Case Report

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Breast Angiosarcoma: Four Case Series and Literature Review

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ABSTRACT

The mammary angiosarcoma is a rare malignant mesenchymal tumor that develops from the vascular tissue of the breast. It represents 0.004 to 1% of all malignant breast tumors and 8 to 10% of breast sarcomas. It can be primary in a 40-year-old woman or radiation-induced in an older woman who has undergone conservative treatment for breast cancer, including conservative surgery and adjuvant radiotherapy. Herein, we present four cases involving breast angiosarcoma in young and relatively older women and the different treatment they received. Our discussion encompasses the epidemiological, diagnostic, and therapeutic facets of this rare and aggressive tumor type.

Keywords: *BRCA1* and *BRCA2* genes; breast cancer; breast imaging; mammography; primary angiosarcoma

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Key Points

- Mammary angiosarcoma (MAS) is a rare malignant tumor of the breast's vascular tissue, accounting for 8–10% of breast sarcomas. It can be primary (PAS) or secondary to radiotherapy (RAS).
- This is a presentation of four MAS cases with varying clinical features, from localized masses to advanced metastatic forms, requiring surgical and chemotherapeutic management.
- MAS is extremely rare (<0.04% of breast cancers), typically affecting young women (PAS) or elderly patients after radiotherapy (RAS).
- It often presents as a rapidly growing mass, skin lesions, or erythematous plaques, which can be mistaken for benign conditions.
- Mammographic and ultrasound features are non-specific, with magnetic resonance imaging being essential for better assessment and staging.

Introduction

Mammary angiosarcoma (MAS) is a rare malignant mesenchymal tumor arising from the vascular tissue of the breast. It accounts for 8–10% of breast sarcomas (1) and 0.004–1% of all malignant breast tumors (2). In women over 40 years who have undergone conservative treatment for breast cancer, such as breast-conserving surgery and adjuvant radiotherapy, MAS may be either radiation-induced (RAS) or primary (PAS) (3). Despite the use of locoregional conservative treatment, the incidence of subsequent angiosarcomas continues to rise. These tumors usually affect the skin and rarely involve the thoracic wall or mammary parenchyma. The vascular nature of angiosarcomas is confirmed through definitive histological diagnosis (1-3).

In this article, we present four distinct cases of MAS in women of varying ages and clinical contexts, along with a review of the literature to better understand the epidemiological, diagnostic, and therapeutic aspects of this rare entity.

Written informed consent was obtained from the patients for publication of these case series.

Case Reports

Case 1

The patient was a 36-year-old unmarried, nulliparous woman with a family history of breast carcinoma. She initially presented with a

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rapidly enlarging right breast mass measuring 11 cm, evolving over one month, without associated axillary lymphadenopathy. Breast ultrasound and mammography revealed a large, heterogeneous, and poorly vascularized solid mass occupying nearly the entire right breast, measuring 11×7 cm, and classified as American College of Radiology/Breast Imaging Reporting and Data System 4B (Figure 1). A core needle biopsy revealed a poorly differentiated angiosarcoma. Immunohistochemical staining showed strong positivity for CD31 and factor VIII-related antigen, confirming the vascular endothelial origin of the tumor, and was negative for pancytokeratin, effectively excluding an epithelial malignancy (Figure 2).

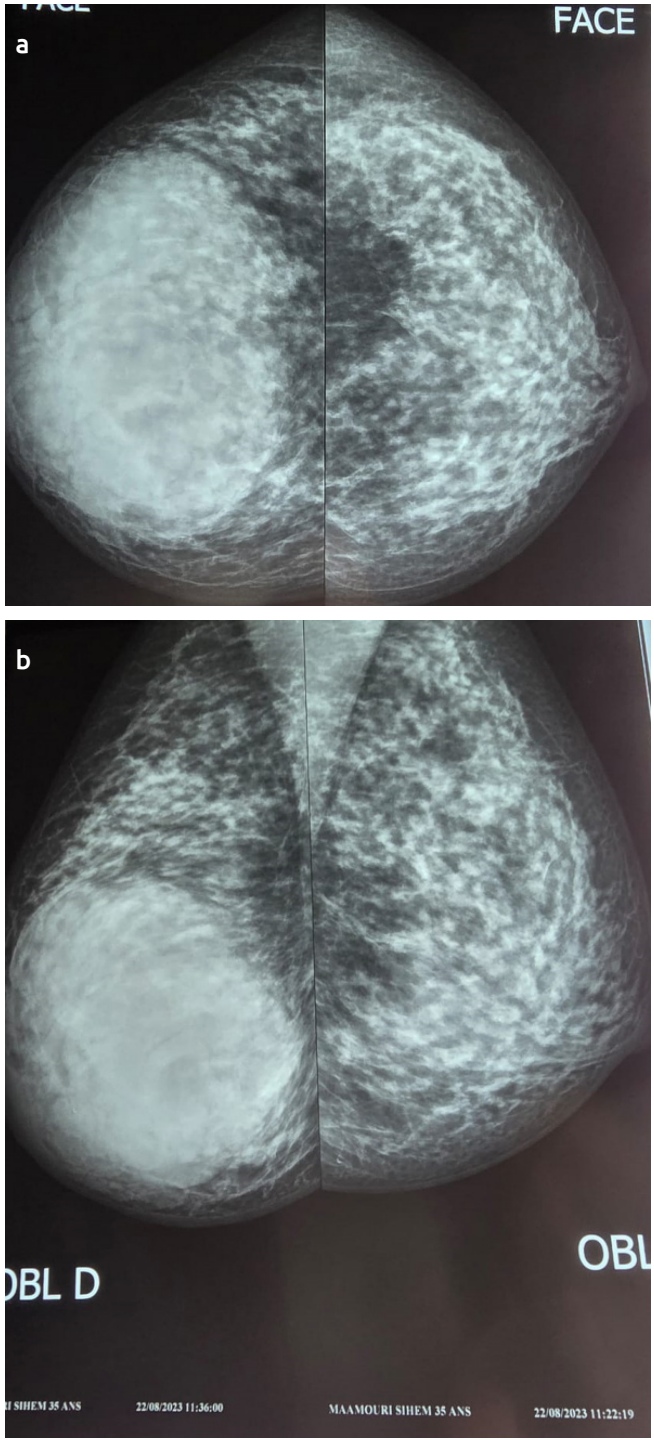

Figure 1. (a+b): Mammography showing a large solid mass occupying nearly the entire right breast (a): Craniocaudal projection, (b): Mediolateral oblique projection

The patient was scheduled for a right mastectomy but was lost to follow-up. Six months later, she presented to the emergency department with a marked deterioration of her general condition and a rapid increase in breast mass volume. Clinical examination revealed a 20 cm exophytic mass involving the entire right breast, with extensive blackish skin discoloration (Figure 3). A thoraco-abdomino-pelvic computed tomography scan demonstrated a large, infiltrative, and necrotic tumor invading the underlying pectoral muscle (Figure 4). The lower portion of the mass contained hydro-aeric components with air bubbles, ulceration, and cutaneous fistulization. In addition, there was right axillary lymphadenopathy and multiple pulmonary (Figure 5) and osseous (Figure 6) metastases.

She was found to have severe anemia (hemoglobin: 1.5 g/dL), necessitating transfusion with eight units of packed red blood cells to achieve a stable condition suitable for major surgery. A right mastectomy was performed, and the defect was reconstructed using a latissimus dorsi muscle flap.

Final histopathological examination confirmed the diagnosis of angiosarcoma, revealing highly irregular, anastomosing vascular channels lined by atypical endothelial cells, with hyperchromatic nuclei and high mitotic activity (Figure 7). The patient was subsequently scheduled for adjuvant chemotherapy and radiotherapy. Unfortunately, she died after four cycles of chemotherapy due to progression of advanced metastases.

Case 2

A 65-year-old patient with a left breast nodule was diagnosed as infiltrating ductal carcinoma. She had undergone conservative

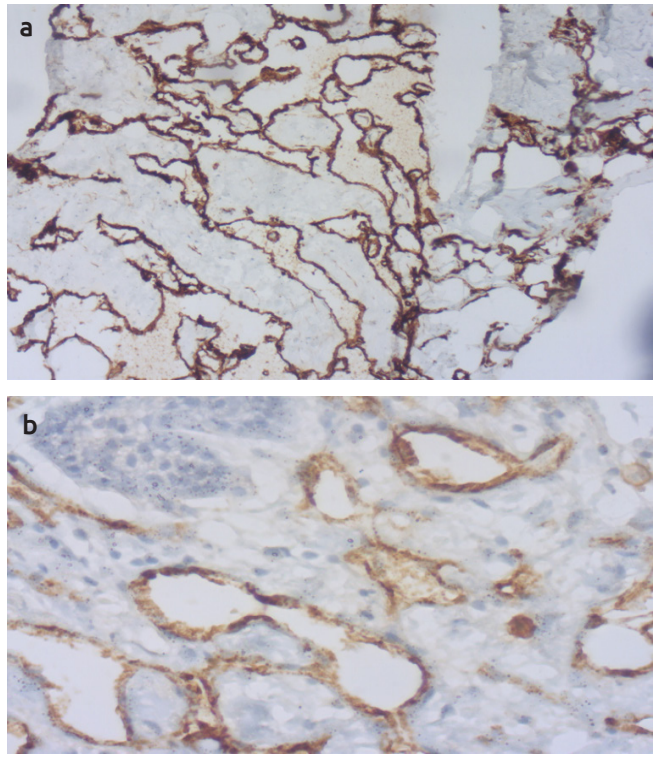

Figure 2. (a): Tumoral cells are positive to CD31, (b): Tumoral cells are positive to fact VIII

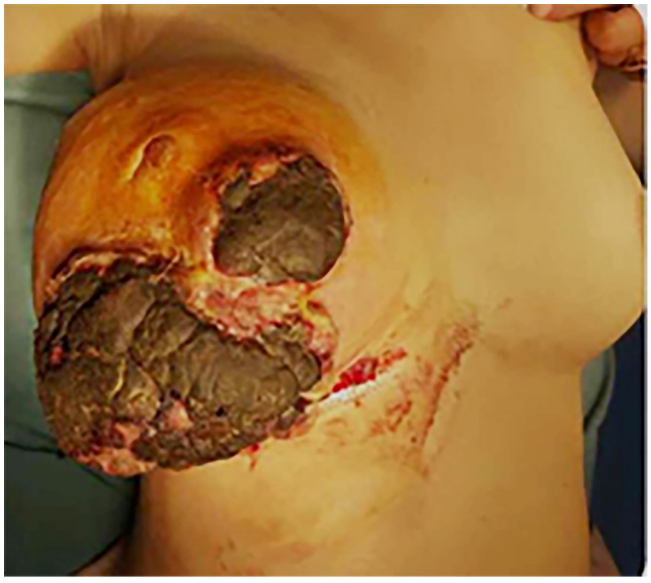

Figure 3. Clinical presentation of an angiosarcoma

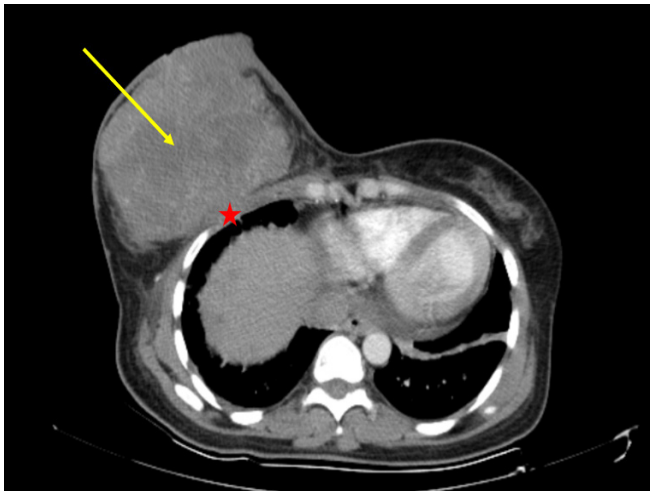

Figure 4. Computed tomography scan showing a large, infiltrative and necrotic tumor of the right breast (arrow) with invasion of the underlying pectoral muscle (asterisk)

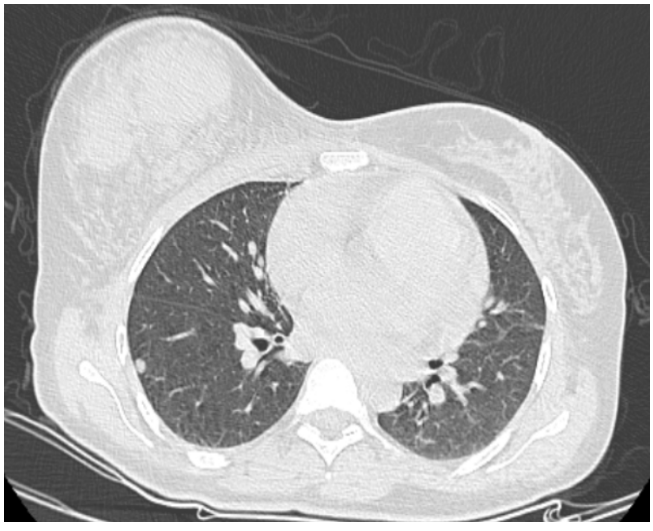

Figure 5. Axial computed tomography scan demonstrating multiple pulmonary metastases

treatment followed by postoperative radiotherapy. Ten years later, at the age of 75 years, she underwent reconsultion for the appearance of a 3 cm lump on the same breast corresponding to histologically confirmed angiosarcoma of the left breast, necessitating radical treatment with total mastectomy followed by chemotherapy.

Follow-up of the patient revealed no evidence of disease recurrence to date.

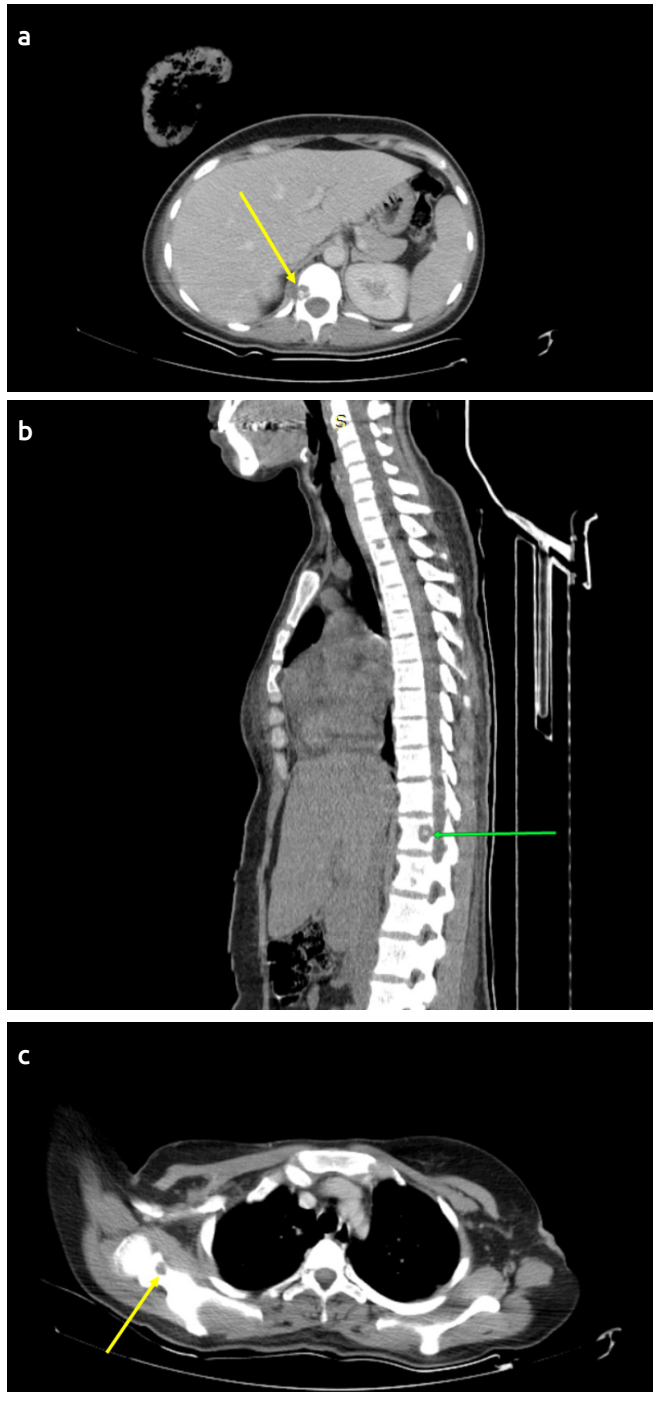

Figure 6. (a): Computed tomography scan axial section demonstrating an osseous metastasis in a thoracic vertebra, (b): Computed tomography scan sagittal section demonstrating an osseous metastasis in a thoracic vertebra, (c): Computed tomography scan sagittal section demonstrating an osseous metastasis in the right scapula

Case 3

A 34-year-old woman with no previous relevant medical history consulted for a rapidly growing breast mass measuring 15 cm with necrotic budding. A biopsy was performed and the result of the histopathology examination showed angiosarcoma of the left breast. She underwent a left mastectomy followed by adjuvant chemotherapy without radiotherapy. The patient has shown no signs of disease recurrence to date during follow-up.

Case 4

A 70-year-old woman presented with a well-circumscribed, 3.5 cm resected mass of the left breast, corresponding to a MAS on histopathology. She subsequently underwent a total mastectomy without receiving chemotherapy or radiotherapy. The patient lived to the age of 79 years and was cancer-free; she died from heart failure secondary to poorly controlled hypertension.

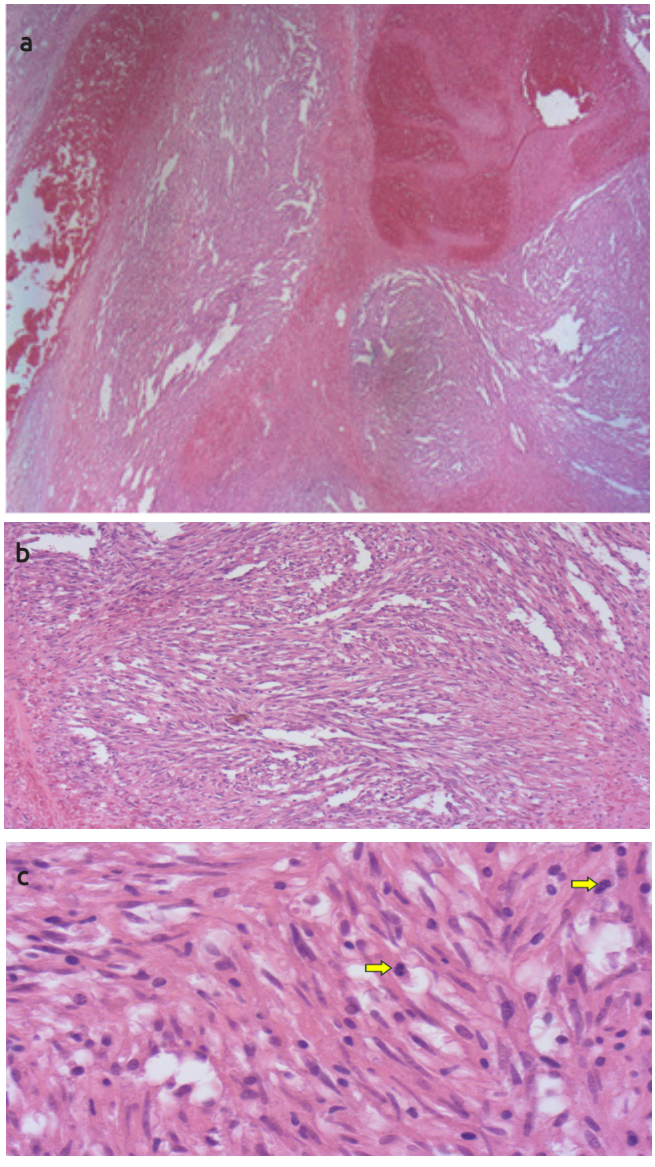

Figure 7. (a): Breast mass composed of anastomosing vascular channels of varying caliber and size, some of which are voluminous and full of blood (HE*10), (b): The vascular channels are lined by atypical endothelial cells (HE*40), (c): Tumoral cells are spindle-shaped with elongated nuclei showing moderate atypia and numerous mitoses (arrows)

Discussion and Conclusion

Epidemiology

Less than 0.04% of all breast cancers are primary breast angiosarcomas (PBAS), an uncommon condition that affects younger women with a median age of 40 years and unknown risk factors. Its frequency is roughly 0.0005% (4). Wang et al. (5) validated its uncommon occurrence in a study that included only 11 instances of MAS, of which only one was a primary MAS, out of a total of over 5,000 cases of breast cancers from 1997 to 2007. There are two types of secondary breast cancer angiosarcomas (SBAS): Post-radiation angiosarcoma and cutaneous angiosarcoma linked to lymphedema. In 1948, Stewart and Treves (6) published the first description of cutaneous angiosarcoma linked to lymphedema. This form typically appears in lymphedematous limbs and chest walls following mastectomy and axillary lymph node dissection. The increased use of sentinel lymph node sampling and breast-conserving therapy has reduced the prevalence of treatment-emergent lymphedema (7). In contrast, post-radiation angiosarcoma typically develops following radiotherapy and breast-conserving treatment. Although it can sometimes form in the breast parenchyma, it primarily affects the breast's dermis in the radiation field in the so-called "twilight zone", where radiation is inhomogeneous and may subsequently invade the underlying breast tissue (7). With a mean age of diagnosis of 70 years, SBAS primarily affects elderly women (4). As more patients are receiving conservative treatment (breast-conserving surgery and adjuvant radiation), its incidence is gradually rising. Although some data suggest that angiosarcoma can develop as early as 1–2 years or as late as 41 years following treatment, the typical interval between radiation and angiosarcoma development is six years (8).

Clinical Presentation

Earlier research reported that SBAS typically manifests as a palpably growing mass that is fast expanding and typically ranges in size from 5.7 cm to 7.3 cm (9). Usually seen in the mammary gland, the tumor can extend to the skin and result in ulceration (10). Rarely, SBAS can manifest as soreness in the breast, a sensation of fullness, or broad induration throughout the entire breast (9, 10).

Furthermore, Kasabach-Merritt syndrome, which is frequently seen in children with large hemangiomas and causes thrombocytopenia and consumptive coagulopathy as a result of platelet sequestration that leads to severe bleeding, may be linked to PBAS. However, rather than a palpable mass, SBAS frequently manifests as skin alterations and lesions in the chest wall or remaining chest parenchyma due to its cutaneous and/or subcutaneous position (5, 11). Erythematous or purplish plaques, nodules, contusions, skin discoloration, erythematous patches, blue to red or black nodules, and edema are the main symptoms of associated skin lesions.

There may or may not be ulceration (11). Diagnosis may be challenging as these lesions may be easily confused with radiodermatitis or other skin conditions.

Imaging Findings

PBAS

In a study into the mammographic features of PBAS, Wang et al. (10) concluded that these findings were non-specific. In particular, the authors describe PBAS as lobulated or oval masses, large diffuse asymmetries with irregular density, skin thickening,

locally thickened arteries, irregular subcutaneous fat density, and changes in the breast's trabecular structure. Notwithstanding these findings, no publication has mentioned the existence of swollen lymph nodes in the axilla. The parenchymal origin of PBAS, as opposed to the ductal structures where calcium is often deposited, and/or their rapid growth may account for the absence of related microcalcifications.

Mammograms may appear falsely normal due to the fact that PBAS primarily affects young women with dense breast parenchyma that may make a lump difficult to see. Naka et al. (12) reported that 33% of the angiosarcomas in their dataset were not detected on mammography. Momand et al. (13) found that 19% of patients had tumors that were apparent on magnetic resonance imaging (MRI) and ultrasonography, but were not evident on mammography. When a palpable anomaly is discovered, ultrasound can be helpful in verifying a mass, particularly in young women with dense breast parenchyma. On color Doppler, masses are typically vascularized and poorly delineated.

Angiomatous pseudo-stromal hyperplasia, galactocele or lactating adenoma, ductal ectasia, apocrine metaplasia, lipoma, angiolipoma, hematoma, seroma, fat necrosis, silicon granuloma, sebaceous or epidermal inclusion cyst, abscess, and ductal ectasia are among the largely benign breast angiosarcomas that can be identified by ultrasound (14).

In situations when MAS is suspected, MRI may be helpful for differential diagnosis and determining the extent of the disease, given the prevalence of false-positive and non-specific results with conventional imaging techniques. A heterogeneous mass with low signal intensity on T1-weighted images and high signal intensity on T2-weighted images is visible in angiosarcoma MRI scans. Higher-grade lesions may have irregular regions of strong T1 signal, which indicate venous lacunae or hemorrhages. MRI helps with surgery planning and is useful for determining the size of a tumor. Moreover, MRI can detect any disease that remains after an incisional biopsy (14, 15).

SBAS

Skin changes during radiation therapy, such as thickness, retraction, and architectural distortion of the breast parenchyma, can obscure or cause angiosarcoma-related skin alterations to be misinterpreted on mammograms. Poorly defined asymmetric masses may be seen in the subset of instances with parenchymal involvement. However, it is important to realize that mammograms can produce false-negative readings. According to Lim and Goei (16), a fully normal mammogram may be evident in about 33% of angiosarcoma cases linked to radiation therapy. Consequently, it is important to remember that skin thickness often declines two years following radiation therapy while monitoring patients undergoing breast-conserving therapy (17).

Beyond this point, any additional increase in skin thickness should raise the possibility of a malignant disease, such as angiosarcoma or carcinomatous mastitis. It can be challenging to differentiate skin lesions from post-radiation skin thickening on ultrasonography. Heterogeneous regions with disturbance of normal tissue planes are recognized as intraparenchymal masses (18). A plateau or washout with delayed imaging and fast gadolinium enhancement are MRI characteristics comparable to those of primary angiosarcoma. Of note, it has been demonstrated that MRI is the most sensitive method for identifying radiotherapy-associated sagittal angiosarcoma (15).

Histopathology

The pathogenesis of angiosarcoma, especially MAS, is complex. *BRCA1* and *BRCA2*, two important genes in breast and ovarian cancer, are thought to play a part in the development of SBAS because they are essential for maintaining cellular equilibrium and protecting DNA from radiation-induced damage. Cases of SBAS have been reported in people with *BRCA1* and *BRCA2* mutations by researchers such as West et al. (19). Both animal models and MAS patients exhibit signs of angiosarcoma development linked to the transcription factor p53 and its inhibitor MDM2 (18). Increased expression of vascular endothelial growth factor may also is also be involved in this particular mechanism (12, 13, 18). In order to differentiate invasive carcinomas from MAS, immunohistochemistry investigations are essential. Angiosarcoma can be indicated by endothelial markers, including CD34, CD31, and factor VIII. A poorer prognosis is linked to a higher ki-67 index (20). A thorough histological and immunohistochemical examination of the entire material is important following surgical excision and is regarded as the gold standard for diagnosis (20). Fine-needle aspiration and needle biopsy can result in false-negative results for malignancy, estimated to occur in 37% of cases because of well-differentiated histological types or the presence of necrotic tissue, fat, or bleeding.

Angiolipomas, hemangiomas, and benign proliferative lesions are examples of the differential diagnoses for low-grade angiosarcomas. Mastitis, fibromatosis, and especially invasive breast cancer are factors to take into account for higher grade angiosarcomas (21). Abnormal endothelial cells in blood vessels proliferate rapidly in MAS. These cells frequently infiltrate the surrounding breast tissue, resulting in necrotic and hemorrhagic patches. Although the cells of well-differentiated angiosarcomas resemble normal endothelium, they also have aberrant vascular patterns and atypia.

Histologically, poorly differentiated types may be more challenging to identify due to their unclear vascular development. MAS typically has a poor prognosis due to its high rate of local recurrence and tendency for hematogenous dissemination. There are three categories of MAS: Low grade, which has well-formed vascular channels; intermediate grade, which has prominent neoplastic vascular development; and high grade, which has localized hemorrhage, infarction, and necrosis (18).

Treatment

For both primary and secondary MAS, surgical excision with mastectomy is usually the accepted course of treatment. For minor primary lesions, breast-conserving treatment may be an option. The rate of local recurrence may be decreased by chemotherapy, and docetaxel shows promise in the treatment of secondary angiosarcoma (22). Hyper fractionated radiation therapy has been demonstrated to be successful in lowering cell repopulation in quickly expanding high-grade secondary angiosarcomas, despite the paucity of available evidence (22).

Prognosis

Although 5-year survival rates may be higher than those of other types of cutaneous angiosarcoma, secondary angiosarcomas often

have a dismal prognosis. The completeness of surgical resection affects the outcome. Local recurrence is frequently linked to distant metastases and is a poor prognostic indication (7).

In summary, MAS, both primary and secondary, are uncommon diseases. The clinical presentation may be skin discoloration, skin plaques or nodules, a palpable mass, or a combination of these symptoms. The diagnosis may be delayed if discoloration is confused with bruising. Findings from ultrasonography and mammography are not specific for angiosarcoma. Particularly in high-grade tumors, MRI can be used to determine the extent of the lesion and can show a rapidly enhancing heterogeneous mass with bleeding or blood pooling. The incidence of post-irradiation angiosarcomas is increasing as breast-conserving therapy is used more often to treat breast cancer. Early intervention, which is important for treatment of this aggressive malignancy, depends on prompt recognition.

Ethics

Informed Consent: Written informed consent was obtained from the patients for publication of these case series.

Footnotes

Authorship Contributions

Surgical and Medical Practices: I.B., S.F., H.A., E.G., D.C., S.B., B.B.; Concept: I.B., H.A., E.G., S.B., B.B.; Design: I.B., H.A., E.G.; Data Collection or Processing: S.F., H.A., E.G.; Analysis or Interpretation: S.F., D.C., S.B., B.B.; Literature Search: I.B., S.F., H.A., E.G.; Writing: H.A., E.G.

Conflict of Interest: No conflict of interest was declared by the authors.

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