

Breast hamartoma: a clinicopathologic analysis of 27 cases and a literature review

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OBJECTIVES: Breast hamartoma is an uncommon breast tumor that accounts for approximately 4.8% of all benign breast masses. The pathogenesis is still poorly understood and breast hamartoma is not a well-known disorder, so its diagnosis is underestimated by clinicians and pathologists. This study was designed to present our experience with breast hamartoma, along with a literature review.

METHOD: We reviewed the demographic data, pathologic analyses and imaging and results of patients diagnosed with breast hamartoma between December 2003 and September 2013.

RESULTS: In total, 27 cases of breast hamartoma operated in the Ankara University Medicine Faculty's Department of General Surgery were included in the study. All patients were female and the mean age was 41.8 ± 10.8 years. The mean tumor size was 3.9 ± 2.7 cm. Breast ultrasound was performed on all patients before surgery. The most common additional lesion was epithelial hyperplasia (22.2%). Furthermore, lobular carcinoma *in situ* was identified in one case and invasive ductal carcinoma was observed in another case. Immunohistochemical staining revealed myoid hamartoma in one case (3.7%).

CONCLUSION: Breast hamartomas are rare benign lesions that may be underdiagnosed because of the categorization of hamartomas as fibroadenomas by pathologists. Pathologic examinations can show variability from one case to another. Thus, the true incidence may be higher than the literature indicates.

KEYWORDS: Breast; Hamartoma; Carcinoma.

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INTRODUCTION

Breast hamartoma is an uncommon breast tumor that accounts for approximately 4.8% of all benign breast masses (1) and that contains lobular breast tissue involving various fibrous, fibrocystic and adipose tissues (2). However, with increasing social awareness and widespread breast cancer screening, hamartomas are being routinely diagnosed with greater frequency. The pathogenesis of hamartomas remains unclear and its diagnosis is underestimated by clinicians and pathologists. In the literature, breast hamartoma is presented only in case reports and reviews of wide series are very rare. Thus, this study was designed to present the

clinicopathologic findings of twenty-seven patients with breast hamartoma.

METHODS

Between December 2003 and September 2013, 27 cases of breast hamartoma operated in the Ankara University Medicine Faculty's Department of General Surgery were included in this study. The histopathology records, clinical follow-up data and previous breast imaging results of the patients were obtained. These data were again analyzed and annotated by clinicians and pathologists.

RESULTS

Demographic features, tumor sizes, preoperative imaging procedures, pathologic results and treatment modalities are shown in Table 1. Clinically, most (24) patients had painless, soft-to-firm, palpable breast lumps and three patients had breast asymmetry. Breast ultrasonography (US) was performed on all of the patients as the first preoperative imaging procedure. In addition to US, mammography was performed in 6 cases and magnetic resonance imaging

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Table 1 - Demographics and clinicopathologic features of 27 patients with breast hamartoma.

Number of patients	27
Age, mean ± SD (min-max)	41.8 ± 10.8 (19-56 years)
Gender	Female (all)
Tumor size, mean ± SD (min-max)	3.9 ± 2.7 (0.3-15 cm)
Additional lesion	
Ductal epithelial hyperplasia	6 (22.2%)
Pseudoangiomatous hyperplasia	7 (25.9%)
LCIS	1 (3.4%)
IDC	1 (3.4%)
Myoid hamartoma	1 (3.4%)
SMA	+
CD34	+
Desmin	+
Preoperative evaluation	
Ultrasonography	27 (100%)
Mammography	6 (22.2%)
FNAC	4 (14.8%)
MRI	1 (3.4%)
Surgery	
Lumpectomy	27 (100%)
Mastectomy + SLNB	1 (3.4%), second surgery for IDC

SD: standard deviation, LCIS: lobular carcinoma *in situ*, IDC: invasive ductal carcinoma, SMA: smooth muscle actin, FNAC: fine-needle aspiration cytology, MRI: magnetic resonance imaging, SLNB: sentinel lymph node biopsy.

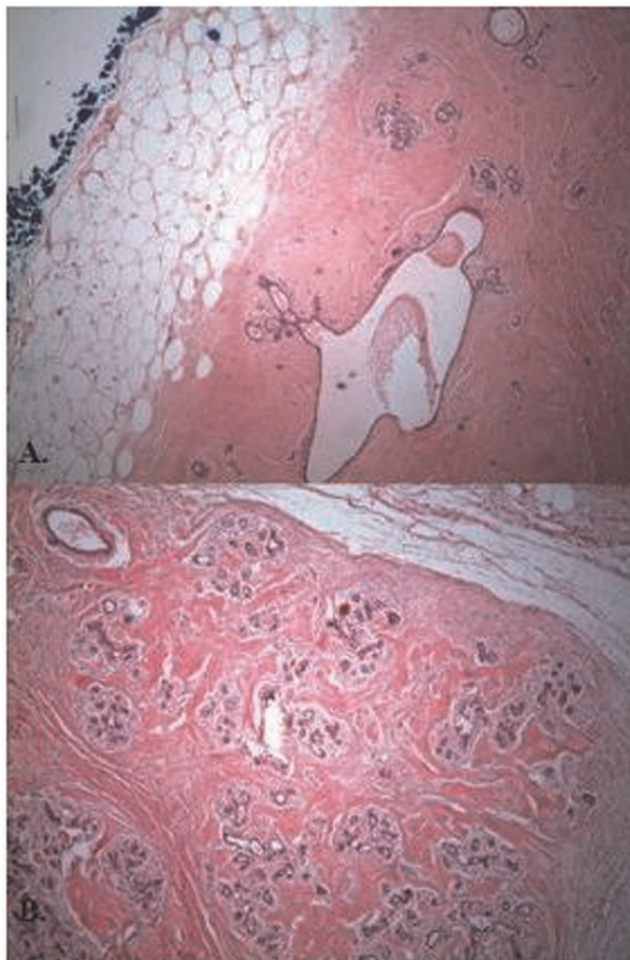


Figure 1 - (A) and (B) Well-circumscribed mass with normal terminal ductal lobular unit, fat and hyalinized stroma, Hematoxylin Eosin (H&E), ×40.

(MRI) was conducted in one case. In total, 23 cases showed features characteristic of fibroadenoma or hamartoma. In 4 patients (14.8%), US revealed a partial irregular border, and fine-needle aspiration cytology (FNAC) was performed and revealed benign lesions. Pathologic examination usually revealed a well-circumscribed mass with normal breast components, such as a terminal ductal lobular unit, fat and a hyalinized stroma (Figures 1A-B). The lesions usually showed fibrocystic changes, columnar cell changes and adenosis. No proliferative lesions were observed in 14 patients (51.9%). The most common additional proliferative lesion was ductal epithelial hyperplasia, which was diagnosed in 6 patients (22.2%) (Figure 2). We identified lobular carcinoma *in situ* (LCIS) in one case and invasive ductal carcinoma (IDC) in another case, near the breast hamartoma (3.7%). Pseudoangiomatous hyperplasia was observed in 7 cases (25.9%) (Figure 3). One case (3.7%) was pathologically reported as breast myoid hamartoma and this hamartoma stained positive for desmin, smooth muscle actin (SMA) and CD34 (Figures 4A-C). Mastectomy and sentinel lymph node biopsy were performed on the patient with IDC and lumpectomies were performed on the other patients.

DISCUSSION

Breast hamartomas are poorly defined, rare, benign breast neoplasms. Hamartomas were initially defined as mastomas in 1928 by Prym (3). Afterward, several cases were reported and classified as adenolipomas, fibroadenolipomas or lipofibroadenomas (4). Arrigoni et al. (5) first used the term hamartoma in 1971. Hamartoma is referred to as myoid hamartoma, a rarer form, when it shows a significant smooth muscle component. This term was first used by Davies and Riddell (6) in 1973.

Articles related to breast hamartoma in the literature are mostly case reports and rarely case series; therefore, they are

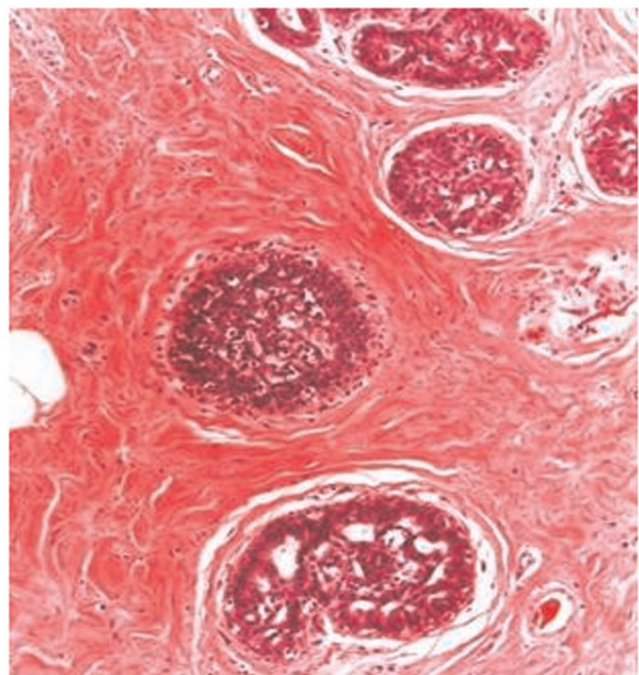


Figure 2 - Ductal epithelial hyperplasia, (H&E), ×100.

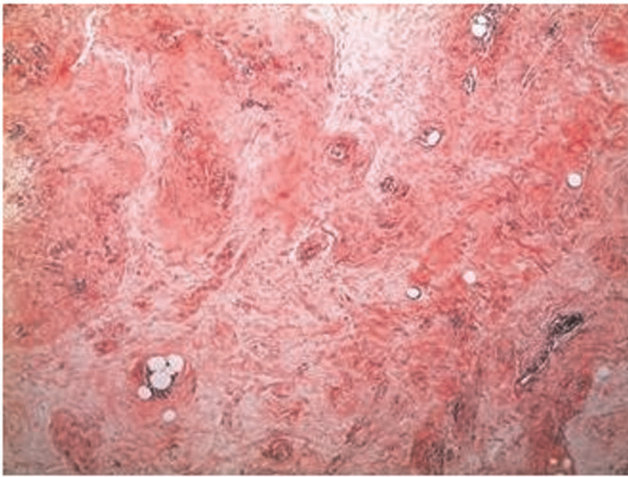


Figure 3 - Pseudo-angiomatous hyperplasia, (H&E), $\times 40$.

limited in number. Thus, there are few data about these tumors. We compiled the published case reports and case series in PubMed from between 1993 and 2013 in terms of demographic features, tumor size, applied imaging procedures, pathology reports and the results of additional staining, which are shown in Table 2 (7-43).

The incidence of breast hamartoma among benign breast tumors was reported to be 4.8% by Charpin et al. (1) in a large case series in 1994. In total, 27 hamartomas (3.1%) were diagnosed among 864 benign breast tumors at our center over the last ten years. In the literature (23,28,29,31,33, 34,37,40-42) the average age of the patients with breast hamartoma ranged between 33.5 and 66.5 years. In our study, the age range was from 19-56 years and the mean age was 41.8 years. There was only one patient under 20 years of age and 7 patients were over 50 years of age.

The etiopathogenesis of breast hamartomas is not clear but they are thought to result from dysgenesis (44) rather than a true tumorous process. However, female sex steroid hormones (34) have been implicated in the development of breast hamartomas. In one study, Herbert et al. (33) reported estrogen receptor (ER) and progesterone receptor (PR) positivity in epithelial cells and stromal cells in all 24 cases with breast hamartomas. Additionally, there are no clear data on the source of smooth muscle for myoid hamartomas, but this muscle could derive from vessels, the nipples, undifferentiated breast stromal tissue or myoepithelial cells (4,14). Another hypothesized smooth muscle source is the metaplasia of breast stromal cells (14) into smooth muscle cells. The existence of CD34 on smooth muscles (21,34) is an important sign of the metaplasia of stromal cells into smooth muscle cells, but there are no clear data on this subject. Myoid hamartomas stain strongly positive for SMA, desmin and vimentin (8) by immunohistochemical staining. In our study, only 1 patient of 27 was diagnosed with myoid hamartoma and immunohistochemical staining for desmin, SMA and CD34 was positive, consistent with the literature.

With increasing social awareness and the use of numerous diagnostic procedures on breast lumps, including mammography, ultrasound, and MRI, it is expected that more hamartomas will be reported. Breast hamartomas have a typical mammographic appearance. The radiolucent

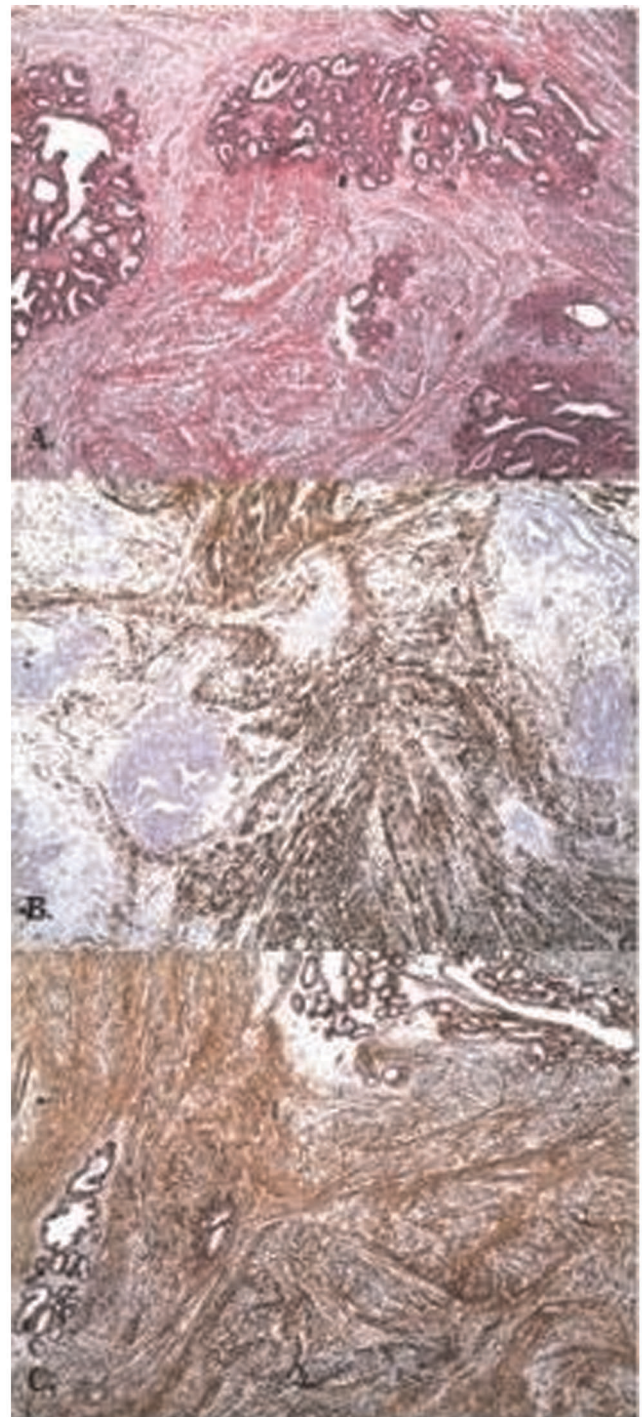


Figure 4 - Myoid hamartoma, (A) (H&E), $\times 40$ (B) desmin, $\times 40$, (C) SMA, $\times 40$.

lesions include fat; various amounts of fibrous and adenomatous tissues, with smooth rims; and occasionally, a thin capsule (4). US evaluates breast hamartomas as having sonolucent fat and a heterogeneous internal echo pattern with echogenic fibrous components (45). Alongside US, MRI characteristically shows a smooth and well-defined hypointense rim, internal heterogeneous enhancement and the presence of fat density (34). In the present study, US was



Table 2 - Literature review for breast hamartoma.

Author and year	Age, gender	Clinical findings	Size (cm)	US (n)	MMG (n)	MRI (n)	FNAC (n)	Pathologic findings (n)	Additional staining	Recurrence
Nasit et al., 2012 (7)	45, F	Lump	9	NR	Well-circumscribed, dense mass	NR	Few mammary lobules and ducts, with a fibrous stroma	Myoid hamartoma	Vimentin +, SMA +, Desmin +, ER, PR + Cytokeratin -, S-100 - CD34 -	No (one-year follow-up)
Mizuta et al., 2012 (8)	38, F	Lump	2.8	Well-demarcated, hypoechoic lesion with slightly irregular margins	Well-demarcated, oval, isodense mass that was partly indistinct (BI-RADS-4)	Well-circumscribed mass with high signal intensity, showing strong enhancement and a microlobulated margin. Dynamic contrast-enhanced imaging demonstrated rapid enhancement of the mass	Fibroadenoma with focal mastopathic change	Myoid hamartoma	SMA +, Vimentin +, Desmin + Cytokeratin -, S-100 -	NR
Kai et al., 2012 (9)	70, F	Lump	3.2	Irregular hypoechoic tumor both within and external to hamartoma	Typical hamartoma	Suspected malignancy	NR	Hamartoma DCIS IDC	NR	NR
Uchôa et al., 2010 (10)	59, F	Lump	2.5	NR	NR	NR	NR	NR	Vimentin +, Desmin +, CD34 + Calponin +, bcl-2 +, SMA - Actin -, S-100 -, CD99 -, CD10 -	NR
Choi et al., 2010 (11)	72, F	Lump	9	Spiculated, non-parallel hypoechoic nodule within hamartoma	Typical hamartoma with focal asymmetry	Suspected malignancy	NR	Hamartoma IDC	NR	No (2-year follow-up)
Ko et al., 2010 (12)	43, F	Lump	2.5	Irregular isoechoic mass with a microlobulated margin	Two oval isodense masses with a partially obscured margins in the left subareolar area	Suspected malignancy	Mammary lobules, ducts, and stroma No malignant component	Myoid hamartoma	Vimentin +, SMA +, CD34 +, S-100 -	Recurrence in the first year
Gupta et al., 2010 (13)	13, M	Lump	10	Solid heterogeneous mass with internal echogenic zones	NR	NR	Non-diagnostic	Hamartoma	NR	No (14-month follow-up)
Kajo et al., 2010 (14)	46, F	Lump	17	NR	NR	NR	Fibroadenoma	Myoid hamartoma	Desmin +, SMA +, Caldesmon +, CD34 -, S-100 -, CD 10 -	NR
Khoo et al., 2009 (15)	46, F	Lump	9	Solid breast mass	Dense, well-encapsulated mass with no calcifications	NR	Fibroadenoma	Myoid hamartoma, chondroid differentiation	Vimentin +, Myoglobin +, SMA + Desmin +, CD34 +, Cytokeratin -, S-100 -	NR



Table 2 - Continued.

Author and year	Age, gender	Clinical findings	Size (cm)	US (n)	MMG (n)	MRI (n)	FNAC (n)	Pathologic findings (n)	Additional staining	Recurrence
Pervatikar et al., 2009 (16)	25, F	Lump	15	NR	NR	NR	Malignant	Hamartoma IDC		No (one-year follow-up)
Lee WF et al., 2008 (17)	48, F	Lump	4.5	NR	Typical hamartoma	NR	NR	Hamartoma	NR	NR
Hernanz et al., 2008 (18)	29, F	Breast asymmetry	14	NR	Well-circumscribed mass	NR	Core biopsy; hamartoma	Hamartoma	NR	NR
Stafylia et al., 2007 (19)	60, F	Lump	11.5	Solid mass	Dense, well-defined mass	NR	NR	Myoid hamartoma	NR	No (4-year follow-up)
Murat et al., 2007 (20)	42, F	No complaints; MMG, US	5	Smooth-edged, solid mass lesion with heterogeneous echogenicity	Smooth-edged, heterogeneous, oval opacity and surrounding radiolucency	Mass lesion with heterogeneous intensity	Core biopsy; hamartoma	Hamartoma	NR	NR
Murugesan et al., 2006 (21)	45, F	Breast pain; MMG, US	1.6	Irregular hypoechoic, lobulated, ill-defined borders	Irregular, partly ill-defined lesion with no microcalcification	NR	Core biopsy; myoid hamartoma	Myoid hamartoma	SMA +, Desmin +, S-100 -	NR
Borges da Silva et al., 2006 (22)	33, F	Axillary mass	10	Compatible with the diagnosis of a voluminous nodule	NP	NP	NP	Hamartoma	NP	No (2-year follow-up)
Ruiz-Tovar et al., 2006 (23)	43.2 (mean), F, 8 cases	Lump (all)	7.25 (mean)	Heterogeneous mass with hypoechoic areas inside (2)	Well-circumscribed masses combining radiolucent and dense areas (all)	NR	Benign (5) Core biopsy; hamartoma (1)	Hamartoma (all)	NR	Recurrence in 1 patient (after 6 months)
Kuroda et al., 2006 (24)	57, F	Bilateral axillary lump	3.5, 3.3	NP	NP	NP	Incisional biopsy; hamartoma (1)	Bilateral hamartoma	NP	NP
Breucq et al., 2005 (25)	42, F	Lump	2	Well-circumscribed, oval heterogeneous nodule	Denser aspect	NP	NR	Myoid hamartoma, LCIS	NR	NR
Barbaros et al., 2005 (26)	36, F	Lump	15	Fibroadenolipoma	Fibroadenolipoma	NR	NR	Hamartoma	NR	NR
Gatti et al., 2005 (27)	43, F	Lump	4.5	Oval shape, well-circumscribed margins and internal echogenicity	No sign of disease	NR	NR	Hamartoma	NR	NR
Giannotti Filho et al., 2004 (28)	51 (mean), F, 3 cases	Lump	1.3 (mean)	Well-circumscribed lump	Well-circumscribed lump	NR	NR	Myoid hamartoma	SMA +, Vimentin +, Desmin +, S-100 -	NR



Table 2 - Continued.

Author and year	Age, gender	Clinical findings	Size (cm)	US (n)	MMG (n)	MRI (n)	FNAC (n)	Pathologic findings (n)	Additional staining	Recurrence
Lee et al., 2003 (29)	66.5 (mean), F, 2 cases	Axillary mass (1) MMG (1)	5.5 (mean)	Well-defined hypoechoic nodule within hamartoma (1) NP (1)	Typical hamartoma	NR	Malignant (1) NP (1)	Hamartoma, DCIS, IDC (1) Hamartoma, IDC (1)	NR	No (6-month follow-up) (1) No (5-year follow-up) (1)
Baron et al., 2003 (30)	54	Lump	5	NP (1) NR	Well-circumscribed, oval, mixed fatty and fibroglandular lesion	NR	Benign epithelial cells	Hamartoma ILC	High ER Low PR	NR
Tse et al., 2002 (31)	50 (mean), F, 2 cases	Lump	2 (mean)	Well-defined lobulated mass (1) NP (1)	NP Circumscribed mass with a thin pseudocapsule, no microcalcification, and no spiculation	NR	NP (1) Cellular atypia (1)	Hamartoma, DCIS (1) Hamartoma, DCIS, mucinous carcinoma (1) Hamartoma, ILC	NR	No (5-year follow-up) (1) No (4-year follow-up) (1)
Kuroda et al., 2002 (32)	53, F	Lump	6	isoechoic solid mass with capsule suspected to be a lipomatous tumor	Circumscribed mass with a thin pseudocapsule, no microcalcification, and no spiculation	NR	NR	Hamartoma, ILC	β -catenin -	NR
Herbert et al., 2002 (33)	48 (mean), F, 24 cases	Lump (all)	2-5 (range)	NR	NR	NR	NR	Hamartoma Focal apocrine metaplasia (in a few cases)	Pseudoangiomatous hyperplasia (7)	NR
NR										
Tse et al., 2002 (34)	38 (mean), F, 24 cases	Lump (23) Breast asymmetry (1)	3.8 (mean)	Typical hamartoma (18)	Mixed fibrous adipose tissue Ovoid-rounded, well-circumscribed masses of mixed heterogeneous density with a mottled center and thin smooth capsules with peripheral radiolucent zones	NR	Typical hamartoma (4) Well capsulated, with a dark smooth rim; ovoid in shape, with internal heterogeneity and heterogeneous gadolinium enhancement	Hamartoma (11) Non-diagnostic (3) Benign (7) More cellular (4)	NR	Recurrence in 1 patient (after 10 months)
Ravakhah et al., 2001 (35)	36, M	Lump	3	NR	NR	NR	Non-diagnostic	Hamartoma	NR	NR
Weinzweig et al., 2001 (36)	15, F	Breast asymmetry	27	Mixed echogenic pattern	NR	NR	NR	Hamartoma (lobular proliferation) Hamartoma (all) Calcifications (4) Ductal hyperplasia (9)	NR	NR
Wahner-Roedler et al., 2001 (37)	50 (mean), F, 35 cases	Lump (18) MMG (18)	3.2 (mean)	Solid hypoechoic lesion (12) Solid hypoechoic with definite cystic areas (5)	Irregular margin (1) Indistinct margin (4) Water density (21) Mixed density (2)	NR	Core biopsy; benign (3)	Hamartoma (all) Calcifications (4) Ductal hyperplasia (9)	NR	NR



Table 2 - Continued.

Author and year	Age, gender	Clinical findings	Size (cm)	US (n)	MMG (n)	MRI (n)	FNAC (n)	Pathologic findings (n)	Additional staining	Recurrence
Takeuchi et al., 2001 (38)	74, F	Lump	1.8	Oval-shaped hypoechoic mass with slightly irregular margin	Well marginated and oval-shaped isodense nodule with no microcalcification	NR	NR	Myoid hamartoma	SMA +, S-100 -, Myoglobin -, Keratin -, Vimentin -	NR
Mester et al., 2000 (39)	59, F	Lump	7	NR	Circumscribed, predominantly fatty mass. Multiple macro- and microcalcifications were contained in the mass	NR	Nondiagnostic	Hamartoma DCIS	NR	NR
Chiacchio et al., 1999 (40)	40.4 (mean) F, 10 cases	Lump	5.4 (mean)	NR	Nodular densities	NR	NR	Hamartoma	Pseudoangiomatous hyperplasia	CK +, S-100 +, Vimentin +
Blomqvist et al., 1997 (41)	NR 33.5 (mean), F, 2 cases	Lump (1) Breast asymmetry (1)	NR	NP	NP	NP	Benign hamartoma (1) Benign (1)	Hamartoma	NP	NR
Anani et al., 1996 (42)	65.5 (mean), F, 2 cases	Lump, skin ulcer (1) Lump (1)	6 (mean)	Hypoechoic absorbing lesion suggestive of carcinoma (1)	Typical hamartoma with irregular opacity containing microcalcifications (1) Typical hamartoma with spiculated mass (1)	NR	NR	Hamartoma IDC (all)	NR	NR
Garfein et al., 1996 (43)	50-59 (range), F, 6 cases	Lump (3) MMG (3)	1.1-7 (range)	Solid lesion (4)	Well-circumscribed lesion (1) Heterogeneous radiodensity (4) Homogeneously radiodense (1) Slightly irregular border (1)	NR	Nondiagnostic (1)	Myoid Hamartoma	Actin +, Desmin +, Vimentin +, Cytokeratin -, S-100 +	No (follow-up of 2-19 months)
This study	41.8 (mean), F, 27 cases	Lump (24) Breast asymmetry (3)	3.9 (mean)	Well-circumscribed, oval heterogeneous nodule (23) Slightly irregular margin(4)	Typical hamartoma (5) Malignant lesion (1)	Malignancy (1)	Benign (4)	Hamartoma (26) Myoid hamartoma (1) IDC (1) LCIS (1)	SMA + (1), Desmin + (1), CD34 + (1)	No recurrence to date

F: female, M: male, NR: not reported, NP: not performed, SMA: smooth muscle actin, ER: estrogen receptor, PR: progesterone receptor, DCIS: ductal carcinoma *in situ*, LCIS: lobular carcinoma *in situ*, IDC: invasive ductal carcinoma, ILC: invasive lobular carcinoma.



used for all patients as the first imaging procedure and in addition to US, mammography was utilized for 6 patients. MRI was used only for 1 patient with IDC.

The pathologic features of hamartomas are not well known. The original definition consisted of a fibrous fatty stroma including various amounts of epithelial elements, as well as nodular lesions. The fibrous and fatty tissues were used for the early classification of hamartomas: McGuire et al. (46) classified breast hamartomas as fibrous, fatty or fibrous-fatty. Jones et al. (47) suggested 4 classification groups for breast hamartomas: encapsulated fibrocystic changes, fibroadenoma with a fibrous stroma, fibroadenoma-like and surrounded adenolipoma. These classifications were not widely accepted. No criteria with detailed explanations of breast hamartomas are used by pathologists. Fechner et al. (48) described the lobular distribution and the presence of fat in breast hamartomas as distinguishing features compared with fibroadenomas. A fibrotic stroma surrounding the lobules and extending into the interlobular areas, causing obliteration, is the most frequently observed feature; most authors (2,47,48) refer to this feature as interlobular fibrosis. However, interlobular fibrosis is not specific to breast hamartomas. In sclerosing hyperplasia, an increasing number of interlobular glands are observed as round masses with interlobular fibrosis, which can mimic breast hamartomas. The absence of fatty tissue in the stromal structure is often associated with fibroadenomas, so this condition can be distinguished from sclerosing lobular hyperplasia and breast hamartomas (33,34,45). Fischer et al. (2) defined the presence of a pseudoangiomatous stroma particularly in breast hamartomas. This condition was revealed to be a consistent observation in subsequent reports and the incidence rate (34,49) varied between 16 and 71% (34). We also found the rate to be 25.9% in our series, in line with the literature.

Malignancies associated with breast hamartomas (9,11,16,29,31,42,50) are rarely observed, and only a few studies have reported invasive breast cancer associated with breast hamartoma. We identified IDC in only 1 case and LCIS in 1 other case. Although epithelial hyperplasia is not a characteristic feature of breast hamartomas, ductal epithelial hyperplasia was identified in 6 cases (22.2%). Wahner-Rodler et al. (37) reported this incidence rate as 26% in their large case series. These high coincidence rates are very important. Patients with a certain or suspected diagnosis of hamartoma must be operated and these patients should never be followed, even if their tumors are small.

In conclusion, we present our institutional experience with breast hamartomas in 27 patients. Although breast hamartomas are rare, benign lesions, these lesions can reach large sizes. A diagnosis can be made by core needle biopsy, along with an appropriate correlation of clinical and radiologic features. Breast hamartomas may be underdiagnosed because pathologists may categorize these lesions as fibroadenomas instead of hamartomas. Thus, the true incidence may be higher than the literature indicates.

■ AUTHOR CONTRIBUTIONS

Sevim Y and Genc V conceived and designed the study. Sevim Y, Kocaay AF, Eker T, Celasin H, Karabork A and Erden E were responsible for data acquisition. Sevim Y, Karabork A, Erden E and Genc V were responsible for data analysis and interpretation. Sevim Y, Celasin H, Karabork A, and

Genc V were responsible for the manuscript writing. Kocaay AF, Eker T, Karabork A and Erden E were responsible for the figures.

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