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Case Report

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PRIMARY ANGIOSARCOMA BREAST WITH INTRACTABLE THROMBOCYTOPENIA

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ABSTRACT

Angiosarcoma of the breast is a rare malignant tumor. It is not easy to accurately diagnose this entity preoperatively because it often shows nonspecific clinical, mammographic and ultrasonography findings. It has high propensity for loco regional and distant metastasis hence very poor prognosis. Surgery in the form of mastectomy or wide excision remains the cornerstone of treatment. We reporting a case of primaryangiosarcoma of the breast who developed severe thrombocytopenia postoperatively three months later. Radiotherapy and chemotherapy have been tried with varying results in adjuvant setting.

KEYWORD: *Angiosarcoma, Breast, Thrombocytopenia.*

INDRODUCTION

Angiosarcomas are rare and aggressive malignant sarcomas of vascular endothelial cell origin, reports < 2% of all sarcomas.[1] It forms 0.04% of all the breast tumors and approximately 8% of breast sarcomas.[2,3] Breast angiosarcomas usually affect women in the thirties or forties 6.[4] Clinically they appear as a painless, irregular breast mass, that occasionally grow fast. The etiology of primary angiosarcoma remains unknown. Secondary angiosarcoma breast usually occurs in elderly women with a history of radiotherapy to the chest wall.

Primary angiosarcoma are associated with higher incidences of distant metastasis hence prognosis is dismal.[5] Here we reporting a case of 50-year-old postmenopausal woman with primary angiosarcoma of the breast presented in our institute. Postoperatively three months later, patient came with complaints of hematemesis and weakness. She was found to have severe anaemia and thrombocytopenia. Despite the best supportive care and repeated blood transfusions, patient died.

CASE REPORT

A 50 year old post-menopausal woman with no significant past medical history presented with a palpable swelling over the left upper inner quadrant of the breast since one year.There was no history of pain or nipple discharge. There was no previous history of radiation or trauma to breast and chest wall. History for familial breast cancer was also absent. FNAC done outside was suggestive of phyllodes tumour. She underwent lumpectomy for the same, and the histopathology report was hemangioma.

She presented at our hospital two months after lumpectomy with recurrence of the lump. On inspection, overlying skin had bluish red discoloration. There was no nipple-areolar retraction, skin puckering or ulceration. On palpation, the patient had a 5 x 5 x4cm lump; located in the upper inner quadrant of the left breast, firm in consistency with bosselated surface. The mass was non tender, and it was adherent to the superficial skin but not fixed to the underlying chest wall. A Single, firm, mobile axillary lymph node was palpable, which was about 1x1 cm size. The rest of the physical examination was normal with contralateral breast showing no abnormalities.

Ultrasonography of the breast showed a 5 x 4 cm hyper echoic lesion in upper inner quadrant, no calcification seen and margins were poorly defined. The diagnosis of inflammatory etiology was suggested.Tru-cut biopsy displayed vascular neoplasm favoring hemangioendothelioma. The slide review of the previous lumpectomy specimen was also suggestive of hemangioendothelioma.

Staging work up done including blood examination (complete blood examination, renal function test, liver function test, blood sugar), and radiological examination (CT scan of chest and upper abdomen) to rule out distant metastasis.

Patient underwent left radical mastectomy. Histopathological report suggested the diagnosis of

angiosarcoma – grade I with dermal invasion, epidermis was intact, no lymph node involvement seen. In Immunohistochemistry, the neoplastic cells expressed CD31,CD34 and ERG antigen, which confirmed the diagnosis of low grade angiosarcoma(fig 1).

Patient was kept on regular follow up. After three months, she came with complaints of severe hematemesis and weakness. Her general condition was very poor, complete blood haemogram revealed severe anemia and thrombocytopenia (Hb: 5.4 gm/dl and platelet count 20,000/mm^2). Despite the best supportive care and repeated blood transfusions, patient could not survive.

Table 1: Adapted from *Donnell et al.*[10]

characteristics	Low grade (type I)	Intermediate grade (type II)	High Grade (type III)
Endothelial tufting	Minimal	Present	Prominent
Papillary formations	Absent	Focally present	Present
Solid and spindle cell areas	Absent	Absent/minimal	Present
Mitoses	Absent/rare	Present in more papillary areas	Frequent
Blood lakes	Absent	Absent	Present
Necrosis	Absent	Absent	Present

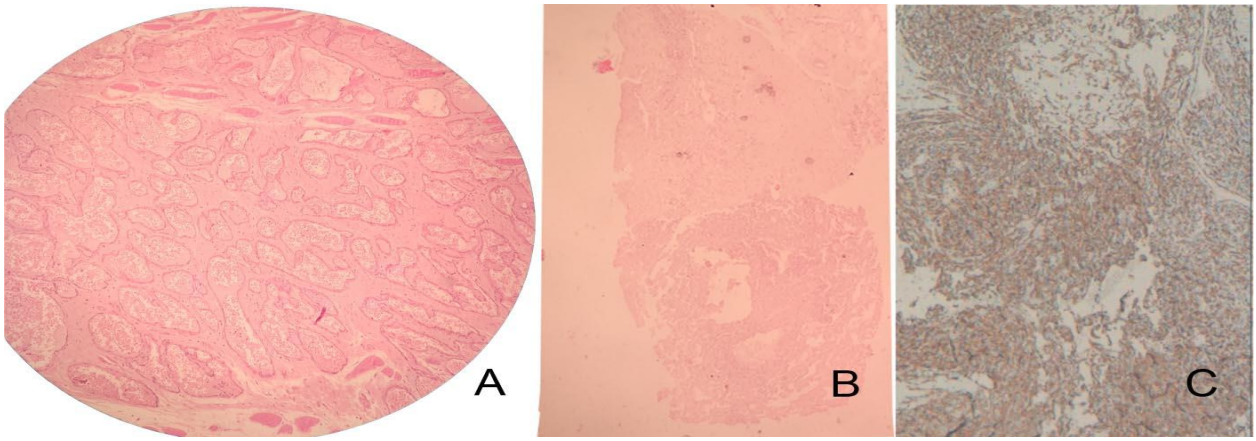

Fig 1: A. Histology (hematoxylin and eosin staining of radical mastectomy specimen angiosarcoma. Histology showing vascular channels with abnormal endothelial cells containing red blood cells) B. Histology hematoxylin and eosin staining of tru-cut biopsy specimen. C. CD31 Immunohistochemical staining for the endothelial cell marker.

DISCUSSION

Angiosarcomas are relatively rare histological subtype of sarcoma and represent less than 2% of all sarcomas.[1] The etiology of primary angiosarcoma remains unknown. Angiosarcomas also occur in special clinical circumstances, including developing in a previously irradiated area and in a chronically lymph edematous extremity i.e Stewart-Treves syndrome.

The age of patients at diagnosis is generally younger than that of patients with ductal cancer. Some investigators have reported that the median age of angiosarcoma ranges from 30 to 40 years[4], However this patient was 50 years old lady.

Patients with primary angiosarcoma breast present with a palpable mass that may be growing rapidly. Bluish skin discoloration occurs in up to a third of patients and is thought to be attributable to the vascular nature of the tumor. In the series by *Yang et al* [4], the mean tumor size of the mass at presentation was 5.9cm, This patient also presented with a lump of size 5X5X4 cm with bluish discolouration of overlying skin.

The prognostic factors for sarcoma of the breast include the tumor size, presence of residual disease or positive surgical margin and grade of tumour.[6, 7] *Rosen et al*[8] reports that the five-year survival rate is 76%, 70% and 15%; respectively for low-grade, intermediate-grade and high-grade lesions. Breast angiosarcomas are graded using a three tier grading system into low, intermediate, and high grades (table 1). Postradiation angiosarcomas are usually high-grade lesions.

However, It was believed that histologic grading of mammary angiosarcomas plays an important role in prognostication, but a recent study, *Nascimento af* et al[9] -Primary Angiosarcoma of the Breast: Clinicopathologic Analysis of 49 Cases, has shown that there is no correlation between histologic grade and patient outcome.

Donnel M et al [10] reported tumour larger than 5 cm are associated with shorter disease-free survival. Indeed, tumors smaller than 5 cm are usually associated with better prognosis even in the presence of worsening factors.

Characteristically, angiosarcoma of the breast metastasizes hematogenously to the lungs, skin, subcutaneous tissue, bone, liver, brain, and ovaries.[5] Metastasis to axillary lymph nodes is very rare (less than 1%).

Although it is a crucial disease, initial misdiagnosis is reportedly common as seen in this case. One of the reasons for misdiagnosis is the variety of possible clinical presentations, mammographic and ultrasonographic findings.[11] Radiographically, Breast angiosarcomas exhibits lots of diagnostic dilemmas as there are no specific pathognomonic features. They often appear as ill-defined masses on mammograms. Calcifications can be seen but differ from those seen with breast carcinomas. In a review of radiologic findings with angiosarcomas, *Liebermane et al*[12] established that the echo texture of these lesions is highly variable. They conclude that Patients with higher-grade lesions at pathologic evaluation were significantly (P less than .05) more likely to have abnormal mammogram. Magnetic resonance imaging (MRI) of angiosarcoma shows a mass with low signal intensity on T1-weighted images, but high signal intensity on heavily T2-weighted images. The latter suggests the presence of vascular channels containing slow flowing blood.[13]

Preoperative diagnosis, by FNAC and biopsy, may be difficult. False-negative rate of percutaneous biopsy is 37%.[14] The differential diagnoses of this rare malignancy include benign hemangioma, cystosarcoma phyllodes, stromal sarcoma, metaplastic carcinoma, fibrosarcoma, liposarcoma, and reactive spindle cell proliferative lesions. Large-core biopsies might facilitate the correct diagnosis as they provide a larger sample, but such a macrobiopsy is often difficult to perform due to the vascular nature of these tumor's. Surgical resection and microscopic examination of sufficient sampling of the tumour are often necessary to render a final diagnosis.

Immunohistochemistry can show positivity for factor VIII antigen, CD34, CD31, Ulex lectin, desmin, and vimentin. CD31 appears to be the most promising marker. In our patient there were three antigens positive CD31, CD34 and ERG antigen confirming the diagnosis of angiosarcoma.

The clinical course of the patient was complicated due to grade IV anemia and grade IV thrombocytopenia. There are two hypotheses that explain this thrombocytopenia. The first is that it was due to antiplatelet antibody. The second is that it may have resulted from antitumoural consumption of platelets. This platelet consumption may have been due to defective synthesis of prostaglandin I_2 by neovascular endothelium or release of a platelet aggregating substance by tumour cells.[15] These observations imply a direct role for the platelet in the pathogenesis of tumour cell metastasis.[15]

Endothelial cells expresses several kinds of cell adhesion molecules, including ICAM-1,VCAM-1, and PECAM-. Over expression of these molecules stimulated by proliferating tumour cells and resultant platelet aggregation may also a reason for this thrombocytopenia.[16] In this case we were not able to evaluate for these molecule.

Kwang-Il Yim et al[17] reported a case of angiosarcoma breast with wide spread skin lesion on the chest wall also observed intractable thrombocytopenia. He deemed that the uncontrolled thrombocytopenia was caused by persistent platelet consumption in the large skin lesion.

The best treatment of breast angiosarcoma is surgery, either by mastectomy or wide local excision with clear margin. The role of adjuvant treatment after surgery is still controversial.

Betty J Barrow et al[18], in a study of 59 patients with sarcoma of the breast (angiosarcoma in 17 patients) reported mastectomy followed by radiation therapy had local failure rate of 13% compared to 34% without radiation therapy. However this study could not show a statistical benefit for adjuvant radiation. Post-mastectomy radiation can be considered for large tumor size and positive surgical margin; as these are associated with high risk of local failure. However in our patient no adjuvant treatment has been given as the tumor size was not large, margins clear and was a low grade disease.

Sher T et al[19], in a retrospective review of 69 patients of primary angiosarcoma breast reported, survival was not favorably associated with chemotherapy or radiotherapy; however, an overall response rate of 48% was seen in metastatic angiosarcoma breast with combination cytotoxic chemo-therapy (anthracycline and ifosphamide or gemcitabine and taxane).

The ANGIOTAX[20] study was the first phase II prospective clinical trial of patients with metastatic or locally advanced angiosarcomas that established the role of weekly paclitaxel, ORR of 19% and non-progression rate of 24% at 6 months. However, this study included angiosarcomas of all sites that were not amenable to radiation or curative intent resection.

Immunotherapy may also play a part in treating this rare type of breast cancer. Recently, an approach to attacking a proliferative endothelium has been extensively investigated. New agents against angiogenesis, such as bevacizumab or rapamycin might also be useful against this tumour.

CONCLUSION

Breast angiosarcoma is a rare disease, which can develop as a primary neoplasm or as a complication due to prior exposure of the breast to either surgery or irradiation. Ultrasound usually shows heterogeneous hyperechogenicity with an associated architectural distorted appearance and typical malignant characteristics should alert the radiologist to a possible diagnosis of angiosarcoma. The best method for making diagnosis is core-cut biopsy. Total mastectomy remains the most effective mode of treatment. There is currently no consensus data for standard adjuvant treatment. No clinical trail has yet proven any benefit from adjuvant chemotherapy or radiation therapy in managing angiosarcoma, however both treatment modalities can be considered in locally advanced and metastatic patients.

CONSENT: obtained consent from patients relative.

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