Pediatric and Adolescent Breast Masses: A Review of Pathophysiology, Imaging, Diagnosis, and Treatment

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OBJECTIVE. Pediatric breast masses are relatively rare and most are benign. Most are either secondary to normal developmental changes or neoplastic processes with a relatively benign behavior. To fully understand pediatric breast disease, it is important to have a firm comprehension of normal development and of the various tumors that can arise. Physical examination and targeted history (including family history) are key to appropriate patient management. When indicated, ultrasound is the imaging modality of choice. The purpose of this article is to review the benign breast conditions that arise as part of the spectrum of normal breast development, as well as the usually benign but neoplastic process that may develop within an otherwise normal breast. Rare primary carcinomas and metastatic lesions to the pediatric breast will also be addressed. The associated imaging findings will be reviewed, as well as treatment strategies for clinical management of the pediatric patient with signs or symptoms of breast disease.

CONCLUSION. The majority of breast abnormalities in the pediatric patient are benign, but malignancies do occur. Careful attention to patient presentation, history, and clinical findings will help guide appropriate imaging and therapeutic decisions.

Keywords: adolescent breast masses, pediatric breast masses, ultrasound

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though breast masses are uncommon in the pediatric population, the detection of an abnormality is often alarming to caregivers and patients. Fortunately, most breast conditions arising in the pediatric age group are benign. Integral to the evaluation of these patients is a thorough clinical examination and history. Key factors that aid in diagnosis include the length of time that the mass has been present, associated pain or other symptoms, whether the mass affects one breast or both, how rapidly the mass is growing, and, finally, any family history of breast disease [1].

Because most breast tumors in young people are benign, a conservative approach is warranted. Diagnosis and treatment must be tailored to avoid damaging developing breast tissue, which can result in hypoplasia or aplasia [1]. In the pediatric population, mammography plays no significant role in the evaluation of breast disease for several reasons. First, the exposure of breast tissue to ionizing radiation can induce cellular changes that may lead to the development of malignancy. Second, young breast tissue can be extremely dense mammographically, reducing the overall sensitivity of the examination. Finally, the incidence of primary breast cancer is extremely low in the pediatric population, reducing the utility of mammography as a diagnostic problem-solving tool [1]. Ultrasound is generally the primary imaging modality used in young patients, aiding in the initial diagnosis, assisting in imaging-guided biopsy when indicated, and offering a safe method of follow-up. In the pediatric patient, MRI of the breast is rarely used, though in select cases, it may be useful for surgical planning or assessing the extent of disease.

Benign Breast Disease
The most common benign pediatric breast lesions can be divided into two main groups: those that arise as part of the spectrum of normal breast development and those that arise as a usually benign but neoplastic process within an otherwise normal breast.

Normal Breast Development
Breast tissue begins to develop at approximately week 5 of gestation, arising from the ectoderm on the ventral surface of the embryo along a curvilinear ridge known as the “Hughes line” or the “milk line,” extending from the axilla to the groin [2]. The majority of the milk line disappears shortly after its
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Premature Thelarche

Breast tissue developing in girls before age 7.5 years is called premature thelarche if there are no associated findings of precocious puberty [1]. Clinically, these patients present with palpable subareolar masses. Most cases are benign and self-limiting, particularly if they are not associated with pre-}

Asymmetric Breast Bud Development

Early normal breast development can be quite asymmetric, with up to a 2-year difference between breasts in the overall timing [1]. The asymmetric breast tissue presents as a unilateral subareolar mass. The role of ultrasound again is to provide verification that normal breast tissue is present and to exclude an underlying mass, reassuring both the patient and parents.

Gynecomastia

Gynecomastia is the excessive development of breast tissue in male patients. In the pediatric population, it can be physiologic or pathologic. Physiologic gynecomastia is generally seen in three age groups: neonates, pubertal boys (who develop pubertal or pathologic gynecomastia), and elderly men. Neonatal breast hypertrophy is a common transient condition seen in up to 90% of all newborns, both male and female [7]. It is presumed to be caused by transient elevations in estrogen due to transplacental passage of the hormone [8]. Parental reassurance is generally all that is warranted, and ultrasound plays little role in treating these patients.

Pubertal gynecomastia can be seen in 3.9–64.6% of boys, depending on the criteria used to define gynecomastia [9]. It is generally seen in boys aged 10–13 years, with typical onset 6 months after the appearance of secondary sex characteristics. Pubertal gynecomastia is a benign process that should regress within 2 years of onset (usually by age 17 years). Half of patients report a family history of gynecomastia [9].

The cause of pubertal gynecomastia is unknown. In the past, an imbalance of testosterone and estrogen concentrations has been used to explain this entity. However, sex hormone profiles have not shown a clear association. More recent data suggest that leptin may play a role in its development [10]. Leptin is found in mammary epithelial cells and can enhance aromatase enzyme activity in fatty tissue and breast tissue, resulting in an increase in estrogen concentrations. Leptin also can activate estrogen receptors in breast tissue.

Pathologic gynecomastia can be caused by an increase in estrogen, a decrease in testosterone, or medication or drug use, or it may be idiopathic [7]. Elevated serum estrogen levels can be caused by increased production of estrogen from testicular tumors (Leydig cell tumors) or adrenocortical neoplasms. Increased aromatization of the precursors of estrogen can result in the elevation of estrogens and accounts for the gynecomastia associated with Sertoli cell and sex-cord testicular tumors and in testicular germ cell tumors, liver disease (cirrhosis), hyperthyroidism, Klinefelter syndrome, and hyperthyroidism. Congenital testicular aplasia or hypoplasia, testicular trauma or torsion, viral orchitis, and congenital anomalies (such as Klinefelter syndrome) can all be associated with decreased testosterone levels and may lead to pathologic gynecomastia. Medications such as spironolactone and ketoconazole can displace estrogen from sex hormone–binding globulin, resulting in elevated free-estrogen levels. Finally, some herbal and skin care products (including those containing lavender and tea tree oil) have weak estrogenic and antiandrogenic activity that may cause gynecomastia [11].

Typically, ultrasound does not play a primary role in the evaluation of the breast in pubertal gynecomastia. If the physical examination is suggestive of gynecomastia, a thorough history and laboratory assessment should follow. However, if the physical findings are questioned, ultrasound allows verification of normal-appearing breast tissue and the exclusion of an underlying mass. Ultrasound is also helpful in revealing a lack of breast tissue in cases of pseudogynecomastia [12], which is breast enlargement caused by fat deposition. Although testicular neoplasms peak in incidence after puberty, testicular cancer can be associated with gynecomastia, which may be the only clinical finding at diagnosis. Ultrasound can be used to evaluate for the presence of testicular neoplasms if indicated in these patients (Fig. 1).

Mastitis and Abscess

In children, mastitis has a bimodal distribution and is seen most frequently in children younger than 2 months and those 8–17 years old [13]. The majority of cases are found in girls, and common pathogens include Staphylococcus aureus (> 75% of cases), gram-negative bacilli, group A Streptococcus species, and Enterococcus species [13]. Neonatal mastitis is rare and is presumed to be caused by mucous membrane and skin pathogens gaining access to the hormonally stimulated infant breast tissue through the nipple or ducts [14]. Pediatric
mastitis in the older age group is generally associated with skin infections, instrumentation or piercings, or lactation. Clinically, the patient will present with erythema, warmth, and focal tenderness in the breast. Leukocytosis may or may not be present.

Ultrasound is helpful in differentiating mastitis from abscess [14]. At sonography, mastitis can show both decreased echogenicity (early phlegmon) or increased echogenicity (usually due to edema of the fatty tissue). Hyperemia is usually present on color Doppler imaging. Enlarged reactive lymph nodes may be present. An abscess can be diagnosed when a round, oval, or irregular hypoechoic collection is evident. The collection often is complex but generally shows decreased flow centrally on color Doppler. Antibiotic therapy is the treatment of choice. Ultrasound can be used to direct needle-guided aspiration of abscess contents for culture and assessment of antibiotic sensitivities or to direct drainage [15] (Fig. 2).

Galactocele
A galactocele is a cystic collection of breast milk. They are frequently seen in lactating women and are rare in children. They usually present as a palpable mass and can be variable in echogenicity, from purely anechoic to isoechoic, depending on fat and protein content. Occasionally, fat-fluid levels can be visualized [16]. Histologically, cuboidal to columnar epithelium is noted within the walls of these cysts, and the adjacent breast tissue may show lactational change [17]. Factors that may play a role in their development in the pediatric population include stimulation by prolactin, epithelial cell secretion forming a cyst after trauma, and ductal obstruction [18]. Treatment consists of either monitoring the galactoceles with serial clinical or ultrasound examinations or aspirating the galactoceles to provide symptomatic relief [16] (Fig. 3).

Neoplastic Processes
Neoplasms in the pediatric population are overwhelmingly benign. The most common benign tumor is a fibroadenoma (seen more commonly in adolescence) or the more rapidly growing juvenile fibroadenoma [17]. Rare benign lesions include pseudoangiomatous stromal hyperplasia (PASH), juvenile papillomatosis, and vascular lesions such as hemangiomas. Malignant neoplasms are rare and include phyllodes tumors, metastatic disease, and breast carcinoma. In the adolescent patient presenting with a breast mass, histologic diagnosis by core biopsy may be appropriate, particularly if the imaging features are atypical or if clinical history shows that the lesion has shown rapid growth.

Fibroadenoma
Fibroadenoma is a benign mass caused by overgrowth of the specialized connective tissue stroma of the breast lobule. It comprises 91% of all solid breast masses in girls younger than 19 years [19]. Fibroadenomas can be microscopic or large; multiple lesions may be present. These estrogen-sensitive tumors are generally not seen before puberty. On physical examination, they usually present as mobile painless “rubbery” masses. At sonography, they often form oval or round well-circumscribed hypoechoic masses with parallel orientation, an abrupt interface, and variable posterior acoustic alteration [19]. They can have a macrolobulated contour. Their internal echotexture can be heterogeneous or homogeneous. Color Doppler may show the lesion as avascular or with mildly increased flow. Management is controversial and varies among institutions. If the sonographic appearance is classic and the lesion does not show rapid growth, short-term follow-up ultrasound can be used to monitor the mass, because up to 10% can regress spontaneously [15].

Complex fibroadenomas are defined as those containing cysts, sclerosing adenosis, epithelial calcifications, or areas of papillary apocrine metaplasia. They are more typically seen in older patients [20]. Children and adolescents with complex fibroadenomas are at slightly higher subsequent risk for developing breast cancer [19] (Fig. 4).

Juvenile Fibroadenoma
Juvenile or cellular fibroadenomas are an uncommon variant of fibroadenoma seen more frequently in the African-American population [21, 22]. A minority of these tumors show rapid growth and can attain large size [21]. Clinically, their presentation is variable, ranging from small mobile painless masses to rapidly growing tumors. Juvenile fibroadenomas are well-circumscribed lesions with hypercellular stroma, accompanied by intraductal epithelial hyperplasia [21]. The sonographic features of a juvenile fibroadenoma may not differ significantly from those of a phyllodes tumor [19, 23]. Generally, surgical excision is advised for any rapidly growing mass in the adolescent breast, even if it has been previously characterized as benign by core biopsy (Fig. 5).

PASH
PASH is a benign tumorlike proliferation of breast stroma exhibiting interconnected channels lined by thin spindle cells [24]. The spaces in these tumors contain a mucopolysaccharide substance and are lined by myofibroblasts. The interconnected slitlike spaces resemble vessels, hence the name “pseudoangiomatosus.” It is a relatively common entity, frequently seen microscopically in normal tissue at breast biopsy and in mastectomy specimens. PASH is often associated with proliferative and nonproliferative fibrocystic changes in areas of gynecomastia and is frequently associated with lobular hyperplasia [25]. Histologically, it can be mistaken for a low-grade angiosarcoma or phyllodes tumor. PASH is most likely to be confused histologically with angiosarcoma if red blood cells are found within the spaces on core biopsy.

PASH has been hypothesized to represent an exaggerated response of estrogen-primed breast tissue to progesterone [24]. Although it is more commonly seen in premenopausal women as an incidental finding at biopsy [26], PASH can present as a clinically or mammographically detected rubbery tumorlike mass [27] and has been reported in children [28].

At ultrasound, tumorlike PASH is most often solid and hypoechoic, oval in shape, and oriented parallel to the chest wall [26]. Sonographically, they are often similar in appearance to a fibroadenoma and can be multiple in number. Posterior acoustic enhancement or no alteration of posterior acoustics is generally seen. In a minority of cases, small anechoic spaces may be evident, corresponding to apocrine-lined cysts at histopathology. Management requires thorough evaluation of the biopsy specimens to ensure that the lesion is benign and not a sarcoma. Generally, imaging follow-up is sufficient for pathologically benign lesions. In the pediatric population, if surgical excision is considered, it should be approached cautiously to avoid injury to the developing breast bud [29]. Rarely, tumoral PASH may grow rapidly in adolescents and require more extensive surgery [23] (Fig. 6).

Juvenile Papillomatosis
Juvenile papillomatosis is a benign rare proliferative breast mass uncommonly seen in children. Histologically, the lesion is characterized by papillary epithelial hyperplasia found within the small ducts and lobules [30]. Numerous cysts and dilated ducts are present, separated by areas of dense stroma, giving
the lesion a “Swiss cheese” appearance [31]. Clinically, patients with juvenile papillomatosis present with a firm but mobile well-circumscribed mass that can be mistaken for a fibroadenoma. Juvenile papillomatosis on ultrasound shows a heterogeneous echotexture with small anechoic areas along the border, representing the numerous small cystic spaces seen histologically [32]. Surgical excision is the treatment of choice. Patients with juvenile papillomatosis are at a slightly increased risk for the development of breast cancer simultaneously or at a later date. This risk is greater if there is bilateral or recurrent disease or there is a family history of breast cancer. Juvenile papillomatosis is also considered a marker for familial breast cancer. With the diagnosis of papillomatosis, there is an increased rate of having a positive family history of breast cancer, ranging from 33% to 58% of cases [23]. Therefore, patients with juvenile papillomatosis should be monitored closely (Fig. 7).

Vascular Lesions

Unlike in adults, vascular lesions in the pediatric breast are usually benign, most commonly hemangiomata [17]. These hamartomatous lesions are extremely rare, and their outcome and clinical features vary with the histologic features. Some lesions grow rapidly and often involute rapidly, whereas others simply grow slowly [33]. In general, pediatric breast hemangiomas do not respond to corticosteroids, and, if the lesions do not resolve spontaneously, excision may be required (Fig. 8).

Phyllodes Tumor

Phyllodes tumor is a rare stromal tumor that, like the fibroadenoma, arises from the specialized lobular connective tissue. It is the most common primary breast malignancy in adolescents [15]. There is a higher incidence of phyllodes tumors in people of Asian heritage [34]. Clinically, these lesions present as rapidly growing breast lumps.

In children and adolescents, most phyllodes tumors exhibit a benign behavior; however, some lesions show a high rate of recurrence or can metastasize. Generally, several histologic features (including increased stromal cellularity, cellular atypia, stromal overgrowth, and the presence of sarcomatous elements, infiltrative margins, and necrosis) are used to predict which tumors have a more malignant behavior [34]. The malignant variety contains sarcomatous elements, infiltrative margins, stromal cell atypia with nuclear pleomorphism, and stromal overgrowth.

Recurrence rates correspond with tumor biology, with more benign phyllodes showing a lower recurrence rate (10–25%), whereas malignant phyllodes tumors have a recurrence rate of up to 40% [34].

At ultrasound, these tumors can appear identical to fibroadenomas and juvenile or giant fibroadenomas, displaying circumscribed borders, low-level internal echoes, and small cysts [35]. Histologic examination with ultrasound-guided core needle biopsy is indicated when children and adolescents present with rapidly growing lesions that may be phyllodes tumors, because imaging findings and fine-needle aspiration do not distinguish between benign and malignant forms.

Metastatic Disease

In the pediatric population, metastatic cancer of the breast is more common than primary breast cancer. Lymphoma, leukemia, and rhabdomyosarcoma are the most common primary tumors that metastasize to the breast in pediatric patients [17] (Fig. 9).

Primary Breast Carcinoma

Primary breast carcinoma is exceedingly rare in pediatric patients, comprising less than 1% of childhood cancers and less than 0.1% of all breast cancers [36]. The tumor most frequently reported in the literature is secretory carcinoma, which is less aggressive than infiltrating ductal carcinoma, though it does possess malignant potential and can recur locally and metastasize to axillary nodes. A recent review of Surveillance, Epidemiology and End Results data [37] included secretory carcinomas in patients ranging in age from 11 to 86 years and noted a 5-year overall survival of 87.2%, with no deaths reported among the patients treated with lumpectomy and radiation therapy. Clinically, secretory carcinoma of the pediatric breast presents as a firm and immobile painless enlarging mass [38]. At sonography, the lesions are most frequently round or oval, with circumscribed or partially microlobulated margins and hypoechoic relative to fatty breast tissue [39]. Treatment is surgical, though there is great debate and variability in the extent of surgery performed for these lesions.

Primary Breast Carcinoma as a Secondary Neoplasm

Children who undergo radiation treatment for cancer are at elevated risk for developing secondary neoplasms [40]. Breast cancer is the most commonly seen solid secondary neoplastic tumor, developing most frequently in young girls who undergo mantle irradiation for the treatment of Hodgkin disease. The breast cancer risk for women who are survivors of Hodgkin disease is 75 times that of the general population [41]. Those at greatest risk are young women who were treated between the ages of 10 and 16 years. The majority of tumors develop within the field of radiation. Because the risk for solid tumors continues to increase with years past survival, screening is integral, and consideration should be given to chemoprevention. American College of Radiology guidelines recommend screening mammography 8–10 years after completion of therapy but not before age 25 years [42]. Women who have received radiation treatment to the chest are at increased risk for development of breast cancer, and MRI screening is recommended in this group as an adjunct to screening mammography [43].

Role of Percutaneous Procedures in Pediatric Breast Lesions

When developmental variations are discovered, biopsy is not indicated and can damage the developing breast bud. With careful sonoographic technique, many lesions can be characterized as benign by ultrasound and can be followed for growth, avoiding biopsy. However, lesions that are growing or atypical in appearance may require biopsy, and core biopsy is preferred as the least invasive method of establishing a diagnosis.

Conclusion

When pediatric patients present to their primary care physician with a possible breast abnormality, parental concern is often high. However, many of the breast findings in childhood are variations of normal development and require reassurance but no imaging. When a patient is referred for imaging, a complete history is essential in guiding management. Ultrasound is the preferred imaging tool and can be used to both characterize benign physiologic changes of the breast (e.g., asymmetric breast development or gynecomastia) as well as more fully characterize neoplastic processes of the breast. When a neoplastic process is evident on imaging, ultrasound can be used to monitor stability or interval growth. Histologic diagnosis by core biopsy is appropriate when the lesion shows rapid growth or has atypical features. As with any needle-guided procedure, careful radiologic-pathologic correlation is required to ensure accurate diagnosis. In the pediatric patient, MRI of the breast...
is rarely used, though in select cases it may be useful for surgical planning or assessing the extent of disease.

References
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Fig. 1—17-year-old boy with unilateral asymmetric gynecomastia of right breast, with pain for 4 years. Patient is of Ashkenazi Jewish descent.
A, Ultrasound of right breast shows hypertrophied tissue (arrow).
B, Comparison image of normal left breast shows normal thickness of breast tissue (asterisk). Because of patient’s elevated risk of BRCA1 and BRCA2 mutations, family history of breast cancer, and psychosocial issues related to significant asymmetry of his breasts, elective unilateral mastectomy was performed.

Fig. 2—19-year-old woman with left breast abscess. Patient was not lactating but had left nipple ring and presented with left breast pain for 2 months with new development of palpable mass and associated erythema.
A, Single ultrasound image shows left breast abscess (arrow) at 4 o’clock radian, 3 cm from nipple. Note peripheral ring of increased vascularity. Abscess is round and hypoechoic with mobile internal debris of mixed echogenicity.
B, Image obtained after ultrasound-guided aspiration shows nearly complete collapse of abscess cavity (asterisk). After needle aspiration, patient underwent incision and drainage of abscess performed by breast surgeon, with placement of drain. Cultures showed gram-positive cocci. Patient was given appropriate oral antibiotic therapy and showed interval improvement during her follow-up examination with no recurrence of abscess.

Fig. 3—19-year-old woman, 2 months postpartum and breast-feeding, who presented with palpable lump in her right breast. Antiradial sonographic image of right breast at 9 o’clock radian, 1 cm from nipple, shows well-circumscribed oval complicated cystic lesion (arrow) with multiple internal septations and posterior acoustic enhancement, consistent with galactoceles. Short-term surveillance was chosen. Ultrasound of left breast performed 6 months later at follow-up (she was still nursing) showed no change in galactoceles. Because this lesion was palpable, it was recommended that patient be monitored with clinical breast examinations.
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Fig. 4—15-year-old girl with complex fibroadenoma. Patient presented with palpable right retroareolar mass. Initial ultrasound showed hypoechoic macrolobulated mass (asterisk) of mixed echogenicity in right breast at 6 o’clock radian, 3 cm from nipple. Mass shows cystic and solid components and mixed posterior acoustic shadowing, and it enhanced through transmission of sound. Given that mass was new, palpable, and complex in appearance, ultrasound-guided core biopsy and surgical consultation were recommended. Patient and her family decided against ultrasound-guided core biopsy and instead chose excisional biopsy. Pathologic analysis confirmed that lesion was complex fibroadenoma.

Fig. 5—16-year-old girl with juvenile fibroadenoma who presented with painless lump in subareolar region in left breast at 3 o’clock radian.
A, At ultrasound-guided biopsy, mass (arrow) proved to be juvenile fibroadenoma. Juvenile fibroadenomas usually present as hypoechoic mass of mixed echogenicity. Short-term (6-month) clinical and imaging follow-up was recommended.
B, Follow-up ultrasound and clinical breast examination showed stability of lesion. Patient opted to have mass excised because of increasing discomfort. Surgical pathologic examination verified presence of juvenile fibroadenoma.
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Fig. 6—16-year-old girl with tumoral pseudoangiomatous stromal hyperplasia (PASH) who presented with painless rapid enlargement of her left breast over 6-month period. A, Initial evaluation was performed with ultrasound of left breast followed by ultrasound-guided core biopsy. Lesion (arrow) was diagnosed as tumoral PASH. B–E, Bilateral breast MRI was then performed to evaluate extent of lesion and to guide surgical therapy. MRI included T1-weighted contrast-enhanced (B), T1-weighted contrast-enhanced with subtraction (C), T1-weighted contrast-enhanced multiplanar reformation (D), and T2-weighted SPAIR (spectral adiabatic inversion recovery) (E) sequences. MRI examinations show large well-encapsulated hypervascular mass (asterisk, B), with large peripheral vessels causing mass effect on adjacent breast tissue. Removal of tumoral PASH was performed by breast surgeon in conjunction with plastic surgery for reconstruction of left breast to achieve breast symmetry.

Fig. 7—14-year-old girl with juvenile papillomatosis. Patient presented with complaint of new soft palpable mass in upper inner quadrant of right breast. Initial diagnostic ultrasound shows oval-shaped mass (arrow) that is parallel in orientation, measuring 4.8 × 2.8 cm, at 1 o’clock radian, 3 cm from nipple, in right breast. Mass is of mixed echogenicity with both solid and cystic components. Patient returned for ultrasound-guided core needle biopsy and surgical consultation. Pathologic analysis of core needle biopsy showed juvenile papillomatosis without atypia. Right breast lumpectomy with wide margins was performed, with surgical pathologic analysis also showing extensive juvenile papillomatosis without atypia. Close clinical follow-up by breast surgeon was recommended because of slightly elevated risk of breast cancer associated with this lesion.
Fig. 8—3-year-old girl with left breast hemangioma. Contrast-enhanced chest CT was performed with positive PPD (purified protein derivative) to evaluate hilar adenopathy. Multiple enhancing masses (arrow) are noted in left breast, supplied by left internal mammary and axillary vessels. Findings are consistent with patient’s known left breast hemangioma, which was being followed clinically.

Fig. 9—12-year-old girl with metastatic rhabdomyosarcoma to left breast. A, There was asymmetric soft-tissue density in left breast (arrow), in comparison with right breast, which increased on subsequent follow-up. B, On follow-up examination, patient also developed metastatic disease (arrow) to ribs, lungs, mediastinal lymph nodes, and other soft tissues, as well as large pericardial effusion, not fully visualized on these single images. She died within few months after this CT examination.

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