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A clinical approach to benign breast lesions in female adolescents

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Summary. The female breast undergoes two phases of growth and differentiation. The first occurs during fetal life and results in the formation of simple branched ducts, which are able to respond to the hormonal stimuli of maternal origin. The second period of growth occurs at puberty, when the ducts elongate, divide, and form terminal duct lobular units. Breast pathology during adolescence is usually benign and therefore management has to be mostly conservative. Familiarity with the spectrum of breast pathology in this age group is essential. Ultrasound is the imaging modality of choice. Open surgical biopsies can damage the developing breast and therefore availability and expertise with fine needle aspiration biopsy can circumvent this problem. (www.actabiomedica.it)

Key words: adolescent breast, nipple discharge, benign breast disease

Introduction

In the 5th week of intrauterine life a 2-4 cell layer 'milk streak' or 'mammary band' appear as lines of thickening in the ectoderm, extending from the axilla to the groin (1). The fact that supernumerary nipples can be found from the groin to the axilla, supports the concept of a milk line or crest (2). They can appear similar to pigmented macules or as a fully developed nipple and areola. These are rarely functioning but can be a cosmetic concern (3). During the 6th to 7th week there is a thickening in the thoracic region where the breast bud forms; the 'mammary crest,' to form a 4 to 6 cell wide ridge and the rest of the milk streak begins to involute (1). The nipple primordium is first seen in 7.0- to 8.0 mm embryos as a narrow collection of ectodermal cells, which by 10 mm has a single layer of closely applied mesenchyme. From 11.0 to 14.0 mm, the mesenchyme differentiates beneath the nipple primordium into four layers. At 14.0 mm, the nipple has moved from a relatively dorsal to a ventral position and the epithelium has proliferated to form a nodule that is pushing into the mesenchyme. The growth of the nodule then continues to form the breast bud. The bud is fully enclosed in the mesenchyme and there is an indentation over the surface (2). Two distinct populations of epithelial cells (central and basal) can be identified. Concomitantly, the mesenchymal cells differentiate to form fibroblasts, smooth muscle cells, capillary endothelial cells, and adipocytes (3).

By 6 months of gestational age, the mammary gland is established as a well-defined tubular structure in a bed of dense fibroconnective tissue stroma. This is the time breast tissue in both boys and girls can be apparent (3).

In the newborn breast, there are very primitive structures, composed of ducts ending in short ductules lined by one to two layer of epithelial and one of myoepithelial cells. Secretory activity does not seem to be confined to the primitive alveolar structures, since the whole ductal system appears dilated, secretion filled, and lined by a secretory-type epithelium. These obser-

vations suggest that secretory activity is a generalized response of all the mammary epithelium to maternal hormonal levels. The secretory activity of the newborn gland subsides within 3-4 weeks (4).

Morphological and functional maturation starts from birth to 2 years. Soon after birth, the nipples become everted from proliferation of the underlying mesoderm, and the areolae increase in pigmentation. Development of erectile tissue in the nipple areolar complex occurs. Nipples that remain inverted until puberty are not uncommon (3).

Studies of infant breast from birth to 2 years of age in both sexes show variable features that have been described in terms of the degree of glandular development and branching complexity (morphological type) and the amount of functional differentiation, relating to secretory activity and glandular involution (functional stage; Table 1) (2). The infant breast is able to respond to the secretory stimuli that arise from maternal hormones and the production of milk by 80-90% of both sexes is due to the effects of prolactin on withdrawal of the sex steroids (2).

Sexual dimorphism of the breast occurs during puberty under the influence of hormones. In females, ductal elongation and formation of lobular structures occurs. In males, no further development normally occurs. The occurrence of gynecomastia in males demonstrates that ductal and stromal (but not lobular) developmental potential is present in the male breast (2).

Breast disorders

Disorders of Breast Growth

• ***Premature thelarche***

The term thelarche refers to the onset of pubertal breast development in females, with estrogen stimulating ductal growth and progesterone promoting lobular and alveolar differentiation, completing the terminal duct lobular unit (5). Breast buds are common at birth secondary to maternal estrogen effect. They can appear as early as 1-3 years of age and can persist from birth. Although most patients with premature thelarche have no associated medical problems, hypothyroidism is a rare cause. Premature thelarche is often an isolated condition, but may be the first symptom of precocious puberty, particularly in girls older than 2 years of age (6). When unilateral, it can mimic a mass and thus frequently comes to clinical attention (5).

• ***Polythelia and Polymastia***

Polythelia (supernumerary nipple or accessory nipple) is an anomaly of breast development affecting 1-2% of the population. It is most often unilateral but can be bilateral in in 30-35% of children with polythelia. They are located along the milk line in 95% of cases. Polythelia has been linked to renal anomalies, so a renal ultrasound is often indicated. Supernumerary nipples are benign but may be removed for cosmetic reasons (7).

Table 1. Summary of morphological types and functional stages of infant breast (2)

Morphological type	
I (MT I)	Rudimentary ductal system composed of elongated ducts with no branching or less than two dichotomous branching
II (MT II)	Branching ductal system with more than two dichotomous branching, but without the development of terminal lobular units
III (MT III)	Branching ductal system and well-developed terminal lobules
Functional stage	
I (FS I)	All ducts and ductules are lined by secretory type of epithelium
II (FS II)	Mixture of ducts lined by secretory epithelium and ducts lined by apocrine type of epithelium
III (FS III)	Almost all ducts lined by apocrine type of epithelium
IV (FS IV)	Mixture of ducts lined by apocrine type of epithelium and involving ducts lined by multilayered epithelium
V (FS V)	Almost all ducts showing involution and often lined by multilayered epithelium

Polymastia (accessory breast tissue) commonly occurs in the axilla or just below the native breast tissue but can be found anywhere along the milk line. Accessory breast tissue is often not appreciated until pregnancy or puberty. Although polymastia is benign, it may require resection for cosmetic reasons or due to cyclic pain or irritation. Polymastia is at risk of developing any breast pathology, including fibrocystic changes, mastitis, fibroadenomas, and malignancies (7). Like polythelia, it is usually sporadic, but can have familial inheritance (8).

• ***Athelia and amastia/hypomastia***

The absence of nipple and/or glandular breast tissue is a rare occurrence. Ectodermal defects may cause bilateral absence of breasts in males and females and is related to the failure of development of the ectodermal layer and its appendages. Bilateral amastia may be an isolated occurrence or be associated with other anomalies of the palate and upper extremities. Unilateral amastia may be a variant of Poland syndrome and should be treated accordingly (8). Very small breasts are fairly common in otherwise normal women. There is some evidence of an association between hypoplastic breasts (defined as a breast size of 200 ml or less) and mitral valve prolapse. Becker's naevus is occasionally associated with unilateral breast hypoplasia, possibly as a result of high androgen receptor activity on the affected side, and with areolar hypoplasia in males. Breast hypoplasia or aplasia is a feature of the AREDYLD (acrorenal field defect, ectodermal dysplasia, and lipoatrophic diabetes) syndrome (OMIM 207780) (9).

• ***Juvenile mammary hypertrophy***

Also known as virginal hypertrophy or juvenile gigantomastia, is a rapid and massive enlargement of one or both breasts (10). The breast growth is rapid, begins shortly after thelarche, and can be dramatic, resulting in breasts that weigh up to 50 pounds each. The number of hormonal receptors in the hypertrophic breast tissue is normal, as are serum estradiol levels. The treatment depends on whether breast growth has been completed; if the patient is still growing, progesterone or antiestrogen can be used to control breast growth. If this is unsuccessful, or if breast growth has been completed, breast reduction surgery is necessary. Lactation may be affected by juvenile hypertrophy, particularly after breast reduction surgery (6). If a reduction mammoplasty is done, hormonal therapy may need to be continued postoperatively as there have been documented cases of recurrence. When the hormonal therapy is discontinued, the patient should be seen at regular intervals. Juvenile hypertrophy carries no increased risk of breast cancer (7).

• ***Tuberous breast***

Key features of tuberous breast deformity include a constricted breast base, reduced breast parenchyma, abnormal elevation of the inframammary fold, and, most characteristically, decreased skin envelope in the horizontal and vertical dimensions with herniation of the breast parenchyma into the areola. The nipple areola complex is expanded and lacks elasticity and firm dermal support (11).

Benign Pediatric Breast Masses

• ***Fibrocystic Changes (FCC) and Columnar Cell Changes (CCC)***

Previously it was referred to as fibrocystic "disease" of the breast. Histologically, fibrocystic change can be identified in up to 90% of all breast tissue examined in women. The most common presenting symptoms are breast pain and palpable nodules or lumps in the breast. FCC is divided into three groups according to their risk of developing breast cancer: nonproliferative lesions (cysts, apocrine metaplasia, mild epithelial hyperplasia, non-sclerosing adenosis), proliferative lesions without atypia (moderate to florid epithelial hyperplasia, sclerosing adenosis, radial scar, papilloma, and papillomatosis), and proliferative lesions with atypia (atypical ductal hyperplasia and atypical lobular hyperplasia). Relative to the general population, women with nonproliferative lesions have no increased risk for developing breast cancer. On the other hand patients with non-atypical proliferative and atypical proliferative lesions have relative risks ranging from 1.3 to 1.9 and 3.9 to 13, respectively (12).

• ***Fibroadenomas***

Fibroadenomas are the most common masses seen in adolescent girls, accounting for 67-94% of

adolescent breast pathology (13). Fibroadenomas arise from breast lobules and surrounding stroma and are estrogen sensitive. The mean age of presentation is 15-17 years old. Fibroadenomas present as a discrete, rubbery, mobile, painless breast mass most often in the upper outer quadrant. They are bilateral in 10% of cases and multiple in 10-15% (7). The physical examination is usually diagnostic. Lesions are well circumscribed, "rubbery," mobile and non-tender. Fibroadenomas have been reported to resolve spontaneously. All presumed fibroadenomas <5 cm can be safely observed for at least 1 or 2 menstrual cycles. If there is growth of the lesion, excisional biopsy is warranted (13).

• ***Juvenile Fibroadenomas***

Juvenile fibroadenoma is a variant of fibroadenoma, representing 7-8% of all fibroadenomas. Juvenile fibroadenomas demonstrate rapid growth with an average size of 5-10 cm. They are often associated with overlying skin changes including ulcerations and distended superficial veins. They cannot be occasionally differentiated from a phyllodes tumor on imaging or biopsy. For both cosmetic reasons and for pathologic confirmation, they should be excised (7).

• ***Juvenile Papillomatosis***

The mean age of onset is 19 years old. It is characterized by papillary epithelial hyperplasia of ductal epithelium. This leads to formation of a mobile mass consisting of multiple cysts in a dense stroma. In contrast to intraductal papillomas, there is frequently no nipple discharge. On pathology and imaging, these masses have a "Swiss cheese" appearance. Treatment of juvenile papillomatosis consists of surgical excision with negative margins. Although this is not considered a precancerous lesion, it is considered a marker for increased risk of breast cancer. Patients should be monitored closely for breast cancer once they reach adulthood (7).

• ***Phyllodes tumours of the breast***

Median age of presentation of phyllodes tumors is 45 years; however, they have been reported to occur in girls as young as 10 years of age (13). Phyllodes tumours of the breast constitute an uncommon group of fibroepithelial neoplasms that have a morphological resemblance to the intracanalicular fibroadenoma at the benign end of the spectrum, but with increased stromal cellularity and leaf-like architecture. Phyllodes tumours are classified into benign, borderline and malignant on the basis of histological parameters, i.e. the degree of stromal cellularity and atypia, mitotic count, stromal overgrowth, and the nature of their tumour borders (14).

• ***Retroareolar cysts***

Retroareolar cysts occur in young adolescent women and the clinical diagnosis is made with the presence of a palpable subareolar or retroareolar nodule. Sometimes it is associated with inflammation, pain, and erythema that extend beyond the areola to the mammary tissue. These lesions tend to resolve spontaneously. Retroareolar cysts are formed by obstruction and dilation of Montgomery's areolar tubercule, a sebaceous gland intimately associated with the terminal portion of a lactiferous duct that arises from the underlying mammary lobules tubercule (15). Symptomatic cysts are managed with oral antibiotics and frequent clinical and ultrasonographic follow-up. Asymptomatic cysts require the same monitoring and reassurance to the patient. Given the relatively benign course of the condition, every effort should be made to preserve the developing breast bud with needle aspiration or incision and drainage considered only in the rare presence of abscess formation unresponsiveness to antibiotics (16).

• ***Pseudoangiomatous Stromal Hyperplasia (PASH)***

PASH can affect persons of any age, ranging from 12 to 75 years, but it occurs more commonly in premenopausal women (17). PASH tumors are benign proliferation of stromal myofibroblasts, which express CD34, vimentin, and at least focally smooth muscle actin, desmin, and bcl-2, but not endothelial markers (CD31, Factor VIII), S100 or cytokeratin. The clinicopathological spectrum of PASH ranges from focal, incidental microscopic findings to clinically and mammographically evident breast masses. It is characterized histologically by interanastamosing angulated and slit-like spaces lined by slender spindle cells and surrounded by dense collagenous stroma. The slits lined by myofribroblastic cells are probably a fixation artifact induced by the retraction of the collagenous stroma,

but, although devoid of red blood cells, these slit-like spaces are apt to be mistaken for vascular spaces, hence the potential misdiagnosis as low-grade angiosarcoma (18). The stromal hyperplasia in PASH results from an exaggerated, aberrant responsiveness of mammary myofibroblasts to hormonal stimuli. The main hormone implicated to stimulate the myofibroblasts is progesterone. The nuclei of myofibroblasts in PASH have been shown to express progesterone receptors (PR) (17).

Bloody nipple discharge

• In the pediatric and adolescent population, bloody nipple discharge is rare, but is also associated as in adults with the same benign histologies of duct ectasia and intraductal papilloma. Duct ectasia is characterized by dilation of the subareolar mammary ducts, with periductal fibrosis and inflammation. Intraductal papilloma is a lesion of breast ducts with epithelium-covered fibrovascular cores (19).

Infection and inflammation may play a role in some cases of bloody nipple discharge where positive bacterial cultures were obtained (Staphylococcus aureus or Staphylococcus epidermidis), with clinical resolution after antibiotic therapy (19).

Inflammatory Lesions

Breast abscesses manifest as tender, indurated, or fluctuant erythematous masses. They may result from obstruction of a mammary duct, infection of a retroareolar cyst, irritation or abrasion of a nipple, or cellulitis of the surrounding chest wall area. Staphylococcus aureus is the major causative agent. These lesions appear on ultrasound (US) as cystic or complex masses. US is not only diagnostic but also helps guide therapeutic needle aspiration. Mastitis may appear as a complex or solid mass on US. By Doppler US, abscesses show only peripheral flow, whereas mastitis shows central flow (20).

Approach to breast lesions in children and adolescents

• Clinical evaluation is the first and essential component for the complete assessment of pediatric breast complaints. With complete history and physical exam, many pediatric breast complaints can be correctly categorized as normal developmental processes or physiologic changes, which require only reassurance (5).

• US is the ideal imaging modality to study the pediatric breast. In contrast to adults, utility of mammography is limited in the pediatric population because of the extremely low risk of breast cancer, the increased risk of radiation-induced malignant changes, and poor image quality due to dense fibroglandular breasts (20).

• Elastography: Sonoelastography is a method that attempts to distinguish benign from malignant masses. Tissue compression results in tissue deformation; the extent of this deformation is measured. Elastography has the potential of reducing the unacceptably high false positive that is a problem in routine use of US as a screening modality (21). Currently, there exist several types of breast elastography; strain imaging by compression, acoustic radiation force impulse (ARFI), and shearwave elastography (SWE) (22). Factors affecting false findings are related to lesion size, breast thickness, and lesion depth. Larger benign lesions tended to have a higher false-positive rate, and small malignant lesions also had similar higher false-negative rate. In large breast and deeper lesions accuracy tended to be lower, correspondingly better for more superficial masses (21).

• Breast magnetic resonance imaging (MRI) is not routinely used for evaluation of an adolescent breast mass. If a patient has a greater than 20% lifetime risk of developing malignancy (strong family history, BRCA1 or 2 genetic mutation carrier, or with a personal history of mantle radiation), breast MRI may be indicated for screening, which usually does not begin before age 25 years or 8 years after chest radiation therapy, whichever is later (23).

• Fine-needle aspiration biopsy (FNA): Open surgery for sampling breasts in adolescents may interfere with the maturation and development of the breast; thus, there is a need for a less invasive, but reliable technique. Compared to open biopsy, FNAs are much more likely to be accepted by the patient for sampling multiple lesions or areas. In addition, the nature of the FNA technique allows samples to be easily evaluated by ancillary studies, such as immunohistochemistry, flow cytometry, or cytogenetics (24).

• Nuclear medicine breast imaging include positron emission mammography (PEM), molecular breast imaging (MBI), and breast specific gamma imaging (BSGI). Although these modalities offer functional rather than anatomic information regarding the breast, which eliminates the issue of dense breast tissue in the adolescent, research has primarily focused on detection of breast malignancy, which has a very low prevalence in the adolescent population. These exams also require an injection of a radioactive tracer, which is to be avoided in children and adolescents when possible (23).

Breast US

The highest quality US images of the breast are obtained with 5-12-MHz linear transducers, depending on the degree of breast development. By US, the fat in normal breast parenchyma is hypoechoic, fibrous tissue is echogenic, and glandular tissue is intermediate in echogenicity (20). Table 2 summarizes the standard terms proposed for breast ultrasound (25).

Breast masses detected by US can be either cystic or solid. A sharply demarcated anechoic lesion with posterior acoustic enhancement is characteristic of a

Table 2. The standard terms proposed for breast ultrasound (25)

Masses						
Shape	☐Oval		☐Round	☐Irregular		
Orientation	☐Parallel		☐Not parallel			
Margins	☐Circumscribed					
	☐Not Circumscribed:		☐Indistinct	☐Angular	☐Microlobulated	☐Spiculated
Echo pattern	☐Anechoic	☐Hyperechoic	☐Complex cystic and solid	☐Hypoechoic	☐Isoechoic	☐Heterogeneous
Posterior features	☐No posterior features		☐Enhancement	☐Shadowing		☐Combined pattern
Calcifications						
☐Calcifications in a mass		☐Calcifications outside of a mass		☐Intraductal calcifications		
Associated features						
☐Architectural distortion						
☐Duct changes						
☐Skin changes:		☐Skin thickening		☐Skin retraction		
☐Edema						
☐Vascularity:	☐Absent		☐Internal vascularity		☐Vessels in rim	
☐Elasticity assessment:	☐Soft		☐Intermediate		☐Hard	
Special features						
☐Simple cyst						
☐Clustered microcysts						
☐Complicated cyst						
☐Mass in or on skin						
☐Foreign body including implants						
☐Lymph nodes-intramammary						
☐Lymph nodes-axillary						
☐Vascular abnormalities:	☐AVMs (arteriovenous malformations/pseudoaneurysm)				☐Mondor disease	
☐Post surgical fluid collection						
☐Fat necrosis						

benign cyst. A thin septum (<0.5 mm) may be seen within a simple cyst. Cysts with walls and/or septations greater than 0.5 mm, intracystic masses or sold masses with cystic areas; are considered suspicious with a recommendation for biopsy. For a solid mass to be considered benign, one of three findings have to be present: intense uniform hyperechogenicity, ellipsoid shape with a thin echogenic capsule, and two to three gentle lobulations with a thin echogenic capsule. Nine malignant features have been described; these include the following (positive predictive value for each is within parenthesis): spiculation [91.8%], a solid mass that is taller than wide [81.2%], a mass with angular margins [67.5%], one that demonstrates posterior acoustic shadowing [64.9%], a mass that demonstrates a branching pattern [64%], hypoechogenicity [60.1%], calcifications [59.6%], duct extension [50.8%], and microlobulations [48.2%]. If malignant features are absent, the benign features are sought. If benign characteristics are seen, a solid mass is classified as being benign. Solid masses which do not demonstrate malignant or specific benign features are then classified as indeterminate with a recommendation for tissue diagnosis (21).

Conclusions

As most breast lesions in the adolescent age group are benign, a conservative approach to management is highly recommended. Knowledge of the spectrum of breast lesions is essential. Good clinical evaluation can narrow the spectrum of suspected lesions.Noninvasive investigations as ultrasound and FNA should be used as first line approach.

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