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Effective Treatment for Primary Locally Aggressive Intermediate and Malignant Soft Tissue Tumors of the Breast

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Objective: This study aimed to examine the rare locally aggressive intermediate tumors and malignant primary breast mesenchymal tumors in patients receiving surgical treatment.

Summary of background data: Locally aggressive intermediate tumors were subdivided into nonmetastasizing and rarely metastasizing, and the malignant group was subdivided as a single subgroup called able to metastasize. A retrospective examination of surgical notes and clinical charts was carried out reviewing gender, age, symptoms, duration of symptoms, tumor size, clinical presentation, radiation history, kind of surgery undergone, adjuvant radiotherapy, adjuvant chemotherapy, local recurrences, systemic metastases, and mortality.

Results: Mitotic index and Ki-67 were statistically different between locally aggressive and malignant groups ($P < 0.001$). One local recurrence occurred in only 1 patient diagnosed as dermatofibrosarcoma protuberans among all patients. None of the entities showed distant metastasis or mortality. In this result, clear margin of surgery in locally aggressive intermediate group and combination of surgery with radiation therapy in the malignant group was the most important determinant for the prospect of the patients with mean follow-up of 28 months.

Conclusion: The main treatment for localized mesenchymal breast tumors is surgery. When the disease is locally advanced or malignant with high mitotic index, radiotherapy with

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surgery is predominantly used. Targeted therapies are promising with the limited place of chemotherapy.

Key words: Breast – Cystosarcoma phyllodes – Dermatofibrosarcoma protuberances – Myxofibrosarcoma – Soft tissue tumors

Breast mesenchymal tumors were classified into categories by the World Health Organization (WHO) in 2019.[1] Concerning the issue of classifying mesenchymal tumors of the breast, it was recommended that it be in conformance with WHO's categorization of soft tissue tumors.[2] Desmoid-type fibromatosis, well-differentiated liposarcoma, and solitary fibrous tumors belonged to the group of locally aggressive intermediate soft tissue breast tumors that are of mesenchymal origin and do not metastasize. Dermatofibrosarcoma protuberances and borderline cystosarcoma phyllodes of the breast belong to the same group and rarely metastasize.[1–5] However, the malignant group of the soft tissue tumors can metastasize. Stromal overgrowth occurs in malignant cystosarcoma phyllodes and, similar to primary sarcomas of the breast, they originate from mesenchymal tissue of the mammary gland. Primary sarcomas of the breast are heterogeneous neoplasms and are considered extremely rare, constituting less than 1% of all breast cancers.[5]

Secondary breast mesenchymal neoplasms occur because of previous radiation exposure. This circumstance arises because of the extensive exposure to radiation following breast-conserving treatment carried out for breast cancer. As these primary diseases are rare, the basis of existing knowledge is mainly various case reports and some comparatively small retrospective studies.

In comparison with epithelial breast cancer, there is a lack of high-level evidence to endorse a standard of care for these rare entities. This article seeks to analyze the patients who have not previously undergone radiation so as to eliminate secondary cases. Reports were obtained for patients registered at the Adana City Training and Research Hospital who underwent surgical treatment between 2010 and 2020. Borderline behavior and the malignant nature of these rare primary tumors were then examined.

Materials and Methods

The cases diagnosed pathologically at the authors' center between 2010 and 2020 were categorized into 2 breast tumor groups: locally aggressive intermediate tumors and malignant soft tissue tumors. The first of these groups was further subdivided into nonmetastasizing and rarely metastasizing, and the second was subdivided into a single subgroup called able to metastasize (Table 1). The hematoxylin-eosin (H&E)-stained sections being examined were obtained from Saglık Bilimleri University, Adana City Training and Research Hospital, Pathology Department. From these H&E-stained sections, the following were examined: surgical margin, mitosis, grade, infiltrative or nodular pattern, S-100, CD34, CD10, Ki-67, actin, desmin, vimentin, H-kaldesmon, myogenin, estrogen receptor, progesterone receptor, factor 13A, vimentin, and CD68. In all cases, H&E-stained sections were analyzed to verify the diagnosis. An average of 6 H&E slides were available for each case (range: 3 to 10).

A retrospective examination of surgical notes and clinical charts was carried out reviewing gender, age, symptoms, duration of symptoms, tumor size, clinical presentation, radiation history, kind of surgery undergone, adjuvant radiotherapy, adjuvant chemotherapy, local recurrences, systemic metastases, and mortality. Patient records were reviewed to obtain follow-up information, including direct phone call records and death certificates. The study did not include patients who had other past primary malignancy in the breast, radiation exposure in the past, or metastatic disease in the breast. Also, informed consent was taken in writing from patients supplied by one-to-one calling the patients to our center. Approval for the study was provided by the Ethics Committee of Adana City Training and Research Hospital in association with Saglik Bilimleri University (ethics committee number: 777-25.03.2020).

Statistical analysis

IBM SPSS Statistics ver. 24.0 (IBM Co., Armonk, New York) was used to perform statistical analysis. Mean (standard deviation) or median (range) was used to present continuous data, and categorical data were depicted as frequency. Normal distributions of the continuous variables were evaluated by using the 1-sample Kolmogorov-Smirnov test. Comparisons between the groups were made using the

Table 1 The demographic characteristics and tumor-specific findings of locally aggressive, intermediate, and malignant soft tissue tumors of the breast

Case	Sex/age (y)	Diagnosis	Gross	Ki - 67	Mitotic Index	Side	Size (cm)	Surgery	Adjuvant Therapy
Locally aggressive intermediate soft tissue tumors of the breast									
Nonmetastasizing									
1	f/60	A desmoid tumor (fibromatosis)	Focal infiltrative	1	1	Right	5.5	Segmental mastectomy	Rt
2	f/62	Solitary fibrous tumor	Well-defined	8	3	Right	3.5	Segmental mastectomy	No
3	m/40	Well-differentiated *liposarcoma*	Focal infiltrative	5	2	Right	2	Segmental mastectomy	No
Rarely metastasizing									
4	f/44	Dermatofibrosarcoma protuberans	Infiltrative	3	2	Right	7	Segmental mastectomy	Rt
5	f/52	Borderline phyllodes tumor	Focal Infiltrative	5	5	Right	10	Simple mastectomy	No
6	f/22	Borderline phyllodes tumor	Well-defined	15	9	Right	3	Segmental mastectomy following wide surgical excision due to positive margin	No
7	f/23	Borderline phyllodes tumor	Focal infiltrative	7	9	Left	5.4	Segmental mastectomy	No
8	f/33	Borderline phyllodes tumor	Focal infiltrative	3	1	Right	7	Simple mastectomy with oncoplastic surgery	No
Malignant soft tissue tumors of the breast									
Capable of metastasizing									
9	f/56	Malignant phyllodes tumor	Infiltrative	20	12	Right	4.5	Segmental mastectomy	Rt
10	f/54	Malignant phyllodes tumor	Infiltrative	15	22	Right	8	Segmental mastectomy	Rt
11	f/34	Malignant phyllodes tumor	Infiltrative	40	30	Right	12	Simple mastectomy	Rt
12	f/26	Malignant phyllodes tumor + invasive ductal carcinoma	Infiltrative	30	23	Right	9	Modified radical mastectomy	Cht/Rt
13	m/60	*Myxoid/round-cell liposarcoma*	Infiltrative	20	16	left	11	Simple mastectomy	Rt
14	f/45	Leiomyosarcoma	Infiltrative	15	15	Left	3.5	Segmental mastectomy	Rt
15	f/74	Myxofibrosarcoma	Infiltrative	20	25	Left	3.3	Segmental mastectomy	Rt

Cht, chemotherapy; f, female; m, male; Rt, radiotherapy.

Mann-Whitney *U* test. Differences were considered statistically significant at $P < 0.05$.

Results

The results of 2 groups are presented as follows (Table 1).

Locally aggressive but nonmetastasizing group

In this group, 1 patient was diagnosed with desmoid-type fibromatosis, 1 with a solitary fibrous tumor, and 1 with a well-differentiated liposarcoma (Figs. 1a and 1b, and 3a).

Locally aggressive but rarely metastasizing group

In this group, 4 patients were diagnosed with borderline cystosarcoma phyllodes and 1 with dermatofibrosarcoma protuberance (Fig. 1c and 1d).

Malignant group

Four patients in the malignant group were diagnosed with malignant cystosarcoma phyllodes (Fig. 2a–2d), 1 patient was diagnosed with myxoid/round-cell liposarcoma, 1 with myxofibrosarcoma, and 1 with leiomyosarcoma (Fig. 3b–3d).

A total of 15 patients were included in the study. Of these, 13 were women and 2 were men. The average age of the patients was 45, 6 ± 15, 7 months (range: 22 to 74). A lump presented in all patients, and 7 of them had complaints of pain. None of the cases had a prior history of radiation, which meant that postradiation sarcoma could be eliminated. Symptoms were experienced for a mean duration of 8, 6 ± 6, 7 months (range: 2 to 24).

In 8 of the cases, surgical treatment involved segmental mastectomy. Segmental mastectomy was carried out on 1 of these patients after a wide surgical excision because of surgical margin positivity diagnosed as a borderline phyllodes tumor. Surgery was carried out again on 1 of the patients diagnosed with dermatofibrosarcoma protuberance because of local recurrence 5 years following the initial wide local excision. A simple mastectomy was performed on 3 patients, and on 1 patient, prosthesis was performed for cosmetic purposes. In 9 cases, adjuvant radiotherapy was performed, and in 1 patient adjuvant chemotherapy was performed. The latter was suffering from invasive ductal carcinoma in the mass burden of a malign phyllodes tumor.

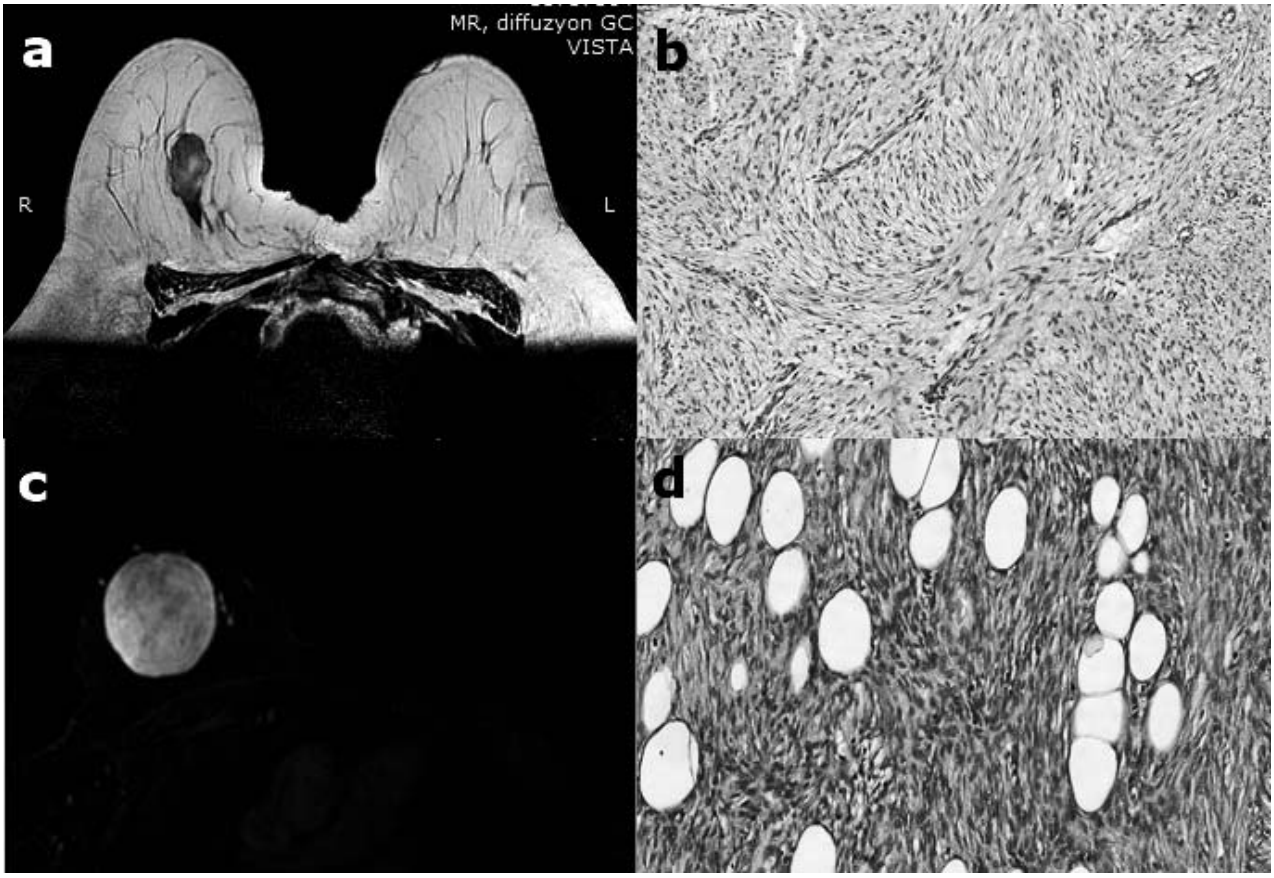

Fig. 1 (a) An ill-defined intensive enhancing solid lesion measuring 41 mm × 21 mm at 12 o'clock in the right breast diagnosed as desmoid-type fibromatosis. (b) Solitary fibrous tumor consists of constricted cytoplasms with unclear margins, with an unclear pattern, randomly distributed, having nuclei in the form of a spindle-oval shape, and showing focal myxoid changes in the background (hematoxylin-eosin [H&E], original magnification ×100). (c) A large homogeneously enhancing mass with circumscribed margins involving most of the upper quadrant of the right breast diagnosed as borderline cystosarcoma phyllodes. (d) Dermatofibrosarcoma protuberans having an infiltrative margin and showing an irregular spread in the form of honeycombs toward the adipose tissue and consists of spindle cells that show a vortex-shaped pattern (H&E, original magnification ×200).

In 10 patients, the right breast was affected (66.6%), and in 5 patients (33.3%) the left breast was affected. The mean tumor size was found to be 6, 3 ± 3, 1 cm (range: 2 to 12). The mean follow-up for all patients was 28 months (range: 3 to 102). Mitotic index and Ki-67 were statistically significant between locally aggressive and malignant groups ($P < 0.001$), whereas age and tumor size were not significant ($P > 0.35$ versus $P > 0.25$, respectively). Distant metastasis and mortality were not observed in any of the patients.

Discussion

A wide spectrum of entities comprise mesenchymal tumors of the breast, which often creates issues in managing them. Breast tumors with adipocytic, fibroblast, or vascular differentiation may be observed in rare cases, and these are encompassed on a spectrum from benign to malignant. However, a few lesions demonstrate borderline features and are present in a gray zone between malignant and benign because it is not possible to predict their behavior accurately. Hence, a significant issue that needs to be addressed is the borderline behavior and malignant attributes of these uncommon tumors. Histopathologically, mitotic index and Ki-67 are the determinant variables between locally aggressive and malignant behavior.

Locally aggressive but nonmetastasizing group

In our study, 1 of the patients in the locally aggressive but nonmetastasizing group with des-

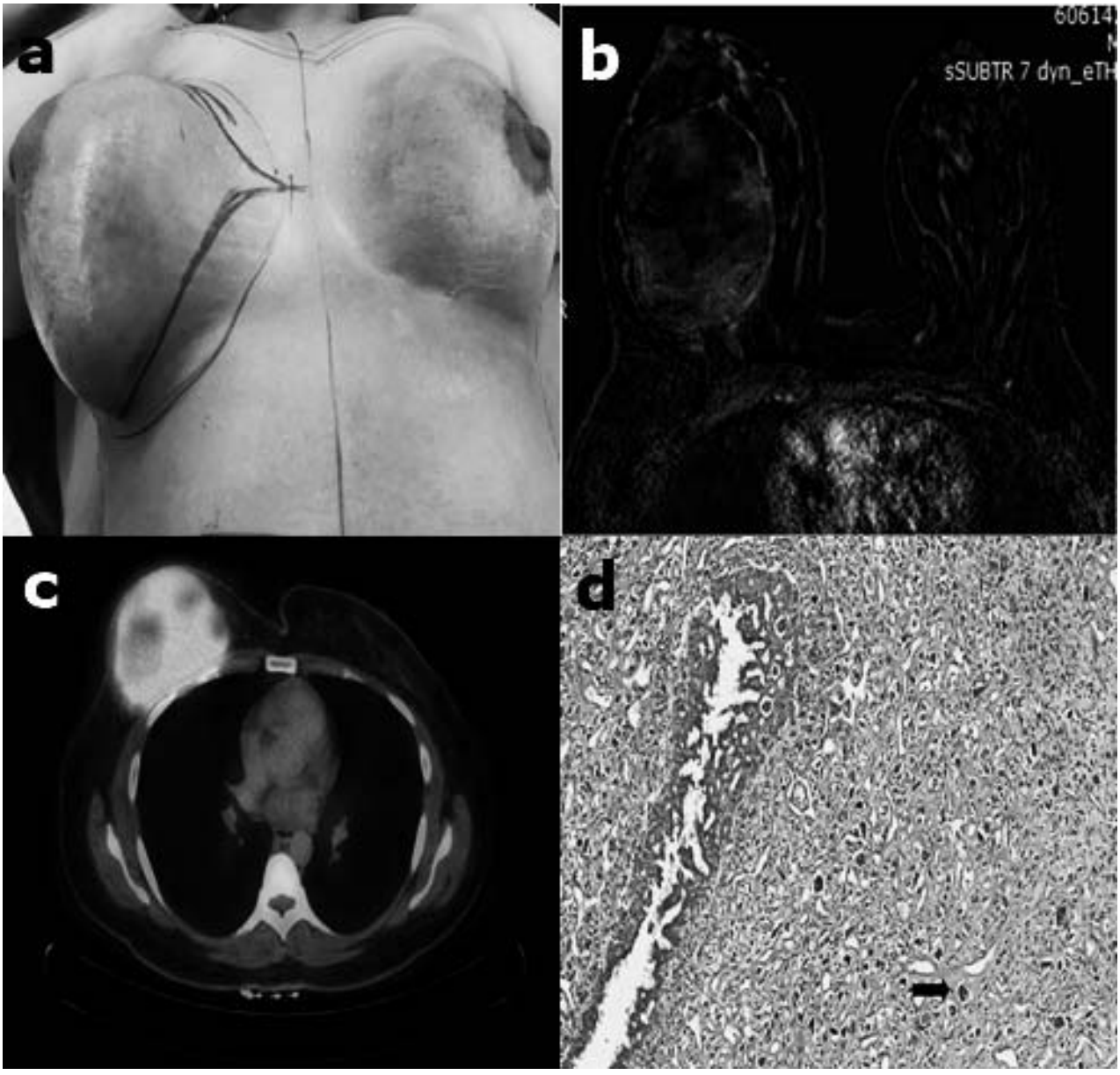

Fig. 2 (a) A large mass encompassing most of the right breast is causing asymmetry of the nipples and inflammation and edema of the skin with a preoperative Tru-Cut biopsy revealing a fibroepithelial tumor. (b) A huge heterogeneously enhancing mass within the center of the right breast and causing retraction of the pectoral muscle in the same patient. (c) 18F-fluorodeoxyglucose (18F-FDG) positron emission tomography (PET) imaging findings of the same tumor encompassing most of the right breast of the patient. (d) Permanent pathology revealing malignant phyllodes tumor (H&E, original magnification ×100). These tumors are biphasic, consisting of long, branching, cleft-like spaces that have an inner layer lined with hyperplastic epithelials, and the outer layer is lined with myoepithelial cells. There are formed mesenchymal cells surrounded by cellular stroma around the ductus structures and ducts. There are many atypical, mitosis (arrow), and stromal overgrowths in the tumor.

moid-type fibromatosis was found to have a close surgical margin following resection and exposure to adjuvant radiotherapy without any local recurrence and metastasis with follow-up at 65 months. In the literature, these tumors make up 0.2% of all breast tumors, and a suitable alternative is to perform extensive surgical resection with broad margins because of the risks of postsurgical recurrences.[4] That is because there is no conclusive evidence for the advantages of chemotherapy, radiotherapy,

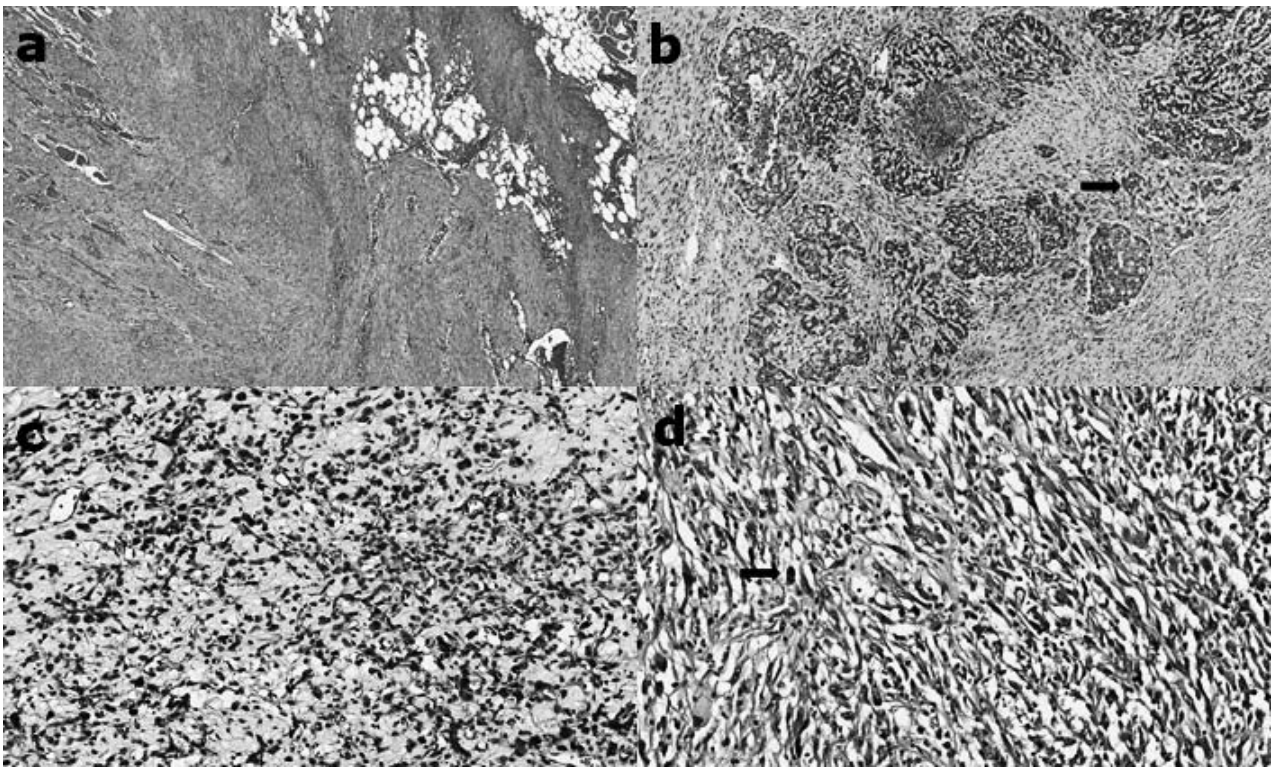

Fig. 3 (a) Desmoid-type fibromatosis tumors are composed of myofibroblastic cells with oval nuclei, which are infiltrated into the surrounding tissue, such as muscle structures and adipose tissue but are still relatively well-bounded, aligned parallel to each other in collagen (H&E, original magnification ×40). (b) The patient with malignant phyllodes and an invasive tumor consisting of epithelial and mesenchymal components, with large areas of necrosis observed. In this biphasic tumor, the focus of infiltrative, invasive ductal carcinoma (arrow) showing abortive glandular structures seen in some areas of the epithelial component (H&E, original magnification ×50). (c) Myxoid liposarcomas are tumors composed of lipoblasts on the myxoid surface, with a moderate cellular, round nucleus-nucleus/cytoplasm ratio, with round and oval nuclei, some of which are multivacuolated cytoplasm (H&E, original magnification ×200). (d) Leiomyosarcomas are tumoral lesions showing a fascicular growth pattern, with eosinophilic cytoplasm, ending with a spindle, blunt tip, with pleomorphic nuclei in most areas, with frequent mitotic activity (arrow) (H&E, original magnification ×200).

cytotoxic agents, and anti-inflammatory or anti-estrogen therapy when these tumors have not been fully excised.[6] Medical treatments that target the PDGFRβ pathway have recently been used in inoperable or recurrent tumors and have been somewhat successful.[7]

Hence, for our patient, diagnosed as solitary fibrous tumor, radiation was not planned and no local recurrence was observed at a 9-month follow-up. The malignant nature of these tumors is depicted in previous studies through mitoses (≥4 mitoses per 10 high-power fields) and/or infiltrative margins and cytological atypia. However, greater cellularity, mitotic activity, pleomorphism, and necrosis were not observed in the current case under review, and so it did not fulfill the criteria for malignancy and is therefore classified as benign. The solitary fibrous tumor is an uncommon mesenchymal neoplasm that typically emerges in the pleura; however, very limited cases do occur in the breast, and the treatment typically focuses on surgical excision with wide margins. It seems that similar to other soft tissue neoplasms, chemotherapy has no effect. A potential targeted therapy is inhibition of vascular endothelial growth factor (VEGF) and its receptor (VEGFR); however further research is required to validate these findings.[8] There are contradictory findings regarding the use of radiation. Radiotherapy may be used in cases that exhibit a large histological grade or incomplete margins at excision.[9]

There was an extensive surgical margin in the patient with a well-differentiated liposarcoma following resection. No local recurrence was experienced by this patient at an 18-month follow-up. This kind of liposarcoma is the most common subtype of

liposarcoma, representing 40% to 45%, and is a primarily locally aggressive malignant mesenchymal neoplasm. Other subtypes include myxoid/round-cell, pleomorphic, and dedifferentiated liposarcomas. However, well-differentiated liposarcomas are rare entities in the location of the breast, and for this subtype, it will be sufficient to perform a resection with high surgical margins.[10]

Locally aggressive but rarely metastasizing group

One of the patients in the locally aggressive but rarely metastasizing group, who had been found to have dermatofibrosarcoma protuberans, underwent a second surgery 5 years after the first extensive local excision was performed. Reexcision of the earlier surgical scar with the underlying breast tissue was carried out to the level of the pectoral fascia and no recurrence was observed at the 20-month follow-up. In general, dermatofibrosarcoma protuberans stems from the dermis, slowly moves toward the deeper soft tissues, and may take place at any anatomic site. According to the literature, there are almost 60 localized cases in the breast. It is recommended that full local surgical resection should involve surgical margins of 2 to 3 cm, and that 3-dimensional resection should involve skin, underlying fascia, and subcutaneous tissue. In addition, the recently recommended neoadjuvant imatinib was effective in reducing the size of the tumor.[11] Imatinib may also help in regulating the disease in patients suffering from metastasis.[12] Although it is not certain how adjuvant radiotherapy performs as a treatment for neoplasm, radiotherapy was preferred in this case because of the initial resection margins.

There were 3 borderline cystosarcoma phyllodes tumors in this study, and once extensive surgical margins were achieved, this group of patients did not experience local recurrence during a mean follow-up period of 35, 6 ± 14, 1 months. Intermediate histological attributes are exhibited by other patients suffering from borderline phyllodes tumors, and it is frequently difficult to differentiate between the two. The behavior of these lesions is frequently unpredictable because they demonstrate most but not all the characteristics of malignancy. A few studies have shown rare instances of metastasis for borderline cystosarcoma phyllodes.[3–13] Borderline phyllodes are differentiated from malignant tumors by grading them across different histological characteristics that include stromal cellularity, tumor border, mitotic activity, stromal atypia, and stromal overgrowth. A risk of metastasis has been found in histologically malignant phyllodes tumors; however, it may be difficult to ascertain the microscopic differences between borderline and malignant phyllodes, and therefore any misidentification causes inaccurate behavior predictions.[13,14]

Malignant group

Four patients were found to be suffering from malignant cystosarcoma phyllodes tumors. Invasive ductal carcinoma was found in one of the patients within the mass burden of malign phyllodes tumors, having 4 positive axillary lymph nodes. This patient went through adjuvant chemoradiotherapy, which was different from other patients who were only receiving adjuvant radiotherapy. This group of patients did not exhibit local recurrence during a mean follow-up period of 45, 5 ± 20, 2 months. It is rare for cancer to develop within phyllodes tumors, a tendency that stems from the epithelial component of this stromal tumor. Past studies have reported a total of 30 patients. Some studies have been carried out recently on the function of molecular analysis, molecular targeting agents (tyrosine kinase inhibitors), and using Taxanes for metastatic malignant cases.[15–17]

There was a wide surgical margin in another patient in the malignant group suffering from myxoid/round-cell liposarcoma. Adjuvant radiation therapy was given preference and the patient did not experience local recurrence at the 18-month follow-up. Myxoid/round-cell liposarcoma is one of the least common malignant breast tumors, constituting only 0.03% of all breast tumors. The literature has reported a very limited number of cases of myxoid/round-cell liposarcoma.[18,19] In cases in which it is not possible to obtain negative margins solely through surgery, and the size of the tumor is larger than 5 cm or is of high grade (for example, pleomorphic or myxoid/round-cell liposarcomas), adjuvant chemotherapy or radiotherapy may be required.[20]

Myxofibrosarcoma is also principally treated with clear surgical margins following radiotherapy and also more recently with pembrolizumab. Our patient with myxofibrosarcoma did not experience recurrence after surgery and subsequent radiotherapy.

The final patient from the malignant group was found to have leiomyosarcoma of the breast, and the mass was resected with a large surgical margin. The patient did not experience local recurrence at 78 months of follow-up. Diagnosis of breast leiomyo-

sarcomas is rare, and only 16 cases have been reported so far. The same approaches as those used in other sarcomas are used to treat breast sarcomas, therefore wide local excision/lumpectomy or mastectomy is used with or without radiotherapy. However, there is a lack of evidence for dissection, chemotherapy, and radiotherapy bringing about improvement in the disease-free rates or overall survival.[21] Adjuvant radiotherapy following surgical resection was provided to the patient, and no recurrence was observed after following up at 5 years. Analysis of eribulin, which is a tubulin-targeting derivative of marine sponges, was examined for use in advanced soft tissue sarcomas that increased following 1 or 2 sessions of chemotherapy. It generated responses in leiomyosarcomas and has the potential to be an effective treatment.[22]

When these 3 groups of patients were evaluated in general, it was seen that the most important inference was the negative surgical margin, but we observed that reexcision, wide surgical resection, and radiotherapy came to the fore in tumors close to the border. Radiotherapy is considered in the case of surgical margin closeness in mesenchymal breast tumors that do not metastasize and rarely metastasize, whereas it comes into the prominence in tumors with metastasis ability after surgery. Because surgery and radiotherapy are considered as the mainstay of treatment in this heterogeneous group of patients, targeted therapies are promising with the limited place of chemotherapy. The efficacy of these current agents should be randomized in larger series to be investigated.

Clinically, according to the metastasis ability of the breast mesenchymal tumors, we recommend the use of radiotherapy, chemotherapy, and/or targeted treatment protocols with multidisciplinary benefits, as a priority of surgery.

Conclusion

Heterogeneity is observed in mesenchymal tumors of the breast, and due to a wide spectrum of entities, it is important to plan treatment in a multidisciplinary manner. Localized disease can primarily be treated through surgery. Concerning locally advanced, metastatic, or inoperable disease, chemoradiotherapy and potential targeted therapies are predominantly used. Mitotic index and Ki-67 are indicators of the aggressiveness and capability of metastasizing of these types of tumors. New treatment plans should be developed based on tumor biology because this group of tumors is heterogeneous. Examination of the extremely rare entities of mesenchymal tumors of the breast provides an understanding of the more problematic cases in order to improve management of the condition as well as determine future courses of action, and for these rare entities further research is required and should be planned.

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