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Biopsied breast masses in adolescents. Analysis of clinical features

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ABSTRACT

Objective: Breast lesions in childhood are mostly benign and self-limiting, and the biopsy indications are restricted in this period. The differentiation between fibroadenomas and phyllodes tumors is difficult with imaging because of their overlap in initial size and growth rate. Therefore, biopsy or excision may be required.

Material and Methods: We retrospectively reviewed data from 531 patients (404 females, 76.1%; 127 males, 23.9%) that were applied to our center between 2009 and 2019. Breast US was performed to all applicants with pain and swelling in the their breast. Patients with fibroadenoma with and without core biopsy were recorded.

Results: Thirty-one solid breast lesions were detected. Twenty-one lesions were performed biopsy (21/531, 3.9 %). The most common mass lesion was fibroadenoma (27/31, 87.1%) and the most frequently biopsied lesion was fibroadenoma (11/21; 52.3%). The 10 simple fibroadenomas, one juvenil fibroadenoma, one benign phyllodes tumors, and two invasive ductal carcinomas have been identified. A statistically significant difference ($p < 0.05$) was detected between the groups with or without core biopsy for the size of fibroadenomas, but there was no statistically significant difference between both groups for patients' age with fibroadenoma.

Conclusion: Malignancies in the breast and lesions such as fibroadenoma that requires a malignancy exclusion are observed in children and adolescents. Large size is a statistically significant parameter in the biopsy decision.

Keywords: child, adolescent, breast, biopsy, fibroadenoma

INTRODUCTION

Breast lesions in childhood are mostly benign and self-limiting (1). Biopsy indications are limited, as they have adverse effects on breast development (1,2). Therefore, radiological findings gain more importance. Those radiologists know normal breast development and pathologies, like clinicians do, can improve the correct management of the process.

Ultrasonography (US) is the primary and major imaging method in childhood (1,2). Mammography is not beneficial in this age group, and it has radiation. Magnetic resonance imaging (MRI), on the other hand, is useful in the evaluation of some malformations and rare breast malignancy (1,2). Not only that; the Breast Imaging Reporting and Data System (BI-RADS) classification, which is useful in breast lesions, is not preferred in children due to the extremely rare occurrence of malignant lesions (0.08/100000 in female younger than 20 years) (3).

Fibroadenoma is the most common pediatric breast mass (4). The various subtypes of fibroadenomas as juvenile and giant fibroadenoma occur in childhood. Fibroadenomas and phyllodes tumors are clinically and sonographically similar. Phyllodes tumors are usually benign but can be borderline and rarely malignant (5). Macrolobulations and microcystic components are suggestive to phylloides tumor on US (6). The phyllodes tumors have more likely than fibroadenomas to rapid growth and large initial size (7). Biopsy can be required for differential diagnosis.

In this study, we discussed factors affecting the breast biopsy decision in fibroadenomas and results of the biopsy in children and adolescents.

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MATERIAL and METHODs

The study was conducted in accordance with the principles of the Helsinki Declaration. As a routine procedure, written informed consent was obtained from each patient for all procedures and publication. Ethics committee approval was received for this study from the Clinical Trials Ethics Committee (2020 / GOKAE / 682).

We retrospectively analyzed the data of 531 patients aged 1-19 years who underwent breast imaging in our center between 2009 and 2019. We saw that all patients had been evaluated with US. Three patients had breast MRI (1.5 Tesla MRI device, General Electric Signa HDx, GE Medical Systems, USA) but none of them had mammography. We used adult breast disease criteria for BI-RADS 3-5 lesions. In cases where there is more than one lesion, we evaluated the largest lesion.

Sonographic assessment and US- guided biopsies

Ultrasonography was examined using a 13 MHz superficial probe and a Hitachi Ezu-MT28-S1 model (Hitachi Inc.Japan) device by an experienced breast radiologist. In US-guided core needle biopsy procedures, 16 gauge tru-cut automatic biopsy needles (Estacore® Geotek Healthcare Products, Turkey) were used. The same radiologist performed the biopsies.

Immunohistochemical analysis

Breast cancers were grouped by hormone receptors into four molecular subtypes. The status estrogen (ER) and progesterone receptors (PR), human epidermal growth factor 2 (HER 2), and Ki 67 index were evaluated.

Statistical analysis

Data were evaluated in the IBM SPSS Statistics 22.0 statistics package program. In addition to descriptive statistical values, we confirmed a normal distribution for age and lesion size between undergoing biopsy and without biopsy in patients with fibroadenoma by Kolmogorov–Smirnov test. Subsequently, independent samples t-test was applied, which is a parametric test. We considered it statistically significant if the P value was <0.05.

RESULTS

The mean age of all cases was 14 ±5.7. 196 (36.9%) of 531 cases who applied were evaluated as completely normal since neither developmental, nor physiological, nor pathological findings were detected. Benign physiological or developmental changes were detected in 191 cases (35.9%). Of these, 182 had early or normal development, 3 had asymmetry, and 6 had neonatal hypertrophy. Gynecomastia (n=82) and adipomastia (n=14) cases were added to this group. Two patients with axillary involvement were reported. Patients diagnosed with Burkitt lymphoma and cat-scratch disease were excluded from the study.

Forty eight mass lesions were detected in 48 patients (9.0 %), (**Table 1**) as BI-RADS 0. Additionally, one patient was reported as BI-RADS 4 and another as BI-RADS 5 (0.4%). Twenty-one patients (3.9%) underwent breast biopsy (**Table1**). FNAB was applied to 4 patients (19 %) in total. These were cases with a prediagnosis of cyst and mastitis (n=2), upon the request of the family and clinician, and two male cases with unilateral gynecomastia. A total of 17 people (80.1 %) underwent core biopsy (**Table 2**). Four (4/17; 23.5 %) masses showed greater than 20% interval growth before tissue diagnosis, with imaging intervals ranging from 6 months to 2 years, and one of these was a benign phyllodes tumor. Two patients had axillary lymphadenopathy (n=2), and the other two had a suspected malignant mass (n=2). All patients who underwent core biopsy were women.

Only 2 of 21 biopsies were performed on male patients. Fibroadenoma was the most common mass lesion (27/48, 56.25%) and the most frequently biopsied lesion (11/21; 52.4%) as well. The mean age of patients with fibroadenoma was 15.5 ± 3.4 (11–19). The mean age of patients who underwent core biopsy was (15.9 ± 2.2); the mean age of the others 15 was (15.4 ± 1.8) in patients with fibroadenoma. There was no statistically significant difference between both groups (p=0.556). The mean sizes of fibroadenomas with 11 core biopsies were 35.4 ± 10.9 (24-46) mm, while the mean size of fibroadenomas that did not undergo biopsy was 16.1 ± 4.2 (8-24) mm. There was a statistically significant difference between the groups (p<0.001).

Both of our primary breast cancer cases were ER positive. A 19-year-old patient with high Ki 67 index (40%) was HER2 positive, and her molecular subtype was luminal B. Tumor's size was 4 cm, and there were multiple lymph nodes with impaired hilus-cortex relations and compatible with metastasis. Two aunts of the patient had a history of breast cancer in the premenopausal period. Chemotherapy and radiotherapy were given to the patient who underwent breast conserving surgery and axillary dissection. The protective chemotherapeutic agent (transtuzumab) was continued in the following year. However, due to recurrence in the same breast at the end of one year, a mastectomy was performed.

The other 17-year-old patient with molecular subtype luminal A had a tumor size of 2 cm and a negative axilla. BRCA 1 and 2 were negative. Breast conserving surgery was performed. After chemotherapy and radiotherapy, prophylactic antiestrogen therapy was started. Clinical, radiological and laboratory findings were normal during the four-year follow-up period.

Table 1: Distribution of developmental anomalies, benign and malignant pathologies by gender.

	Female (n)	Male (n)
Neonatal hypertrophy	6	-
Early or normal development	182	-
Asimetry	3	-
Gynecomastia	-	82
Adipomastia	-	14
Fibroadenoma	27	-
Phyllodes tumor	1	-
Cyst	18	-
Mastitis	3	1
Malignancy	2	-
Other *	2	-

*: Burkitt lymphoma , Cat-Scratch disease

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Table 2: Gender and diagnosis distribution of patients that underwent fine needle aspiration and core biopsy.

	Female (n)	Male (n)
Fibroadenoma	11	-
Phyllodes tumor	1	-
Mastitis	2	-
Malignancy	2	-
Gynecomastia	-	2
Cyst	1	-
Other *	2	-

*: Burkitt lymphoma, Cat-Scratch disease

DISCUSSION

In childhood, lesions that most frequently require biopsy are fibroadenomas, which are also the most common lesions. However, even a little, biopsy is performed due to malignancy, granulomatous and lymphoproliferative diseases, too. We showed that patient's age does not affect the biopsy decision of fibroadenomas but large lesion size is a statistically significant parameter in this study.

It has been reported in various series that the most common pediatric breast mass is fibroadenoma (54% - 94%) (8-11). Because these masses are estrogen sensitive, they are not usually seen before puberty (12). The management of the pediatric breast masses has a wide spectrum. In this period, the management strategies show differences for BI-RADS 3 lesions from adult management (2,13,14). The frequency of sonographic follow-up is shorter, and the referral size of surgical resection is larger than adults. It is stated that a 20% increase in size in six months during the follow-up period cannot be accepted as in adults (10). It is argued that doubling of the lesion size in children should be an indication for biopsy. The size increase in our patients was between 20 and 50%. On the basis of the recommendations for surgical resection, size cutoffs of 4 cm or 5 cm (2,13,14). However the sensitivity is around 67% for the detection of phyllodes tumors.

While taking a biopsy decision, risk factors such as family history; are taken into consideration. The primary criteria in the biopsy decision are the presence of one or more of the features such as the first dimension being above 3 cm, inhomogeneous internal echo, increased size during follow-up, increased vascularization and lobulation, millimetric cystic components and microcalcification (15).

Fibroadenomas, which are often defined as oval, well-defined, homogeneous hypoechoic lesions parallel to the chest wall on US, are usually simple fibroadenomas (16,17). We included simple fibroadenomas under US follow-up for at least two years, once every six months in the first year. In these lesions, spontaneous regression can be observed at the level of 10% during the follow-up period (8). Juvenile fibroadenomas and phyllodes tumors cannot be distinguished sonographically, and complex fibroadenomas may be seen in childhood and may be associated with breast cancer (17).

In our study, all lesions except the diagnosis of simple fibroadenoma were surgically excised. There was no upgraded lesion. Upgrade can develop after excision in juvenile fibroadenomas, which is also defined as cellular fibroadenoma, or in some phyllodes tumors (2). Phyllodes tumors are rare, of which 9–35% are malignant (18-20). Additionally, phyllodes tumors may have a recurrence, less in benign ones (10% - 25%), therefore, continuous follow-up is required (21). In cases of fibroadenoma and phyllodes tumor differentiation, core biopsy should be performed, as FNAB will not be sufficient. The negative effects of core biopsy on normal breast development are negligible (13,22).

It has been reported that the most common primary breast cancer in children is cystosarcoma phyllodes, and the most common breast malignancy is metastatic masses originating from extra-breast neoplasms (23). The literature reports that the main breast carcinomas are secretory carcinomas with a good prognosis in the pediatric age group (3). However, as in our cases, invasive ductal carcinomas constitute the majority of cases and their prognosis is poor (24).

One of our two breast cancer cases was luminal A and the other was luminal B. In a large series of studies by Warner et al. the relationship of the molecular breast cancer subtypes in childhood and young adults with body size and body mass index was compared (25). This study reported that breast cancers belonging to four molecular subtypes were seen at similar rates compared to adults.

There is no consensus on treatment in the literature. Breast-conserving surgery is usually preferred (3). It has been reported that axillary metastasis is observed in 20% - 30% of cases (26).

Breast US examinations always include the axilla. Most of the breast lymphatic drainage (75% - 97%) goes to the axillary lymph nodes (27). Therefore, a pathology in the breast is expected to affect the axilla first. However, large axillary masses can cause edema in the breast through the obstruction. Two of our cases had complaints of swelling in the armpit and ipsilateral breast fullness and pain. No malignant lesions were observed in the breasts in sonographic examinations. In the unilateral axilla, multiple lymph nodes with a diameter of 3-5 cm with impaired hilus-cortex relations were observed. A case (17-year- old, female) had scratches on the ipsilateral hand and arm. Upon learning that a house cat had scratched her, "Cat-scratch disease" was considered, and core biopsy was performed from the axilla. Histopathological findings included granulomas, diffuse polymorphous core leukocytes, and focal necrosis areas consistent with the initial diagnosis (28). Findings regressed with short-term antibiotic therapy.

The axillary core biopsy diagnosis of the other case (16-year-old, female) was high-grade Burkitt lymphoma, which accounts for approximately 40% of childhood non-Hodgkin lymphomas. Survival rates in this disease have increased dramatically recently, an achievement attributed to the use of chemotherapy and immunotherapy (29). However, in this study, the disease progressed very rapidly, and the patient died within three months.

One of the limitations in our series is that our hospital is not a pediatric or oncology-specific hospital. However, our series still gives an idea about the frequency of pediatric patients who resort to hospitals in a general population. Other limitations are that our series is a retrospective and single-center study. Since our case number was small, we could only evaluate lesions with and without biopsy in terms of size and age. We could not evaluate them in terms of features such as

inhomogenity, increased size on follow-up, increased vascularization and lobulation, millimetric cystic components and microcalcification.

CONCLUSION

In childhood up to 19 years of age, there may be malignancies in the breast and lesions such as fibroadenoma that require malignancy exclusion.

Age is not decisive in the biopsy decision. Large size is a statistically significant parameter. Additionally, it should be kept in mind that lymphoproliferative diseases and granulomatous pathologies, which are more common in these ages, may cause secondary complaints in the breast.

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Ethical approval: All procedures performed in studies involving human participants were in accordance with the institutional and/or national research committee's ethical standards and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The local ethics committee approved this research (01.10.2020, 171). No funds were used from any institution.

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