BREAST FIBROADENOMAS: ULTRASOUND APPEARANCE AND POTENTIAL ASSOCIATION WITH PERIPHERAL VEIN THROMBOSIS

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BREAST FIBROADENOMAS: ULTRASOUND APPEARANCE AND POTENTIAL ASSOCIATION WITH PERIPHERAL VEIN THROMBOSIS (Abstract): The **aim** of this study was to characterize the ultrasound appearance of breast fibroadenomas and explore a potential association with peripheral vein thrombosis. **Materials and methods:** We retrospectively studied between January 2021 and December 2022 the imaging records and reports of 159 women with fibroadenomas who underwent breast ultrasound (US) with an 11-18 MHz linear transducer and 7 of them lower extremity US for suspicion of peripheral vein thrombosis with an 11-18 MHz linear or a 3-6 MHz curved transducer. **Results:** We found a total of 293 fibroadenomas, and the most frequent pattern was: isoechoic (69.62% lesions), homogenous (77.47% lesions), with well-defined (100%), macrolobulated margins (51.88%), oval-shaped (95.22% tumors), with a Solbiati index greater than or equal to 2 (51.19%), without Doppler signal (73.72%). We studied the correlation between the Doppler signal and contour pattern, the number of lobulations, and the Solbiati index using a function in Python, and we found the following results: the dimensions of the fibroadenoma (r = 0.117438) and the number of lobulations (r = 0.282) have a positive correlation, but the Solbiati index (r = -0.012) and contour pattern (r = -0.243945) have a negative correlation with the presence of the Doppler signal. The association of multiple breast fibroadenomas with peripheral vein thrombosis was rare (7.46% cases). We monitored 147 patients with simple fibroadenomas every six months for two years, and none of them had a significant variation in the dimensions. **Conclusions:** The association of multiple breast fibroadenomas with peripheral vein thrombosis was rare, so we considered it to be a random association. In our study, the most frequent pattern of fibroadenomas was isoechoic, homogenous, oval-shaped lesions with macrolobulated margins, a Solbiati index greater than or equal to 2, and no Doppler signal. According to our experience, we offered, for typical fibroadenomas, the option of conservative management. A fine needle biopsy was advised in one case with atypical-appearance lesions at ultrasound.
Keywords: FIBROADENOMAS, VEIN THROMBOSIS, ULTRASOUND.

INTRODUCTION

Fibroadenomas are benign lesions with minimal or no malignant potential (malignant transformation 0.01-0.3%), frequent between ages 15 and 35, with predilection for the upper outer quadrant, and a slightly

variable dimension in time or with the period. There are at least two special types of breast fibroadenomas: complex fibroadenomas (which can grow over time) and giant fibroadenomas (growing quickly to a diameter larger than 5 centimeters) (1). Multiple fibroadenomas account for 20% of breast fibroadenoma cases, and their management presents particular challenges because they may have other associated diseases and it is difficult to follow up on every single lesion (2, 3).The cause of fibroadenomas is not known, but the relationship with ovarian hormones is considered important. Simple fibroadenomas are predominantly encountered in women of reproductive age (the incidence is 7-13% in women from adolescence through the mid-20s) (4). The hormonal fluctuations during the menstrual cycle, puberty, pregnancy, menopause, and oral contraceptives increase the risk of fibroadenomas, may stimulate fibroadenomas' growth, and increase the risk for peripheral vein thrombosis (2, 5). Typically, ultrasound depicts a round or ovoid, homogeneous, hypoechoic, well-circumscribed, or macrolobulated mass; intralesional calcification in (~10% of cases) and a thin echogenic rim (pseudocapsule) may be seen (6). Mammography and MRI contribute to the diagnosis (7, 8). When a lesion has the typical features of a fibroadenoma on ultrasound and there are no clinical issues, it can be safely followed. When lesions enlarge or have atypical imaging findings, an ultrasound-guided core biopsy will give a diagnosis (9).

MATERIALS AND METHODS

We retrospectively studied between January 2021 and December 2022 the imaging records and reports of 159 women with fibroadenomas who underwent B mode and Doppler mode breast US with an 11-18 MHz linear transducer and 7 of them lower extremity US for suspicion of deep vein thrombosis with an 11-18 MHz linear or a 3-6 MHz curved transducer (which provides a deeper field view) using a General Electric Voluson E6 ultrasound machine.

Breast US study protocol included bilateral examination with transversal, longitudinal, radial, and antiradial sections of the breast and evaluation of the axillary, subclavian, supraclavian, and internal mammary regions; the patient is lying down in supine position (with right and left oblique rotation in case of large breasts), with the hands above the head (for better exposure of the breast and evaluation of internal mammary and axillary regions), and with the hands nearby the body (for the examination of subclavian and supraclavian regions). For a better visualization of the pathology, the focal zone of the probe must include the lesion, the power of the ultrasound waves, time gain compensation, and gain carefully adjusted for optimal visualization of the deep structures of the breast, for compensating the rapid attenuation of the waves when high frequencies are used, and for well-differentiating the solid and cystic lesions, respectively. The compression of the lesions with the transducer is useful to determine the hardness of the solid ones and to demonstrate the mobility of the internal echoes of the cysts.

The ultrasound report must include the exact location of the lesions, echogenicity (compared with the fatty tissue), number, dimensions (at least two: the longest dimension and the transversal dimension), structure, compressibility, associated acoustic changes, and Doppler signal characteristics. This study was focused on lesion number,

echogenicity, the longest dimension (L), ratio between the longest (L) and the transversal (T) dimensions (L/T ratio, Solbiati index), structure, presence and location (central and peripheral) of the Doppler signal, and lesion growth over time.

If after the first ultrasound examination the patient had lesions with a typical pattern for fibroadenomas, we indicated follow-up at a 6-month interval, and if the lesions did not grow more than 10%, we considered them to be stable, and the diagnosis of fibroadenoma was made with confidence. Conservative treatment with follow-up every 6 months for 2 years was applied. If, in time, one of the fibroadenomas grows more than 10%, we return to a 6-month follow-up for another two years. If the lesions have an odd feature (anechoic components, micro calcifications, poorly defined margins), the patient was referred to a fine needle biopsy to correlate with morpho-pathology.

Ultrasound examination for lower limb deep vein thrombosis was extended from the common femoral vein to the anterior tibial, posterior tibial, and peroneal veins, with transversal and longitudinal sections and segmental compression every 2 cm. The patient lies down in supine position with the head elevated to help with venous pooling, and the examined leg is externally rotated with the knee slightly bent (for better access to the femoral and popliteal veins) (10, 11).

RESULTS

We studied 159 women, age range17 to 74 years, who had 293 fibroadenomas, among them 67 had multiple fibroadenomas, and we studied the US pattern of the lesions, the associated breast diseases (fibrocystic breast disease, mammary duct ectasia) and peripheral vein thrombosis (which was found in 5 cases).Most of the woman (121 -76.10%) had at diagnosis ages between 26 and 49 years, accordingly to the literature (1)(fig. 1).

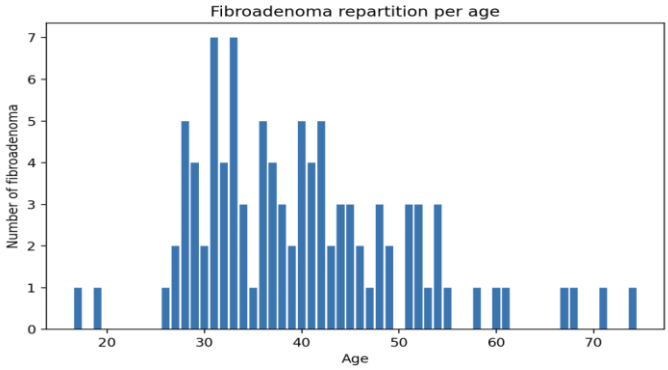

Fig. 1. Number of fibroadenomas - repartition per age

The average number of fibroadenomas was 1.85 per person, and the highest number of lesions was in the case of a 21-year-old woman (7 lesions). Among the 159 patients, we found 92 (57.86%) (age range 27 to 60 years) with a single fibroadenoma and 67 (42.14%) (age range 27 to 50 years) with multiple fibroadenomas, most of them associating fibrocystic breast disease (61.95% and 76.11%, respectively), and 62 (38.99%) presented mammary duct ectasia.

In the case of 7 patients with multiple

fibroadenomas, we also depicted lower extremity edema and referred them to the cardiologist, who found at clinical examination unilateral lower extremity edema, tenderness, erythemas or cyanosis, dilated superficial veins, palpable thrombotic veins, and suspected deep vein thrombosis of the lower extremity confirmed by B mode and Doppler mode US in 5 cases. The association of multiple breast fibroadenomas with peripheral vein thrombosis was rare (7.46% cases), so we considered it to be a random association, results that are similar to the literature data (12) (fig. 2).

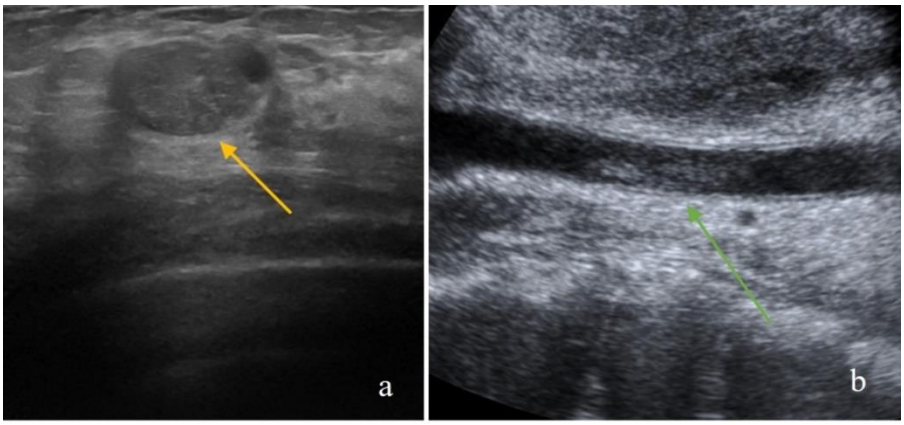

Fig. 2. B mode breast ultrasound- isoechoic, macrolobulated, oval shaped inhomogeneous (yellow arrow) fibroadenoma (a); B mode thigh ultrasound femoral vein thrombosis

The most frequent pattern of fibroadenomas was: isoechoic (204-69.62% lesions), homogenous (227-77.47% lesions), with well-defined (100%), macrolobulated margins (152-51.88%), oval-shaped (279-95.22%) tumors, with a Solbiati index greater than or equal to 2 (150-51.19%), and without Doppler signal (216-73.72%). A small number of tumors were round 14 (4.78%), with Solbiati index smaller than 2 (142-48.46% cases), microlobulated (42-14.33%) or regular (99-33.79%) margins, hipoechoic (89-30.38%), and inhomogenous structure in 66-22.29% of lesions (the most special types of inhomogeneities being macrocalcifications 4.09%, microcalcifications 1.70%, or anechoic inclusions 1.70%). In our study, most of the tumors had the largest diameter smaller than 2 cm (255-87.03%), and only 38 (12.97%) tumors had L diameter between 2 and 7 cm; 77 (26.28%) had Doppler signal present (mostly peripheral, 47-16.04%) (fig. 3). Microlobulated margins (found in 14.33% of the tumors) are considered in the literature a problem for a confident diagnosis of fibroadenoma, but the microlobulated lesions did not grow over time, so in the end, this pattern was also included in benign lesion features (6). No lymphadenopathies were found.

One special case was a 27-year-old female who had four hypoechoic lesions: two lesions were simple fibroadenomas (followed-up at a 6-month interval for 24 months), and two mases had an uncertain appearance (hypoechoic, inhomogeneous, one of them containing an irregular anechoic area, and the other one with microcalcifications) and were referred to a fine needle biopsy, which established the diagnosis of complex fibroadenomas (fig. 4).

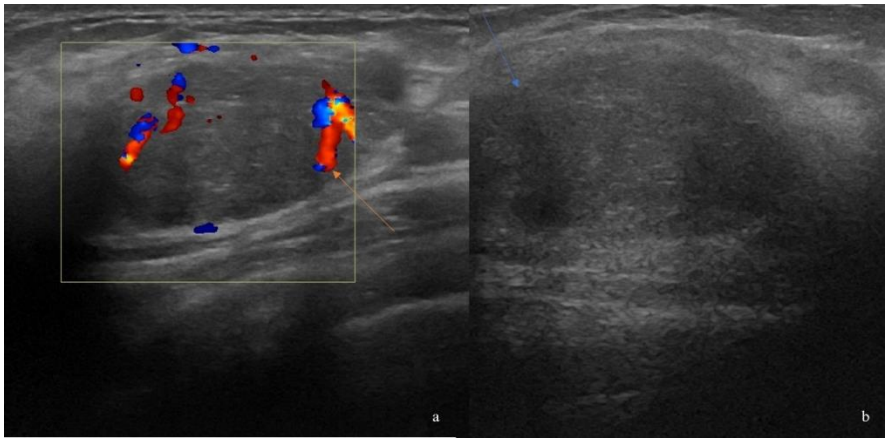

Fig. 3. B and Doppler mode breast ultrasound: isoechoic, well-circumscribed fibroadenoma with central and peripheral Doppler signal (orange arrow) (a); B mode breast ultrasound: isoechoic fibroadenoma, with macrolobulated margins (blue arrow) (b)

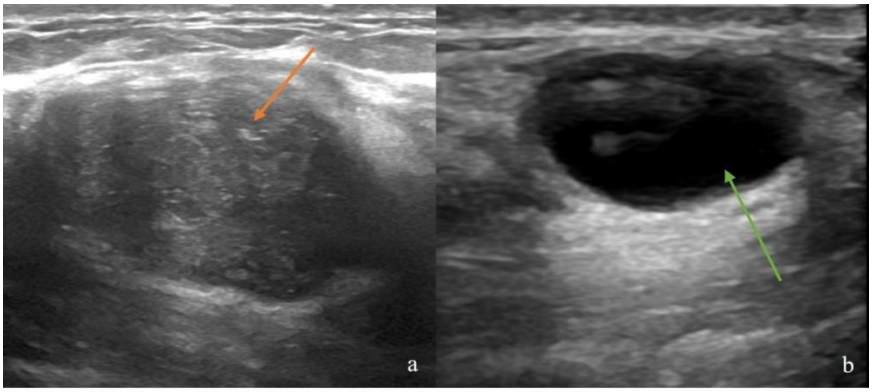

Fig. 4. B and Doppler mode breast ultrasound, BI-RADS 4a lesions: hypoechoic, macrolobulated, oval shaped lesion, with microcalcifications (orange arrow) (a); inhomogeneous hypoechoic, microlobulated, oval shaped lesion, containing an irregular anechoic area (green arrow) (b)

We studied the correlation between the Doppler signal and the following features of the lesions: contour pattern (regular or lobulated margins), number of lobulations, dimensions, and length-to-thickness ratio using a function in Python that has the following definition: correlation is used to summarize the strength and direction of the linear association between two quantitative variables. It is denoted by r and has values between -1 and +1. A positive value for r indicates a positive association, and a negative value for r indicates a negative association. We found the following results: lobulated margins (r = -0.243945), the number of lobulations (r = 0.282), dimensions (r = 0.117438), and length-to-thickness ratio (r = -0.012), and we concluded that the larger the dimensions of the fibroadenoma and the higher the number of lobulations will corre-

late with the presence of the Doppler signal; the length-to-thickness ratio and contour pattern have a negative correlation with the Doppler signal.

To correlate Doppler signal with three variables at once (contour pattern, number of lobulations, and dimensions), we used the algorithm Ordinary Least Squares Regression, and the most interesting of all results was the coefficient (Coef), which suggests a moderately positive correlation between Doppler signal and the number of lobulations (tab. I).

According to all the features we had studied, we concluded that 182 (62.12%) patients had simple fibroadenomas, which had to come for follow-up every 6 months for two years; nine (3.07%) patients with complex fibroadenoma and one (0.34%) patient with a giant fibroadenoma came every 3 months for 6 months, and then at a 6-month interval, and one (0.34%) patient with an uncertain lesion was referred to a fine needle biopsy, which confirmed the diagnosis of complex fibroadenoma (13). The compliance for follow up was good enough: we monitored 158 lesions for at least 2 years; among them most fibroadenomas (116-73.42%) had stationary dimensions, 23 (14.56%) fibroadenomas were increasing in size, 14 (8.86%) fibroadenomas had decreasing sizes, 5 (3.16%) fibroadenomas had variable size over time (increasing and decreasing) (fig. 6).

TABLE I.

Correlation between Doppler signal and contour pattern, number of lobulations and dimensions with Ordinary Least Squares Regression algorithm

Doppler signal	Coef.	Std. errs.	T
Dimensions (cm)	0.048	0.049	0.981
Contour pattern	-0.048	0.233	-0.207
No. of lobulations	0.379	0.167	2.267

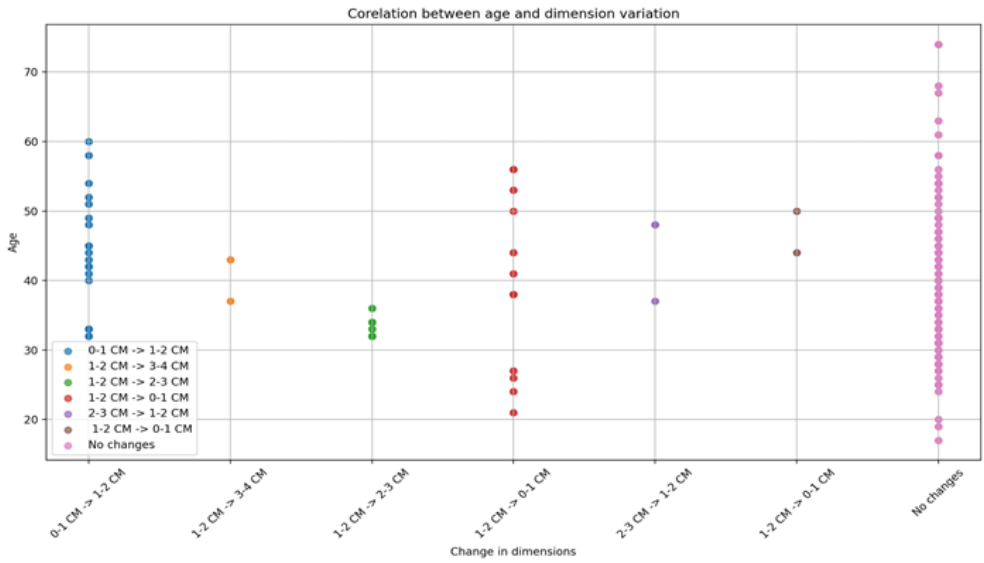

Fig. 6. Correlation between age and dimension variation over time

DISCUSSION

The most frequent pattern of fibroadenomas was isoechoic, homogenous oval-shaped lesions with a Solbiati index greater than or equal to 2, well-defined margins, and no Doppler signal, which was similar to the literature data (4). Other features of the lesions were discordant with the literature data: macrolobulated margins (51.88%) were more frequent than regular margins (33.79%) (1).

The association between multiple breast fibroadenomas and peripheral vein thrombosis was rare (5-7.46% cases), so we considered it to be a random association, despite the fact that both lesions have hyper estrogenism among the etiology (12).

Most of the lesions were homogeneous, slightly inhomogeneous, or contained macrocalcifications; only 10 (3.38%) tumors had microcalcifications or anechoic inclusions, which raised the suspicion of complex fibroadenomas and indicated follow-up at a 3-month interval (nine cases) and a fine needle biopsy (in one case) (4).

Most of the tumors had the largest diameter smaller than 2 cm (87.03%), and the number of tumors with diameters between 2 and 7 cm was fewer (12.97%), according to the literature data (9). The only lesion considered to be a giant fibroadenoma was an isoechoic 7/3 cm tumor with central Doppler signal present in the case of a 29-year-old woman, which was followed up initially at 3 months with insignificant growth (0.5 cm) over this period of time.

We studied the correlation between Doppler signal and contour pattern, number of lobulations, largest dimensions, and length-to-thickness ratio using a function in Python; lobulated margins ($r = -0.243945$) and Solbiati index ($r = -0.012$) have a negative correlation, but the number of lobulations ($r = 0.282$) and lesions' largest dimension ($r = 0.117438$) have a positive correlation with the presence of Doppler signal.

In terms of follow-up, our data were similar to those in the literature (13). We managed to monitor the simple fibroadenomas (according to the compliance of the patients) in 147 cases every 6 months for two years, and none of them had a significant variation of the dimensions in order to raise diagnostic issues; nine with complex fibroadenomas and one with giant fibroadenoma came every 3 months for 6 months, and then at a 6-month interval for two years, and one patient with complex fibroadenomas was referred to a fine needle biopsy.

CONCLUSIONS

The association of multiple breast fibroadenomas with peripheral vein thrombosis was rare, so we considered that a random association.

In our study, the most frequent pattern of fibroadenomas was an isoechoic, homogenous oval-shaped lesion with a Solbiati index less than 2, well-defined macrolobulated margins, and no Doppler signal. A small number of tumors were round, microlobulated, hypoechoic, with inhomogeneous structure due to macrocalcification, microcalcifications, or anechoic inclusions, with a Solbiati index larger or equal to 2, and a Doppler signal present, mostly in the periphery of the lesions. Most of the tumors were smaller than 2 cm; less frequently, we encountered tumors with the largest diameters between 2 and 7 cm.

We found, using a function in Python, that the Doppler signal has a negative correlation with lobulated margins and the L/T ratio and a positive correlation with the

number of lobulations and lesions' largest dimension.

According to our experience when offered the option of conservative management, in our study, most women preferred follow-up and not biopsy. A fine needle biopsy was advised in one case with atypical-appearance lesions at ultrasound.

CONFLICT OF INTEREST AND FUNDING

The authors declare no conflicts of interest. This research received no external funding.

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