Original Article

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Breast Sarcomas: Rare but Challenging Entity for Diagnosis

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ABSTRACT

Background: Breast sarcomas are extremely rare, can be primary or secondary, pose a high risk of recurrence with an overall poor prognosis. Primary breast sarcomas constitute < 1% of all primary breast malignancies and less than 5% of all sarcomas. Sarcomas arising in phyllodes tumors account for < 6 % of all phyllodes tumors. The most common subtype of both primary and secondary sarcoma is angiosarcoma.

Methods: This was a retrospective study of patients diagnosed as sarcoma of breast (excluding malignant phyllodes and metaplastic carcinoma) during the period from January 2016 to July 2019. The demographic and clinical features were noted from the medical records. The details of gross specimens (grossed in strict accordance with CAP protocols) were noted. The haematoxylin and eosin-stained slides along with immunohistochemistry (IHC) (pan cytokeratin, calponin, vimentin, SMA, CD117, Ki 67, desmin, CD10, CK5/6, EMA, p63, CD34, CD56, myogenin, CD99, p16, S100, BCL2, CD31, caldesmon and CD68) were reviewed and categorized according to WHO (2019) criteria.

Result: The median age of patients was fifty years. There were fourteen breast sarcomas including one arising in phyllodes tumor during the study period. These included undifferentiated pleomorphic sarcoma (4), liposarcoma (2), myxofibrosarcoma (2), angiosarcoma (2), one each of leiomyosarcoma, rhabdomyosarcoma, fibrosarcoma and stromal sarcoma. Despite using a wide panel of IHC markers, 4/14 (28.57%) sarcomas were classified as undifferentiated pleomorphic sarcoma.

Conclusion: Primary breast sarcomas are rare tumors and pose diagnostic challenge. It is important to categorize these entities in view of the differing biologic behavior and molecular profiles. Morphology along with IHC is important for diagnosis, treatment and prognosis.

Keywords: *Breast Sarcoma, Mesenchymal Tumor, Immunohistochemistry, Undifferentiated Pleomorphic Sarcoma*

Introduction

Breast sarcomas are rare and comprise less than 1% of all breast tumors and less than 5% of all soft tissue sarcomas. They may be primary or secondary. Female predominance and higher incidence in fifth to sixth decade is observed in primary breast sarcomas, whereas secondary sarcomas occur in older age. Primary sarcomas occur de-novo and secondary sarcomas are associated with chronic lymphedema, radiotherapy or genetic syndromes like neurofibromatosis, Li-Fraumeni syndrome and familial adenomatous polyposis.[1] The diagnostic criteria for secondary sarcomas occurring post radiotherapy are established by Cahan et al and they include a history of malignant tumor of different histology, sarcoma developing in irradiated fields and a latent period of more than four years. [1, 2] Immunohistochemical studies remain the gold standard in diagnosing and sub-categorizing these heterogeneous entities. [1] There are only a limited number of case reports and no large series on breast sarcomas from India. [3-7] We report a series of 14 sarcomas of the breast, characterized on morphology and immunohistochemistry (IHC) in view of the rarity.

Materials and Methods:

This was a retrospective study carried out on patients diagnosed as sarcoma of breast, including both primary and secondary during the period from January 2016 to July 2019. The demographic and clinical features and details on gross specimen were noted from the medical records. Surgical specimens were fixed in 10% formalin and processed for paraffin embedded sections. 4 **µm** sections were cut and stained with hematoxylin and eosin (H&E).

Additional 4 **µm** sections were mounted on poly-l-lysine coded slides and IHCs were performed on the Leica Bond 3 autostainer with HIER (heat induced epitope retrieval) along with a positive control. The reaction product was visualized after counterstaining with hematoxylin. The markers performed were pan cytokeratin, calponin, vimentin, SMA, CD117, Ki 67, desmin, CD10, CK5/6, EMA, p63, CD34, CD56, myogenin, CD99, p16, S100,

BCL2, CD31, caldesmon and CD68 based on initial histological subtypes and differential diagnoses. The list of antibodies, source and dilution were provided in Table 1. The morphology on H&E stained slides was reviewed along with IHC and tumors were categorized according to WHO classification of tumors of the breast (2019) criteria.[8] Extensive sampling was done in cases of diagnostic dilemma to rule out malignant phyllodes tumor and metaplastic carcinoma.

Results

During the study period a total of 14 breast sarcomas were diagnosed, which constituted 0.2% of all the breast malignancies. These included 12 (86%) primary and 2 (14%) secondary breast sarcomas. The risk factors for the secondary sarcomas included prior radiotherapy and chronic lymphedema. All the 14 were females (100%) with age ranging from 19 to 73 (median 51) years. Seven tumors were in the left, 6 in the right breast and the laterality was not available in one. The size varied from 3-28 cm. The specimens received included 5 core biopsies, 4 wide local excisions, 4 mastectomies and one modified radical mastectomy. The histology with IHC features were as given below (Table 2).

Liposarcoma (n=2): Grossly, both the tumors were large and lobular with pale yellow areas, areas of hemorrhage and necrosis. On microscopy, there were mature adipocytes with fibrous septae and an atypical spindle cell component. Few multinucleated cells, vacuolated cells, areas of necrosis and hemorrhage were seen. One case was a secondary dedifferentiated liposarcoma which on microscopy showed papillary proliferation of oval to cuboidal cells harboring vesicular nuclei and moderate amount of eosinophilic cytoplasm with an abrupt transition to lipomatous and spindle cell component with moderate atypia. Brisk mitoses (7-8/10 high power fields), areas of necrosis and hemorrhage were seen. The tumors were positive for vimentin, p16 and MDM2 (**Figure 1 A, B, C**).

Myxofibrosarcoma (n=2): Grossly, the tumors were partially circumscribed with grey white, firm fleshy and focally necrotic areas. Microscopically the tumors showed atypical spindle cells in a myxoid background with curvilinear vessels and brisk mitoses. The tumors showed positivity for vimentin with a **Ki-67 index of 25% in each.**

Angiosarcoma (n=2): Grossly the tumors were nodular and hemorrhagic. Microscopy showed atypical vascular spaces lined by spindle to cuboidal cells with atypia along with atypical mitoses and areas of myxoid change. The tumors showed positivity for CD31, CD34, ERG and vimentin with a **Ki-67 index of 30-40%.** One case showed axillary lymph nodal metastases (**Figure 1 D, E, F, G, H, I**).

Leiomyosarcoma (n=1): Microscopy showed round to spindle atypical cells arranged in sheets, trabeculae and bundles with binucleated and multinucleated giant cells and brisk mitoses(6-8/10 high power fields). The tumor showed positivity for SMA, desmin, CD10 and caldesmon (**Figure 2 A, B**).

Rhabdomyosarcoma (n=1): On microscopy the tumor showed diffuse sheets of round to oval cells with pleomorphic hyperchromatic nuclei and few multinucleated giant cells. Mitoses were 5-6/10 high power fields. The tumor showed positivity for desmin and CD56 (**Figure 2 C, D**).

Fibrosarcoma (n=1): Grossly, the tumor was solid and fleshy with hemorrhagic and glistening areas. Microscopically the lesion was composed of short fascicles of monomorphic spindle cells in herring bone pattern with brisk mitoses, areas of hemorrhage and necrosis. The tumor showed positivity for SMA, vimentin and a **Ki-67 proliferation index of 25%.**

Stromal sarcoma (n=1): Grossly, the lesion was grey white and ill-defined. Microscopy revealed a diffuse proliferation of plump spindle cells harboring vesicular nuclei and moderate amount of eosinophilic cytoplasm. The tumor showed positivity for vimentin, CD 10 with a **Ki-67 index of 12%.**

Undifferentiated pleomorphic sarcoma (n=4): Grossly the tumors were circumscribed and solid with grey white, fleshy and hemorrhagic areas. Microscopy revealed sheets and short fascicles of markedly atypical and pleomorphic spindle cells with few giant cells, brisk mitoses (8-10/10 high power fields) and necrosis. The tumors showed positivity for vimentin and all other markers were negative (**Figure 2 E, F**).

Secondary sarcomas: The secondary sarcomas included one each of angiosarcoma and liposarcoma (dedifferentiated).

Follow-up: Follow-up details were available for 9 patients (5 years to 2 weeks). Four patients including one each of alveolar rhabdomyosarcoma, secondary dedifferentiated liposarcoma, fibrosarcoma and undifferentiated pleomorphic sarcoma, underwent six weeks of external beam radiation therapy with no recurrence. Two patients including one each of angiosarcoma and undifferentiated pleomorphic sarcoma responded to resection followed by neo-adjuvant chemotherapy and had an uneventful

recovery. One patient with myxofibrosarcoma was on palliative chemotherapy, and completed the sixth cycle. One patient with undifferentiated pleomorphic sarcoma underwent right radical mastectomy followed by adjuvant radiotherapy for which she defaulted and presented with bilateral lung metastases. She was admitted for the third cycle of chemotherapy. One patient with secondary angiosarcoma presented with recurrence, seven months after completion of treatment. Five patients were lost to follow up.

Tables 1: Antibody names, clones and vendor details for IHC.

S.No.	Antibody name	Abbreviation	Clone	Company
1.	Pankeratin	PanK	AE1/AE3	Dako
2.	Cytokeratin 5	CK5	EP1601Y	Cell Marque
3.	Calponin	Calponin	CALP	Thermo
4.	Vimentin	Vimentin	V9	Thermo
5.	Smooth Muscle Actin	SMA	IA4	Cell Marque
6.	Cluster of Differentiation 117	CD117	YR145	Cell Marque
7.	Cluster of Differentiation 10	CD10	56C6	Dako
8.	Cluster of Differentiation 34	CD34	QBEnd10	Dako
9.	Cluster of Differentiation 56	CD56	MR-42	Cell Marque
10.	Cluster of Differentiation 99	CD99	EPR3097Y	Cell Marque
11.	Cluster of Differentiation 31	CD31	JC70A	Dako
12.	Cluster of Differentiation 68	CD68	KP1	Cell Marque
13.	Ki67	Ki67	MIB-1	Dako
14.	Desmin	Desmin	D33	Biocare
15.	Epithelial Membrane Antigen	EMA	E29	Biocare
16.	p63	p63	4A4	Biogenex
17.	p16	p16	E6H6	Ventana
18.	Myogenin	Myogenin	MYG007	Biocare
19.	S100	S100	Polyclonal S100	Dako
20.	B Cell Lymphoma 2	BCL2	124	Dako
21.	Caldesmon	Caldesmon	h-CD	Dako
22.	Anaplastic Lymphoma Kinase 1	ALK1	54A	Biocare
23.	Erythroblast transformation-specific [ETS] Related Gene	ERG	ERG9FY	Biocare

Table 2: Individual number of cases and IHC findings of various histological subtypes of breast sarcomas.

S.No.	Histological subtype	Number of cases	IHC (positive markers)	IHC (negative markers)
1.	Liposarcoma	2	Vimentin, p16, MDM2	PCK, CD10, ALK1, SMA, CD117, PCK, Caldesmon
2.	Myxofibrosarcoma	2	Vimentin, Ki67: 25% (both)	CD34, Desmin, SMA, PCK, p16, S-100, BCL2
3.	Angiosarcoma	2	CD31, CD34, ERG, Ki67: 30-40%	

S.No.	Histological subtype	Number of cases	IHC (positive markers)	IHC (negative markers)
4.	Leiomyosarcoma	1	SMA, desmin, CD10, caldesmon	CD117, CK5, EMA
5.	Rhabdomyosarcoma	1	Desmin, CD56, Myogenin	CD99
6.	Fibrosarcoma	1	SMA, vimentin, Ki67: 25%	CD34, Desmin, Caldesmon, CD117
7.	Stromal sarcoma	1	Vimentin, CD10, Ki67: 12%	CD117, PCK, SMA, CD34
8.	Undifferentiated pleomorphic sarcoma	4	Vimentin	PCK, CD34, Caldesmon, SMA, p63, CD68, S-100, CD117

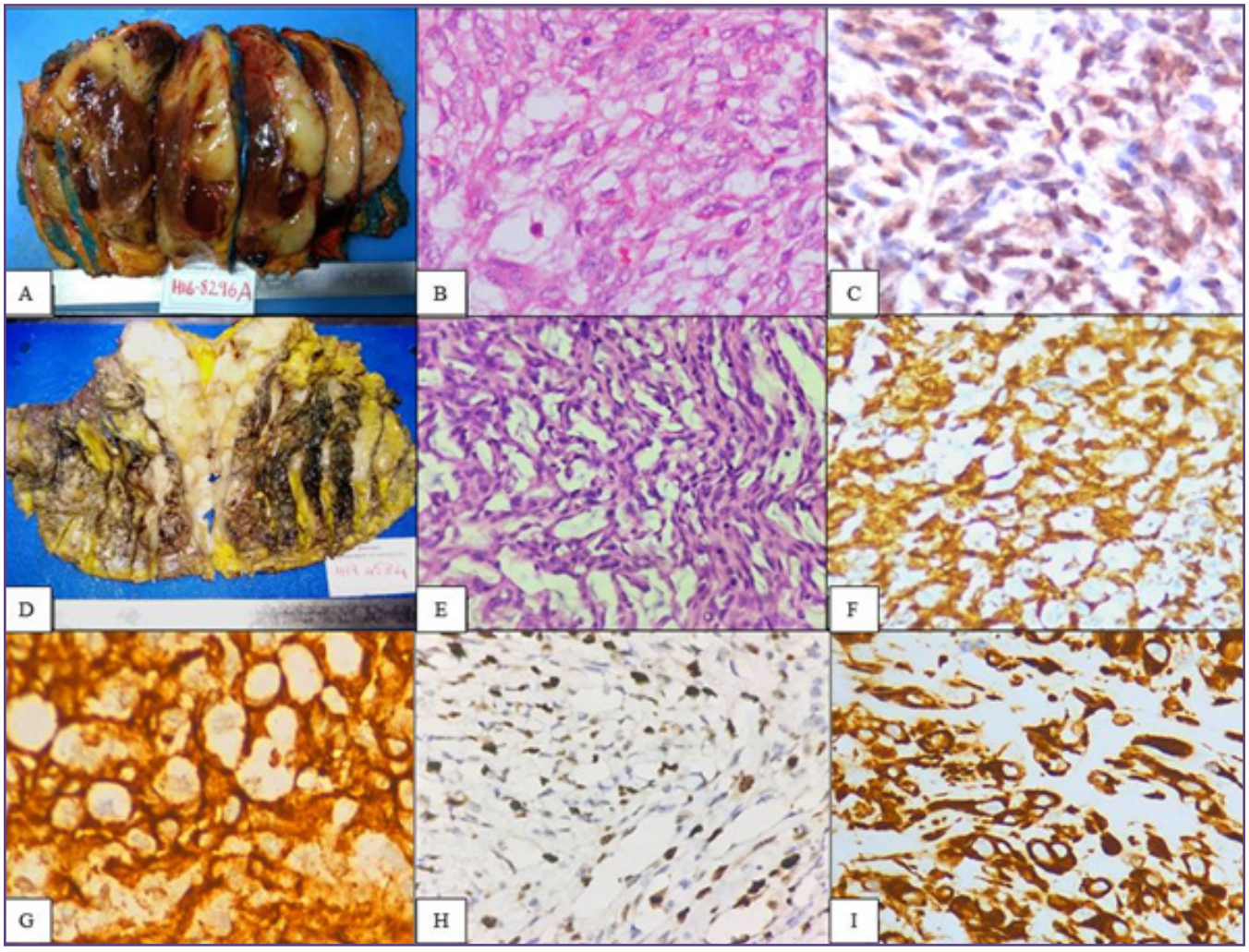

Fig. 1:A. Gross specimen of liposarcoma of breast showing a large grey white lobulated mass with glistening areas, B. Photomicrograph of the same showing sheets of atypical polygonal cells with abundant pale cytoplasm and hyperchromatic nucleus with occasional lipoblasts (Hematoxylin and eosin [H&E]x400), C. Immunohistochemistry (IHC) with MDM2 expression in liposarcoma (MDM2 x100), D. Gross specimen of angiosarcoma of breast showing an ill-defined grey white lesion with tiny microcystic spaces, E. Photomicrograph of the same showing tiny anatomizing vascular channels lined by flattened epithelium (H&Ex100); Photomicrographs of IHC expression of CD31 (F), CD34 (G), Ki67 (H) and Vimentin (I) in angiosarcoma (IHCx100).

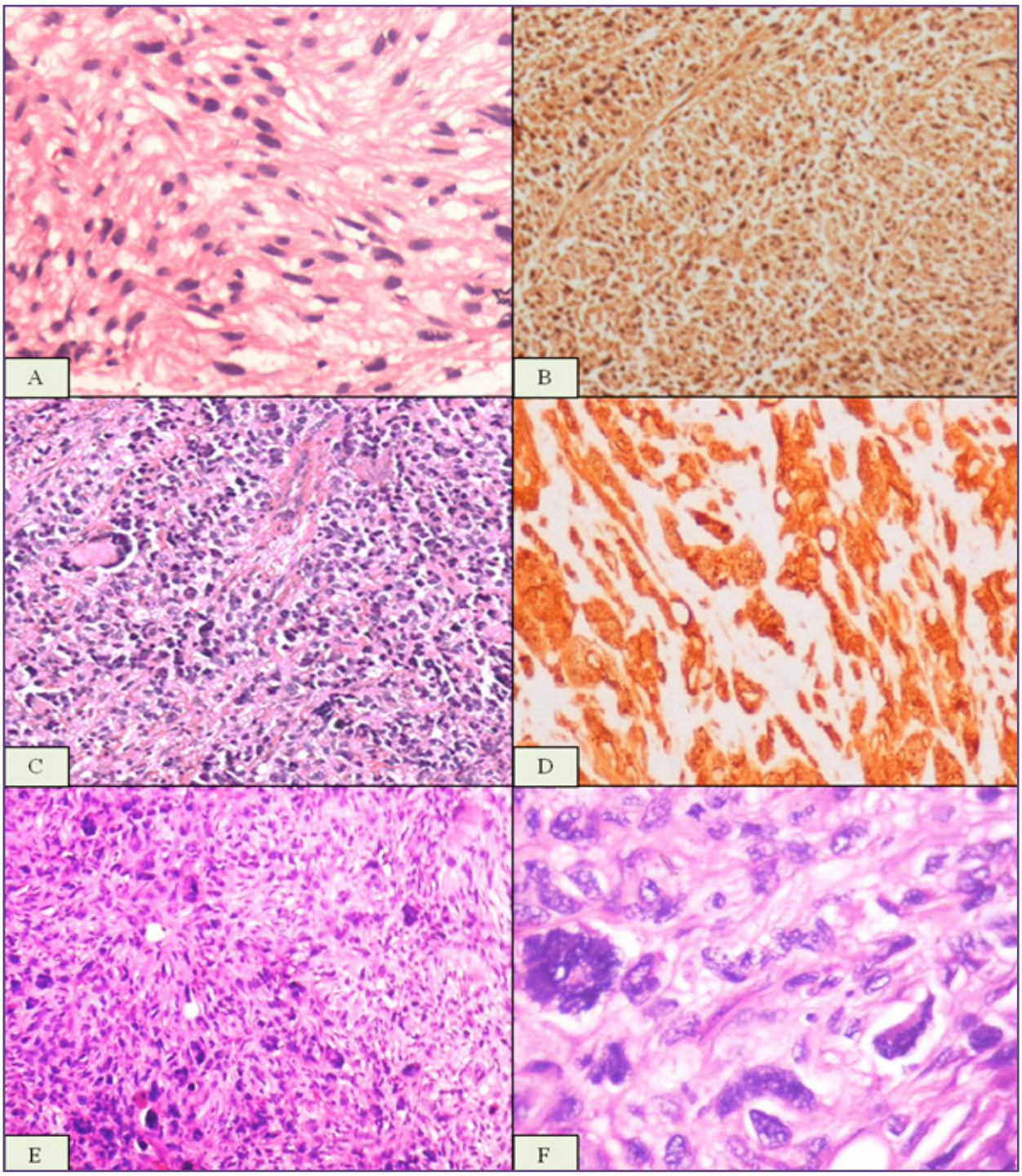

Fig. 2: A. Photomicrograph of leiomyosarcoma of breast showing spindle cells arranged in fascicles and bundles with elongated hyperchromatic nuclei (H&Ex400); B. SMA expression in leiomyosarcoma(SMAx400); C. Photomicrograph of rhabdomyosarcoma showing fascicles of spindle to oval cells with abundant cytoplasm, pleomorphic nuclei and interspersed large rhabdoid cells with abundant eosinophilic cytoplasm (H&Ex100); D. Desmin expression in rhabdomyosarcoma(Desmin x400); E. Photomicrograph of undifferentiated pleomorphic sarcoma showing fascicles and whorls of pleomorphic cells with moderate amount of cytoplasm and hyperchromatic pleomorphic nuclei (H&Ex100);F. Photomicrographs of the same showing large cells with pleomorphic bizarre nuclei and multinucleate cells (H&Ex400).

Discussion

Breast sarcomas are extremely rare and constituted 0.2% of all the breast malignancies in the present study. The median age of 51 years and female gender predilection are in agreement with earlier studies. [1, 4] Breast sarcomas are histologically diverse with high risk of recurrence and an overall poor prognosis. [9, 10] Angiosarcoma was reported to be the most common primary breast sarcoma. [8, 11] The present study showed that undifferentiated pleomorphic sarcoma was the most common (4/14 (28.57%) subtype, despite using a wide panel of IHC markers. This was followed by angiosarcoma, myxofibrosarcoma and liposarcoma, and others. Lim et al made similar observation. [9]

The gross, microscopic and IHC features of breast sarcomas are similar to soft tissue sarcomas. However, the differential diagnosis includes poorly differentiated carcinoma, metaplastic carcinoma and malignancy in phyllodes tumor. Metaplastic carcinoma can be ruled out by absence of diffuse or significant expression of cytokeratin and myoepithelial markers. [12]

Malignancy in phyllodes tumor shows malignant mesenchymal component and benign epithelial component. [8, 9, 13, 14] Extensive sampling, along with IHC, as done in the present study helped resolve the diagnosis.

Primary angiosarcomas of breast are located deep within breast parenchyma and may or may not present with cutaneous involvement. Both primary and secondary angiosarcomas show similar features and cannot be distinguished on gross and microscopic examination. Both the angiosarcomas in the present study showed infiltrative and poorly defined margins, with hemorrhagic and cystic areas. Histologically vaso-formative and anastomosing vascular channels were seen. IHC showed positivity for endothelial markers like CD31 (strong, membranous), ERG (nuclear) and variable CD34, as reported in the literature. [8]

Present study showed 2 cases of low-grade myxofibrosarcoma. Both patients were elderly (55 and 56 years old). The pattern of growth was multi-nodular with a prominent myxoid matrix, atypical fibroblastic cells, elongated curvilinear capillaries, and pseudo-lipoblasts. IHC has limited role. It needs to be differentiated from its close mimic, low grade fibro-myxoid sarcoma, due to differing clinical behavior. Ki-67 proliferation and cyclin E expression is higher in myxofibrosarcoma, as seen in the present study. Both can be reliably differentiated on molecular studies, where FUS-CREB3L2 rearrangement is seen in low grade fibro-myxoid sarcoma whereas this fusion gene is not expressed in low-grade myxofibrosarcoma. [15] Diagnosis was made on morphology in both cases and molecular studies were not performed in the present study.

Primary liposarcomas of the breast are exceedingly rare with less than 50 reported cases. Malignant phyllodes tumor with lipo-sarcomatous differentiation is more common than atypical lipomatous tumor/well differentiated liposarcoma of the breast. In the present study, one case was a primary liposarcoma and the other was a secondary dedifferentiated liposarcoma. Both showed positivity for p16 and MDM2.

Primary or metastatic rhabdomyosarcoma to the breast is very uncommon and usually occurs in children. Our patient was a 19 years old female with alveolar variant of rhabdomyosarcoma. Histologically, the appearance of a small round cell tumor with IHC positivity for actin, desmin, myogenin, and myoD1 helps in the diagnosis. [8]

Leiomyosarcoma of the breast can occur in the dermis, nipple areola complex or parenchyma. IHC positivity for smooth muscle markers like SMA, desmin and caldesmon help in making the diagnosis, as in our patient. [8]

Fibrosarcoma, stromal sarcoma and undifferentiated pleomorphic sarcomas of the breast are also rare and show histological features similar to their soft tissue counterparts. IHC is particularly important in making the diagnosis. Undifferentiated pleomorphic sarcomas require a wide panel of IHC. All markers, except vimentin were negative in the 4 undifferentiated pleomorphic sarcomas in the present study. Similar observations were made earlier. [8, 9, 13, 14] The risk factors for secondary sarcomas of the breast include radiotherapy, post mastectomy lymphedema and association with genetic syndromes.[1] Higher

radiotherapy dose, early age of exposure, chemotherapy along with radiotherapy are implicated in the pathogenesis. [12] There were two secondary sarcomas in the present study and the risk factors included prior radiotherapy and chronic lymphedema. Histologically they comprised of one each of angiosarcoma and dedifferentiated liposarcoma.

Angiosarcoma is the most common radiation induced secondary breast sarcoma and differs from primary angiosarcoma in showing high MYC and FLT4 gene amplification. The other radiation induced secondary breast sarcoma subtypes include undifferentiated pleomorphic sarcoma, leiomyosarcoma and liposarcoma. [12]

Tumor diameter, distant metastasis and histological grade have an immense impact on the prognosis of breast sarcomas. [4] Tumors were large and varied in size from 3-28 cm in the present study. Surgery is the main therapeutic modality and the type of procedure depends on the tumor size and its relationship with the breast. Axillary

involvement is seen in less than 5%.In our study axillary lymph node metastasis was discerned in only one case of angiosarcoma of the breast (7%). The benefit of adjuvant radiotherapy and its role in disease free survival is not clear due the rarity of these entities. [1] Four patients who underwent radiotherapy and two patients who received chemotherapy were disease free in the present study. Metastases and recurrence were observed in one each.

Conclusion

Breast sarcomas are rare tumors and pose a diagnostic challenge. Due to their rarity, there are limited reports in the literature. It is important to adequately categorize these entities histologically in view of their differing biologic behavior, molecular profiles and aggressive nature. Morphology along with IHC is important for diagnosis, treatment and prognosis.

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Competing Interests

None declared

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