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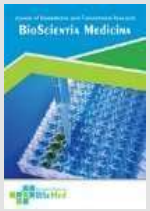

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Primary Breast Angiosarcoma: Serial Cases

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A B S T R A C T

Background: Breast angiosarcoma is a rare malignancy arising from endothelial cell lining, approximately 0.04–0.05% of all breast malignancies and less than 1% of all sarcomas. Consisting of primary breast angiosarcoma (PAS) and secondary breast angiosarcoma (SAS). Diagnosis is often delayed because the case is rare and asymptomatic, the lump is painless, grows quickly, progressive disease can develop distant metastasize, and the prognosis is reportedly poor. **Case presentation:** This case series presents two cases of primary breast angiosarcoma; the first patient is a patient who needs to obtain a diagnosis through physical examination, imaging, surgery, histopathology, and immunohistochemistry. The second patient is how to reconstruct the surgical defect using the Latissimus dorsi flap, and interestingly, with thirteen years of survival without recurrence, Surgery is the main treatment with high local recurrence. Wide excision in the form of a simple mastectomy is recommended if a tumor-free margin of 2-3 cm cannot be achieved. Tumor excision, or cosmesis, is not achieved, which is related to the proportion of breast and tumor size. The use of radiation therapy and neoadjuvant or adjuvant chemotherapy is still controversial. **Conclusion:** Establishing a diagnosis with a thorough examination starts with anamnesis, physical examination, radiological examination, and histopathology, including immunohistochemistry, which is an important examination in confirming the diagnosis.

1. Introduction

Breast angiosarcoma is a rare mesenchymal malignancy arising from endothelial cell lining. approximately 0.04–0.05% of all breast malignancies and less than 1% of all sarcomas. It has a poor prognosis, with a 5-year survival rate of 40%. It can be divided into primary and secondary angiosarcoma. Primary breast angiosarcoma (PAS) develops from the breast parenchyma endothelial cells and can infiltrate the skin. Secondary breast angiosarcoma (SAS) first appears from skin tissue and gradually invades the breast parenchyma. SAS may occur after radiation therapy for breast cancer and lymphedema after axillary lymphadenectomy (Stewart-Treves syndrome). It is a mesenchymal neoplasm with local recurrence and can distantly metastase. Breast Angiosarcoma has a wide spectrum of morphologic variations; thus, recognizing its common morphologic features is crucial in facilitating correct diagnosis, especially in biopsy specimens. In histopathologic features, a highly atypical cell, haemorrhage, or necrosis helped to define high-grade lesions. Immunohistochemistry has an important role in establishing the diagnosis of angiosarcoma.[1-3]

The diagnosis of breast Angiosarcoma is often delayed because cases are rare and asymptomatic; the lump is painless, grows quickly, occurs in women aged 30-50 years, has high local recurrence and distant

metastasis, and reportedly has a poor prognosis. Surgery is the main treatment. Several cases reported the use of neoadjuvant and adjuvant chemotherapy and radiotherapy, but the effectiveness remains controversial. Due to the low incidence, there is no standard treatment regimen for breast angiosarcoma, and recurrence and mortality are high. Wide excision as a mastectomy is recommended if a tumor-free margin of 2-3 cm cannot be achieved during tumor excision or cosmetics cannot be achieved due to the proportion of breast and tumor size. Despite achieving a tumor-free margin, local recurrence and distant metastasis occurred in some cases.[4-7]

2. Case Presentation

Case 1

A 37-year-old woman with the chief complaint of a lump in the left breast, which was felt 5 months before entering the hospital. The lump initially felt like a ping pong ball, which progressed to the size of a tennis ball. The patient underwent surgery to remove the lump three months ago at the local hospital with anatomical pathology results suspicious of hemangioma with a diagnosis of differential well-differentiated angiosarcoma in the left breast region. Two months after removal, the lump was felt to appear again, and the wound on the post-operative scar became an ulcer, bled, progressed, and became painful. There were no complaints of lumps anywhere else. There were no complaints of upset stomach, nausea, or pain in the groin and back. There were no complaints of heavy breathing and shortness of breath after heavy activity, dizziness, and no complaints of vomiting. There were no headaches that got worse every day. From the physical examination, the general status was normal. In localized status, there was a mass in the left breast measuring 20x17x10 cm with an ulcer in the postoperative wound. On palpation examination, it was found that the mass boundaries were not clear, the edges were uneven, the consistency was solid, there was tenderness, and it was not fixed on the chest wall. On examination of the axilla, no lump was found. (Figure 1).

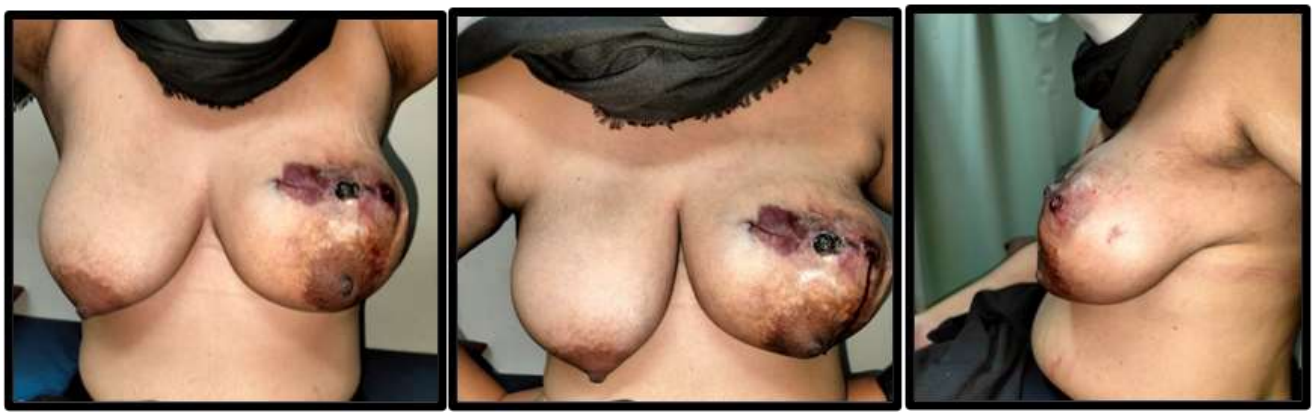
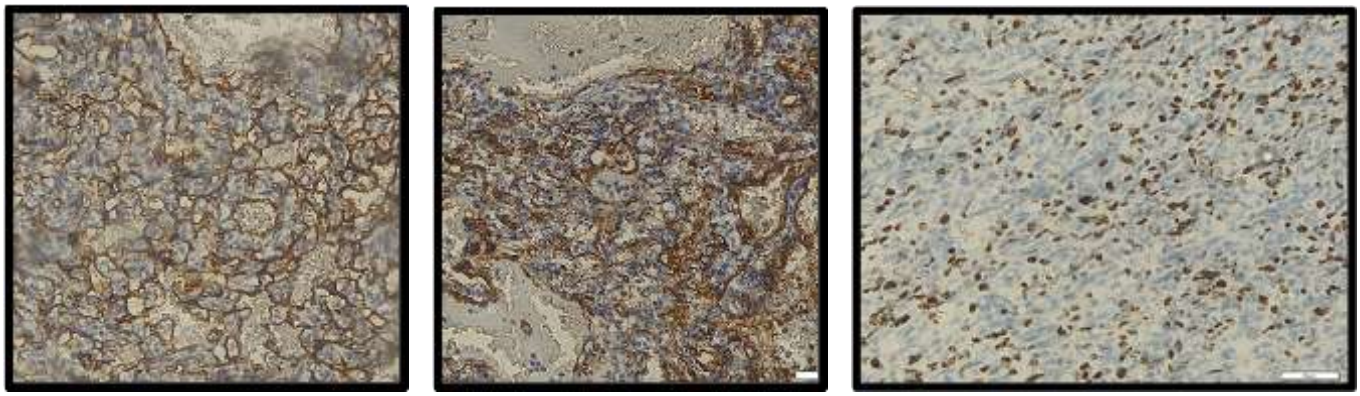


Figure 1. Clinical appearance of the patient: a tumor mass appears in the left mammary area with an ulcer on the postoperative scar.

An immunohistochemical examination was confirmed at Dr. Hasan Sadikin General Hospital with results: CD31 positive, CD34 positive, and Ki67 positive, with high proliferation. With the conclusion that the tumor is angiosarcoma (Figure 2).



IHC CD31 IHC CD34 IHC Ki67

Figure 2. Immunohistochemistry CD31, CD34, and Ki67 results with results: the tumor is angiosarcoma.

MRI of the Thorax was performed (Figure 3), and it was found that a solid mass appears in the left mammary, in the left fibroglandular mammary, which infiltrates the cutis and subcutis anteriorly, accompanied by thickening of the cutis around the left mammary e.c. No intrapulmonary metastases were seen. No bone destruction was seen. There was no visible enlargement of the mediastinal lymph nodes. The patient underwent a simple mastectomy with a 3 cm margin from tumor to healthy tissue; there was no infiltration to the pectoral fascia (Figure 4), and the surgical defect can be sutured primarily.

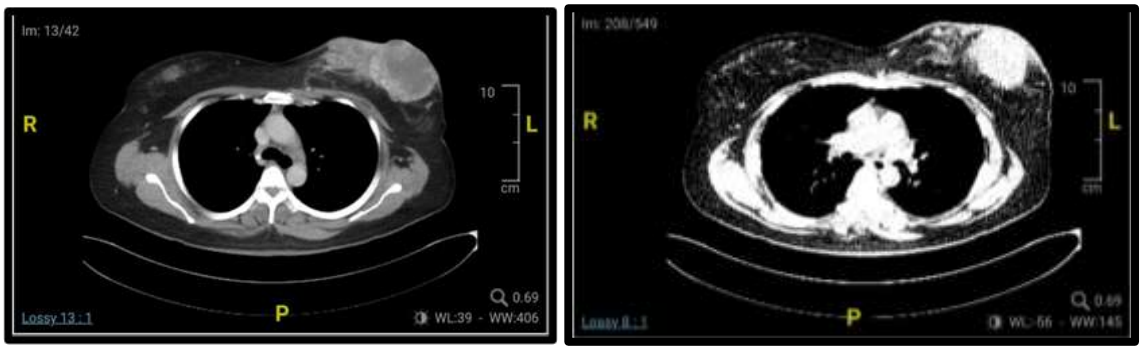


Figure 3. Thoracic MRI with contrast.

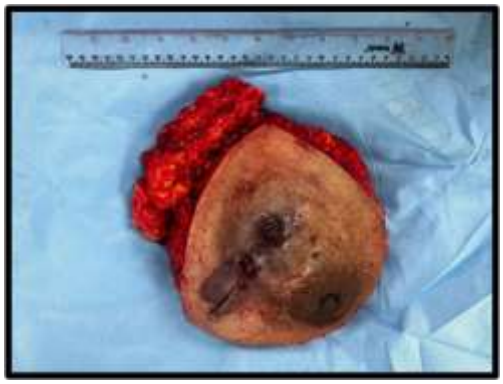


Figure 4. Extensive post-excision specimen after simple mastectomy.

Microscopic examination of the anatomical pathology post-wide excision in the form of a simple mastectomy shows Microscopically: The mass preparation was lined with stratified squamous epithelium, keratinized, and the core was within normal limits. The subepithelium consists of fibro-collagen connective tissue stroma, which experiences extensive hemorrhage and necrosis in contact with lymphocyte cells, and PMN cells. Among them are round, oval to spindle-shaped cells that grow hyperplastic and condense, some of which form small cavity structures containing erythrocytes. Pleomorphic, hyperchromatic, and mitotic cell nuclei were found. No mammary gland ductuli were visible. Conclusion: Left mastectomy, primary angiosarcoma of the breast a/r left breast. The Oncologic diagnosis for this patient is Primary Angiosarcoma of the left breast; the next treatment was planned for external radiation.

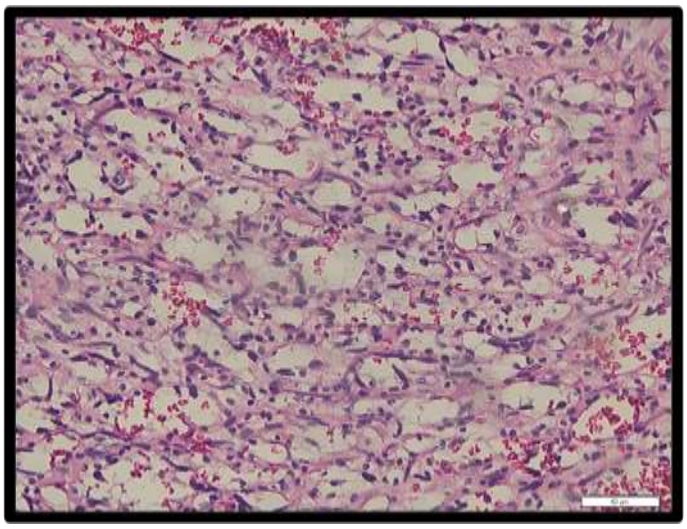


Figure 5. Microscopic histopathological examination.

Case 2

A 19-year-old woman with the chief complained of a lump in her right breast, which was getting bigger, and then an ulcer appeared above the lump, which had not healed 6 months before entering the hospital. The lump was initially felt to be the size of a chicken egg, which progressed to the size of a volleyball. The bluish colour lump then bursts, causing ulcers on the skin that do not heal, and the bleeding was profuse. Complaints of a lump the size of a marble in the right axilla. Because of his complaint, the patient then went to Hasan General Hospital for treatment. There were no complaints of nausea or breathing. There was no history of receiving radiation treatment in the breasts, no history of lumps in the breasts since birth, and no history of previous trauma to the breasts. From the physical examination, the generalist status was normal. In localized status, there is a bluish colour mass in the right breast with an ulcer that profusely bleeds, a palpable mass, 8 x 5 x 4 cm, solid consistency, uneven edges and infiltration into the pectorales major musculus, there was no infiltration to the chest wall. a/r axilla dextra, there were palpable lymph nodes with a size of 1 x 1 x 1 cm, firm boundaries, and mobile (Figure 6).

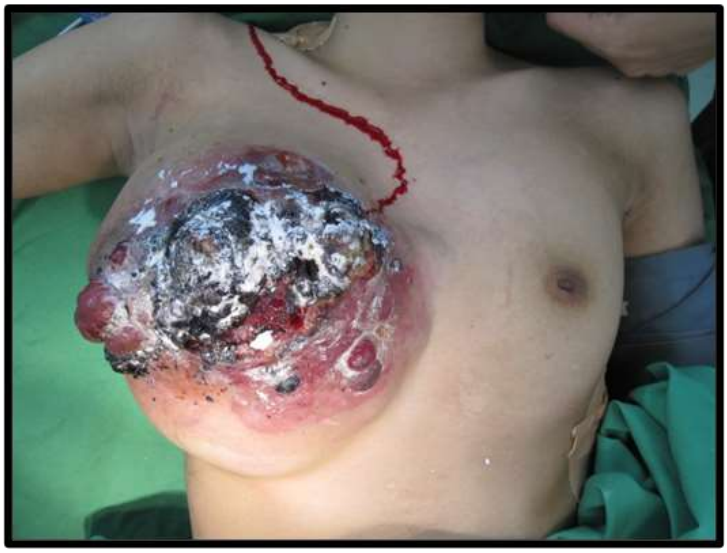


Figure 6. The clinical appearance of the patient shows a tumor mass in the right breast with bleeding ulcers.

Then, a CT scan of the thorax with contrast was performed (Figure 7) and found There was a solid mass in the right mammary gland, in the right fibro glandular mammary gland, which infiltrated the cutis and subcutis anteriorly, accompanied by thickening of the cutis around it, e.c. left mammary gland. No intrapulmonary metastases were seen. No bone destruction was seen. There was no visible enlargement of the mediastinal lymph nodes. The patient underwent a wide excision with 3 cm of margin from the tumor. The radicality was achieved, and the tumor mass was excised along with the pectorales major muscle and pectorales minor muscle. because of the large post-operative defect that could not be closed primarily, and the base was ribs and intercostal muscle, the defect was closed with a Latissimus dorsi flap (Figures 8 and 9).

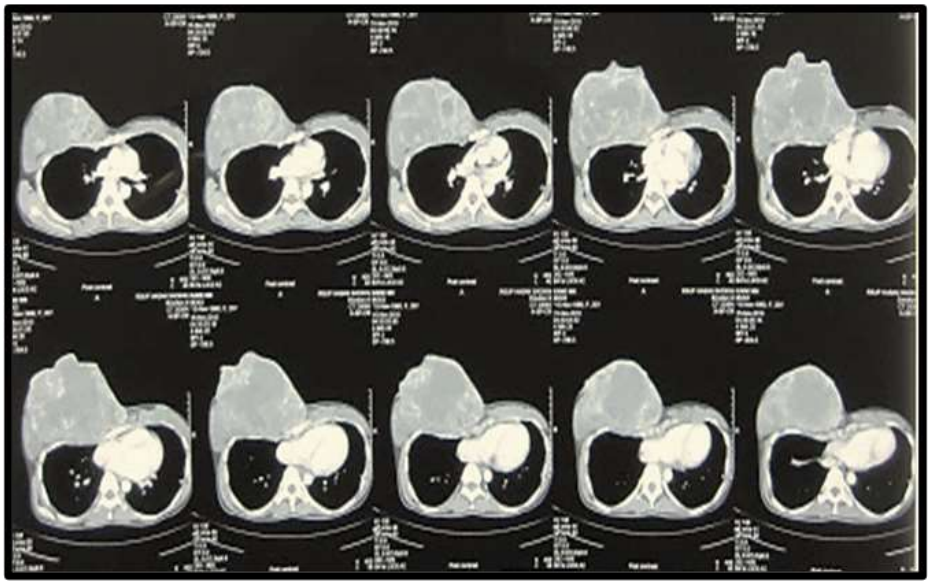


Figure 7. CT scan of the chest with contrast.

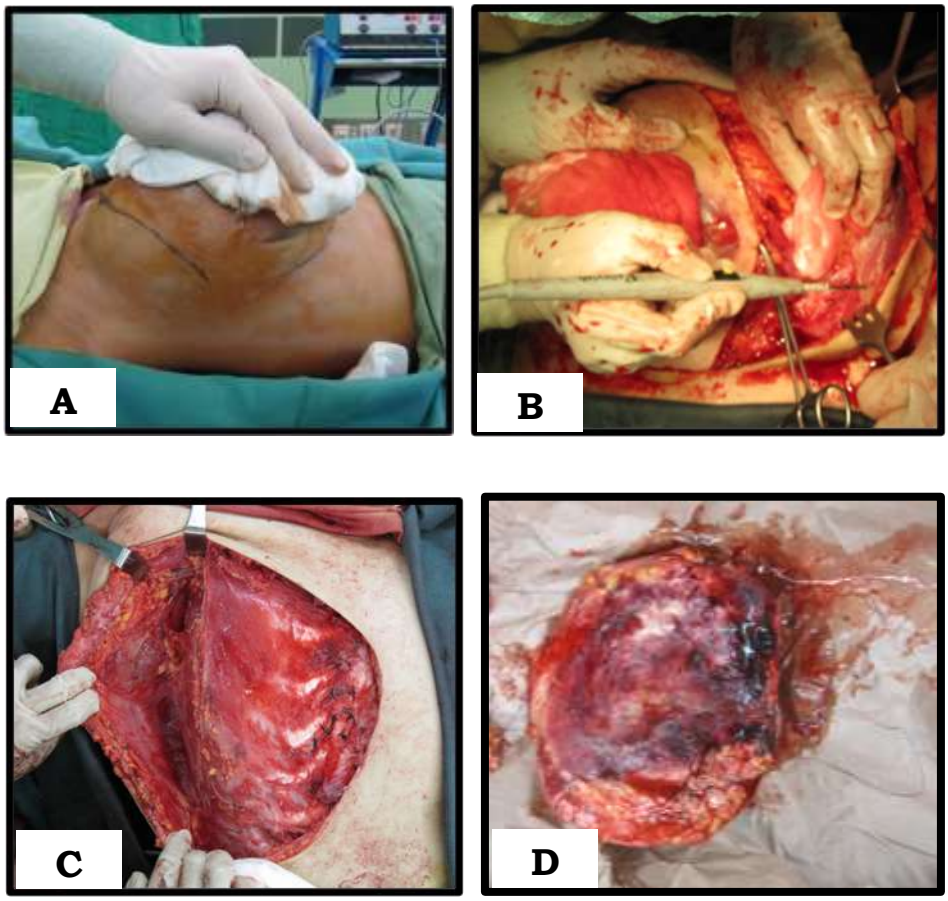


Figure 8. Wide excision surgery. A. Incision design 3 cm from the tumor edge of the tumor mass, B. Wide excision is carried out, C. After wide excision leaves a wide defect, D. Tumor mass after wide excision.

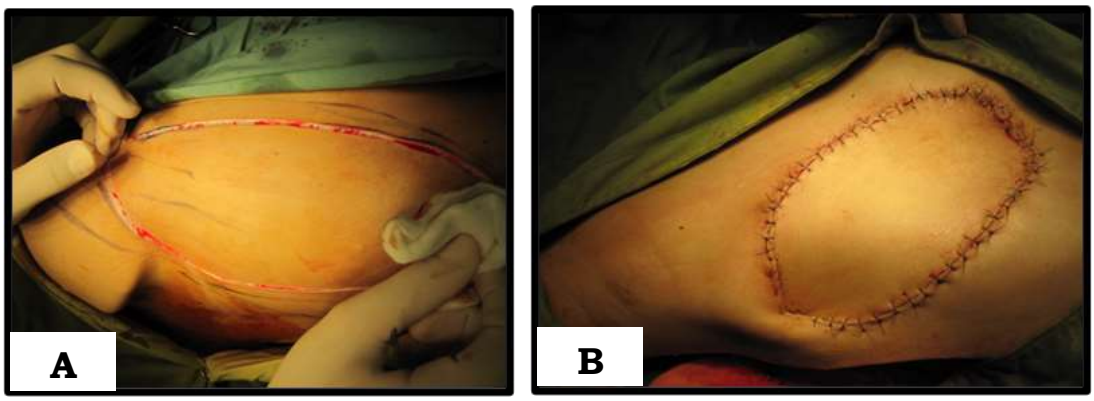


Figure 9. Wide excision defect closure. A. Latissimus dorsi flap incision design, B. After closing the defect with a Latissimus dorsi flap.

Microscopic examination of the anatomical pathology post-wide excision in the form of a simple mastectomy shows microscopically: Most of the tissue is blood clots, only small groups of irregular blood vessel cavities are found, lined with endothelium with pleomorphic nuclei, hypervascular and hyperchromatic with blood-filled lumens. On review, low piston-shaped cells were found that made up the

cavities, some of which formed a hobnail structure, polymorphous nuclei, hyperchromaticity, and mitosis were found. The Oncologic diagnosis for this patient was Primary Angiosarcoma a.r. mamma dextra, the next treatment was planned for external radiation.

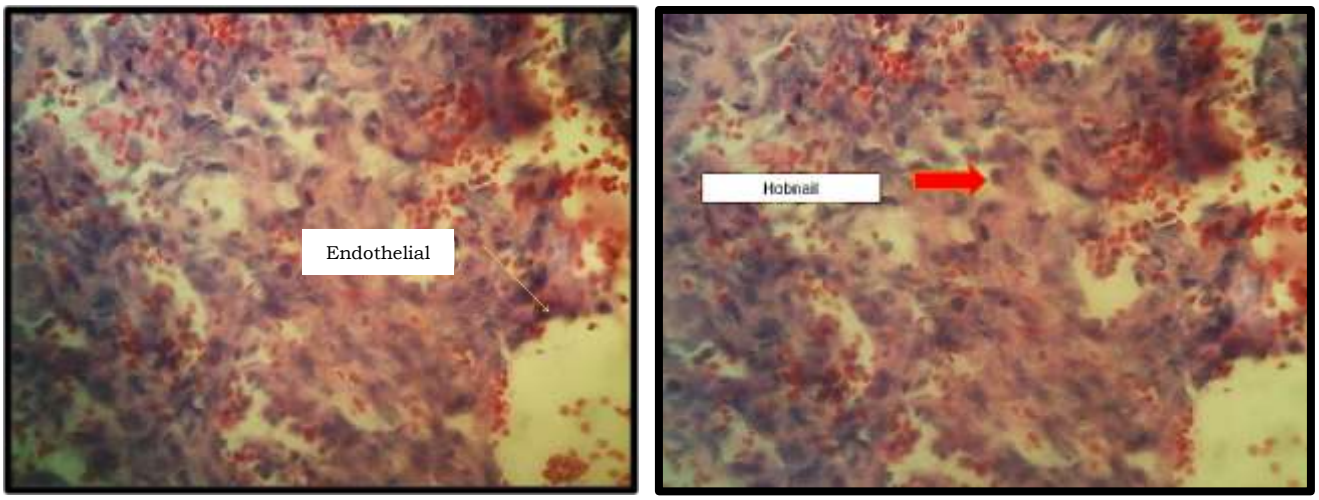


Figure 10. Microscopic examination of anatomical pathology, pleomorphic nuclei, and Hobnail structures.

3. Discussion

Breast sarcoma is a tumor of mesenchymal origin, accounts for approximately 1% of breast malignancies, and consists of several different histopathological types. Understanding of the etiology and prognosis of this tumor is limited due to its rarity. The common histopathologies are angiosarcoma and malignant phyllode tumors. Phyllode tumors consist of the epithelium and stroma of connective tissue. Malignant phyllodes have a high proportion of mesenchymal proliferation and have a genetic profile similar to other breast sarcomas but not to angiosarcoma. Angiosarcoma consists of hemangiosarcoma and lymphangiosarcoma; Phyllodes consist of malignant and borderline. Angiosarcoma of the breast is a very rare case but is a malignant case, approximately 0.04–0.05% of all breast malignancies and less than 1% of all sarcomas. The incidence occurs 6.8 per 100,000 population in one year. First described as mammary angiosarcoma, it was published by Schmidt in 1887. Clinically, angiosarcoma is a fast-growing tumor with skin discoloration and bluish or purplish nodules; the tumor is diffuse and can be multifocal. Diagnosis of breast angiosarcoma is often delayed due to rare cases and asymptomatic. Of all breast malignancies, angiosarcoma has the worst prognosis, with a 5-year survival rate of 40%. Getting worse with metastasis within 24 months postoperatively. Primary breast angiosarcoma (PAS) develops from the breast parenchyma and can infiltrate the skin. PAS is de novo with no prior radiotherapy. PAS originates from the endothelial blood vessels and does not involve lymph nodes. There are no known risk factors for PAS, possibly due to trauma and radiation. There is no definitive data to support this claim. PAS grows quickly, is a painless lump, occurs in women aged 30-50 years, has high local recurrence and distant metastasis, and has a poor prognosis.[8,9]

Secondary breast angiosarcoma (SAS) first appears from skin tissue and gradually invades the breast parenchyma. SAS has 2 possible causes: previous radiation therapy for breast cancer and lymphedema after axillary lymphadenectomy (Stewart-Treves syndrome). SAS occurs during radiation therapy, which is part of breast-conserving therapy in the treatment of breast cancer. Mostly occurs in women

aged 60 and 70 years. Breast Angiosarcoma has a wide spectrum of morphologic variations; thus, recognizing its common morphologic features is crucial in facilitating correct diagnosis, especially in biopsy specimens. Common differential diagnoses for breast AS include benign vascular lesions like atypical vascular proliferation (AVP), angiomatosis, angiolipoma, or hemangioma, and malignant lesions like breast carcinoma with or without metaplastic features, malignant phyllodes tumors, melanomas, or other sarcomas, etc. In addition, two distinct histogenesis have been described for both AS and AVP, including lymphatic type (positive for lymphatic markers like D2- 40, Prox-1, or LVYE-1) and conventional type (negative for lymphatic markers), which is based on both morphology and expressions of differentiation markers.[10,11]

Imaging examination and mammography are not specific; in cases of breast sarcoma, there is a fill-defined mass without calcification. It is often not diagnosed because, at a young age, it has high-density breast tissue. Mammography only shows a thickening of the skin. Ultrasound showed hypoechoic, hyperechoic, or heterogeneous echogenicity, with or without acoustic shadow. Hypervascularization on ultrasound is found in cases of breast angiosarcoma, often misinterpreted as granulomatous mastitis or fibromatosis. MRI is the most sensitive imaging examination in evaluating breast sarcoma. Breast angiosarcoma has a round or irregular shape and firm edges; due to hypervascularization of the tumor, rapid inhomogeneous enhancement is obtained with a plateau or washout pattern on the enhancement curve. In histopathologic features, a highly atypical cell, haemorrhage, or necrosis helped to define high-grade lesions. As compared to SAS, PAS did not show prominent vesicular nuclei and/or conspicuous nucleoli. In addition, some cases of epithelioid SAS with lymphatic differentiation showed pseudo-papillary appearance, which could be a potential diagnostic pitfall for breast carcinoma with papillary features. Immunohistochemical examination for endothelial expression markers (CD31, CD34, factor VIII, vimentin, D2-40, and Fli-1) is often positive in epithelioid carcinoma. CD31 has good sensitivity and specificity, with 90% expressing all types of angiosarcoma and Ki67 >30% indicating a tumor with high proliferation.[2] In this case, CD31 and CD 34 were positive in angiosarcoma and Ki67>20%, which indicates high proliferation. SAS showed consistent positivity for c-MYC on immunostains, while PAS was negative or only had rare weak positivity in high-grade areas. Epithelioid SAS, especially cases with lymphatic differentiation, tended to have stronger or more diffuse c-MYC positivity.[12,13]

Surgery is the main treatment. Shiraki et al. recommend an incision margin of at least 3 cm, recommended 4-5 cm, with a depth of at least up to the pectoral fascia, and combined with radiotherapy, local recurrence occurs at 40 days and 1 year after surgery. Gutkin et al. performed the surgical procedure with margins > 5cm and autologous reconstruction, with low recurrence results. Optimal surgery with R0 achieved is the best approach. Recurrence in 10 of 15 patients. The main principle of surgical management is wide excision with a tumor-free incision. To reach the tumor-free margin, the incision taken is 2-3 cm from the edge of the tumor. National Comprehensive Cancer Network (NCCN) guidelines recommend at least 2 cm or more of tumor-free margin. Mastectomy is a surgical treatment option recommended if a tumor-free margin of 2-3 cm cannot be achieved, or cosmetics cannot be achieved with wide excision.[7] The first patient surgery, wide excision as a simple mastectomy, was done with a 3 cm safety margin and without infiltration to the pectoral fascia. For the second patient, surgery was done with wide excision; the tumor mass was removed along the pectoralis major muscle and pectoralis minor muscle, and the base of the surgery field were ribs and intercostal muscle. Because of a large surgery defect, the latissimus dorsi flap was performed as a reconstruction.[11,12]

The role of radiotherapy and chemotherapy is unclear. Several cases have been reported using neoadjuvant and adjuvant chemotherapy and

radiotherapy, remains controversial. Due to the low incidence, there is no standard treatment regimen for breast angiosarcona, recurrence and mortality are high. In some studies, adjuvant radiotherapy has better local control. In a meta-analysis, adjuvant radiotherapy after surgery had a statistically significant effect on recurrence-free survival. In both breast angiosarcomas in the cases above, radiotherapy was planned. Previous studies have shown that the addition of chemotherapy has a significant benefit in reducing the risk of local recurrence; other research therapies have shown no statistical benefit. The effectiveness of adjuvant chemotherapy is uncertain. Neoadjuvant chemotherapy and hyperfractionated radiation with concurrent hyperthermia, however, show promising results. Need to have confirmed the findings to date on a relatively large sample. In this case report, two cases of breast angiosarcoma were planted radiation for local recurrent control even though the safety margin was achieved. In breast angiosarcoma, a high percentage of local recurrence occurs (15% - 40%), and distant metastases occur in some cases after surgery. The first patient has been observed for six months without any recurrence. Interestingly, the second patient has been observed for thirteen years without any complaints or recurrence. The most common metastasis in breast angiosarcoma is to the lung. Other metastatic locations include bones, liver, thyroid gland, pancreas, and distant soft tissue, such as the forearm.[14,15]

4. Conclusion

The cases emphasize the importance of early diagnosis through MRI and immunohistochemistry, followed by aggressive surgical management with wide margins and potential reconstruction. Radiotherapy might also play a role in certain cases. However, due to the rarity of PAS, long-term follow-up data is necessary to establish definitive treatment protocols.

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