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BREAST IMAGING

ORIGINAL ARTICLE

Breast diseases in children: the spectrum of radiologic findings in a cohort study

Emel Durmaz
Murat Alp Öztek
Hatice Arıöz Habibi
Uğur Kesimal
Hakkı Timur Sindel

PURPOSE
We aimed to investigate the spectrum of radiologic findings and referral reasons for breast diseases in children considering age-appropriate presentation.

METHODS
Our retrospective cohort study included 348 consecutive pediatric patients aged <19 years (median, 13 years) referred to radiology with a clinical presentation between 2005 and 2016. Radiologic findings were reviewed in four age ranges (0–2 years, 2–8 years, 8–15 years, >15 years).

RESULTS
Of 348 patients, 257 had a referral reason. The most frequent referral reason was a palpable mass (35%). Developmental abnormalities accounted for 48% of all radiologic findings in 348 patients. We did not detect any breast malignancy. According to age groups, the most common radiologic findings were neonatal hypertrophy (0–2 years), early breast development (2–8 years), developmental abnormalities by a majority of gynecomastia (8–15 years), and normal findings or developmental abnormalities (>15 years). Interestingly, the frequency of gynecomastia was only 4% in neonatal period or early childhood. Fibroadenomas and fibroadenoma-like solid masses were seen after 8 years and constituted the majority of solid masses (65%). Cysts were seen at a rate of 7% and majority of them were of simple type, which tends to resolve in time.

CONCLUSION
In our study, the most common referral reason to radiology was a palpable breast mass. Neonatal hypertrophy and early breast development in younger children, and developmental abnormalities in older children may be kept in mind as the most common radiologic findings. Our study confirms the substantial absence of malignancies in children as well as a widely different disease spectrum in comparison with the adult population.

Breast diseases in the pediatric population are uncommon conditions and many radiologists lack familiarity with their characteristic imaging features, which may lead to diagnostic challenges. Understanding normal breast development and the spectrum of pediatric breast lesions is the key to correct diagnosis and management.

In our daily practice, clinicians refer children with breast complaints or pathologic findings to breast radiology departments. Although we know that these conditions are usually self-limited and benign, management of breast lesions in children differs from that in the adult population. Although, we tend to avoid breast biopsy in children, in some cases it may be necessary. Breast tissue is vulnerable in children and biopsy can damage the developing tissue and prevent its normal growth. Thus, radiologists should carefully choose proper modality and management. Ultrasonography is the appropriate initial imaging modality in children (1–3). Mammography should be used rarely due to particularly high sensitivity of the developing breast to radiation. Moreover, increased fibroglandular tissue density makes mammography less helpful (4, 5). Magnetic resonance imaging (MRI) of the breast is not widely used in pediatric population but might be helpful in vascular and lymphatic malformations (1, 2).

In addition to avoiding unnecessary biopsies, diagnosing breast diseases directly and distinguishing benign and malignant breast lesions becomes important when parents have a fear of cancer in their children. It will be easier to handle these challenges, if we as

From the Department of Radiology (E.D. ✉ *ealimoglu@akdeniz.edu.tr*, M.A.Ö., U.K., H.T.S.), Akdeniz University School of Medicine, Antalya, Turkey; Department of Radiology (H.A.B.), İstanbul University Cerrahpaşa School of Medicine, İstanbul, Turkey.

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radiologists know the most common findings or diseases in pediatric patients. Here, we aimed to investigate the most common breast findings and referral reasons considering age-appropriate clinical presentation in pediatric patients.

Methods

Data collection and patient selection

Our institutional review board approved this retrospective cohort study in accordance with the Helsinki Declaration. We searched patient information and images between January 2005 and October 2016 from picture archiving and communication system (PACS) of our hospital. We used 3 different radiology/patient information programs since our hospital updated PACS in 2014 and information for some patients had been kept in previous databases. The following programs were used: Medi Hasta. (16.53, 1997/2014, A.U. Hospital); Mia-Med (version 1.0.1.2808, Mia Technology); Sectra (dedicated only to radiology PACS, IDS7, version 17.3).

Data from 358 patients <19 years, referred from pediatrics or pediatric surgery outpatient clinics to radiology department were evaluated by three radiologists. Data collection comprised digital images, radiology reports, notes from pediatricians or pediatric surgeons such as breast symptoms and examination findings, referral reasons, demographic information such as age at the time of diagnosis and sex, and pathology results (when available). Ten of 358 patients were excluded from the analysis due to absence of radiologic findings and referral reasons in the database. Remaining 348 patients having unilateral or bilateral radiologic findings in their breasts constituted our study population. Referral reasons were analyzed in 257 patients for whom data were available.

Imaging methods and review of radiologic findings

Radiologic findings were categorized into six groups; a) normal, b) solid masses, c) cysts, d) non-neoplastic lesions (ductal dilatation, lipomastia), e) inflammatory lesions (mastitis, abscess), f) developmental abnormalities (juvenile hypertrophy, asymmetric growth, early breast development [premature thelarche], neonatal hypertrophy, and gynecomastia). These six groups and their subgroups were addressed in four age ranges (0–2 years, 2–8 years, 8–15 years, >15 years).

The characteristics of the mass such as shape, contour, parallel or not parallel alignment, and multiplicity were evaluated on sonography images or videos. We recommended a short-term follow-up for probably benign masses (BI-RADS category 3 assessment in initial diagnosis). Biopsy was recommended in case of any suspicious finding at the initial diagnosis or interval changes for malignancy during follow-up of probably benign masses. Biopsy type and pathologic results were noted. Also, the number of patients who underwent biopsy at the discretion of the parents or the pediatric surgeon were taken into account. Patients underwent either percutaneous ultrasonography (US)-guided core biopsy (14 gauge needle, Magnum, C.R. Bard Medical) or surgical excision biopsy.

Cysts were subcategorized as simple, clustered, complicated, and complex cysts. Biopsy was recommended for complex cysts, if not corresponding to benign lesions like oil cyst. The status of axilla was evaluated for inflammatory lesions such as abscess or mastitis in terms of lymphadenopathy.

Fibroglandular echogenicity on US was considered as "gynecomastia" in boys. The diagnosis was "early breast development" in girls <8 years old. Findings were considered "normal" in case of: a) no remarkable US findings in males, b) no remarkable US findings in girls <8 years of age, and c) only fibroglandular tissue in girls >8 years of age (peripubertal and adolescents girls). We did not use the US findings compatible with the stage of thelarche adopted from Tanner's classification, since this kind of evaluation would not contribute to our purpose (2, 5, 6).

US was performed using high-frequency broadband linear transducers with central frequencies of 12 MHz or 9 MHz (MyLab70 XVG and MyLab Classic C) by three radiologists who had experience in breast radiology. Mammography was taken only in one projection if necessary to seek any additional malignant finding. The mammograms were obtained as full-field digital mammography (Giotto, IMS).

We used descriptive statistics, frequency, and crosstabs analyses. Positive and negative predictive values and false positive rate were calculated.

Main points

- The spectrum of breast diseases in children is quite different from that in adults.
- Radiologic findings are benign, almost half of them being developmental abnormalities.
- We suggest that benign solid masses can be periodically followed-up with a conservative approach similar to adults.

Results

Of 348 patients, 126 (34%) were male and 222 (64%) were female. The mean age was 12.2±4.5 years (median, 13 years; ranging from 6 months to 19 years). The distribution of age ranges was as follows: 9.5% of the patients were 0–2 years of age, 11.5% were 2–8 years of age, 43.7% were 8–15 years of age, and 35.3% were >15 years of age.

Of 348 patients, 257 had a referral reason on our digital database. The most frequent referral reason was palpable mass with a rate of 35% (n=90) and the second most common reason was gynecomastia with 22% (n=57). The distribution of referral reasons is listed in Table 1. Of 90 patients referred to radiology with a palpable mass, 24 (27%) had no real lesion in their breasts reported by negative or normal radiologic findings.

In 6 patients with breast enlargement, although clinicians did not clearly specify the finding or complaint as asymmetrical, radiologic diagnosis consisted of asymmetrical lesions including one gynecomastia, two juvenile hypertrophies, one cyst and two neonatal hypertrophies. Thus, we think there is an overlap between asymmetrical enlargement (6.6%) and breast enlargement (2.3%) and swelling (2.3%) symptoms. However, palpable mass was again the most frequent reason by far in our study, even if we add premature thelarche (2.7%) as a referral reason to others mentioned above (Table 1).

Of 257 patients with a referral reason, 17 (6.6%) were referred because of nipple discharge. The most common findings in these children were fibroglandular tissue or normal US findings (n=10), followed by focal US abnormalities, namely gynecomastia (n=1) and simple or multiple cysts (n=6).

Of 348 patients, the most frequent findings were gynecomastia in males and normal findings in females (no remarkable US findings in females <8 years, and/or only fibroglandular tissue in those >8 years). The second most frequent finding was developmental abnormalities in female chil-

Table 1. Referral reasons of pediatric patients to radiology department for breast examination

Referral reason	n (%)
Palpable mass*	90 (35)
Localized pain	14 (5.4)
Gynecomastia	57 (22.2)
Nipple discharge	17 (6.6)
Asymmetrical enlargement	17 (6.6)
Tenderness	10 (3.9)
Breast enlargement	6 (2.3)
Precocious puberty	11 (4.3)
Premature thelarche	7 (2.7)
Mastitis	5 (1.9)
Metastasis	5 (1.9)
Breast hypoplasia	1 (0.4)
Erythema	2 (0.8)
Bilateral mastalgia	2 (0.8)
Hemangioma	1 (0.4)
Big areola	1 (0.4)
Trauma	1 (0.4)
Swelling	6 (2.3)
Poland syndrome	1 (0.4)
Lymphadenopathy	2 (0.8)
Neurofibromatosis	1 (0.4)
Total	257 (100)

*Almost one-third of patients with palpable mass had no real lesion like solid mass or cyst.

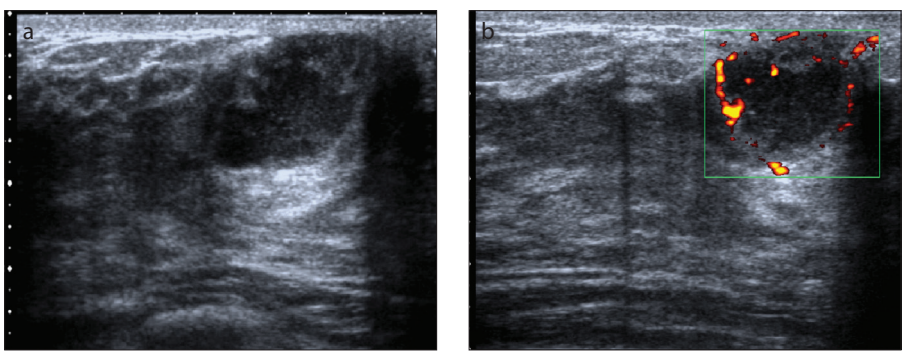

Figure 1. a, b. An 11-year-old girl with a complex cyst with asymmetrical thick wall and irregular margins **(a)**. Power Doppler US **(b)** reveals intensive vascularity in wall. She had localized pain. Core biopsy from wall of cyst with a 14-gauge needle yielded reactive stromal changes. The diagnosis after needle aspiration was abscess.

dren. The most common radiologic findings were neonatal hyperthrophy in 0–2 years of age, early breast development in 2–8 years, and developmental abnormalities in 8–15 years. We diagnosed mostly developmental abnormalities or normal findings regarding age and gender in children >15 years. The histologic spectrum of breast diseases was quite different from that in adults (Table 2). One patient with juvenile fibroadenoma underwent dynamic breast MRI and four patients with juvenile fibroadenoma were further evaluated by mammography in addition to US. In these four patients, we investigated the presence of microcalcifications and other additional findings by mammography.

In our series, gynecomastia was the most frequent diagnosis (30% of all cases) on US. We regard it as a developmental abnormality. It was seen mostly in peripubertal (8–15 years of age) or adolescent period (>15 years of age) in our study. Interestingly, the frequency of gynecomastia was only 4% (4/106) in neonatal period or early childhood. Gynecomastia was unilateral in 19% and bilateral in 48% of children aged 8–15 years. On the other hand, gynecomastia after 15 years was not as often as in the 8–15 years age group. In children aged >15 years, gynecomastia was 16% unilateral and 19% bilateral.

Developmental abnormalities accounted for 48% of all radiologic findings in 348 patients. Non-neoplastic conditions and inflammatory lesions were not so frequent, seen in 5% and 2%, respectively. Cysts were seen at a rate of %7 and majority of them were simple type. Almost half of them were multiple (11/26). During the follow-ups, we realized 9 cysts showed interval regression: two regressed in 5 years, five in 1 year, and two in 6 months. These cysts were seen in pubertal girls. We realized that cysts regressed when the girls developed an adult type breast structure (Table 2). Only one patient had a complex cyst with a localized pain. We performed needle aspiration and core biopsy from wall. Needle aspiration showed an abscess content in this lesion (Fig. 1).

Of 42 patients with solid breast masses, 15 underwent either core or excisional biopsy. We recommended biopsy for 5 of 15 solid masses. Pathology yielded 7 classic fibroadenomas, 2 juvenile fibroadenomas, 2 tubular adenomas, 1 nodular sclerosing adenosis (Fig. 2), 1 peripheral papilloma, and 2 fibroadenomatous hyperplasia (Fig. 3). There were no malignant lesions in our study. Fibroadenomas or fibroadenoma-like solid masses (probably benign solid masses) constituted the majority of solid masses (65%) and they were seen mostly in adolescents. We did not find any fibroadenoma under the age of 8 years. Most of the hemangiomas were found in patients 0–2 years of age (Fig. 4). In solid masses, false-positive rate was 11.9% (95% CI, 2.1–21.7) since we recommended biopsy for 5 lesions. The distribution of solid masses according to age groups is listed in Table 3.

Sample cases

a) In a 15-year-old boy, we found simple multiple cysts along with gynecomastia. Af-

Table 2. Radiologic findings according to sex and age groups in children

US findings	Age range (years) 0–2	2–8	8–15	>15	Female	Male	n (%)
Normal*	1	6	37	43	84	3	87 (25)
Developmental abnormalities							169 (48)
Neonatal hypertrophy	17	-	-	-	17	-	
Early breast development	-	27	-	-	27	-	
Asymmetrical development	-	1	10	2	13	-	
Juvenile hypertrophy	-	-	2	4	6	-	
Gynecomastia	2	2	67	35	-	106	
Solid mass	6	-	12	24	40	2	42 (12)
Cyst							26 (7)
Simple	3	-	12	4	16	3	
Clustered	-	-	2	2	4	-	
Complicated	-	-	-	-	2	-	
Complex	-	-	-	-	1	-	
Non-neoplastic							18 (5)
Ductal dilatation	2	1	2	-	5	-	
Lipomastia	2	3	3	5	2	11	
Inflammatory lesions						6 (2)	
Mastitis	-	-	-	1	-	1	
Abscess	-	-	5	-	5	-	
Total, n (%)	33 (9.5)	40 (11.5)	152 (43.7)	123 (35.3)	222 (64)	126 (36)	348 (100)

* Cases were defined as "normal" in the absence of focal abnormalities in males at any age and females <8 years of age and in the presence of normal breast tissue in girls >8 years.

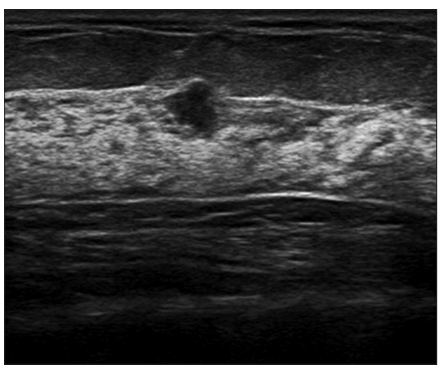

Figure 2. An 18-year-old girl with a small solid mass with indistinct margins, not parallel to skin. We recommended biopsy with BI-RADS category 4 assessment. Excisional biopsy yielded nodular sclerosing adenosis.

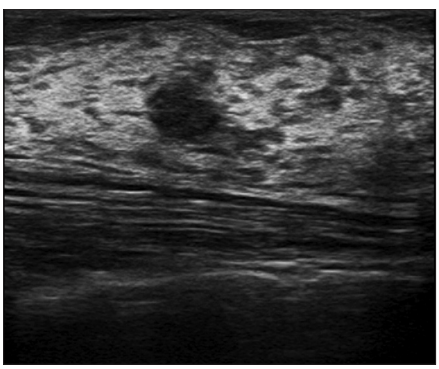

Figure 3. A 16-year-old girl with 8×7×7 mm sized, irregular shaped mass diagnosed as fibroadenomatous hyperplasia by excisional biopsy. A distinct capsule that is expected in fibroadenomas is not seen on US image.

ter 3 years, gynecomastia and cysts disappeared completely.

b) A 16-year-old girl presented with a 8×7×7 mm size solid mass with irregular shape, indistinct margin, and non-parallel alignment to skin. There was no family history or high risk of breast cancer. We recommended core needle biopsy under ultrasound guidance. The surgeon preferred to excise the mass completely. Biopsy yielded fibroadenomatous hyperplasia very similar to fibroadenoma without a capsule (Fig. 3).

c) A 12-year-old girl had a high family risk. Her grandmother, mother, aunt, and the daughter of aunt had history of breast cancer. We found a very big mass that did not fit on the screen. Biopsy yielded a juvenile fibroadenoma. Surgeons decided to proceed with mastectomy in a multidisciplinary meeting by preserving nipple and breast skin. We detected recurrent masses of fibroadenoma during the follow-up after surgery in this patient.

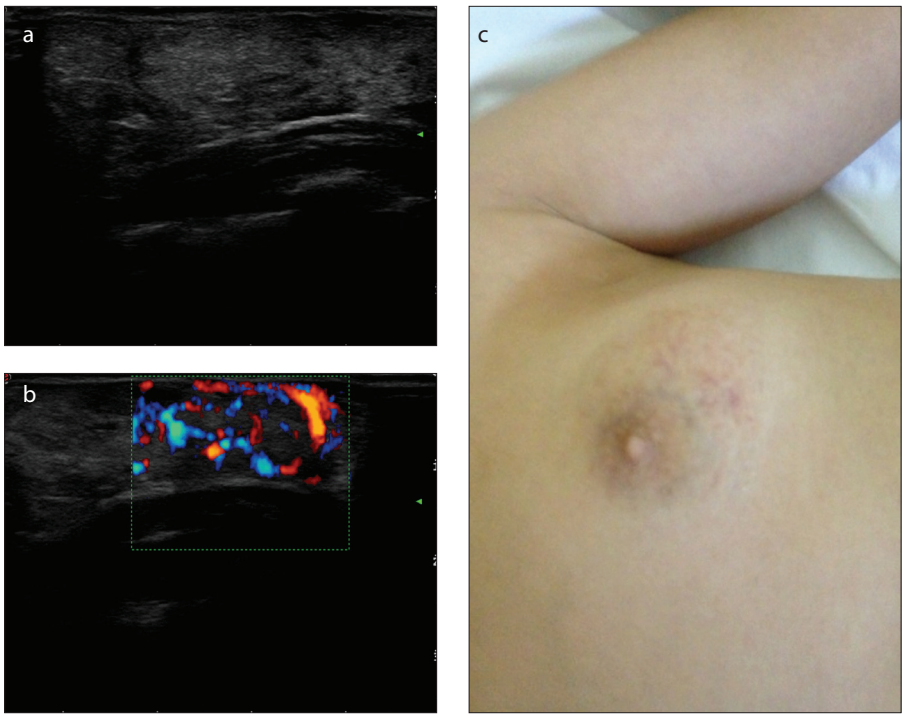

Figure 4. a–c. A one-year-old girl with a parenchymal, slightly hyperechoic solid mass filling outer quadrants of the breast **(a)**. This mass showed hypervascularity with high-flow **(b)**. Also she had a breast skin involvement **(c)**. Our final diagnosis was hemangioma.

Table 3. The distribution of solid masses according to sex and age groups

	Age range (years)						
Solid masses	0–2	2–8	8–15	>15	Female	Male	n (%)
Fibroadenoma[a]	-	-	2	7	9	-	9 (22)
Tubular adenoma	-	-	1	1	2	-	2 (5)
Probably benign mass[b]	1	-	7	10	18	-	18 (43)
Hemangioma	5	-	1	-	6	-	6 (14)
Peripheral papilloma	-	-	-	-	1	-	1 (2)
Hamartoma	-	-	-	1	1	-	1 (2)
Nodular sclerosing adenosis[c]	-	-	-	1	1	-	1 (2)
Fibroadenomatous hyperplasia	-	-	-	2	2	-	2 (5)
Lipoma	-	-	1	1	-	2	2 (5)
Total	6	0	12	23	40	2	42 (100)

[a]Biopsy yielded seven classic and two juvenile fibroadenomas.
[b]Probably benign masses (BI-RADS category 3) were followed up at least 2 years at 6-month intervals (one mass 7 years, three masses 5 years). At the end of follow-ups, no interval progression suggesting malignancy was seen.
[c]Found in an 18-year-old girl (Fig. 2).

Discussion

Clinical research presenting radiologic findings of breast diseases in children are not common (7, 8). We would like to address this issue, since familiarity of the radiologist with breast diseases or developmental variations matching different age groups, would make differential diagnosis easier. Moreover, the need for biopsy arising from uncertain diagnosis could be reduced.

Our retrospective cohort study showed that radiologic findings in childhood were benign and almost half of them were due to developmental abnormalities. In a study by Harth et al. (7), the most frequent radiologic findings were gynecomastia in boys and normal gland tissue in girls. But they did not classify diagnoses into neonatal hypertrophy, asymmetrical breast enlargement, or early breast development as we did for cases of glandular tissue.

Based on our results, the most frequent reasons for referral to radiology were palpable mass and gynecomastia. These results are different from those reported by Harth et al. (7) who found that the most frequent referral reasons were premature thelarche and asymmetric breast enlargement in children. On the other hand, 25% of our patients did not have any focal abnormality, although they were referred with a symptom (mostly a palpable mass). We defined normal breast development as absence of focal abnormalities in males at any age and in females <8 years old, and only thelarche or normal breast tissue in girls >8 years. The majority of our cases were >8 years and normal breast development is called thelarche after 8 years of age in girls. Breast development is usually completed by 2–4 years after thelarche (9). In our opinion, some children may have a palpable mass or pain complaints during normal breast development. These cases cannot be solved by only physical examination without sonography.

Sixty-five percent of all solid masses were fibroadenomas or fibroadenoma-like lesions (probably benign solid masses), mostly in adolescents, similar to the findings reported by other investigators (2, 8). Notably, we did not detect any solid masses in patients <8 years of age. In two boys, we saw only lipoma as a solid mass in the breast. In a study, authors pointed out that biopsy yielded 10 fibroadenomas in 17 palpable masses (10). Our rate of fibroadenoma was lower, probably due to our preference for a follow-up protocol instead of needle biopsy in cases of high probability of benign lesions. Interestingly, we reported a case of fibroadenomatous hyperplasia, a rare well-described benign lesion with composite features of fibroadenoma and fibrocystic change (11) in two girls of 15 and 16 years old. To the best of our knowledge, fibroadenomatous hyperplasia has not been reported in children, so far.

According to the BI-RADS classification, probably benign masses should have a very low probability of (<2%) being malignant (12–14). The chance of such a lesion being malignant in a pediatric patient is even lower, thus explaining our low rates of biopsy. We underline that developing pediatric breasts are prone to iatrogenic injury and biopsy may lead to untoward outcomes. In our experience, a mass located parallel to skin with oval shape and well-distinct margins can be periodically followed-up

similar to adults, unless an interval change during surveillance prompts tissue diagnosis. Of note, no malignant lesions were diagnosed at follow-up in our young patients. However, biopsy should be preferred over follow-up to clarify the nature of masses in children with leukemia or lymphoma, even if they present with a benign appearance. Core or vacuum-assisted biopsy should be recommended for solid breast masses with suspicious features or progressive growth.

Hormones influence the breast tissue in the prepubertal and pubertal phases. While estrogen stimulates the growth of ducts and fibroadipose tissue, progesterone stimulates the development of lobular tissue. Neonatal breast hypertrophy may result from maternal estrogen stimulation, and can occur in either sex. It may persist for 12 months. The role of US is to rule out real breast masses (1, 2, 5, 15, 16).

Gynecomastia may occur in neonatal or pubertal period while it is most commonly encountered in adolescence (2, 5, 6, 17). However, in our study, gynecomastia, generally bilateral, was detected mostly in the 8–15 years age group, one or two years after the onset of puberty. Interestingly, the frequency of gynecomastia was only 4% in neonatal period or early childhood. When gynecomastia is unilateral and shows dendritic shape, it may be confused with carcinoma, which tends to be more eccentric than gynecomastia (1, 18). On the other hand, we found lipomastia in 11 male patients with the symptoms of gynecomastia or breast swelling. Pediatricians did not ask for further work-up for these patients: US alone was sufficient for diagnosis.

Our study confirms that in children, breast cysts tend to be simple and resolve in time. We noted that 9 simple cysts showed interval regression in time when the pubertal breast structure became an adult type breast. Thus, a conservative approach to cysts should be adopted. However, for complex cysts mammography was performed, particularly to differentiate oil cysts from suspicious lesions. When a malignancy is suspected, we recommend core or vacuum-assisted biopsy.

In a study with limited sample size, the underlying reasons of bloody nipple discharge in children were ductal ectasia, gynecomastia, and fibrocystic changes (19). In our study, bloody nipple discharge was seen in 7% of patients, mostly without any focal US abnormality except one case of gynecomastia and 6 cases with simple or multiple cysts. Nipple discharge may occur due to drugs, exercise, trauma and a conservative approach is usually recommended (16, 20, 21).

Early breast development does not always correspond to precocious puberty. It may remain isolated for a time period and then it may progress or regress. To clarify if puberty is accompanied by early breast development, it should be evaluated clinically (22). Our early breast development rate was only 8% (27/348) and it was seen between the ages of 2 and 8 years. Juvenile hypertrophy is another condition presenting with breast growth. It emerges rapidly at the onset of puberty and may be inherited. If asymmetric, differential diagnosis from other possible masses is crucial (16, 23, 24).

The spectrum of our results was different than the ones mentioned in the literature. We did not report congenital anomalies like polythelia or hematoma conditions, which can be readily diagnosed by clinical examination and therefore not referred to us.

In the field of pediatric breast diseases, there is some confusion regarding terminology. For example, gynecomastia in newborns up to 2 years of age can be named neonatal hypertrophy or normal gland tissue in the literature (7). Confusion also exists between early development of breast bud and premature thelarche (3). Clinicians referred to us patients having the same symptoms interchangeably using the terms "breast enlargement" or "breast swelling." In 6 patients with breast enlargement, although clinicians did not clearly specify that the findings or complaints were asymmetrical, a possible asymmetrical lesion was visualized radiologically. Thus, we think there are overlaps between asymmetrical enlargement, breast enlargement, and swelling. Similar considerations hold for asymmetrical breast enlargement and premature thelarche in children >8 years. However, premature thelarche is also defined as the onset of breast development before the age of 8 years (25). Finally, an overlapping meaning can be noted for pseudogynecomastia, also called lipomastia or augmented adipose tissue (1, 7, 17, 18), as well as for pediatric macromastia, which is also known as juvenile hypertrophy (23).

In conclusion, the most frequent reason for referral to radiology for breast symptoms in children was a palpable mass. Radiologic findings were benign, with almost half of them being developmental abnormalities. Thus, conservative approach will be appropriate to protect the developing breast tissue in female children. The most common radiologic findings were neonatal hyperthrophy in 0–2 years, early breast development in 2–8 years, and developmental abnormalities in 8–15 years. Children >15 years of age mostly had developmental abnormalities or normal findings regarding age and gender. Our study confirms the substantial absence of breast tissue malignancies in children as well as a widely different disease spectrum in comparison with the adult female and male population. Also, our study shows that terminology is confusing regarding children's breast diseases. We strongly believe that this confusion can be solved with a standardization effort similar to the standardization provided with BI-RADS in adults.

Conflict of interest disclosure

The authors declared no conflicts of interest.

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