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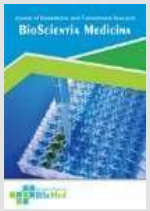

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A Rare Primary Breast Angiosarcoma with Bone Metastasis: A Case Report

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A B S T R A C T

Background: Angiosarcoma is a rare and aggressive malignant tumor originating from endothelial cells. Primary breast angiosarcoma (PBA) is exceedingly uncommon, accounting for less than 1% of all breast malignancies. Bone metastasis from PBA is even rarer, making it a unique clinical entity. **Case presentation:** We present the case of a 37-year-old woman who initially presented with a rapidly enlarging breast mass. A biopsy confirmed the diagnosis of PBA, and she underwent a modified radical mastectomy followed by radiotherapy. Seventeen months later, she developed progressive lower extremity weakness and urinary and bowel incontinence. Imaging revealed a spinal metastasis at the Th4-Th6 level. Biopsy and immunohistochemistry confirmed metastatic angiosarcoma. The patient underwent laminectomy and posterior stabilization. **Conclusion:** This case highlights the rarity and aggressive nature of PBA with bone metastasis. It emphasizes the importance of early detection, comprehensive treatment, and long-term surveillance in managing this challenging disease. Further research is needed to understand the underlying mechanisms and develop effective therapeutic strategies for PBA with bone metastasis.

1. Introduction

Angiosarcoma, a rare and aggressive malignancy arising from endothelial cells lining blood or lymphatic vessels, constitutes less than 1% of all sarcomas. This heterogeneous group of tumors can manifest in various anatomical locations, with the skin, soft tissues, and viscera being the most common sites. The rarity and diverse clinical presentations of angiosarcoma pose significant diagnostic and therapeutic challenges, necessitating a comprehensive understanding of its underlying pathobiology and clinical behavior. Primary breast angiosarcoma (PBA) is an exceedingly uncommon subtype of angiosarcoma, accounting for a mere 0.04% of all malignant breast tumors. This distinct entity originates within the breast parenchyma, distinguishing it from secondary breast angiosarcoma, which typically arises in the skin following radiation therapy. PBA predominantly affects young women in their third or fourth decade of life, often presenting as a rapidly enlarging, painless breast mass. The aggressive nature of PBA, coupled with its rarity, underscores the importance of early detection and prompt intervention to optimize patient outcomes. The etiology of PBA remains poorly understood, with hormonal factors, particularly pregnancy, implicated in its development. A significant proportion of PBA cases are diagnosed during or shortly after pregnancy, suggesting a potential role for hormonal dysregulation in tumorigenesis. However, the exact mechanisms

underlying this association remain elusive, warranting further investigation to elucidate the complex interplay between hormonal influences and the development of PBA. The diagnosis of PBA can be challenging due to its rarity and overlapping clinical features with other breast malignancies. A high index of suspicion is crucial, especially in young women presenting with rapidly growing breast masses. Imaging modalities, such as mammography and ultrasound, may provide initial clues, but definitive diagnosis relies on histopathological examination and immunohistochemical analysis. The latter plays a pivotal role in differentiating PBA from other vascular tumors and establishing the diagnosis with certainty.[1-3]

The management of PBA is complex and often tailored to the individual patient's clinical presentation and disease stage. Surgical resection with wide margins remains the cornerstone of treatment for localized PBA. However, the extent of surgery and the need for adjuvant therapies, such as radiotherapy and chemotherapy, are subjects of ongoing debate. The rarity of PBA has precluded the conduct of large-scale randomized controlled trials, leaving clinicians to rely on retrospective studies and expert consensus to guide treatment decisions. Bone metastasis from PBA is an exceptionally rare event, with limited cases reported in the literature. The most common sites of metastasis for angiosarcoma are the lungs and liver, with bone metastasis typically occurring in the late stages of the disease. The presence of bone metastasis is associated with a poor prognosis, highlighting the need for novel therapeutic approaches to address this aggressive malignancy.[4,5] In this case report, we present a unique and instructive case of PBA with bone metastasis to the spine. This rare clinical scenario underscores the importance of maintaining a high index of suspicion for PBA in young women presenting with rapidly growing breast masses. Furthermore, it emphasizes the need for comprehensive staging and long-term surveillance to detect and manage metastatic disease promptly. By sharing this case, we aim to contribute to the existing body of knowledge on PBA and stimulate further research into the underlying mechanisms and potential therapeutic targets for this challenging disease.

2. Case Presentation

A 37-year-old woman presented to our outpatient clinic with a chief complaint of a rapidly enlarging, painless mass in her right breast. The patient first noticed the mass three months prior to her presentation, and it had grown significantly during that time, from the size of a ping pong ball to the size of a baby's head. The patient denied any associated symptoms such as breast pain, nipple discharge, or changes in the skin overlying the mass. She also denied any history of breast trauma. The patient's medical history was notable for one prior pregnancy, during which she breastfed for two years. She had a history of using hormonal contraception containing progesterone for one year, followed by the use of an intrauterine device (IUD). She denied any other significant medical conditions or family history of breast cancer. On physical examination, the patient's vital signs were within normal limits. Inspection of the breasts revealed asymmetry, with the right breast noticeably larger than the left. The skin overlying the right breast appeared erythematous and shiny compared to the surrounding skin. Additionally, an ulceration was observed on the right breast, accompanied by nipple retraction. There was no evidence of peau d'orange (orange peel-like appearance of the skin) or skin dimpling. Palpation of the right breast revealed a large mass measuring 22x20x7 cm. The mass was partially solid and partially cystic, with ill-defined borders and no associated tenderness. There was no palpable axillary lymphadenopathy on either side. The left breast examination was unremarkable.

Given the concerning clinical presentation, a biopsy of the breast mass was performed. Histopathological examination of the biopsy specimen revealed a highly cellular tumor with infiltrative growth. The tumor cells exhibited pleomorphic, hyperchromatic nuclei, some with prominent nucleoli.

Numerous blood vessels were observed, with lumens that appeared partially anastomosed or contained papillary projections. Notably, there was no evidence of normal breast glandular tissue within the tumor. To further characterize the tumor, immunohistochemical (IHC) staining was performed. The tumor cells showed strong positive staining for vimentin, CD31, and CD34, which are markers of endothelial differentiation. Staining for cytokeratin (CK) and epithelial membrane antigen (EMA) was negative, ruling out the possibility of a carcinoma. These findings, in conjunction with the histopathological features, confirmed the diagnosis of primary breast angiosarcoma (PBA).

To assess the extent of the disease and rule out distant metastasis, the patient underwent additional imaging studies. A chest X-ray and liver ultrasound were performed, both of which were normal. These findings indicated that the angiosarcoma was localized to the breast at the time of diagnosis. Following the confirmation of PBA, the patient underwent a modified radical mastectomy to remove the tumor and surrounding tissues. The surgical margins and all biopsy sites were meticulously examined and found to be free of malignant cells. Additionally, four axillary lymph nodes were identified and excised, none of which showed evidence of metastasis. After the mastectomy, the patient received adjuvant radiotherapy to the chest wall to reduce the risk of local recurrence. She completed a course of 25 cycles of radiotherapy, which was well-tolerated. Seventeen months after the initial diagnosis and treatment, the patient presented to the clinic with new-onset progressive weakness in both lower extremities. The weakness had worsened over time and was accompanied by pain in both shoulder blades and numbness extending from the lower chest to the feet. She also reported experiencing urinary and bowel incontinence, which significantly impacted her quality of life.

Physical examination at this time revealed no evidence of a recurrent mass at the mastectomy site or any deformity or ulceration of the vertebrae. However, there was mild tenderness upon palpation of the thoracic spine, and the patient had a limited range of motion due to pain. Neurological examination confirmed the presence of hypoesthesia (decreased sensation) starting from the T4 vertebral level downwards. Motor strength in both lower extremities was significantly reduced, with a Medical Research Council (MRC) grade of 1/5. To investigate the cause of the patient's neurological symptoms, imaging studies were performed. A chest X-ray and ultrasound of the liver and chest wall showed no signs of distant metastasis or local recurrence. X-rays of the thoracic and lumbar spine were also normal. However, magnetic resonance imaging (MRI) of the lumbosacral spine revealed a significant finding: a mixed cystic mass with well-defined borders and irregular margins located in the extradural space. The mass extended into the intradural space at the Th4-Th6 level on the left side, infiltrating the pedicle, spinous process, posterior longitudinal ligament, interspinous ligament, left posterior soft tissue, and spinal canal. The mass was compressing the spinal cord, causing stenosis and explaining the patient's neurological symptoms.

Given the suspicion of metastatic disease, a biopsy of the vertebral lesion was performed. Histopathological examination of the biopsy specimen revealed features consistent with metastatic angiosarcoma. However, metastatic carcinoma was considered a differential diagnosis. To differentiate between these two possibilities, IHC staining was performed on the biopsy specimen. The results showed positive staining for CD31, CD34, and vimentin, and negative staining for CK and EMA. These findings were identical to the IHC profile of the primary breast tumor, confirming the diagnosis of metastatic angiosarcoma to the spine.

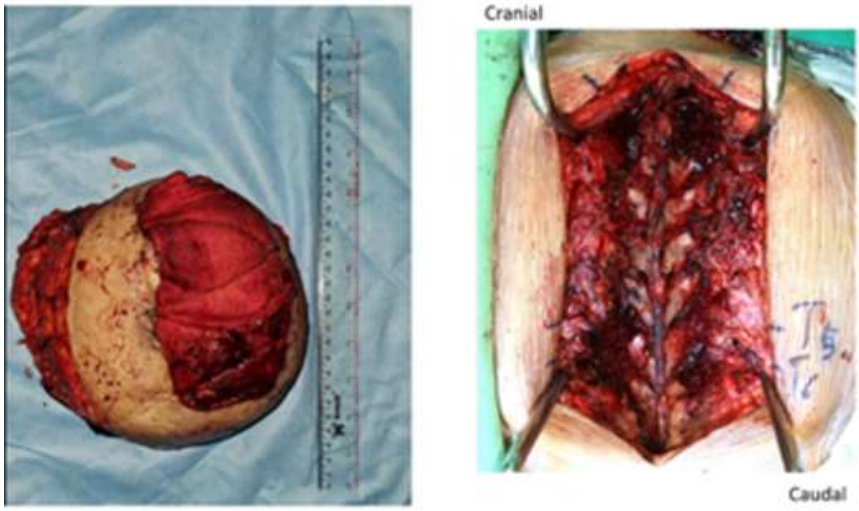
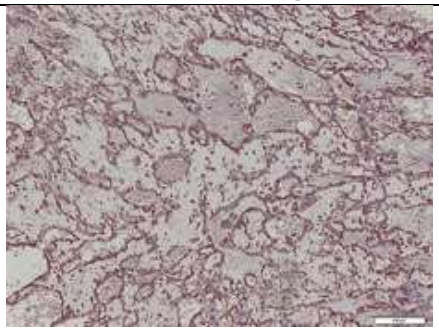
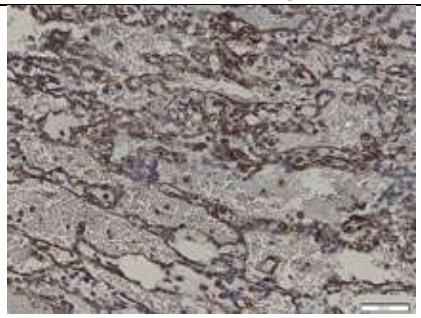
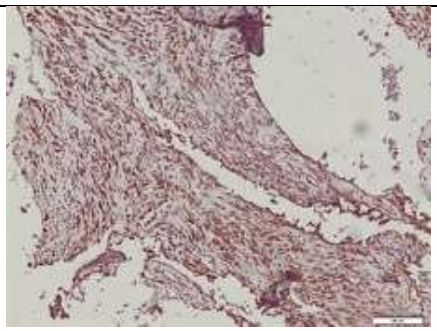
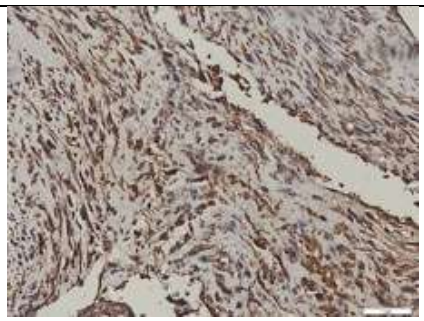
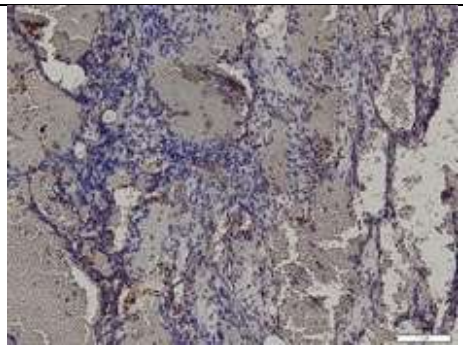
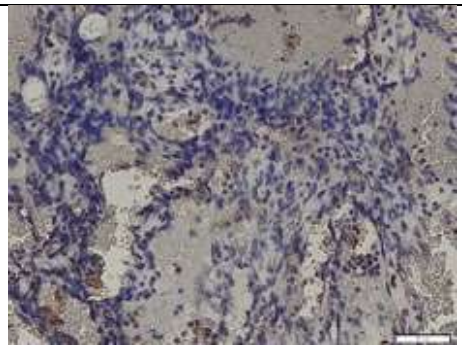
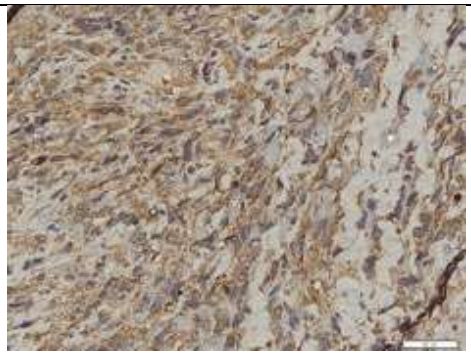
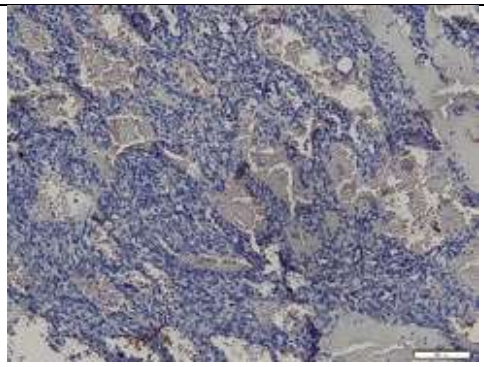
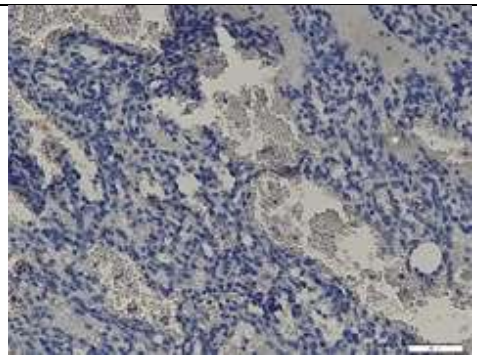
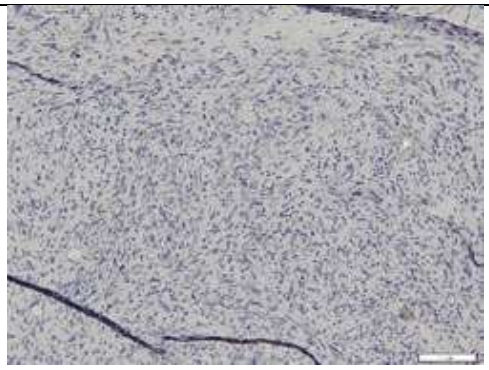
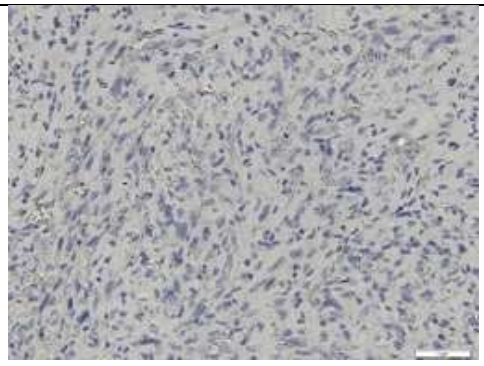
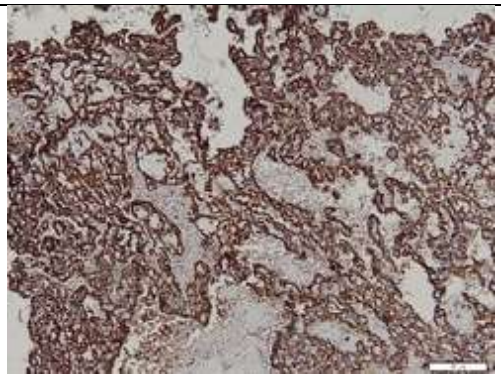
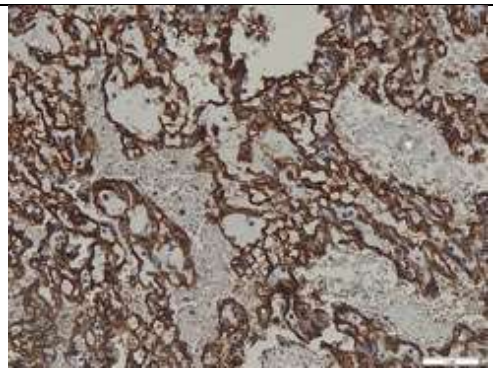
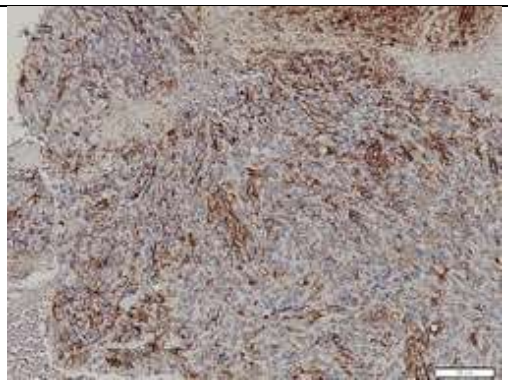
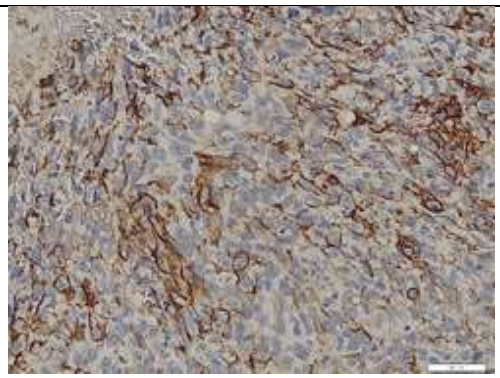
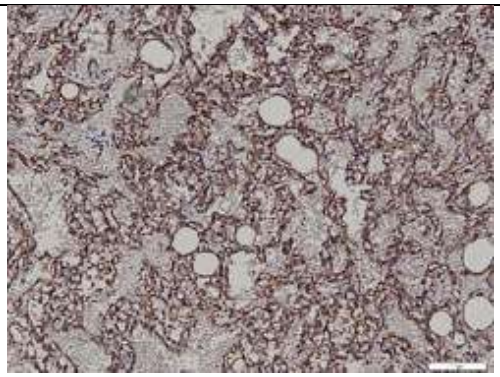
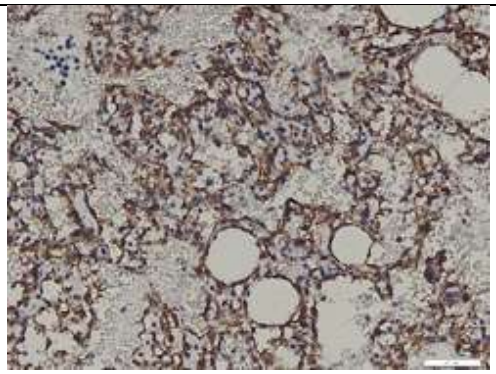
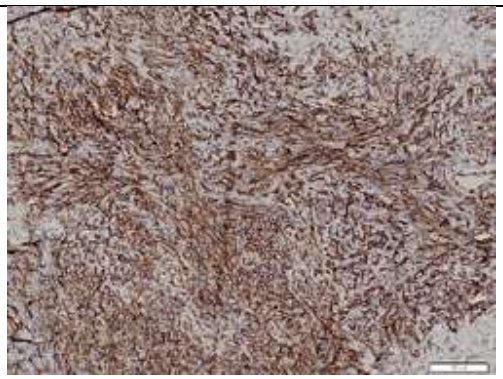
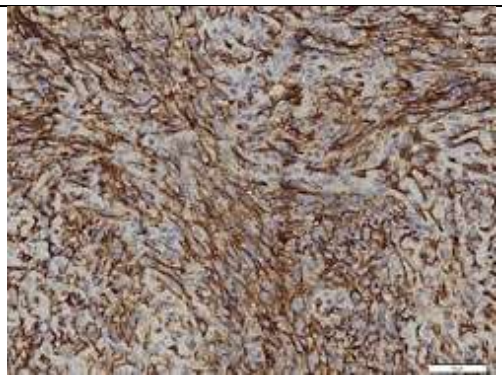


Figure 1. (Left) Intraoperative findings of mastectomy; (Right) Intraoperative findings of laminectomy.

Table 1. Immunohistochemistry assessment.

Mastectomy specimen	**Vertebrae biopsy specimen**
CK: negative Vimentin: positive CD31: positive CD34: positive EMA: negative Impression: consistent with angiosarcoma	CK: negative Vimentin: positive CD31: positive CD34: positive EMA: negative Impression: consistent with angiosarcoma
 VIM 100x	 VIM 200x
 VIM 100x	 VIM 200x

 EMA 100x	 EMA 200x
 EMA 100x	 EMA 200x
 CK 100x	 CK 200x
 CK 100x	 CK 200x

 CD34 100X	 CD34 200X
 CD34 100x	 CD34 200x
 CD31 100x	 CD31 200x
 CD31 100x	 CD31 200x

3. Discussion

Angiosarcoma of the breast is an exceedingly rare and aggressive malignancy, constituting a mere 0.04% of all malignant breast tumors. This translates to approximately 1 in every 2,500 cases of breast cancer being diagnosed as angiosarcoma. The rarity of this disease poses significant challenges in terms of diagnosis, treatment, and research, as the limited number of cases makes it difficult to conduct large-scale studies and establish definitive treatment guidelines. Angiosarcomas are malignant tumors that arise from the endothelial cells lining blood vessels or lymphatic channels. In the breast, they can be classified into two distinct types: primary breast angiosarcoma (PBA) and secondary breast angiosarcoma. This distinction is crucial as it reflects different underlying etiologies, clinical presentations, and potentially, treatment approaches. PBA originates within the breast parenchyma, the glandular tissue responsible for milk production. It is a de novo malignancy, meaning it arises spontaneously without any identifiable predisposing factors in most cases. However, there is a notable association between PBA and pregnancy, with a significant proportion of cases diagnosed during or shortly after pregnancy. This association suggests a potential role for hormonal fluctuations in the development of PBA, although the exact mechanisms remain unclear. In contrast, secondary breast angiosarcoma arises in the skin overlying the breast, typically as a late complication of radiation therapy for breast cancer. This type of angiosarcoma is thought to be induced by radiation exposure, with a latency period of several years, often 7-10 years, between radiation treatment and the development of the tumor. The pathogenesis of radiation-induced angiosarcoma is complex and involves a series of genetic and molecular alterations that ultimately lead to malignant transformation of endothelial cells. The clinical presentation of breast angiosarcoma can vary depending on the type and stage of the disease. PBA often presents as a rapidly enlarging, painless mass in the breast. The mass may be accompanied by skin changes, such as discoloration, thickening, or ulceration. In some cases, there may be nipple retraction or bloody nipple discharge. Due to the rapid growth of PBA, patients often seek medical attention relatively early in the disease course. Secondary breast angiosarcoma, on the other hand, typically presents as skin changes in the area previously treated with radiation therapy. These changes may include erythema, ecchymosis, telangiectasias (spider veins), or the development of multiple nodules. The skin lesions may be painful or pruritic, and they may progress to ulceration and necrosis.[6-8]

The diagnosis of breast angiosarcoma requires a high index of suspicion, especially in young women presenting with rapidly growing breast masses or in women with a history of radiation therapy for breast cancer. Imaging studies, such as mammography and ultrasound, may provide initial clues, but definitive diagnosis relies on histopathological examination of a biopsy specimen. Immunohistochemical staining for endothelial markers, such as CD31 and CD34, is essential to confirm the diagnosis and differentiate angiosarcoma from other vascular tumors. The diagnosis of angiosarcoma, particularly primary breast angiosarcoma (PBA), presents a formidable challenge due to its exceptional rarity and diverse clinical manifestations. This diagnostic complexity is further compounded by the tumor's ability to mimic other, more common breast pathologies, leading to potential delays in diagnosis and appropriate treatment. In the case of PBA, patients often present with a rapidly enlarging, painless breast mass, as was observed in the case described earlier. This clinical presentation, while suggestive, is not pathognomonic for PBA, as it can also be seen in various benign and malignant breast conditions. Consequently, a high index of suspicion is paramount, especially in young women who present with such a rapidly growing mass. The initial evaluation of a suspected PBA typically involves imaging modalities such as mammography and ultrasound. Mammography may reveal a nonspecific mass or an area of architectural distortion, while ultrasound may demonstrate a complex cystic

and solid mass with irregular margins. However, these imaging findings are not specific for PBA and can be seen in other breast lesions, such as phyllodes tumors or metaplastic carcinomas. Therefore, a definitive diagnosis of PBA necessitates a histopathological examination of the breast mass. This involves obtaining a tissue sample through either a core needle biopsy or an excisional biopsy. The histopathological features of PBA can vary considerably, ranging from well-differentiated tumors with recognizable vascular channels to poorly differentiated tumors with atypical cells and a high degree of pleomorphism. In well-differentiated PBA, the tumor cells form anastomosing vascular channels lined by atypical endothelial cells. These cells may exhibit hyperchromatic nuclei, prominent nucleoli, and increased mitotic activity. In poorly differentiated PBA, the tumor cells may lose their endothelial characteristics and appear as spindle-shaped or epithelioid cells with a high degree of pleomorphism. The presence of necrosis and hemorrhage is also common in PBA, reflecting the tumor's aggressive nature.[9-11]

Immunohistochemistry (IHC) plays a crucial role in confirming the diagnosis of PBA and differentiating it from other vascular tumors and breast malignancies. The tumor cells in PBA typically express endothelial markers such as CD31 (PECAM-1) and CD34. CD31 is a transmembrane glycoprotein expressed on the surface of endothelial cells and platelets, while CD34 is a cell surface glycoprotein expressed on hematopoietic progenitor cells and endothelial cells. The strong and diffuse expression of CD31 and CD34 in the tumor cells is a hallmark of PBA and helps to distinguish it from other vascular tumors, such as hemangiomas and lymphangiomas, which may show only focal or weak staining for these markers. In addition to CD31 and CD34, other endothelial markers, such as von Willebrand factor (vWF) and FLI1, may also be expressed in PBA. However, the expression of these markers is less consistent than that of CD31 and CD34. Therefore, a panel of IHC markers, including CD31, CD34, vWF, and FLI1, is often used to confirm the diagnosis of PBA. The absence of staining for epithelial markers, such as cytokeratin (CK) and epithelial membrane antigen (EMA), is another important feature that helps to differentiate PBA from breast carcinomas. CK and EMA are typically expressed in epithelial cells, which are the cells that line the ducts and lobules of the breast. The absence of these markers in PBA confirms its mesenchymal origin and distinguishes it from carcinomas, which are of epithelial origin. In the case presented earlier, the diagnosis of PBA was established based on the characteristic histopathological features of the tumor and the positive IHC staining for CD31 and CD34. The absence of staining for CK and EMA further supported the diagnosis of PBA and ruled out the possibility of carcinoma.[12-14]

The accurate and timely diagnosis of PBA is crucial for initiating appropriate treatment and improving patient outcomes. The rapidly growing nature of PBA necessitates prompt intervention, as delays in diagnosis can lead to increased tumor size, local invasion, and distant metastasis. The use of a multidisciplinary approach, involving clinicians, radiologists, and pathologists, is essential for the optimal management of patients with PBA. The management of primary breast angiosarcoma (PBA) presents a formidable challenge due to the rarity of the disease and the lack of high-quality evidence to guide treatment decisions. The absence of large-scale randomized controlled trials (RCTs) necessitates reliance on retrospective studies, case reports, and expert consensus to formulate optimal treatment strategies. This often leads to a personalized approach, where treatment is tailored to the individual patient's clinical presentation, disease stage, and overall health status.[13,14]

Surgical resection with wide margins remains the cornerstone of treatment for localized PBA. The primary goal of surgery is to achieve complete removal of the tumor with negative margins, minimizing the risk of local recurrence. The extent of surgery, however, is a subject of ongoing debate. Some advocate for mastectomy, while others suggest that

breast-conserving surgery (BCS) may be appropriate in select cases where the tumor is small and well-circumscribed.

The decision between mastectomy and BCS is complex and requires careful consideration of various factors, including tumor size, location, grade, and patient preferences. Mastectomy offers the advantage of ensuring complete tumor removal and reducing the risk of local recurrence. However, it is associated with significant physical and psychological morbidity. BCS, on the other hand, preserves the breast but carries a higher risk of local recurrence, necessitating close surveillance and potentially additional treatments. In cases where the tumor is large or involves multiple areas of the breast, mastectomy may be the preferred option. However, for smaller, well-defined tumors, BCS may be considered if the patient is willing to accept the increased risk of local recurrence. Ultimately, the decision regarding the extent of surgery should be made on an individual basis, taking into account the patient's values and preferences, as well as the surgeon's expertise and experience.[15,16]

The role of adjuvant therapies, such as radiotherapy and chemotherapy, in the management of PBA is less clear. Radiotherapy is often recommended after surgery to reduce the risk of local recurrence, especially in cases where the surgical margins are close or positive. However, the optimal timing and dose of radiotherapy remain unclear. Chemotherapy is typically reserved for patients with high-risk features, such as large tumor size, high grade, or positive lymph nodes. However, the efficacy of chemotherapy in PBA is uncertain, as there is limited evidence to support its use. Several chemotherapy regimens have been used in PBA, including anthracyclines, taxanes, and gemcitabine-based combinations. However, the response rates are variable, and the optimal regimen remains to be determined. The decision to administer adjuvant radiotherapy or chemotherapy should be made on a case-by-case basis, considering the individual patient's risk factors and the potential benefits and risks of each treatment modality. Close collaboration between the surgeon, radiation oncologist, and medical oncologist is essential to develop a personalized treatment plan that maximizes the chances of cure while minimizing the risk of complications.[16,17]

The management of PBA is fraught with challenges due to the rarity of the disease and the lack of high-quality evidence to guide treatment decisions. The absence of large-scale RCTs has hindered the development of standardized treatment protocols, leaving clinicians to rely on retrospective studies and expert consensus. Furthermore, the heterogeneity of PBA, with varying clinical presentations and biological behaviors, adds another layer of complexity to its management. Some tumors may be indolent and slow-growing, while others may be highly aggressive and rapidly metastatic. This heterogeneity makes it difficult to predict the course of the disease and determine the optimal treatment approach for each patient. To address these challenges, there is a pressing need for collaborative research efforts to collect and analyze data on PBA patients from multiple institutions. This would enable the identification of prognostic factors, the development of risk stratification models, and the design of prospective clinical trials to evaluate the efficacy of different treatment modalities. In addition, advances in molecular profiling and targeted therapies hold promise for improving the management of PBA. Identifying specific molecular alterations that drive tumor growth and progression could lead to the development of targeted therapies that are more effective and less toxic than traditional chemotherapy. The management of PBA is a complex and evolving field. Surgical resection with wide margins remains the cornerstone of treatment, but the role of adjuvant therapies is less clear. The rarity and heterogeneity of PBA pose significant challenges to clinicians, necessitating a personalized approach to treatment. Further research is needed to develop standardized treatment protocols and identify novel therapeutic targets for this rare and aggressive malignancy.[16-18]

Following the definitive diagnosis of primary breast angiosarcoma (PBA), a multidisciplinary team approach was adopted to formulate a comprehensive treatment plan for the patient. Given the localized nature of the tumor and the absence of distant metastasis, the decision was made to proceed with a modified radical mastectomy. This surgical procedure involved the removal of the entire breast tissue, including the tumor, along with the axillary lymph nodes. The pectoralis major muscle was preserved, distinguishing this approach from a traditional radical mastectomy. The modified radical mastectomy aimed to achieve complete resection of the tumor with negative margins, ensuring the removal of all microscopic disease. The axillary lymph node dissection was performed to assess the extent of regional nodal involvement and guide further treatment decisions. Meticulous attention was paid to achieving hemostasis and minimizing postoperative complications. Following the mastectomy, the surgical specimen was sent for histopathological examination. The margins of resection were carefully evaluated and found to be free of malignant cells, indicating complete excision of the tumor. Additionally, the four axillary lymph nodes that were removed were examined and found to be negative for metastasis, confirming the localized nature of the disease. To further reduce the risk of local recurrence, the patient was recommended to undergo adjuvant radiotherapy. Radiotherapy is a standard component of the treatment regimen for PBA, as it has been shown to improve local control and overall survival. The patient received a course of 25 cycles of radiotherapy, which was delivered to the chest wall and regional lymph nodes. The radiotherapy was well-tolerated, with no significant acute or late toxicities reported.[17,18]

The combination of modified radical mastectomy and adjuvant radiotherapy represents the standard treatment approach for localized PBA. This multimodal approach aims to achieve complete eradication of the tumor while minimizing the risk of local recurrence and improving long-term outcomes. However, despite the initial success of the treatment, the patient's clinical course took an unexpected turn 17 months later. The patient presented with new-onset progressive weakness in both lower extremities, accompanied by pain in both shoulder blades and numbness extending from the lower chest to the feet. These symptoms raised concerns for spinal cord compression, a potentially devastating complication of metastatic disease. Further investigation with magnetic resonance imaging (MRI) of the lumbosacral spine revealed a mixed cystic mass with well-defined borders and irregular margins located in the extradural space. The mass extended into the intradural space at the Th4-Th6 level on the left side, infiltrating the pedicle, spinous process, posterior longitudinal ligament, interspinous ligament, left posterior soft tissue, and spinal canal. The mass was compressing the spinal cord, causing stenosis and explaining the patient's neurological symptoms. The presence of a spinal metastasis in this patient represented a rare and ominous complication of PBA. Bone metastasis from angiosarcoma is uncommon, with the lungs and liver being the most frequent sites of distant spread. The development of bone metastasis usually occurs in the late stages of the disease and is associated with a poor prognosis. The unexpected occurrence of bone metastasis in this patient highlights the aggressive nature of PBA and the importance of long-term surveillance. Despite the initial successful treatment with surgery and radiotherapy, the tumor cells had disseminated to the spine, leading to significant neurological impairment. This case underscores the need for ongoing vigilance and a high index of suspicion for metastatic disease in patients with PBA.[19,20]

4. Conclusion

This case report highlights the rarity and aggressive nature of PBA with bone metastasis. It emphasizes the importance of early detection, comprehensive treatment, and long-term surveillance in managing this challenging disease. Further research is needed to understand the underlying mechanisms and develop effective therapeutic

strategies for PBA with bone metastasis.

5. References

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