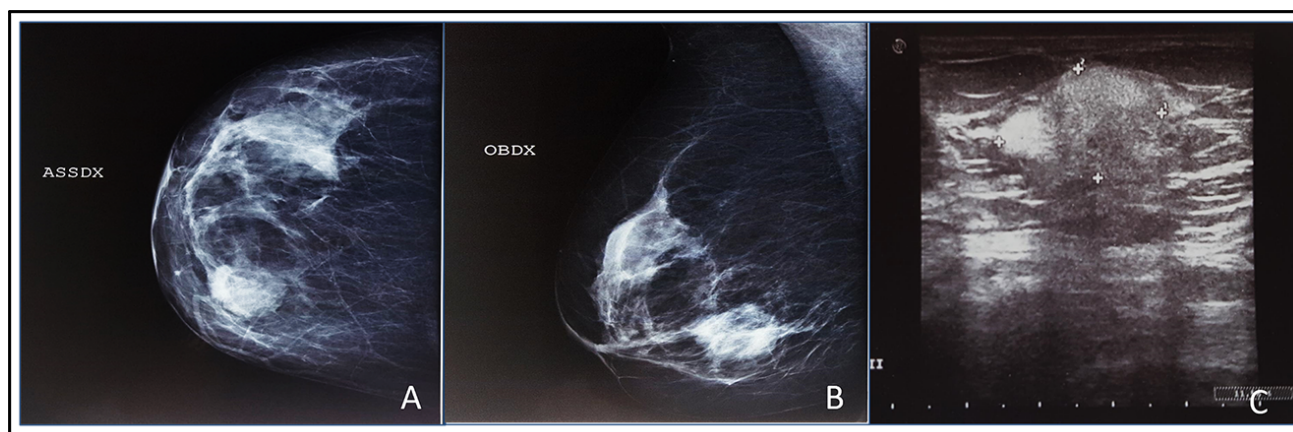


Fig. 1. Imaging findings. (A,B) Mammography showed a heterogeneous radiopacity on the right craniocaudal (CC; ASSDX) and right mediolateral oblique (MLO; OBDX) views, respectively. (C) Ultrasound showed a mixed hyper- and hypoechoic lesion with ill-defined margins.

This case has been reported in line with the case report guidelines: Case Report (CARE) Guidelines to ensure the accuracy and completeness of the report (**Supplementary Material**).

Clinical Findings

Physical examination revealed medium-to-large, ptotic breasts. No visible skin changes or alterations of the nipple–areolar complex were observed. A palpable nodule was detected in the lower inner quadrant of the right breast, approximately 4 cm in diameter. No suspected nodes were detected in the bilateral axillary, supraclavicular, or cervical regions.

Diagnostic Assessment

The patient underwent an ultrasound-guided core needle biopsy using a 14-gauge needle. Histopathological examination revealed the presence of an angiomatous lesion with atypia (B3, breast lesion of uncertain malignant potential). Tumor markers, including CA 15-3 and CA 125, were within normal limits. In the absence of a confirmed malignant diagnosis, no further diagnostic or staging investigations were performed.

Therapeutic Intervention

The histological findings were discussed with the patient, and a nodulectomy was performed in December 2015. The macroscopic exam revealed a reddish, polypoid nodular lesion measuring approximately 1 cm, protruding from the superficial cut surface, with fibrous areas occasionally displaying a reddish-brown coloration. The differences in lesion dimensions reflect the different assessment methods and targets (clinical examination, imaging findings, and gross pathological measurement). The approximately 1-cm measurement referred specifically to the protruding polypoid nodular component rather than the entire lesion.

Histologically, the lesion corresponded to a proliferative vascular neoplasm with a proliferative index (Ki-67) of 30%. Immunohistochemically, the newly formed vascular structures showed diffuse immunoreactivity for CD31 and CD34, with alpha-smooth muscle actin (ASMA)-positive pericytic elements (shown in Fig. 2). Stains for AE1/AE3, Melan-A, HMB45, and Desmin were negative.

Factors that suggested a diagnosis of primary low- to intermediate-grade (G1–G2) angiosarcoma, with infiltrated surgical margins (inked margins).

Furthermore, three weeks after surgery, the patient developed a hyperpigmented lesion in the lower inner quadrant of the right breast, clinically resembling ecchymosis (shown in Fig. 3) not associated with blood collections in the surgical field and consequently considered a cutaneous localization of angiosarcoma.

In view of the diagnosis, the R1 status (microscopically positive surgical margins, with tumor involvement of the inked margins) and the clinical finding of the cutaneous lesion, the case was discussed at a multidisciplinary meeting and a completion mastectomy was suggested.

The patient underwent a skin-reducing mastectomy with tissue expander reconstruction in March 2016. During the procedure, exploration of the axilla revealed several enlarged and firm lymph nodes, which led to a targeted axillary dissection.

The final histopathological examination showed no evidence of residual glandular neoplasm but confirmed cutaneous involvement by low-grade angiosarcoma, with no evidence of lymph node metastasis (0/5).

Follow-up and Outcomes

According to the comprehensive disease status, adjuvant chemotherapy with 12 cycles of Taxol was suggested.

The post-operative course was complicated by a wound dehiscence one month after the initial procedure which required surgical revision.

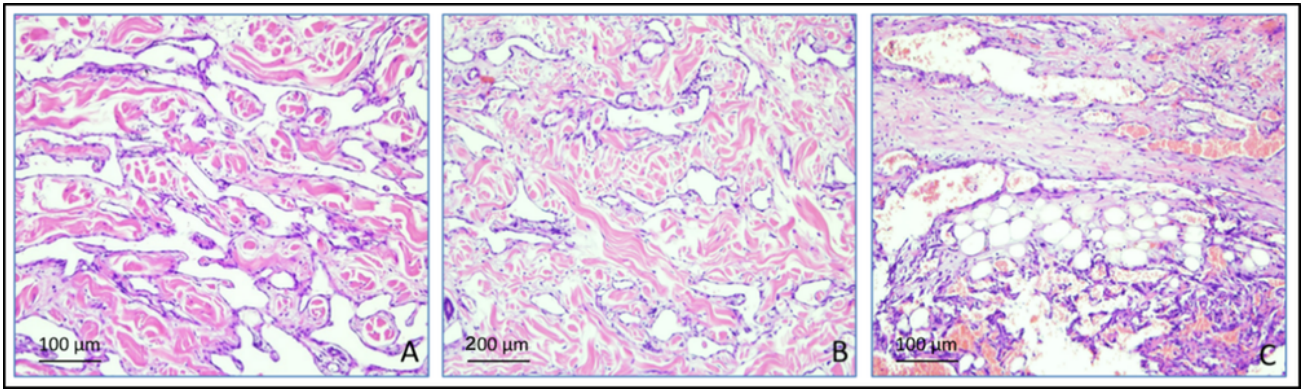


Fig. 2. Pathological findings. (A–C) Vascular proliferative lesion consisting of innocent-looking vascular spaces densely packed and anastomosing that insidiously infiltrate the dermis (A, B, H&E 10 $\times$, 5 $\times$) and the adipose tissue (C, H&E 10 $\times$). H&E, Hematoxylin and Eosin.

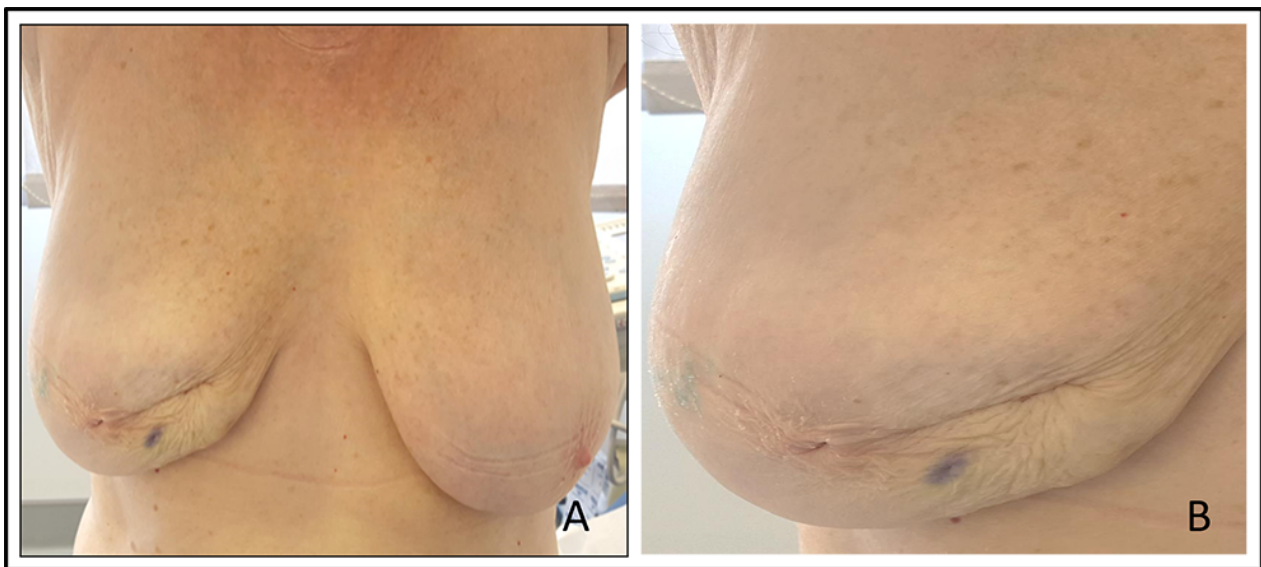


Fig. 3. Clinical findings. (A,B) Hyperpigmented lesion in the lower inner quadrant of the right breast.

Due to this adverse event, Weekly Taxol administration started approximately six months after surgery.

On July 2018 (28 months after surgery) a multicentric hematoma-like swelling was noted in the upper -inner quadrant, without any palpable masses or axillary lymphadenopathy (shown in Fig. 4).

Breast ultrasound and mammography revealed, in the upper-inner quadrant of the right breast, two iso/hyperechoic subcutaneous lesions corresponding to the clinically visible hematoma-like areas. Both lesions measured approximately 1.5 cm and demonstrated mild internal vascularity (shown in Fig. 5).

An incisional biopsy was performed, and histopathological analysis confirmed recurrent angiosarcoma.

Locoregional and systemic staging with magnetic resonance imaging (MRI) and whole-body computed tomography (CT) showed no evidence of lymphadenopathies or distant metastases.

In April 2019, the patient underwent a wide skin excision of the right hemithorax with thigh skin graft reconstruction (shown in Fig. 6).

Histological examination revealed two heterogeneous brownish nodules, with a maximum diameter of 40 mm, located in the upper area of the right breast. Microscopically, the lesion showed increased vascularity and slit-like vascular channels, associated with areas of hemorrhage. Margins were free of disease.

A final diagnosis of recurrent intermediate-grade angiosarcoma of the breast was established.

After surgery, adjuvant radiotherapy was planned. However, during CT simulation for radiotherapy planning, a new cutaneous lesion was identified beneath the skin graft, highly suggestive of local recurrence (LR). Consequently, the patient started taxane -based chemotherapy (paclitaxel 50 mg/m² weekly), which was discontinued after the fifth week because of treatment-related skin toxicity and grade 3 febrile neutropenia.



Fig. 4. Clinical findings. (A,B) A multicentric hematoma-like swelling in the upper inner quadrant of the right breast.

The patient subsequently received radical radiotherapy to the right chest wall, including the residual right breast tissue and the medial chest wall thickening. Treatment was delivered with 6-MV photon beams according to ICRU Report 83 recommendations, with a prescribed dose of 50–60 Gy in daily fractions of 2 Gy. The planned total radiation dose was 60 Gy; however, radiotherapy was interrupted before completion after a cumulative dose of 58 Gy had been delivered. Following treatment, a complete clinical and radiological response was achieved, and a whole-body CT scan performed in February 2020 showed no evidence of disease. In March 2022, following the appearance of cutaneous discoloration on the right chest wall, mammography and breast ultrasound were performed, revealing a poorly defined area measuring 37 mm. Positron emission tomography-computed tomography (PET-CT) scan demonstrated increased metabolic activity corresponding to a heterogeneous enhancing solid mass measuring 83×37 mm. The lesion extended to the overlying thickened skin and infiltrated the adjacent muscular planes, findings consistent with a highly metabolically active neoplastic process (shown in Fig. 7).

In April 2022, the patient started Gemcitabine, which was discontinued after four cycles due to local progression. The lesion had become ulcerated and necrotic, involving the inframammary fold and occupying approximately three-quarters of the right hemithorax (shown in Fig. 8).

Accordingly, the patient was started on oral palliative chemotherapy with Vinorelbine, which was discontinued in March 2023 due to further disease progression and increased risk of infection. The patient was managed with multiple sequential wound dressings.

After one year, disease progression occurred with the development of a contralateral breast lesion clinically sug-

gestive of angiosarcoma, pulmonary metastases, and death due to respiratory failure. The nature of the contralateral breast lesion could not be definitively established as either metastatic disease or a second primary angiosarcoma.

The complete clinical course is summarized in **Supplementary Table 1**.

Discussion

Epidemiology and Clinical Features

PBA is an exceptionally rare and highly aggressive endothelial malignancy, accounting for less than 0.05% of all breast malignancies and approximately 8–10% of breast sarcomas [2,10].

Its rarity, biological heterogeneity, and wide spectrum of clinical presentations make diagnosis and management particularly challenging [6,10].

PBA typically presents in younger women and can manifest as a palpable mass or cutaneous discoloration. Although PBA typically occurs in younger women, our patient was 70 years old, highlighting that this diagnosis should also be considered in older patients without prior radiotherapy or other known risk factors.

Pathogenesis and Classification

The pathogenesis of PBA remains poorly understood. Unlike secondary breast angiosarcoma, which is associated with prior radiotherapy and chronic lymphedema, PBA arises *de novo* and no well-established risk factors have been identified. Although the molecular mechanisms underlying tumor development are not fully elucidated, alterations in angiogenesis-related pathways and vascular endothelial growth factor (VEGF) signaling have been implicated in tumor progression [11].

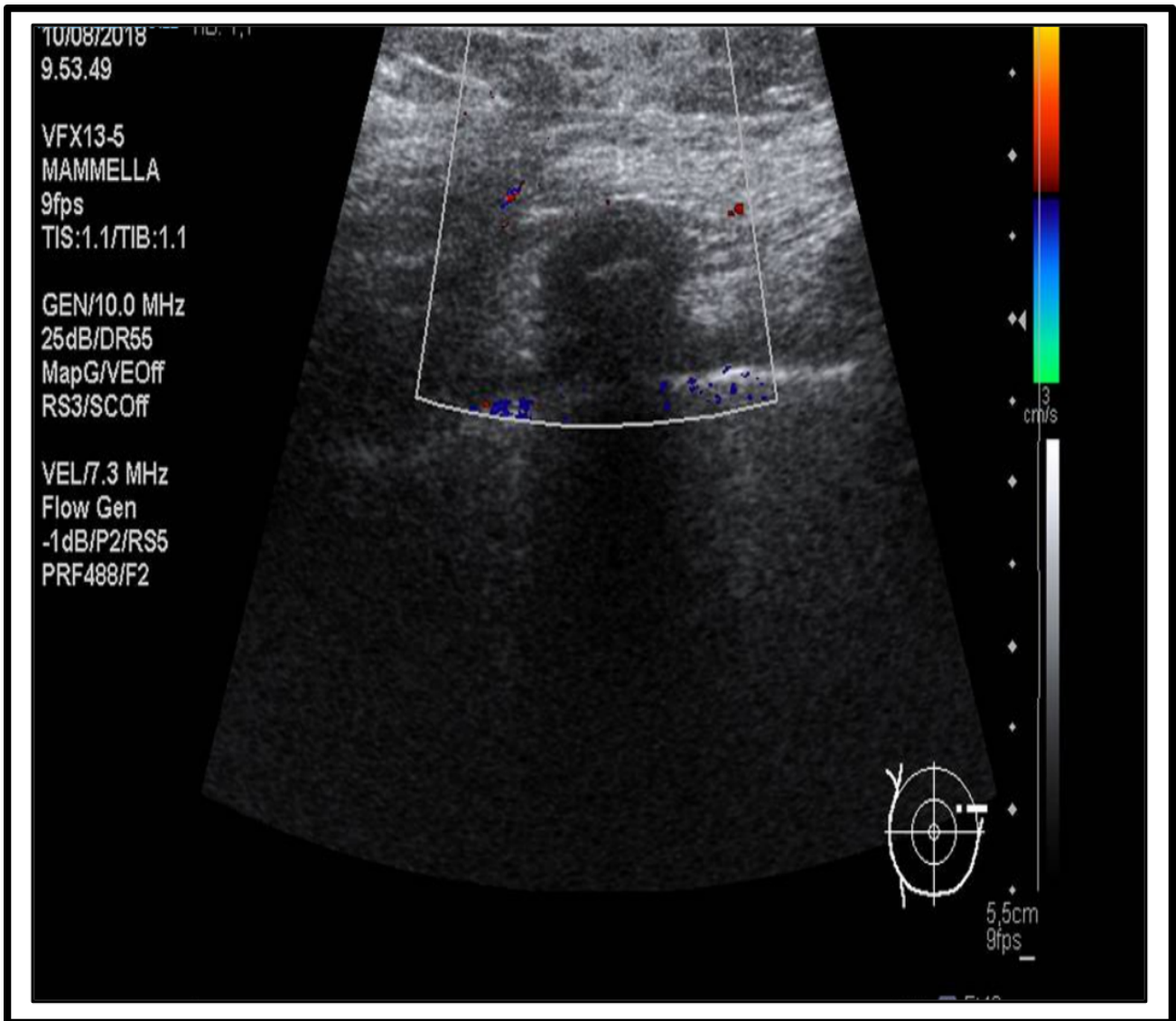


Fig. 5. Imaging findings. Ultrasound showed an iso/hyperechoic area with mild internal vascularity.



Fig. 6. Surgery and surgical specimen. (A,B) Wide excision of the right hemithorax with thigh skin graft reconstruction. (C) Two heterogeneous brownish nodules, with a maximum diameter of 40 mm, located in the upper area of the right breast.

Histologically, PBA is further categorized into low-, intermediate-, and high-grade tumors based on the degree

of vascular differentiation, cellular atypia, mitotic activity, and the presence of necrosis. Low-grade tumors are

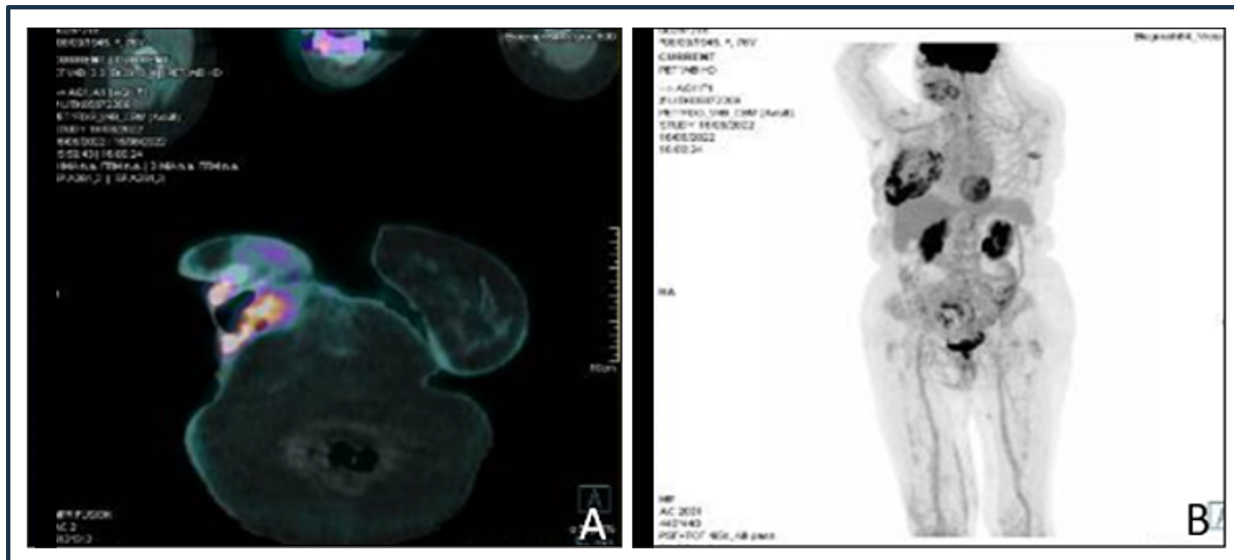


Fig. 7. Imaging findings. (A,B) PET-CT showed increased metabolic activity corresponding to a solid, heterogeneously enhancing mass. PET-CT, positron emission tomography-computed tomography.

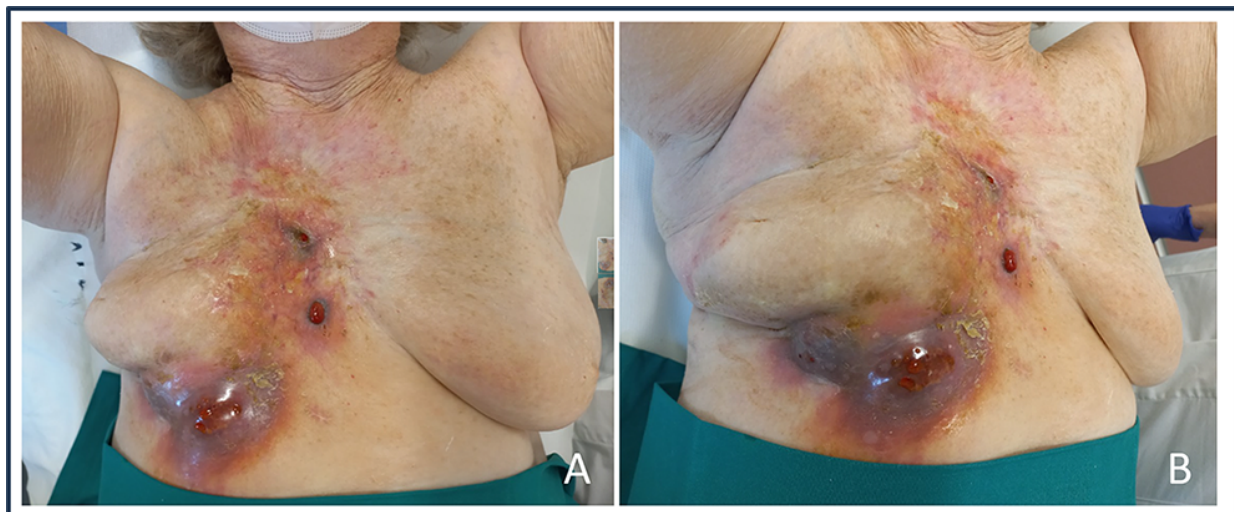


Fig. 8. Clinical findings. (A,B) Lesion ulcerated and necrotic, involving the inframammary fold.

characterized by well-formed anastomosing vascular channels; intermediate-grade angiosarcoma (characterized by an important neoplastic vascular growth); and high-grade angiosarcoma, that show localized necrosis, infarction, and hemorrhage [12].

In our case, the histopathological findings were consistent with a low- to intermediate-grade primary angiosarcoma.

Diagnosis and Differential Diagnosis

Radiologic features are nonspecific and often mimic benign vascular lesions or inflammatory conditions.

Mammography and ultrasound typically reveal a poorly defined heterogeneous mass, while MRI can demonstrate high T2 signal intensity and rapid contrast enhancement corresponding to the tumor's vascular nature [6,13,14,15].

Histopathological examination remains the cornerstone of diagnosis. The hallmark of PBA is the proliferation of anastomosing vascular channels lined by atypical endothelial cells that invade the breast parenchyma. Immunohistochemical staining shows strong expression of CD31, CD34, and ERG, confirming endothelial differentiation, while epithelial and myogenic markers are negative [16,17].

In our case, the lesion demonstrated these characteristic findings, consistent with a low- to intermediate-grade primary angiosarcoma.

Staging is crucial to confirm the non-metastatic nature of the disease and to exclude systemic dissemination, which occurs in up to 60% of patients [18], most commonly involving the lungs, liver, and bones [19,20].

It is routinely performed with contrast-enhanced CT scans of the chest, abdomen, and pelvis, while 2-Deoxy-2-

[18F]fluoro-D-Glucose (FDG) PET-CT is indicated as a problem-solving tool in cases where findings are equivocal [21].

Treatment and Follow-up

Currently, there are no clear guidelines defining the optimal surgical management of PBA; however, complete surgical excision with negative margins (R0) remains the cornerstone of curative treatment for localized, non-metastatic disease [21,22]. Several studies have reported no statistically significant differences in recurrence-free survival or overall survival between mastectomy and breast-conserving surgery (BCS), suggesting that the choice of surgery should primarily be guided by tumor size, location, and the feasibility of achieving negative margins [23,24,25].

Axillary lymph node dissection is not strictly indicated, as nodal involvement is observed in fewer than 10% of cases [26,27,28].

In our case, the patient underwent skin-reducing mastectomy due to the extension of the disease and cutaneous involvement in order to achieve negative surgical margins, in accordance with recommendations.

Despite optimal surgery, early LR justified the addition of radiotherapy (RT) and systemic chemotherapy.

The role of RT in PBA is controversial; some series suggest improved local control and longer local recurrence-free survival (LRFS) when RT follows incomplete excision or R1 resection [3], whereas others failed to demonstrate improved disease-free survival (DFS) and overall survival (OS) [26]. In our case, RT was delivered following early local recurrence, achieving transient disease stabilization. Similarly the role of adjuvant or palliative chemotherapy has not been clearly established.

Our patient initially received adjuvant taxane-based chemotherapy followed by vinorelbine and gemcitabine, agents that have demonstrated limited but clinically meaningful palliative activity in recurrent or metastatic disease [29,30].

However, multiple recurrences and subsequent systemic progression occurred during treatment, underscoring the aggressive biology of PBA and the need for more effective biologically driven, multimodal therapeutic strategies to overcome resistance mechanisms and enhance clinical outcomes.

Prognosis and Outcome

However, the prognostic significance of tumor grade in primary breast angiosarcoma remains controversial, given the limited number of cases and heterogeneous clinical behavior reported in the literature. PBA has a poor prognosis influenced by tumor size, tumor grade, and resection margins, and is characterized by high local recurrence (LR) rates and early systemic spread [22].

Recurrences are most commonly reported within the first few years after surgery, often involving the dermal or subcutaneous tissues of the chest wall [23,31], as observed in our case, where the first LR occurred 28 months postoperatively.

Recent series report a median overall survival (OS) of approximately 38 months, with 1-, 3-, and 5-year OS rates of 80%, 39%, and approximately 25–31%, respectively [31,32].

Despite the history of multiple recurrences, related to the aggressive and refractory nature of PBA, our patient experienced an unusually long survival, with death occurring due to systemic dissemination 102 months after the initial diagnosis, well beyond the median survival reported in the literature.

However, this favorable outcome should be interpreted with caution. In a single case report, prolonged survival cannot be directly attributed to individualized multimodal treatment alone. Tumor biology, including the low- to intermediate-grade histological features observed in this case, may have contributed to the prolonged clinical course, although the prognostic impact of tumor grade in PBA remains difficult to determine due to the rarity and heterogeneity of this disease.

According to the ESMO-EURACAN-GENTURIS guidelines, follow-up for soft tissue sarcomas should include clinical and imaging assessments every 3–6 months during the first 2–3 years, every 6 months until 5 years, and annually thereafter [33].

Conclusions

Primary breast angiosarcoma is a rare and aggressive vascular malignancy characterized by high rates of local recurrence and early metastasis. Diagnostic evaluation is often challenging due to its nonspecific radiologic features and heterogeneous histopathologic presentation. Prompt recognition, wide-margin surgical excision, and multidisciplinary management are critical for optimal outcomes, as achieving negative margins remains the strongest predictor of durable local control. Despite multimodal treatment, prognosis remains poor once recurrence or metastasis occurs. The marked therapeutic resistance of this tumor underscores the need for biologically guided, multimodal strategies and the inclusion of patients in collaborative, molecularly driven clinical trials aimed at improving survival in this rare and challenging malignancy.

Availability of Data and Materials

All data generated or analyzed during this study are included in this published article.

Author Contributions

CVP, AMS, and AB contributed to the conceptualization of the study. FDL, NB, AS and GF contributed to data

collection and curation. CVP, AMS, AB, FDL, NB, AS, and GF contributed to the manuscript design and discussion. Writing—original draft preparation: CVP and AB. Writing—review and editing: AMS and CVP. All authors have been involved in revising the manuscript critically for important intellectual content. All authors gave final approval of the version to be published. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

The study was conducted in accordance with the Declaration of Helsinki. According to our institutional practice, formal Ethics Committee approval was not required for this retrospective single-patient case report. The patient signed a written informed consent form while she was alive for the publication of this case report and the associated images. All images have been fully anonymized to protect patient privacy.

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Conflict of Interest

Alejandro Martin Sanchez and Gianluca Franceschini were members of the Editorial Board of this journal at the time of acceptance. Alejandro Martin Sanchez and Gianluca Franceschini had no involvement in the peer review of this article and have no access to information regarding its peer review. Other authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at <https://doi.org/10.62713/ai.c.4777>.

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