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Case Report

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Primary Angiosarcoma of the Breast: Case Report of Uncommon Tumor and Brief Review of the Literature

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Abstract

Primary angiosarcoma of the breast is uncommon and only diagnosed in roughly 0.04% of all malignant breast tumors. Only 20% of these cases are primary malignancies while the remaining are complications of radiation therapy. Diagnosis is difficult because it tends to mimic benign characteristics on mammogram and histology. Although it can appear benign, breast angiosarcoma is an aggressive, malignant tumor with a poor prognosis. Radiologic imaging along with immunostaining with Factor VIII and CD31 can confirm the presence of angiosarcoma. Currently, surgery is the only treatment option that improves the clinical outcome of the disease, with little help from chemotherapy.

KEYWORDS: Angiosarcoma, Breast, Primary, High grade

ABBREVIATION

AS: Angiosarcoma, **CNB**: core needle biopsy, **IHC**: Immunohistochemistry

INTRODUCTION

Angiosarcoma (AS) of the breast is a neoplasm of vascular origin that represents only 0.04% of all malignant breast tumours[1]. Despite angiosarcomas being the most frequent type of sarcomas, this tumor is still extremely uncommon. Primary malignancies represent only 20% of these cases while the remaining 80% occur as a complication from breast radiation therapy[2]. This tumor is most commonly found in young women aged 20-30 and many are discovered while the patient is pregnant or breastfeeding[3]. Angiosarcomas are typically a palpable mass in the breast, however, 17% of cases may present with a bluish discolouration or bruising of the overlying skin[4]. It has been reported that most primary malignancies are found in younger females with no skin changes and secondary malignancies are found in older women and are more likely to have associated skin changes[5]. Notably, the right breast is more commonly involved than the left in women aged 20 to 30 years[3].

Although it can mimic breast adenocarcinoma clinically, breast angiosarcoma is a more aggressive tumor with rapid proliferation and infiltration into surrounding tissues and possesses a worse prognosis[6]. Due to its variable appearance on radiology and cytopathology, angiosarcoma of the breast is difficult to properly diagnose and distinguish from benign malignancies. Here, we present a case of a primary high grade angiosarcoma of a 21-year-old woman and we review the literature.

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CASE PRESENTATION

A 21-year-old woman presented with a slowly growing mass in her right breast over a period of six months. The mass was recently rapidly enlarging. She had no personal or family history of breast cancer, ovarian cancer or other cancer. Physical exam showed an irregular firm palpable mass at the lower medial aspect of right breast. The mass appeared to be fixed to the overlying skin with no changes of the skin itself. The mass measured approximately 9 x 7 cm and no axillary lymphadenopathy was noted.

Imaging studies with ultrasound showed a diffuse irregular hyperechogenic infiltrating mass located in the lower medial quadrant of the right breast which appeared hypervascular on doppler sonography. Mammography showed a non-specific and diffuse dense area of about 10 cm. No calcification was identified. Imaging studies concluded a malignant neoplasm with recommendation of tissue sampling.

A core needle biopsy (CNB) was performed and showed histomorphologic features of non-malignant vascular lesion, possibly large hemangioma or hamartoma. Due to discrepancy between imaging finding and histological findings, additional larger tissue biopsies were obtained from two different areas of the mass. Histomorphology of the additional biopsies showed an infiltrating tumor composed of empty, slit-shaped neoplastic vessels invading the fat, mammary stroma and lobules (**Figure 1A**). Scattered in the background of the irregularly anastomosing

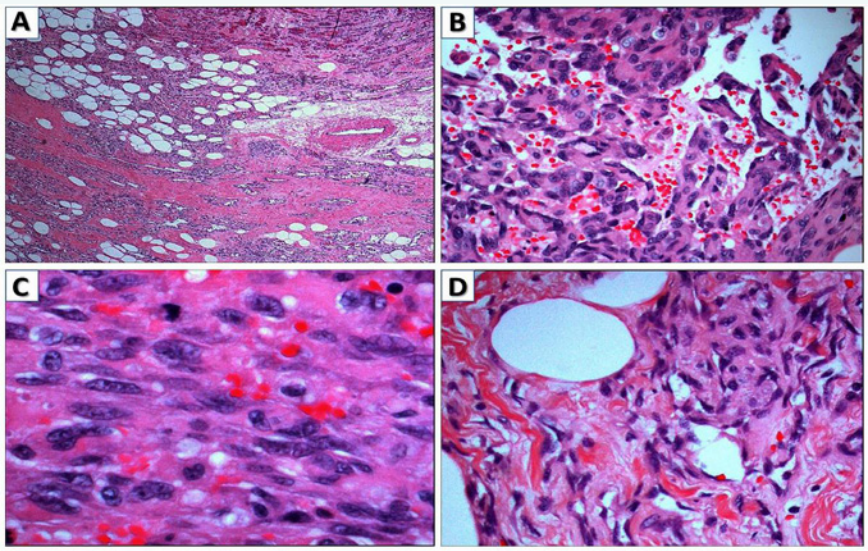

Figure 1 Pathological examination of the breast tissue biopsy of angiosarcoma
1A: Vascular tumor infiltrating the fat, mammary stroma and lobules, low power view (H&E stain x20)
1B: Irregularly anastomosing vascular channels lined up by malignant endothelial cells (H&E stain x40)
1C: High power view showing areas with prominent high-grade malignant features of the tumor (H&E stain x60)
1D: High power view showing areas with low-grade malignant features of the tumor (H&E stain x60)

vascular channels was substantial areas of more cellular growth with hemorrhage, necrosis and increased abnormal mitotic activity (**Figure 1B**). The features were consistent with a high grade angiosarcoma. Other areas of the tumor showed less prominent malignant features, which explained the non-malignant findings in the first biopsy. The tumor was determined to show spectrum of morphology ranging from low (**Figure 1C**) to high (**Figure 1D**) grade malignant features.

Immunohistochemistry (IHC) studies were performed, and the tumor cells were strongly positive for CD31 (**Figure 2A**), CD34 (**Figure 2B**) and were Negative for Cytokeratin, S-100, Desmin, SMA, and HHV-8. The high-grade malignant areas showed up to 40% nuclear staining with Ki-67 (**Figure 2C**). The histomorphology and IHC studies were diagnostic of high grade angiosarcoma. Total body CT scan didn't show any metastasis and the tumor was diagnosed as a primary breast tumor. Due to the high-grade nature of the angiosarcoma, and broad infiltration of breast tissue, mastectomy with adequate safe margins was recommended. Right mastectomy was performed, and post-operative adjuvant chemotherapy was prescribed. Follow up for 19 months showed no evidence of metastasis or recurrence after which the patient was lost to follow up.

DISCUSSION

The first description of angiosarcoma of the breast in the literature was by Schmidt in 1887[7]. This tumor is exceedingly uncommon with a heterogenous presentation, thus most of the available literature is in the form of single case reports with limited data[5]. The incidence of primary breast angiosarcoma is roughly 17 new cases per million women[8]. Due to the deceptively benign appearance of angiosarcomas, studies tend to include patients with a diagnosis of angiosarcoma along with other benign malignancies such as hemangiosarcoma and hemangioendothelioma[9]. The radiologic imaging findings tend to be non-specific which is why they are often misdiagnosed, especially for certain benign malignancies[10].

The clinical presentation is also non-specific, with symptoms such as a palpable mass (~5cm), and a bluish skin discolouration[11]. The right breast is more commonly involved than the left breast, especially in younger patients[2]. Notably, breast angiosarcoma tends to metastasize haematogenously to the contralateral (left) breast, the liver, lungs, bones, and skin[4].

Between 6-12% of cases of primary breast angiosarcoma are diagnosed during pregnancy or shortly after during breast feeding, which suggests hormonal involvement. However, several case reports have examined estrogen and progesterone receptors along with cases of primary breast angiosarcoma which were negative[13]. The hormonal dependency of breast angiosarcoma has yet to be proven, thus, this is suggested as an area of further investigation.

Breast angiosarcomas are often misdiagnosed because they are not seen often and have deceptively benign characteristics on mammograms and histological analysis[9]. Preoperative diagnosis by biopsy is extremely difficult and has a false negative rate of approximately 37%[4]. These numbers can be justified since higher grade angiosarcomas may contain elements of lower grade tumors, especially at the periphery, and remain well differentiated[2].

Angiosarcoma of the breast has been described as well-formed vascular channels lined by endothelial cells[14]. For this reason, immunohistochemical staining tends to surround markers for

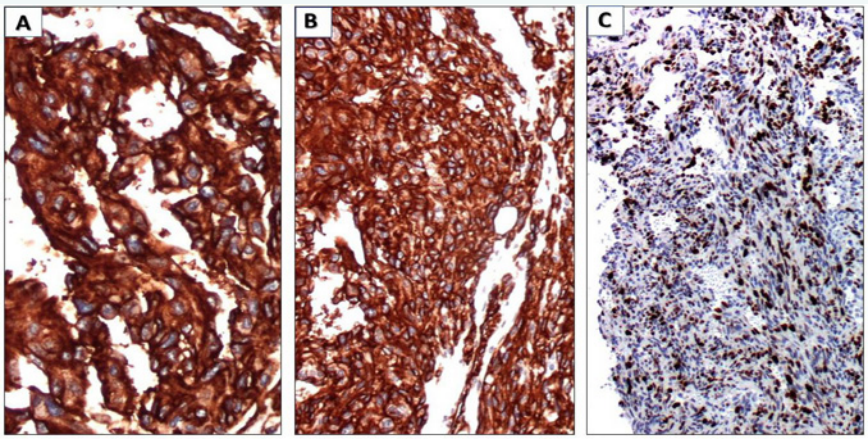

Figure 2 Immunohistochemistry studies of the breast angiosarcoma
2A: Tumor cells positive for CD31
2B: Tumor cells positive for CD34
2C: Tumor cells with high (40%) nuclear staining with Ki-67

endothelial cells. Endoglin is known to be mainly expressed on the surface of endothelial cells and this marker was positive in previous cases of breast angiosarcoma[12]. Endothelial cells have also showed positive reactivity to markers such as CD31, CD34 and von Willebrand factor (factor VIII), with CD31 being the most sensitive and specific marker[2]. Other studies have documented the presence of cytokeratin and P63 markers in angiosarcomas[15].

Initial examination of these tumors has consistently given the false impression of benign vascular tumors, however, there are some unique histological characteristics for angiosarcomas. Some of these features include endothelial tufting, infiltration into adipose tissue, scattered hyperchromatic endothelial nuclei and free anastomosis of the vascular channels[14]. The differential diagnosis of this uncommon tumor includes benign hemangioma, phyllodes sarcoma, stromal sarcoma, fibrosarcoma, liposarcoma, squamous cell carcinoma with sarcomatoid features, myoepithelioma, fibromatosis, reactive spindle cell proliferative lesion and high-grade mammary carcinoma[2]. Immunohistochemical stains for epithelial markers such as pancytokeratin, CD34, CD31 and other sarcoma markers can aid in making the correct diagnosis[2].

Radiologic examination of the tumor can also aid in the diagnosis of breast angiosarcoma. On ultrasound, the masses could present with hyperechoic, or a mixed echogenicity pattern based on their vascular channels or cellular components. Benign lesions typically have a hyperechoic pattern, and this is one of the reasons why breast angiosarcoma can be misdiagnosed as benign[16]. Following a biopsy, angiosarcoma of the breast is commonly misdiagnosed as benign hemangioma[3] and in one case was misdiagnosed as capillary cavernous hemangioma[17]. On a mammogram, angiosarcoma appears as an ill-defined mass and there can be calcifications, however, it lacks the spiculations often seen in breast carcinomas[4]. MRI confirms the presence of vascular channels with slow flowing blood because the mass has low signal intensity on T1-weighted images but has high signal intensity on heavily T2-weighted images[18].

Angiosarcoma of the breast can be separated into three grades, with all three showing inter-anastomosing vascular channels and hyperchromatic endothelial cells. Grade I tumors are well-differentiated with no mitotic figures, necrosis, nor papillary projections. Grade II tumors have endothelial tufting, increased mitotic figures, and focal papillary projections. Grade III tumors on the other hand have distinct blood lakes[3]. Irregular areas of high intensity on T1-weighted images represent these hemorrhagic lakes[18]. The prognosis for breast angiosarcoma is poor with an average survival of 2-3 years and a 5-year survival rate of 50-66% for well differentiated tumors[19]. Age appears to be the only accurate prognostic factor for primary breast angiosarcoma with age > 60 years correlating with a worse prognosis[5]. Other reports have indicated that gross tumor size did not correlate with survival[12].

Despite the recent progress accelerated by the next generation sequencing methodology, the underlying pathogenesis of most AS remains undefined, particularly of primary AS and AS occurring in younger patients. Shih-Chiang Huang et al [20] studied recurrent CIC gene abnormalities in angiosarcomas, which included a molecular study of 120 cases with concurrent investigation of PLCG1, KDR, MYC, and FLT4 gene alterations. They reported that in total, the CIC, PLCG1, KDR, MYC and FLT4 genetic abnormalities account for around 50% of their study cohort. However, the molecular alterations of a significant number of cases remain to be elucidated. The divergent genetic abnormalities emerging in different AS subsets promise both challenges and opportunities in designing future clinical trials of targeted therapy in this disease[20].

There is currently no gold standard for the treatment of angiosarcoma of the breast as it is so uncommon, however the limited research points to surgery being the most effective[4]. Notably, performing a total mastectomy rather than a more limited surgery (such as a quadrantectomy), has shown no advantage in terms of overall prognosis[21]. Chemotherapy on the other hand, has not been proven to have any benefit against this

malignancy, especially if the disease has already disseminated[3]. However, studies have found that paclitaxel was well-tolerated by patients and had an excellent clinical outcome[22]. Newer therapies involving immunotherapy have also been implemented to target angiogenesis, such as bevacizumab or rapamycin[4]. The positive endothelial cell surface marker for endoglin also raises the possibility of treating breast angiosarcoma with anti-endoglin monoclonal antibodies[12].

Prognosis of angiosarcoma is dependent on primary tumor site, size, mitotic activity, stage and cellularity. Poor prognostic factors include lesions larger than 5 centimeters in size and bleeding. Generally, EAs have a poor prognosis due to the ability to grow quickly and metastasize to brain, bone, lung, lymph nodes and soft tissue[24]

Advancement in technology and diagnostic measures is promising for more opportunities to study the pathogenesis, management, and diagnostic parameters of breast angiosarcoma, and that continued investigation drives further development of efficacious and safe treatments for improving patient outcomes.

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REFERENCES

1. S.A. Vorburger, Y. Xing, K.K. Hunt, *et al.* Angiosarcoma of the breast. Cancer, 104 (12) (2005), pp. 2682-2688
2. Bennani, A., Chbani, L., Lamchahab, M. *et al.* Primary angiosarcoma of the breast: a case report. *Diagn Pathol* **8,** 66 (2013). https://doi.org/10.1186/1746-1596-8-66
3. Johnson, C., & Garguilo, G. (2002). Angiosarcoma of the breast: A case report and literature review. *Current Surgery*, *59*(5), 490-494. http://doi.org/10.1016/s0149-7944(02)00629-3
4. Bhosale, S., Kshirsagar, A., Patil, M., Wader, J., Nangare, N., & Patil, P. (2013). Primary angiosarcoma of breast: A case report. *International Journal Of Surgery Case Reports*, *4*(4), 362-364. http://doi.org/10.1016/j.ijscr.2013.01.016
5. Abdou, Y., Elkhanany, A., Attwood, K. *et al.* Primary and secondary breast angiosarcoma: single center report and a meta-analysis. *Breast Cancer Res Treat* **178,** 523–533 (2019). https://doi.org/10.1007/s10549-019-05432-4
6. Ginter PS, McIntire PJ, Shin SJ (2017) Vascular tumours of the breast: a comprehensive review with focus on diagnostic challenges encountered in the core biopsy setting. Pathology (Phila.) 49(2):197–214 https://doi.org/10.1016/j.pathol.2016.11.003
7. Schmidt GB: Ueber das Angiosarkom der Mamma. Arch Klin Chir 1887; 36:421-427.
8. Pairet, G., Tilman, G., Sciot, R., Schubert, T., Perlepe, V., Poirel, H. A., & Galant, C. (2018). Case reports in oncological medicine myoepithelioma: a new rearrangement involving the LPP locus in a case of multiple bone and soft tissue lesions. *Case reports in oncological medicine*, *2018*. https://doi.org/10.1155/2018/3512847
9. Rainwater, L. M., Martin, J. K., Gaffey, T. A., & van Heerden, J. A. (1986). Angiosarcoma of the breast. *Archives of surgery*, *121*(6), 669-672.
10. Taghipour Zahir, S., Sefidrokh Sharahjin, N., & Rahmani, K. (2014). Primary breast angiosarcoma: pathological and radiological diagnosis. *The Malaysian journal of medical sciences : MJMS*, *21*(5), 66–70.
11. Glazebrook, K. N., Magut, M. J., & Reynolds, C. (2008). Angiosarcoma of the breast. *American Journal of Roentgenology*, *190*(2), 533-538.
12. Masatoshi Ohta, Yutaka Tokuda, Soichi Kuge, Akira Okumura, Makiko Tanaka, Mitsuhiro Kubota, Tomoo Tajima, Akira Akatsuka, R Yoshiyuki Osamura, Norikazu Tamaoki, Toshio Mitomi, A Case of Angiosarcoma of the Breast, *Japanese Journal of Clinical Oncology*, Volume 27, Issue 2, April 1997, Pages 91–94, https://doi.org/10.1093/jjco/27.2.91
13. Sher, T., Hennessy, B. T., Valero, V., Broglio, K., Woodward, W. A., Trent, J., ... & Gonzalez-Angulo, A. M. (2007). Primary angiosarcomas of the breast. *Cancer*, *110*(1), 173-178.
14. Chen, K. T., Kirkegaard, D. D., & Bocian, J. J. (1980). Angiosarcoma of the breast. *Cancer*, *46*(2), 368-371.
15. Lin, X. Y., Liu, Y., Zhang, Y., Yu, J. H., & Wang, E. H. (2012). The co-expression of cytokeratin and p63 in epithelioid angiosarcoma of the parotid gland: a diagnostic pitfall. *Diagnostic pathology*, *7*(1), 1-4.
16. Taghipour Zahir, S., Sefidrokh Sharahjin, N., & Rahmani, K. (2014). Primary breast angiosarcoma: pathological and radiological diagnosis. *The Malaysian journal of medical sciences : MJMS*, *21*(5), 66–70.
17. Varghese B, Deshpande P, Dixit S, Koppiker CB, Jalnapurkar N. Primary Angiosarcoma Of the Breast: A Case Report. J Radiol Case Rep. 2019 Feb 28;13(2):15-25. http://doi.org/10.3941/jrcr.v13i2.3449
18. Glazebrook, K. N., Morton, M. J., & Reynolds, C. (2005). Vascular tumors of the breast: mammographic, sonographic, and MRI appearances. *American Journal of Roentgenology*, *184*(1), 331-338. http://doi.org/10.2214/ajr.184.1.01840331
19. Sasahara, A., Tanabe, M., Hayashi, K. *et al.* A case of primary breast angiosarcoma with multiple discontinuous small lesions. *surg case rep* **5,** 157 (2019). https://doi.org/10.1186/s40792-019-0704-8
20. Shih-Chiang Huang, Lei Zhang, Yun-Shao Sung, Chun-Liang Chen, M, Yu-Chien Kao *et al.* Recurrent CIC Gene Abnormalities in Angiosarcomas: A Molecular Study of 120 Cases with Concurrent Investigation of PLCG1, KDR, MYC, and FLT4 Gene Alterations. Am J Surg Pathol. 2016 May; 40(5): 645–655. doi:10.1097/PAS.0000000000000582. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4833528/pdf/nihms734593.pdf
21. Pasta, V., Monti, M., Cialini, M. *et al.* Primitive sarcoma of the breast: new insight on the proper surgical management. *J Exp Clin Cancer Res* **34,** 72 (2015). https://doi.org/10.1186/s13046-015-0190-1
22. Penel, N., Bui, B. N., Bay, J. O., Cupissol, D., Ray-Coquard, I., Piperno-Neumann, S., ... & Blay, J. Y. (2008). Phase II trial of weekly paclitaxel for unresectable angiosarcoma: the ANGIOTAX Study. *Journal of Clinical Oncology*, *26*(32), 5269-5274 http://doi.org/10.1200/JCO.2008.17.3146
23. Green C, Mohtadi M, Russo J, Watkins B, Aziz M, et al. (2021) Epithelioid Angiosarcoma in the Inguinal Canal Region of an 81-year-old man. Case Report of a Rare Tumor with Challenging Diagnosis and Review of the Literature. SM J Sarcoma Res 5: 4. https://www.jsmcentral.org/sm-sarcoma/smjsr694704.pdf
24. Sundaram M, Vetrichevvel TP, Subramanyam S, Subramaniam A. Primary multicentric cutaneous epithelioid angiosarcoma. Indian J Dermatol Venereol Leprol. 2011;77(1):111. doi:10.4103/0378-6323.74990 https://pubmed.ncbi.nlm.nih.gov/21220905/