# Physiological and Pathological Aspects of Full Breast Ultrasonography in Men and Children

# 10

## 10.1 Male Breast Gynecomastia

*Gynecomastia* represents the development of the mammary bud in true mammary glandular structures in male, similar but usually incompletely developed as compared with female breast.

The normal male breast is represented by a small mammary bud, located retroareolarly, with hypoechoic aspect, usually with acoustic shadowing, surrounded by various amount of subcutaneous fatty tissue. No vascular signal could be detected by Doppler examination with usual transducers. Clinically, there is normal sensibility in the mammary area.

Gynecomastia may be suspected clinically by increasing of the mammary volume, simultaneously with the development of the nipple-areolar complex; the development may be continuous, but frequently it has alternate stages of calm and acute evolution. The active development is usually painful, and the patient addressability is increased, or the size of the breasts determines esthetical complaints.

Anatomically, gynecomastia is structured by the developed glandular parenchyma represented by branching ducts of the retroareolar bud; the breast ducts may have multiple branches, from the main ducts to ductules, but rarely the lobular structures can be identified, such as in severe hyperestrogenism. As in the female breast, the galactophorous ducts are surrounded by normal stroma containing new formation vasculature. The vasculature is proportional with the size of the breast and is more salient during the evolutive stage. These three elements in various proportions (mammary parenchyma, glandular stroma, and new formation vasculature) can be identified by Doppler DE and represent the essential findings for the positive diagnosis of gynecomastia [1].

The most frequent differential diagnosis is the *pseudogynecomastia*, which appears as an enlarged "breast tissue" represented by fatty tissue hypertrophy surrounding the small mammary bud. The other rare differential diagnosis is *mass-forming tumors*, and breast cancer in male is the most severe and usually the unique lesion treated. Breast tumors related to the mammary parenchyma are rare and develop almost always in preexistent changes of benign gynecomastia. Other tumors in the same area with no mammary origin are rare and are not correlated with the glandular mammary development.

*Physiological gynecomastia* has peak frequencies at three periods during the lifetime: in the neonatal period, in the adolescence, and in elderly men.

In the neonatal period, gynecomastia is due to influences from maternal estrogens across the placenta, and the spontaneous resolution occurs in 2–3 months.

During puberty, the peak frequency occurs at about the age of 13–14 years, and as many as 60 % of male adolescents are affected. Gynecomastia in a male adolescent typically resolves within months to 2 years. Logically, after 16 years, florid gynecomastia could be considered pathological.

In elderly men, physiological gynecomastia is not well defined, either concerning the limits of age or the evolution. In fact, it is generally difficult to differentiate the physiological from the pathological gynecomastia in elderly men, because the etiologic factors are combined. When present, the positive diagnosis of the physiological gynecomastia is made by exclusion of the main pathological etiologies.

*Pathological gynecomastia* is represented either by the "true" benign gynecomastia, which occurs in childhood, adulthood or elder male in other lifetime periods than the physiological changes, or by the malignant gynecomastia with associated malignant mass forming tumor; 65 % of breast masses are found in elderly man.

There are many conditions for the pathological breast development in boys and men, well known and with many classifications. Most authors admit that estrogen, acting through its receptor (ER), promotes ductal growth, while progesterone, also acting through its receptor (PR), supports alveolar development. It seems that low level of testosterone and the disequilibrium between estrogens and male hormones raise the risk of breast cancer in male, conditions found in undescended testes, orchiectomy, orchitis, testicular injury,



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late puberty, and infertility [2]. Moreover, the association of the high blood cholesterol, rapid weight gain, benign breast conditions, and possibly obesity may be correlated with hormonal disequilibrium in some metabolic diseases including diabetes. Dyslipidemia combined with hyperestrogenemia is associated with men infertility [3]; similarly, in boys, adiposogenital syndrome associates the testosterone insufficiency with obesity. Any type of goiter is more frequently present in people with breast pathology of both sexes, but the mechanism is not very well explained [4, 5]. However, there are studies that demonstrate the correlation between hyperestrogenemia, goiter, and adrenal hyperplasia [6].

Rare cases present male hyperprolactinemia usually due to a pituitary microadenoma, with ductal ectasia containing milk secretion, but the nipple surges are usually absent due to hypoplastic pores [7].

Many patients without any internal endocrine pathology could present gynecomastia due to the food contamination with estrogens. Despite the negation of food producers, it seems that restriction to some contaminated aliments improves the patients' complaints and the clinical evolution is at least stopped. The ubiquitous environmental contaminants bisphenol A (BPA) and 4-nonylphenol (NPH) may promote adverse effects in humans triggering estrogenic signals in target tissues; thus, the results of the hormonal tests indicate that *the biological action of environmental estrogen such as BPA and NPH should be taken into account for the potential impact on human disease-like hormone-dependent breast cancer* [8]. The estrogenic effects of such industrial agents together with an increasing widespread human exposure should be taken into account for the potential influence also on hormone-dependent breast cancer disease [9].

Familial cases of gynecomastia could be assigned to some nutritional factors (food contaminants of estrogens), rather than to genetic factors; the differential diagnosis may be the clinical evolution after several months of dietary treatment.

The correct diagnosis of the pathological gynecomastia, either benign or malignant, includes the evaluation of its etiology; some cases may be considered as symptoms of a distant tumor that require for further examination. In some cases, gynecomastia is a sign of adrenal or testicular feminizing tumors with hyperestrogenism; in other cases, milk-secreting gynecomastia may reveal a pituitary prolactinoma [1].

**The clinical appearance** as a retroareolar painful lump has usually asymmetrical development, but rarely is found unilateral. Breast glands under estrogenic stimulation tend to grow, be sensitive, and be tender and may hurt. Usually, the diagnosis of gynecomastia is made by the physician by just simple observation and the presenting history. The visual inspection may identify as stages I–IV based on the Tanner grading system (Fig. 10.1). The breast is always palpated to ensure there are no hard masses present.

**Mammography** is sometimes used but without a significant role in the evaluation of breast mass in males, because a mammogram requires fairly decent sized breasts to be placed between the two mammographic plates and it is difficult to differentiate the eventual opacity as simple gynecomastia or tumoral lesion [10]. In addition, mammography could not be used in children.

The radiological findings of the breast male were classified according to the aspect of projections of the breast tissues on the plain-film or digital acquisitions [11, 12]:

- *Nodular glandular opacity (acute/florid phase)*
- *Dendritic opacity (chronic fibrotic phase)*
- *Diffuse glandular* (Fig. 10.2)

**The Classical US** The classical US is usually recommended for the identification of cysts, other fluids, or solid masses, but neglecting the glandular anatomy, it was not possible to analyze the types of benign gynecomastia, and being operator dependent, US was not considered as a reproducible, accurate method of diagnosis [13].

Usually, gynecomastia is presented on classical US scans performed directly over the palpable area in the breast as *hypoechoic tissue* in the subareolar region, considered as *breast tissue;* this appearance mimics the US findings of early breast development in female adolescents. US scan of the opposite breast may present a similar appearance, although the *hypoechoic tissue* may be less prominent, almost always coexisting bilateral more or less symmetrical gynecomastia.

The differential diagnosis of gynecomastia with other pathological masses is difficult to perform in the classical US, because the breast cancer usually is hypoechoic too, similar to the fatty tissue; the Doppler usefulness is not widely accepted, and most cases of breast cancer in males are usually misinterpreted. The lack of imaging diagnosis is compensated by breast biopsies, which are painful, with risk of hematoma up to 94 % 1 week after vacuum-assisted biopsy and 55 % after 3 weeks [14]; otherwise, because malignancies are rare in male breast, biopsies are usually unnecessary.

**The FBU** aspects of the three essential anatomical elements of gynecomastia are easily demonstrated; the technique of radial and antiradial scanning and the images' analysis are similar to the female breast [15]:

1. *The true mammary parenchyma* is represented by the retroareolar bud; it appears as a hypoechoic mass of pyramidal shape, the basis on the thoracic wall and the apex to the nipple; when gynecomastia is developing, the periphery of the bud is branching in ducts, more extended in the upper-outer quadrant; the initial branching is less specific, but the advanced stages present typical ducts with the hyperechoic central line representing the virtual lumen of

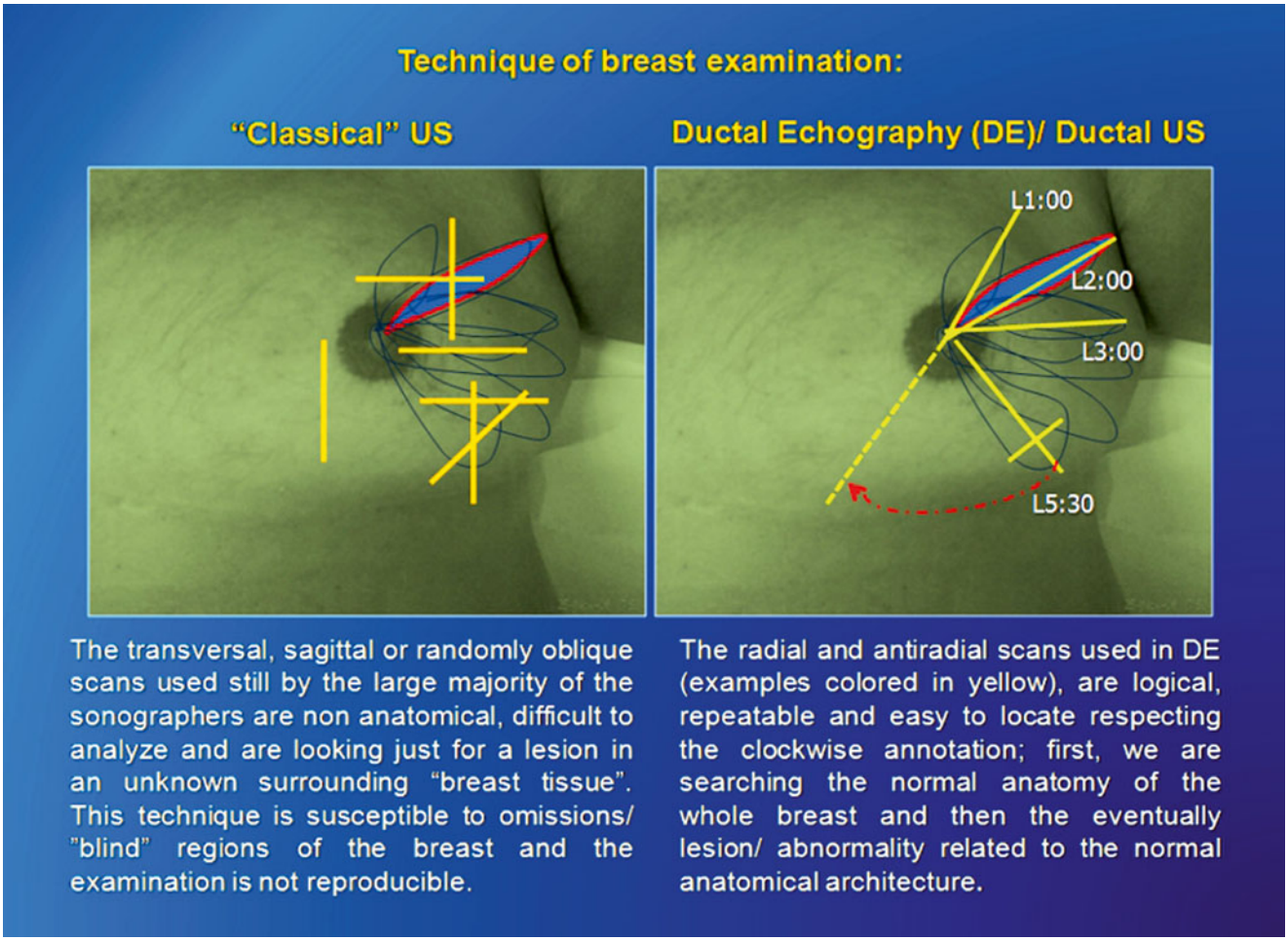


**Fig. 10.1** Technique of examination of the male breast: "classical" US versus ductal echography (based on [16])

the "normal" ducts. The ducts may contain fluids, determining the ductal ectasia with the same appearance as in women: the secretions may appear transonic or more echoic, corresponding to serous up to milk secretions that are found in men with pituitary microprolactinoma. The lobules are usually not visualized, but they may appear in the advanced stages of gynecomastia or in relation with high hyperestrogenism. The salient lobules are associated with ductal thickening which is presumed as hyperplasia; in these cases, an adrenal or testicular feminizing tumor may be responsible for.

2. *The stromal component*, representing the connective, functionally supportive framework of the biological glandular cells (the mammary parenchyma); stroma represents in fact an amount of tissues containing connective cells, fibers, the arterial and venous vasculature, the lymphatic vessels, and the nerves, determining a general hyperechoic aspect. The presence of stroma in FBU appears as a hyperechoic structure surrounding the parenchymal bud and prolonged between its branches.

Stromal development is simultaneous and proportional with the branching bud evolution, and its presence is essential to confirm a mammary glandular architecture, both in "true" gynecomastia and in premature thelarche; the specific glandular stroma is thick and with irregular borders, while the fatty tissue has only a thin hyperechoic conjunctive septae between large areas of hypoechoic fat.

3. *The new formation vasculature* is essential in the developing breast, such as gynecomastia or thelarche. Color and power Doppler are useful in confirming the diagnosis. The number and the size of the detected vessels are correlated with the size of the male breast and with the developing process intensity; the increasing vasculature becomes salient in the forming stages and the decreasing of the vascular network is significant for the stabilized, inactive stages. In gynecomastia, the spectral Doppler illustrates arterial velocimetry with low resistance and pulsatility flux indices, specific for the breast as "normal" anatomical organ, but this is unusual for the subcutaneous fatty tissue in pseudo-gynecomastia. The follow-up FBU

| Clinical presentation | Age 60's, soft or hard, mobile or fixed, usually painless, subareolar usually eccentric, usually unilateral, recent evolution |
|---|---|
| Mammography | Limited applications due of breast size, does not visualise the ducts, rarely evidence of micro - calcifications, requires biopsy [10]:<br>• Large mass: lobulated border<br>• Small mass: spiculations |
| Breast MRI: | Less availability, does not visualise the ducts, use of paramagnetic contrast agents, requires biopsy |
| Classical US | The hypoechoic retroareolar eccentric mass similar to the "breast tissue" (incomplete characterisation), more or less regular contour, requires biopsy |
| Doppler Ductal US with RTSE = FBU | Pathological mass connected to ducts, new vasculature with tortuous shape, plunging artery with incidental angle and centripetal orientation; RTSE with score 4 or 5 Ueno/Tsukuba and high FLR over 5.00; biopsy ± |

**Fig. 10.2** The methods of diagnosis of gynecomastia (based on [16])

examination is useful in assessing the therapeutic response or the spontaneous resolution in newborn or teenager boy.

In a study of 2009, we presented an analysis of 47 cases of "true" benign gynecomastia examined by the FBU technique [1]; all the patients aged 8 months to 67 year old presented the elements of breast anatomy described, and particular cases were observed:

- Five cases of ductal ectasia correlated with hyperprolactinemia, from which one case had pituitary microprolactinoma.
- Seven cases of ductal-lobular hyperplasia, up to 3 mm, correlated with hyperestrogenism: one case presented an adrenal adenoma, three cases presented diffuse adrenal hyperplasia with hypercortisolemia and hyperestrogenemia, and three cases without internal hormonal disorders were considered as food hormonal contaminant changes and responded to dietary treatment (2 boys of 8 months and 4 years old, respectively, and a man of 38 years old).
- The rest of the 35 patients presented "simple" gynecomastia, with the three structural anatomical elements in various degrees of development; some cases were considered as "physiological," with spontaneous remission; others were included in various "pathological" degrees; some correlated with diabetes, obesity, goiter, liver insufficiency (increased conversion of androgens to estrogens in severe liver disease [17]), hormonal treatment of prostatic cancer, or dietary factors, especially particular animal fats (Figs. 10.3, 10.4, 10.5, 10.6, 10.7, 10.8, 10.9, 10.10, 10.11, 10.12, 10.13, 10.14, 10.15, 10.16, 10.17, 10.18, 10.19, 10.20, and 10.21).

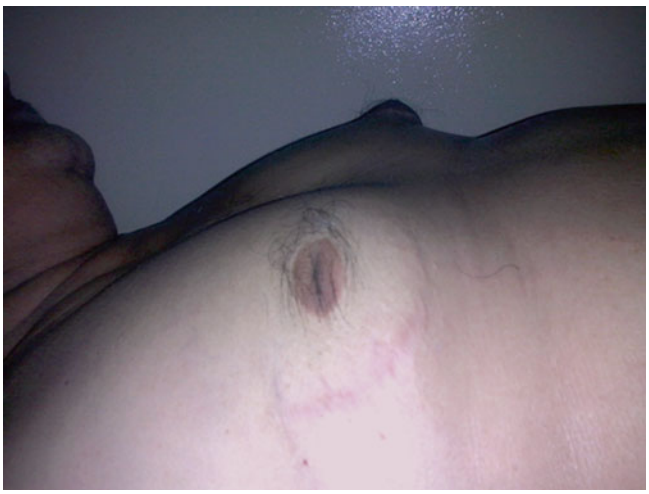

**Fig. 10.3** Gynecomastia in adult with Tanner IV stage visible to the left breast; inverted right nipple following conservative surgery (unnecessary, because of the benign findings and bilateral evolution), with peripheral arcuate scar in the lowers quadrants

The treatment with spironolactone (Spironolactonum) determines a side effect as antiandrogenic activity, with about 5–30 % of male patients complaining of gynecomastia, impotence, or diminished libido [18]; the increased risk of male breast cancer was signaled about 40 years ago [19], but the incidence of cases is reduced because of the rare overall incidence of this disease.

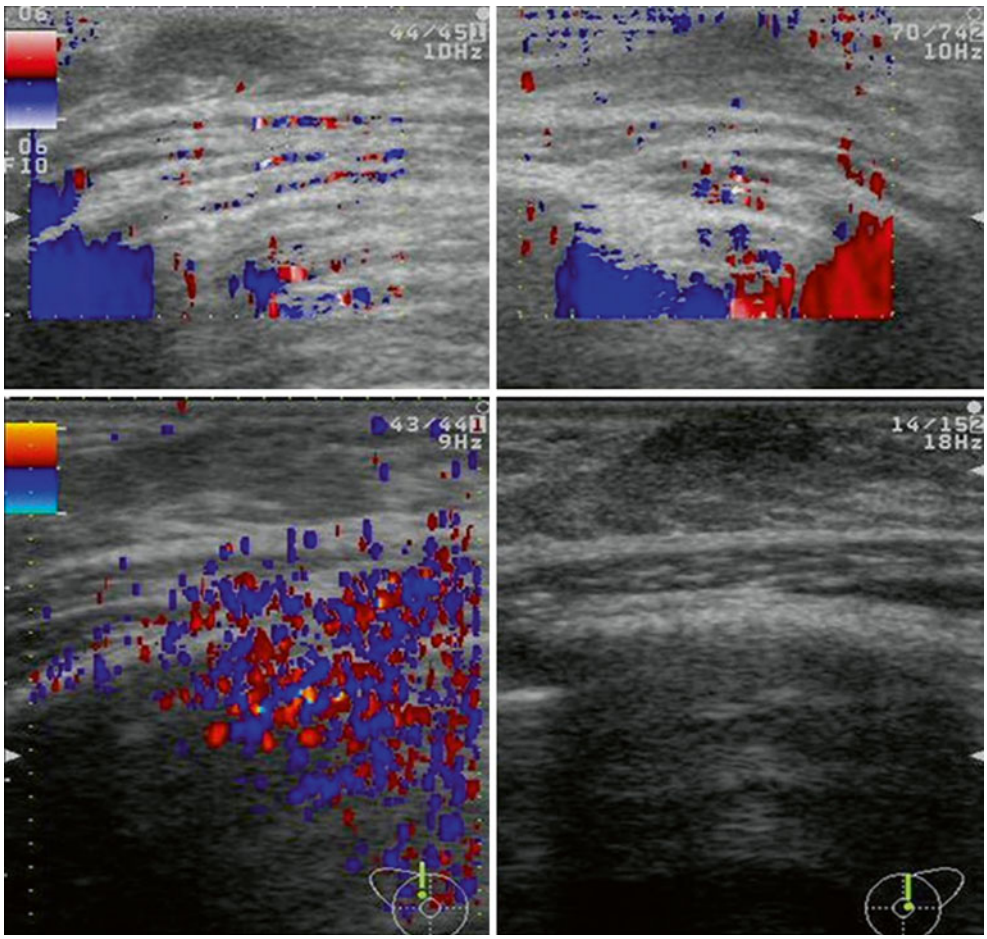


**Fig. 10.4** Infantile gynecomastia: 1-year-old male with bilateral symmetrical mammary bud, probable of exogenous etiology (nutritional); motion Doppler artifacts are the inconveniences of the examination at this age, but the anatomy is well demonstrated (based on [16])

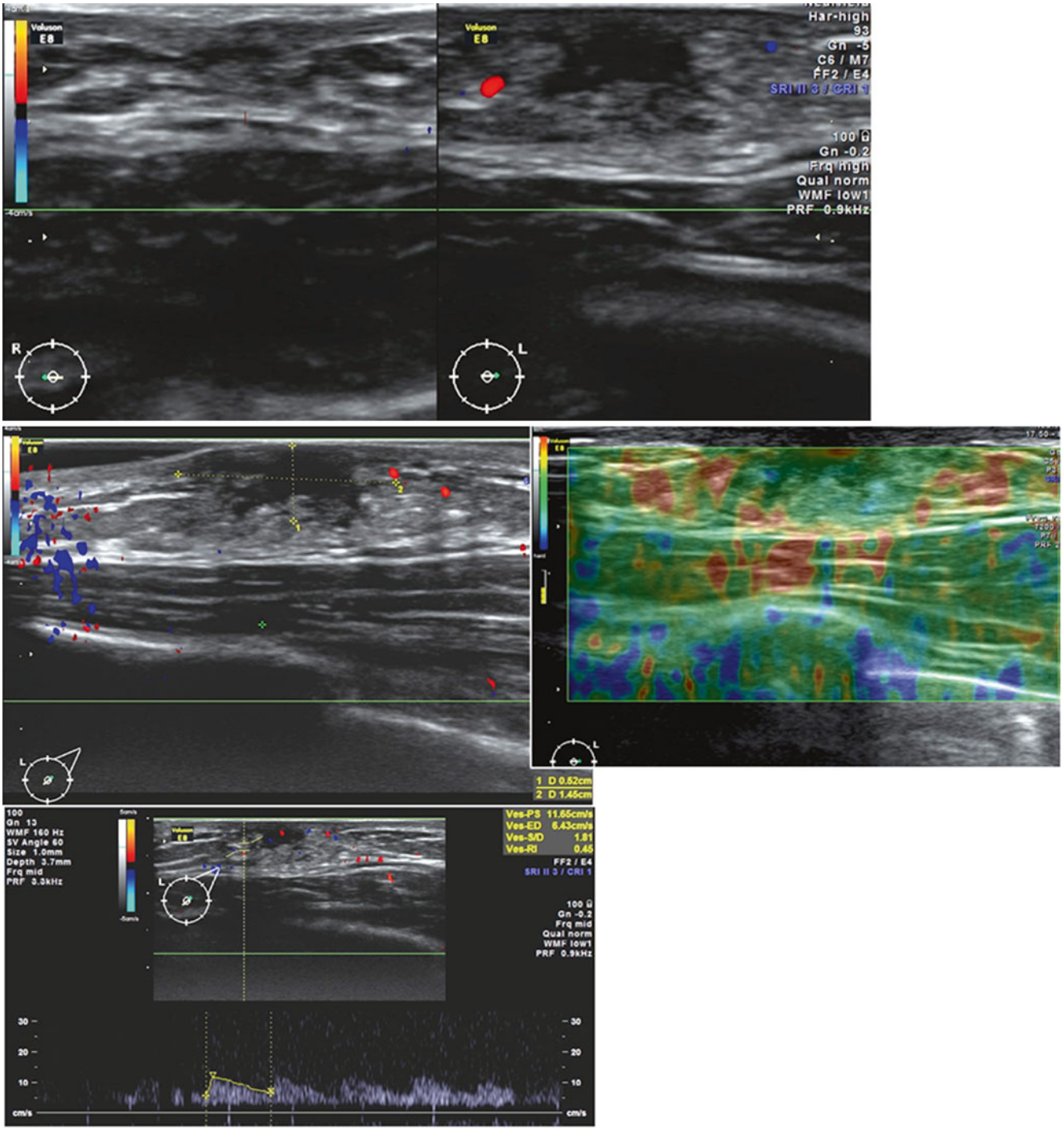


**Fig. 10.5** Asymmetrical precocious pubertal gynecomastia in a 9-year-old boy: first development of the left breast, with the three anatomical elements (the branching bud, surrounding stroma, and new formation vasculature of low resistance velocity). Sonoelastography demonstrates the benign type of mammary strain

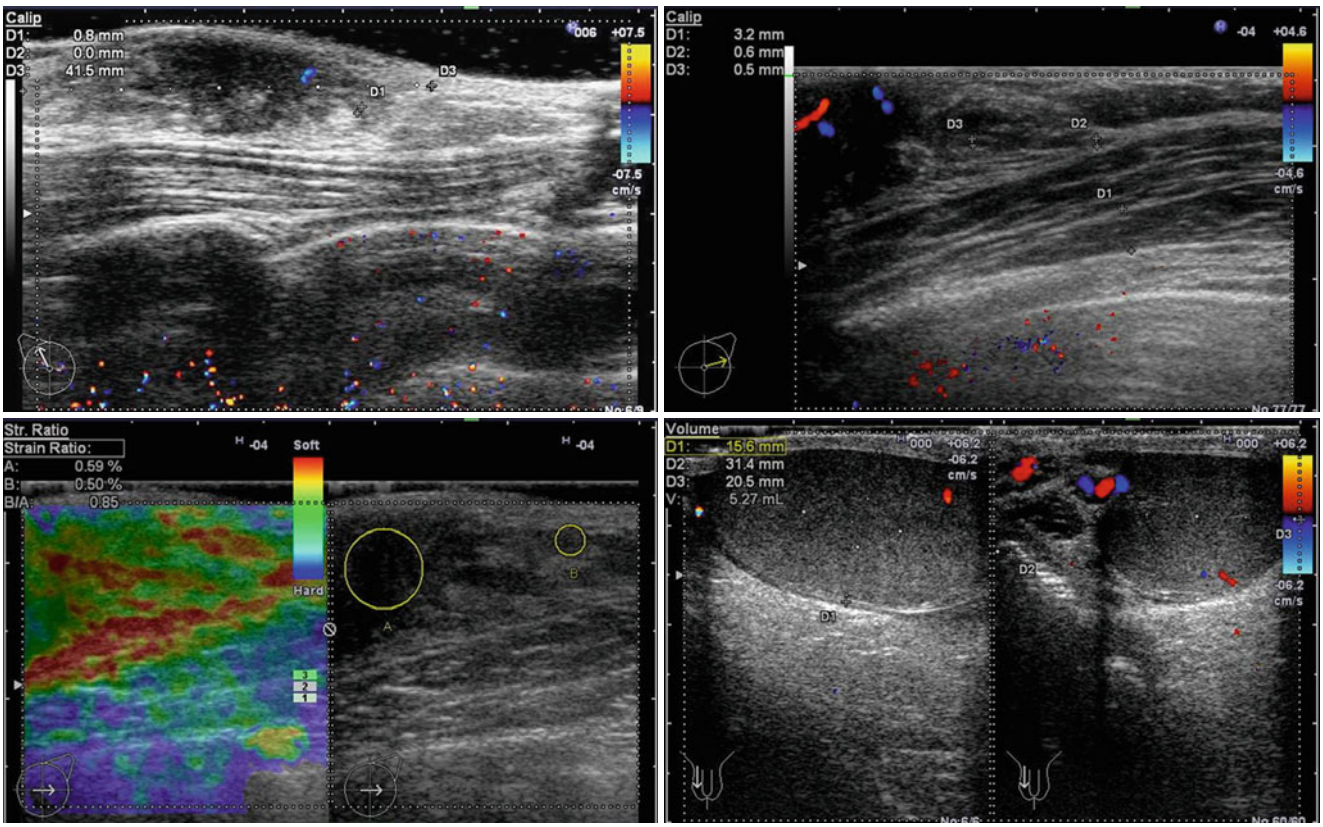


**Fig. 10.6** Physiological pubertal gynecomastia in a 14-year-old boy: the testicular and epididymal size and vasculature are normal in puberty

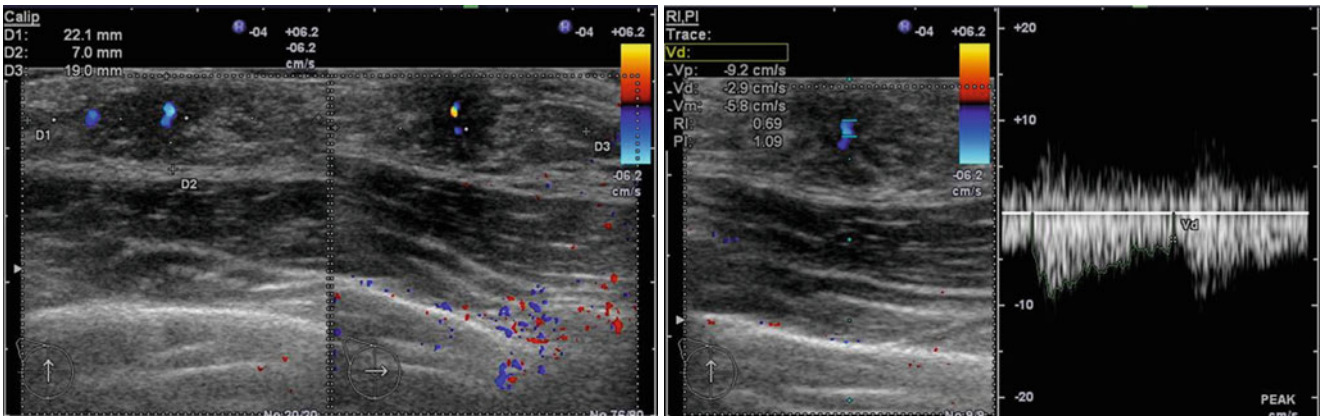


**Fig. 10.7** Pubertal gynecomastia in a 13-year-old boy, with illustration of the three elements: parenchyma (branching of the mammary bud), glandular hyperechoic stroma, and new formation vasculature

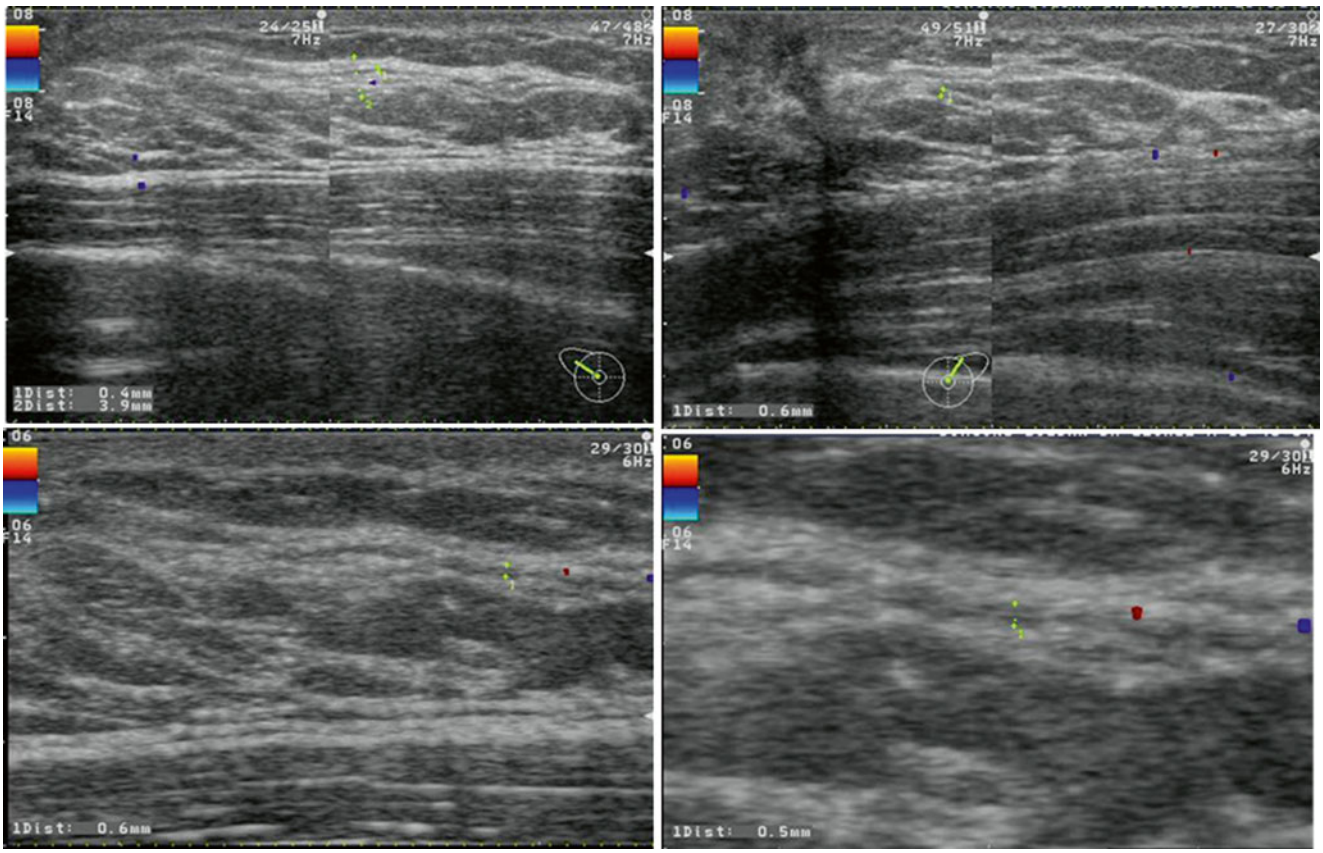


**Fig. 10.8** Advanced pubertal gynecomastia in a 16-year-old boy: true mammary lobes with stroma and ducts containing the hyperechoic central line, a specific sign corresponding to the virtual lumen; despite the age, the size of the breasts is abnormal

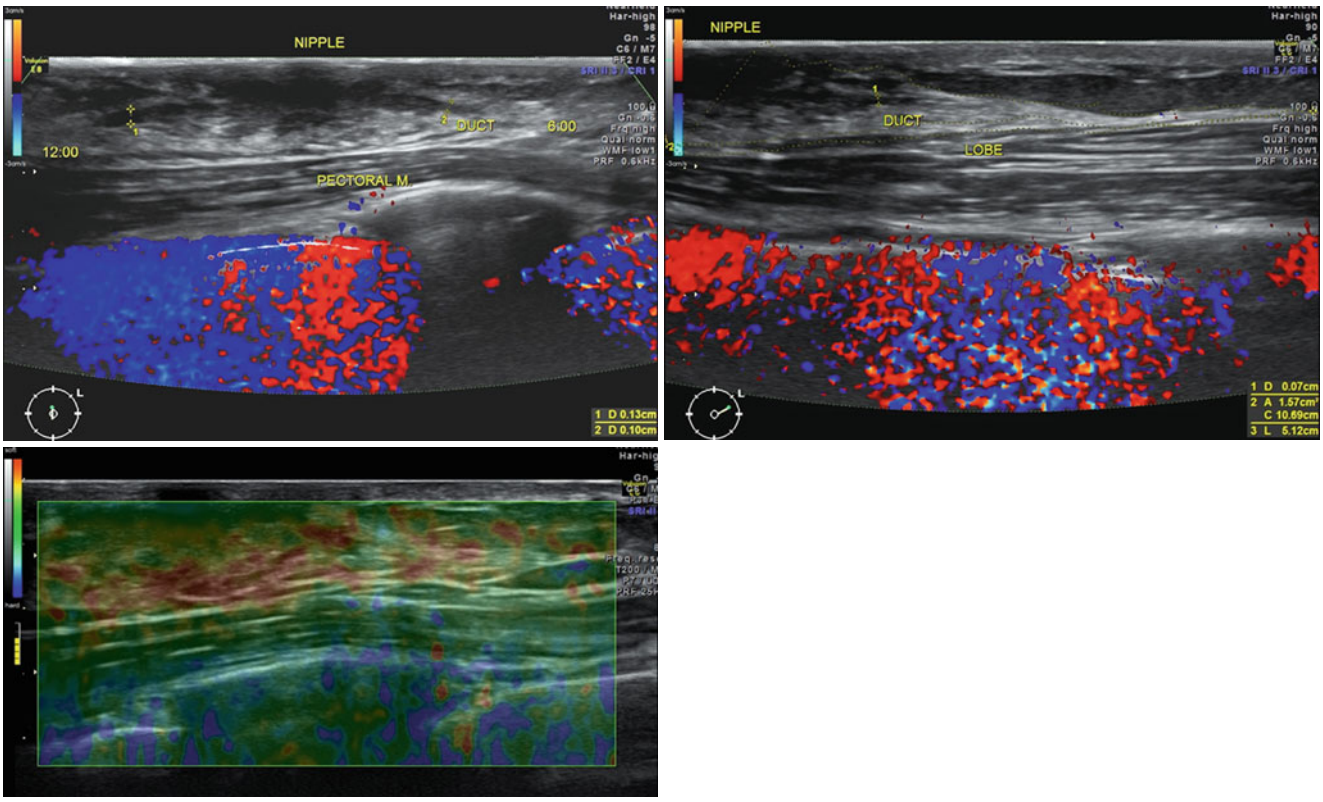


**Fig. 10.9** A 65-year-old man with gynecomastia, without any pathologically proved etiology; the lobar anatomy is similar to the female pubertal breast, but the ductal diameters are usually thinner. Diagnosis: physiological gynecomastia in an older man

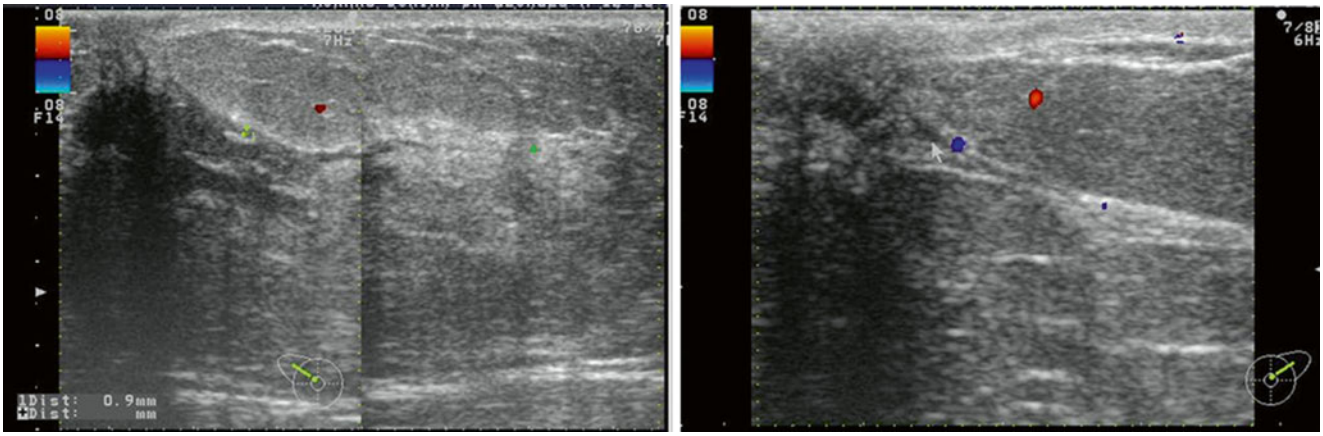

**Fig. 10.10** Familial gynecomastia: 19-year-old son, presenting recent/florid gynecomastia with the three developing elements: branching ducts from the mammary bud, small amount of stroma, and visible new vasculature (based on [16])

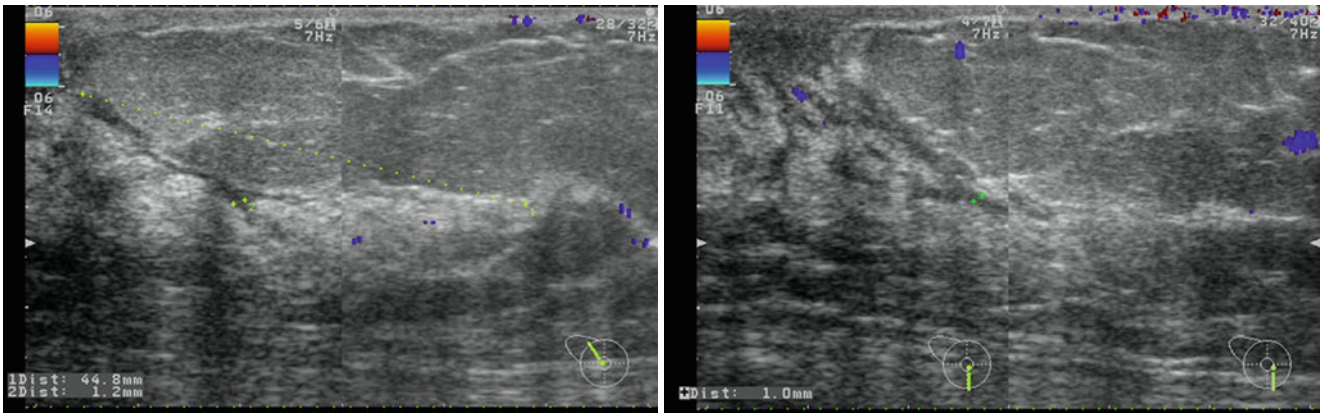

**Fig. 10.11** Familial gynecomastia: 52-year-old father, with chronic gynecomastia for 4 years, presents mammary lobes with elongated ducts, irregular ductal thickening/hyperplasias; the hyperechoic stroma is larger, and there are thick premammary and retromammary fatty layers (type of heterogeneous breast in woman) (based on [16])

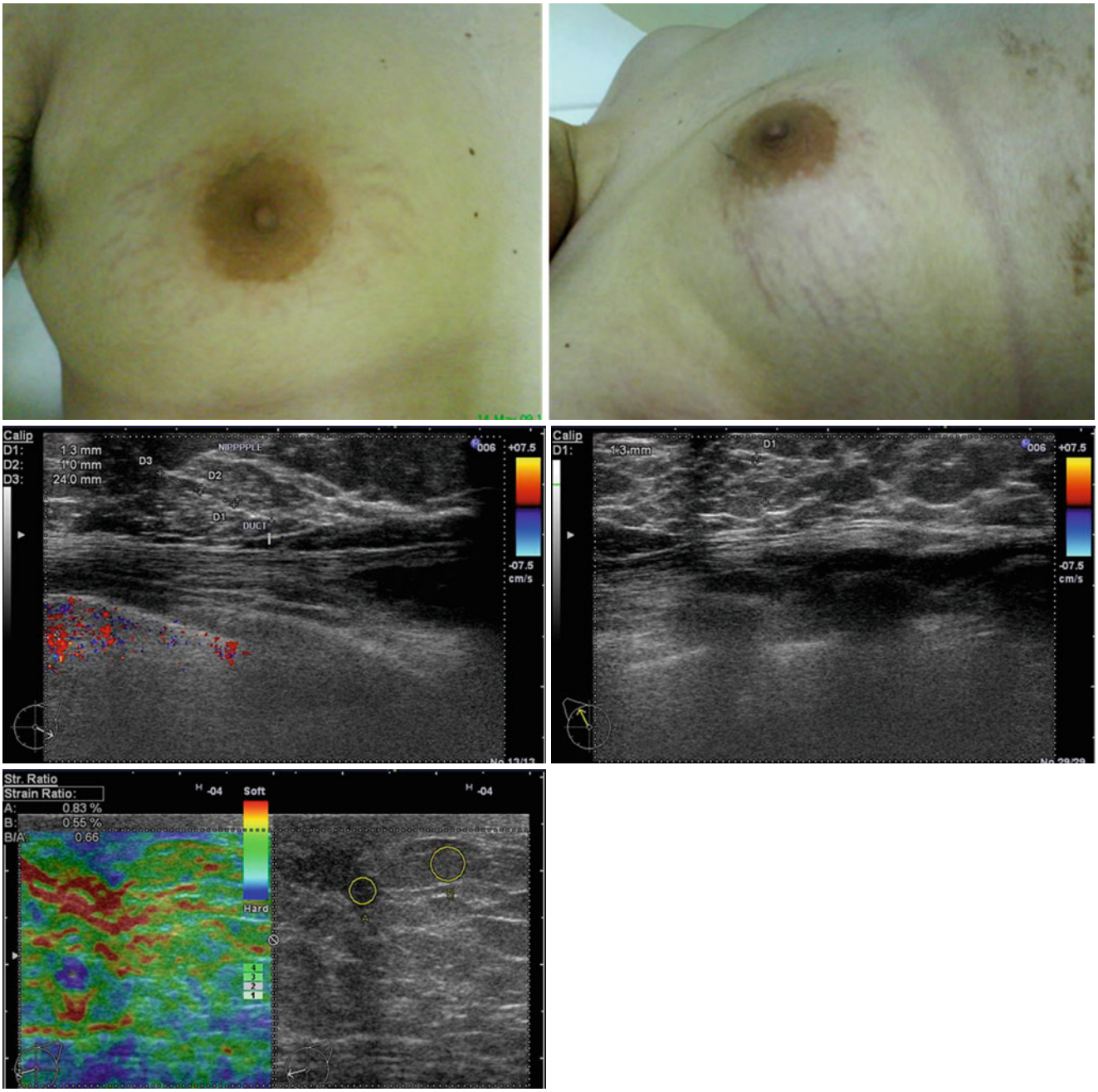


**Fig. 10.12** "True" gynecomastia in a 54-year-old patient, with clinical signs of hypercortisolemia, the Cushing's syndrome: enlarged breasts with large areola demonstrate reddish stretch marks. FBU illustrates retroareolar branching bud: the ducts are typical, with the central hyperechoic line at DE, and sonoelastography delimits the breast parenchyma with score 1 Ueno and low FLR (based on [16])

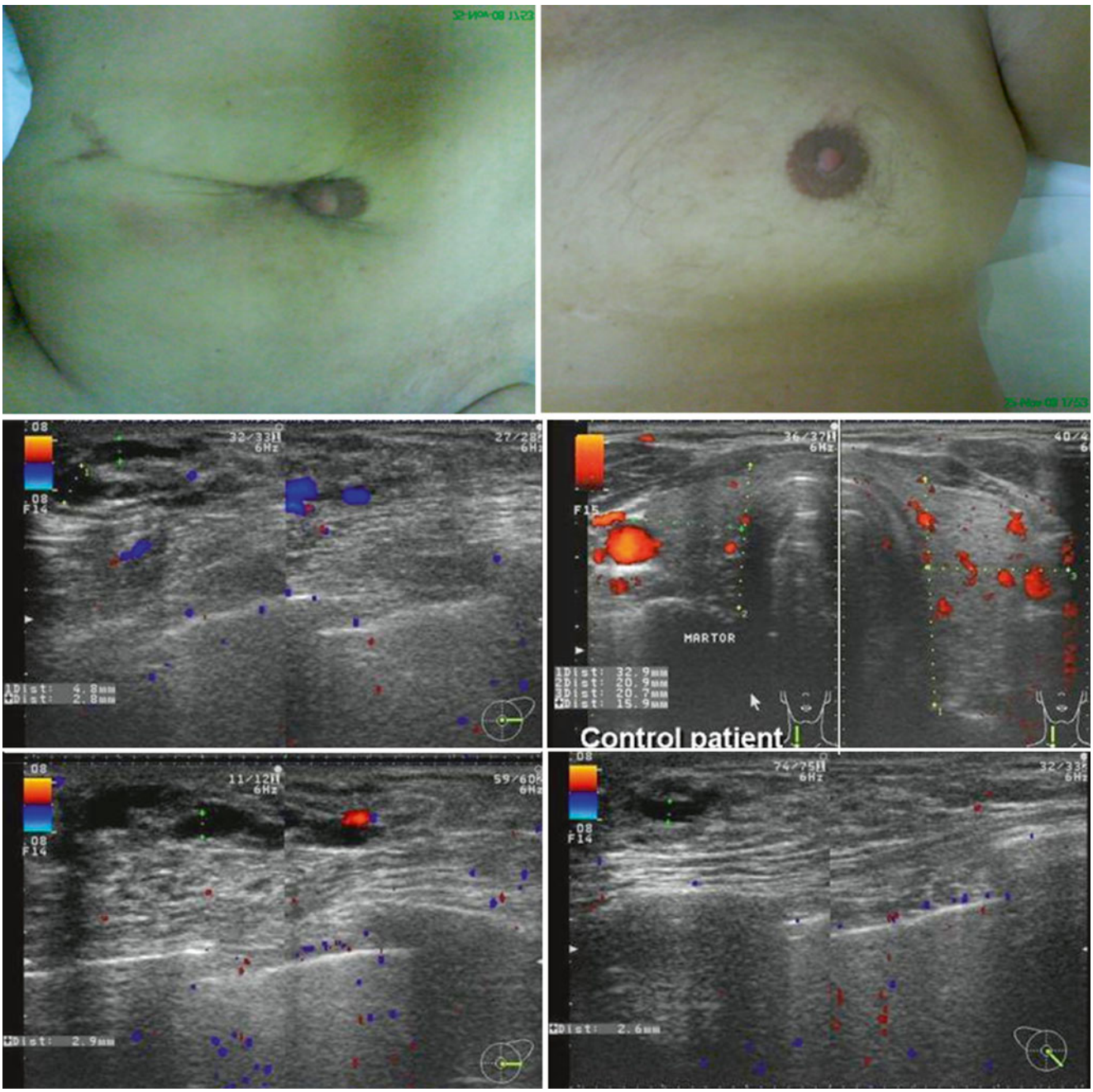


**Fig. 10.13** Galactorrhea in man: 54-year-old male patient after right gynecomastia, misdiagnosed and partially removed (segmentectomy), with local evolution and finally contralateral development equally. The patient presented exophthalmia and Doppler US demonstrated diffuse goiter with moderate increasing of the Power Doppler signal compared to a control patient

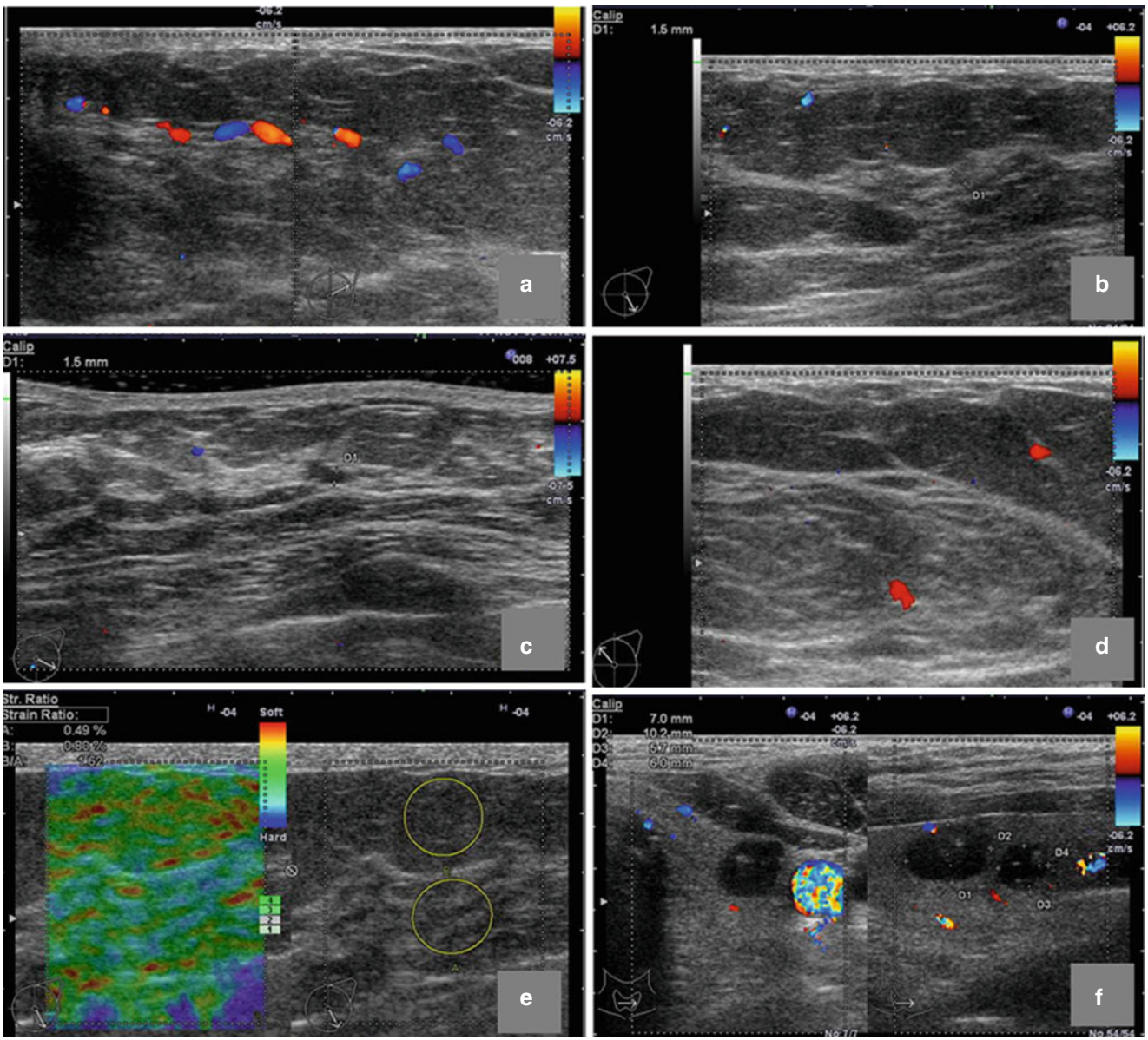


**Fig. 10.14** FBU in a 43-year-old male: gynecomastia with stroma, ducts, and new vasculature (**a**); advanced stage presents terminal ductal-lobular specific units (**b**), small lobular hyperplasias (**c**), and Cooper ligaments with salient vasculature (**d**). Sonoelastography illustrates the normal parenchymal architecture in red-green and the mammary stroma in light blue, while the fatty tissue is more homogeneous (**e**). An associated colloid nodular goiter is present; a complex etiologic-pathogenic correlation has to be demonstrated (**f**) (based on [16])

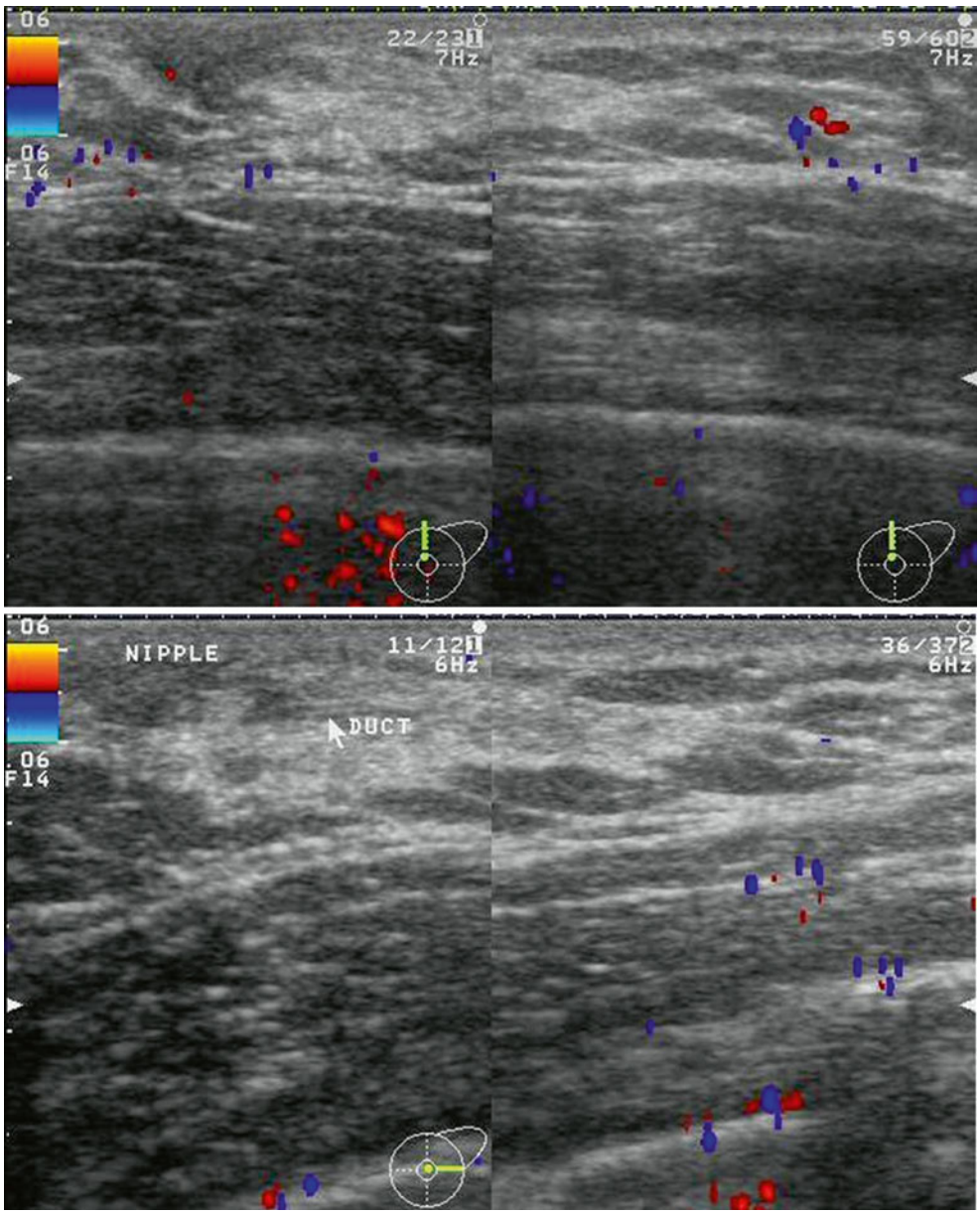


**Fig. 10.15** Recent gynecomastia in a 33-year-old male patient with Cushing's syndrome: obesity, round-shaped face, cutaneous reddish stretch marks, folliculitis, and arterial hypertension; breast DE was performed in the general investigation for an associated infertility that could be correlated with these endocrine disorders [3]

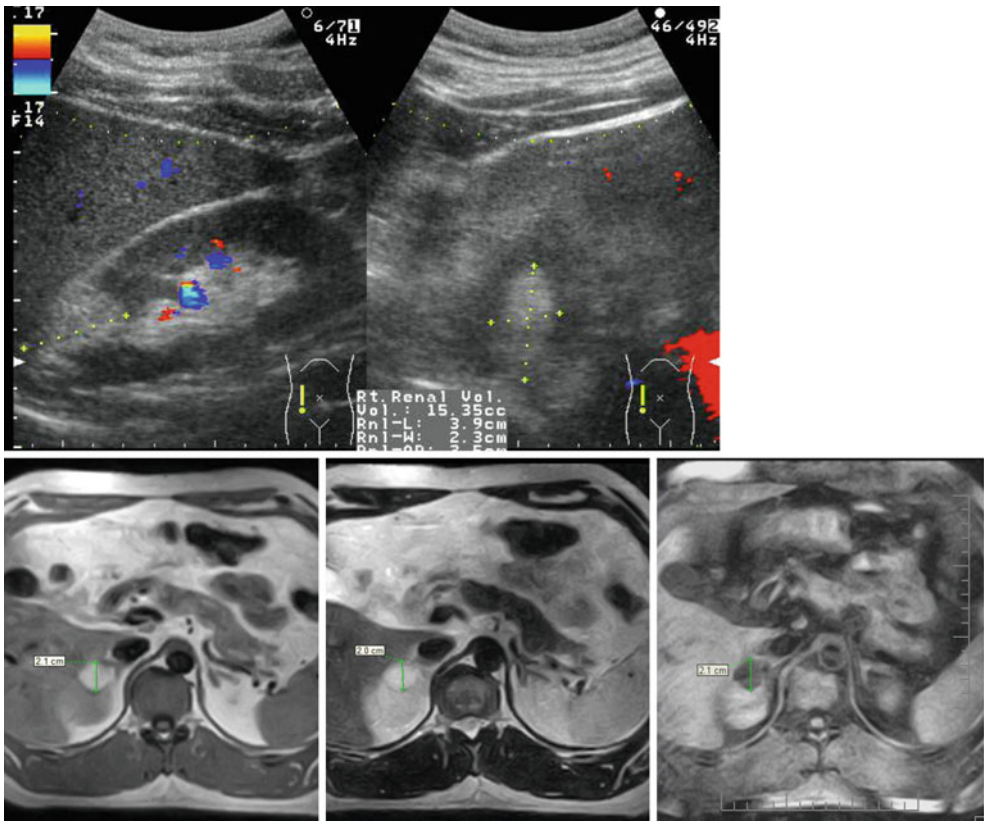


**Fig. 10.16** Recent gynecomastia, the same case: increased values of E2 and plasmatic cortisone determined the research of the adrenals; first intention US demonstrated a right adrenal mass of 15.35 cc, with a lobulated contour, compression of the upper pole of the kidney parenchyma (pseudo-renal tumor), hyperechoic aspect, and no salient vasculature

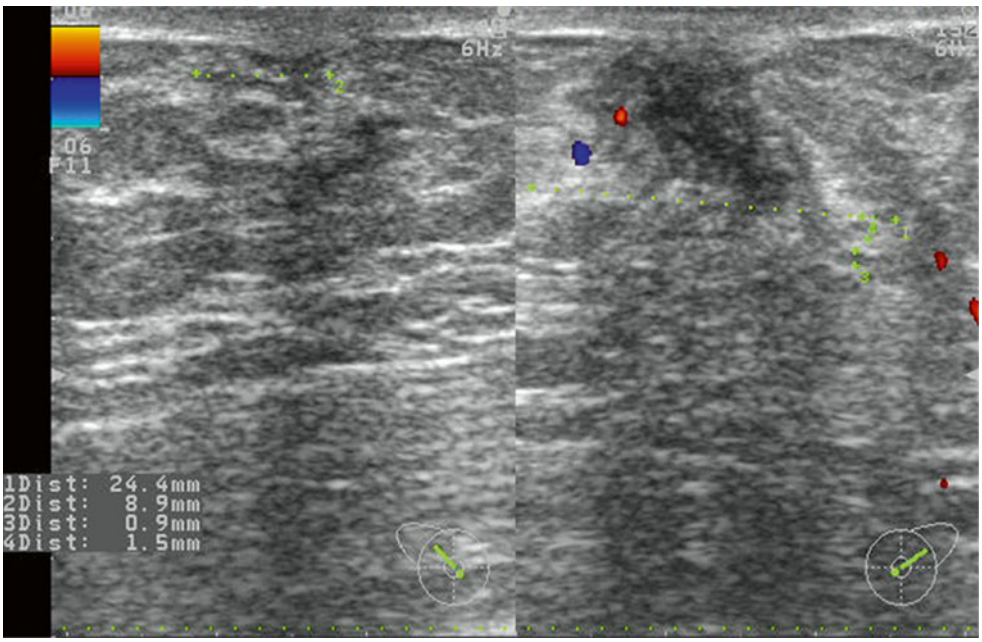


**Fig. 10.17** Asymmetrical gynecomastia in a 58-year-old patient, with left breast branching mammary bud, new vasculature, and glandular stroma; the right mammary bud is typical "normal"

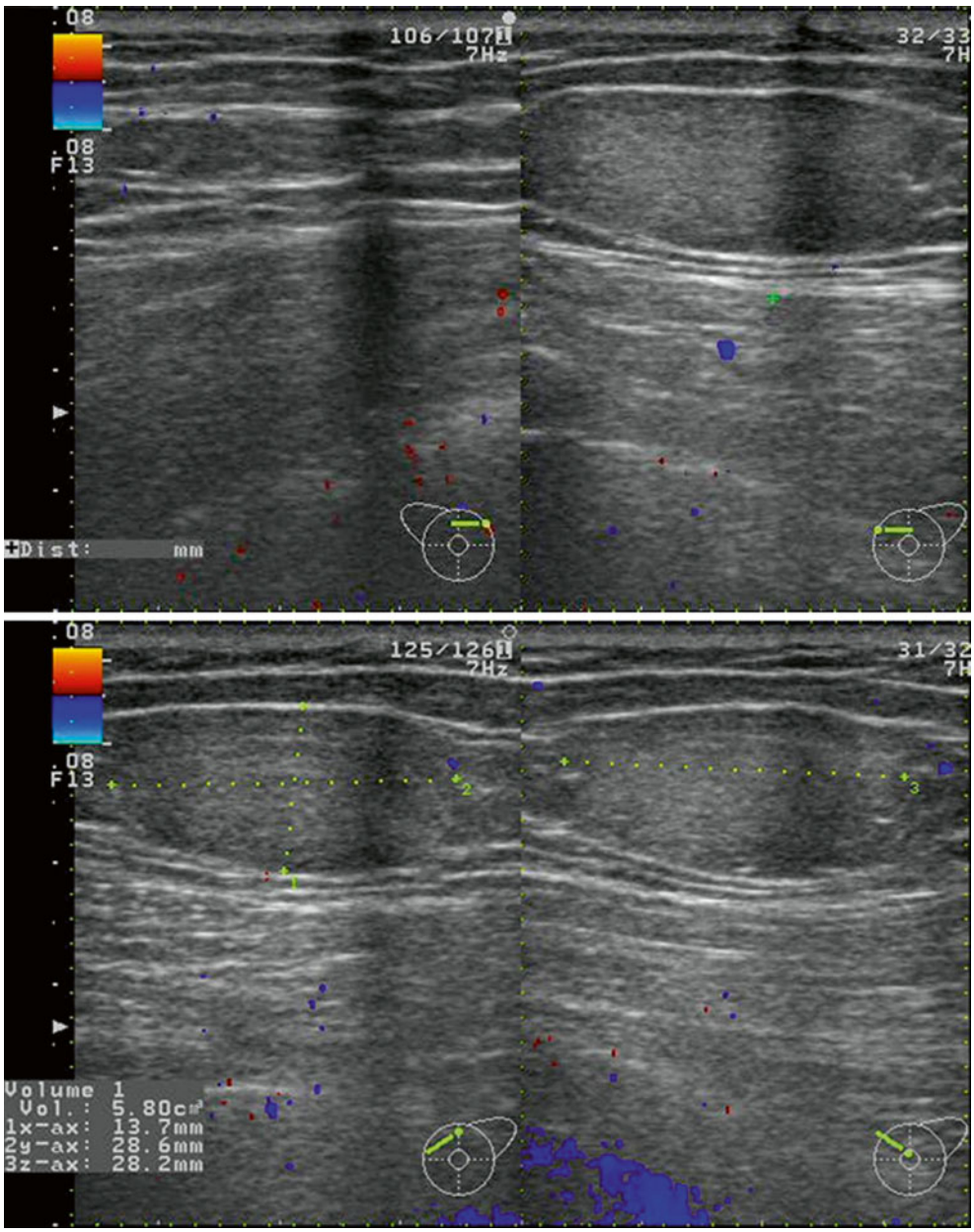


**Fig. 10.18** Pseudo-gynecomastia: typical lipoma in the upper-inner left breast quadrant: homogeneous mass, izo-/hyperechoic, without salient vasculature

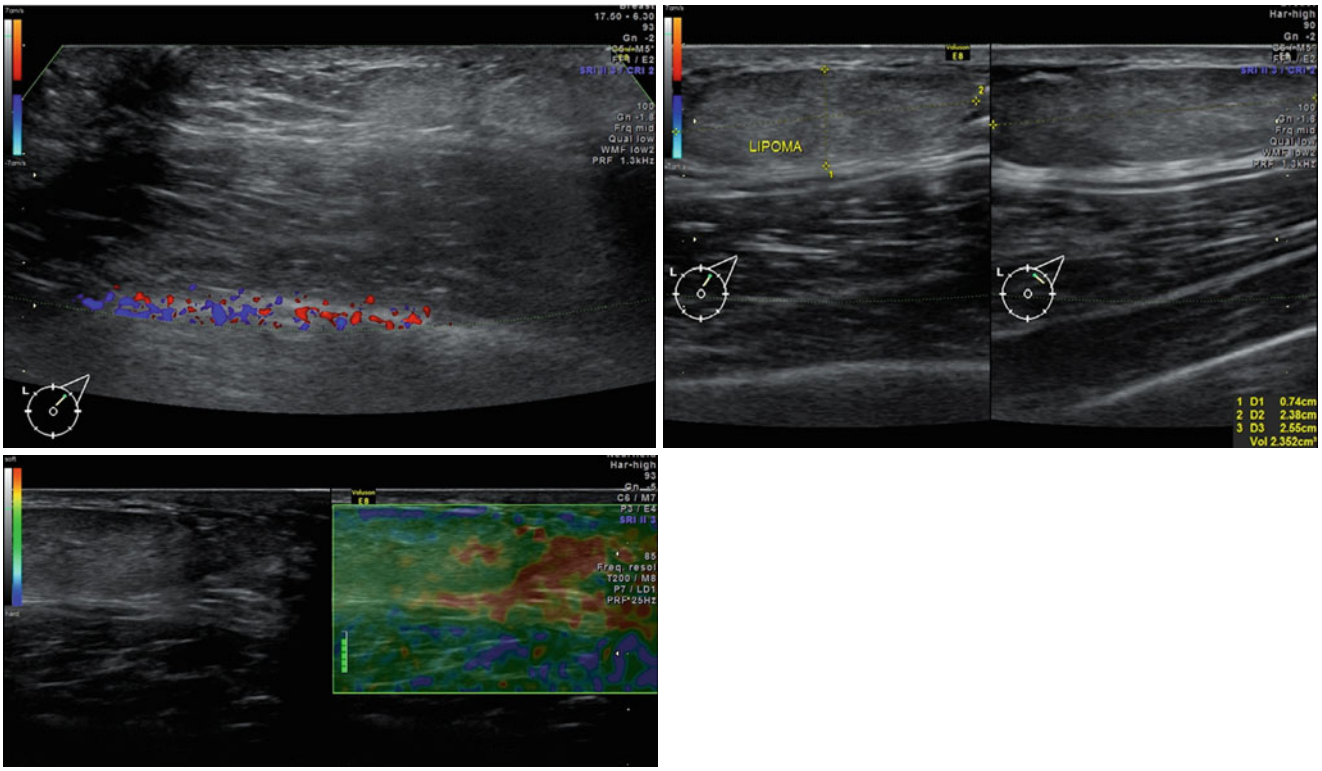


**Fig. 10.19** FBU aspect of pseudo-gynecomastia in a 31-year-old man with a lipoma in the upper-outer left breast quadrant

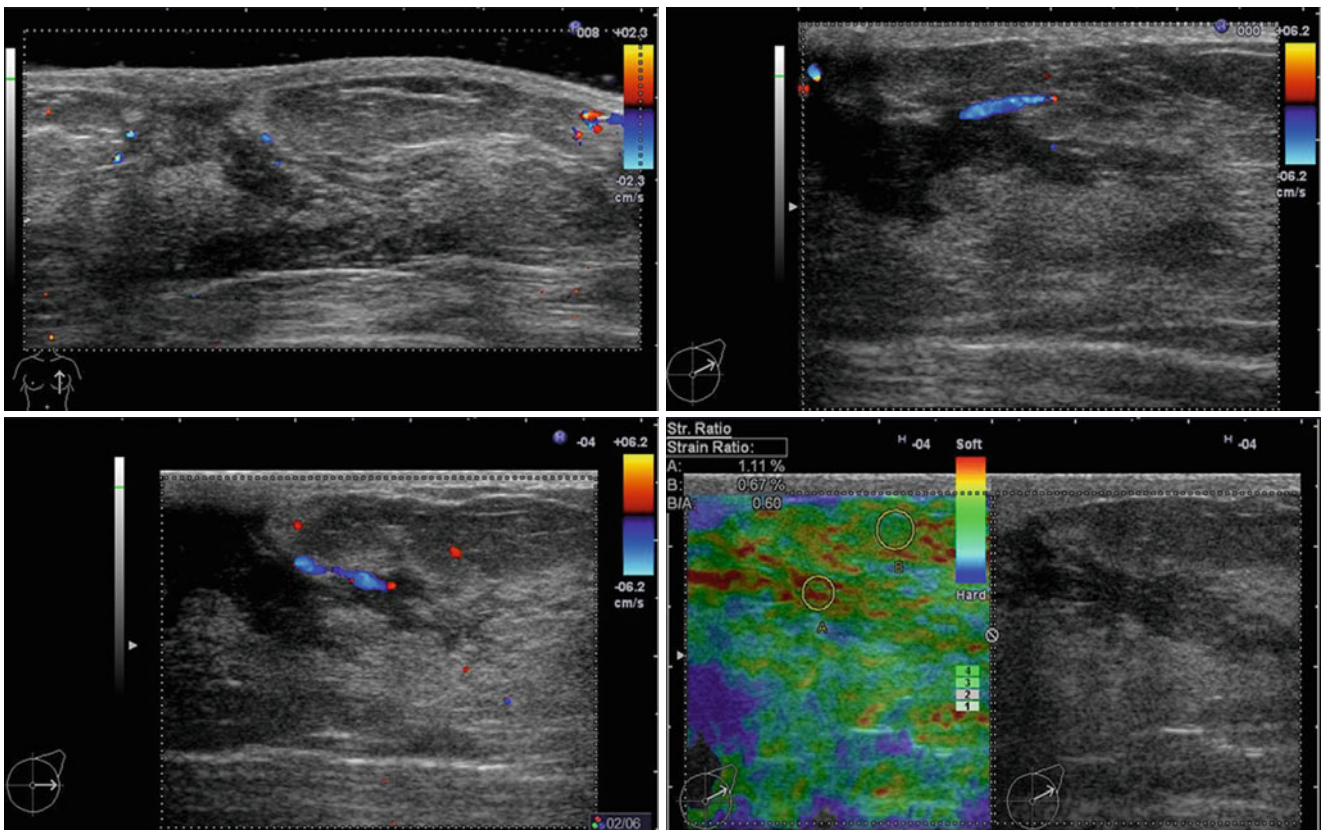


**Fig. 10.20** FBU in a 63-year-old male: asymmetrical gynecomastia with advanced differentiation of the ducts and stroma on the right side, while the left mammary bud has a pseudotumoral hypoechoic aspect, with irregular margins, represented by the developing ducts, demonstrated by the RTSE with score 1 Ueno and very low FLR (0.60)

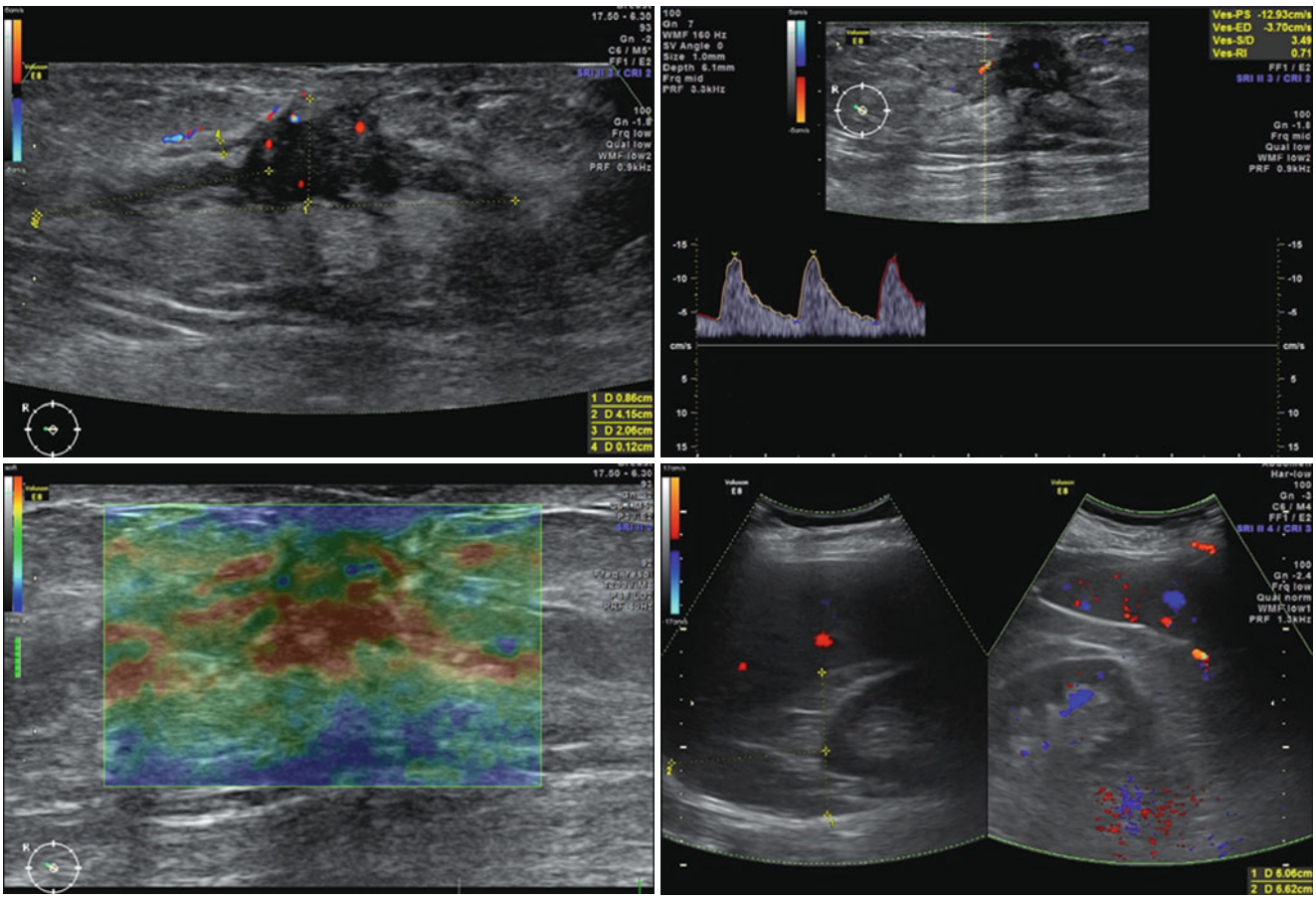

**Fig. 10.21** FBU in a 64-year-old male, with pseudomalignant gynecomastia in 2D US; however, the new formation vasculature is peripheral, according to the periareolary vascular circle, and sonoelastography demonstrates a scoring type 1 Ueno for the branching bud, with normal increasing strain of the nipple-areolar complex

## 10.2 Breast Cancer in Man

The differential diagnosis of the "simple," benign gynecomastia with the male breast cancer or malignant gynecomastia is made using the same criteria as in women. Breast cancer in men is a rare disease, accounting for ≈1 % of all breast cancer cases [20], but it is severe because usually it is diagnosed in advanced stages or it is misinterpreted.

The risk factors for breast cancer in men may be grouped in genetic, metabolic, dishormonal, and environmental. Thus, the major genetic factors are acting similar to woman and include BRCA2 mutations, which are believed to account for the majority of inherited breast cancer in men; in some cases, Klinefelter syndrome and a positive family history may be present. There are suspected genetic factors such as AR gene mutations, CYP17 polymorphism, Cowden syndrome, and CHEK2 [20].

There are some general assumptions largely accepted in the literature:

- When it does occur, male breast cancer occurs in one breast and it is seen in elder males.
- In the majority of cases of gynecomastia, there is no cancer associated; however, any male over the age of 50 with a sudden increase in a single breast is suspected.
- Breast cancer in males presents just like in females: a mass is identified in a single breast, there is generally no pain or nipple discharge, but the mass may be hard to touch.
- The only way to tell if it is cancer is by a biopsy.

FBU aspect of breast cancer in men is similar to the cancer descriptors in woman; this technique is useful especially in demonstrating the connection between the abnormal mass/lesion with the ductal tree for certifying the breast etiology, and the radial scanning is helpful to precise the location upon the clockwise rotation; the aspect of the vasculature must be carefully analyzed to avoid overdiagnosis, and sonoelastography is recommended before any biopsy or surgical treatment. The ductal connection demonstration is essential in the diagnosis of male breast cancer, because similar to women, the majority of men's cancers are invasive ductal carcinomas [21, 22]. Papillary carcinomas are comparatively more common, and lobular carcinomas are rarer in men [23].

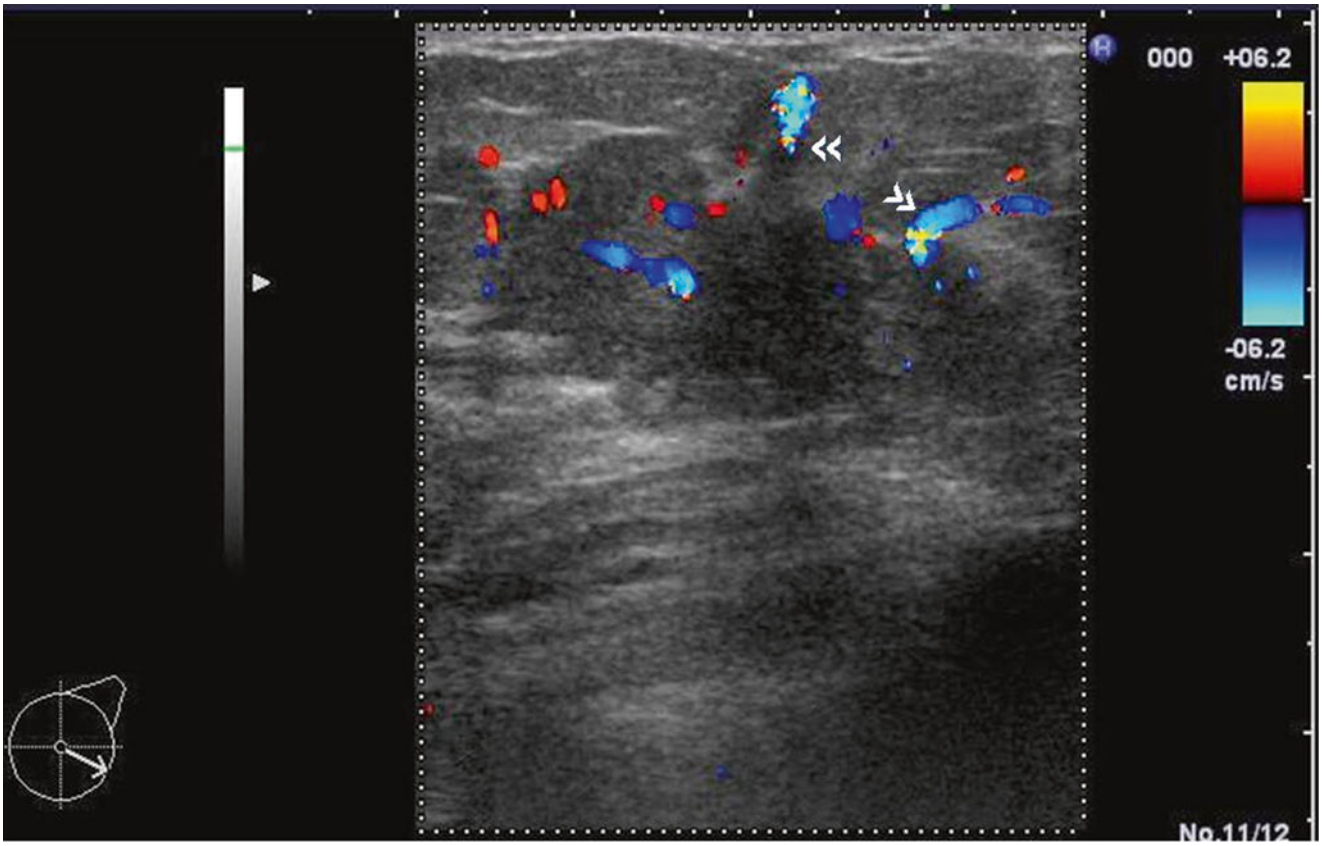


**Fig. 10.22** Doppler US in a 52-year-old male demonstrates at L 4:00 a hypoechoic eccentric mass, with irregular spiculated borders represented by thickened connected ducts, the long axis parallel with the lobar radius and presenting malignant-type new vasculature: multiple vascular poles, with incident plunging angle, and tortuous course. The extension of the tumoral margins following the ducts and the vessels along the Cooper ligaments («) is highly predictive of malignancy. Sonoelastography would be concluding as an additional tool, avoiding unnecessary biopsies (based on [16])

In our experience, breast cancer in men is easier to detect than in women, because of the small breast volume usually without dense glandular structures surrounding the tumor; thus, the sensibility of the method is ≈100 %; the tumor stages of development at the patient presentation are earlier, due to the psychological factors; the associated axillary lymphadenopathy is detected in rare cases. We did not find multicentric or multifocal breast cancer in men, and the literature is poor relative to this aspect (Figs. 10.22, 10.23, and 10.24).

The vascular analysis by Doppler techniques is useful in the positive diagnosis of recent/florid gynecomastia and in the diagnosis of the pathological masses; some observations may be noted [16]:

- An overestimation of Doppler as a unique US finding should be avoided; however, the incident angle of the plunging artery may be considered as malignant sign [24], as well as enlarged tumoral vessels with aliasing flow.
- The value of Doppler or contrast-enhanced US (CEUS) is similar to contrast MRI of the breast, but Doppler is less expansive; however, the use of CEUS proved better results in the "classical" US and DE.
- Doppler characterization is useful in addition to the Stavros [25] and US BI-RADS criteria, because most pitfalls in breast US are due to neglecting the new formation vasculature (present in malignant lesions with benign Stavros criteria, absent in pseudomalignant lesions on classical US, or variant in indeterminate breast lesions).
- Doppler DE supplemented with sonoelastography represents the FBU, the only accomplished US examination of the breast and of the soft tissues, but there are some problems related to the not yet standardized technique: there are different machines with different software and scales of interpretation for the strain, and there are not yet enough trained sonographers in DE and sonoelastography.
- FBU is recommended before the biopsy and surgical treatment, especially in painful gynecomastia or pediatric patients, avoiding the inconvenient side effects such as pain, hematomas after biopsies [14], or scars.

It is assumed that men with gynecomastia may suffer from absolute or relative estrogen excess, and their risk for different associated malignancies may be increased.

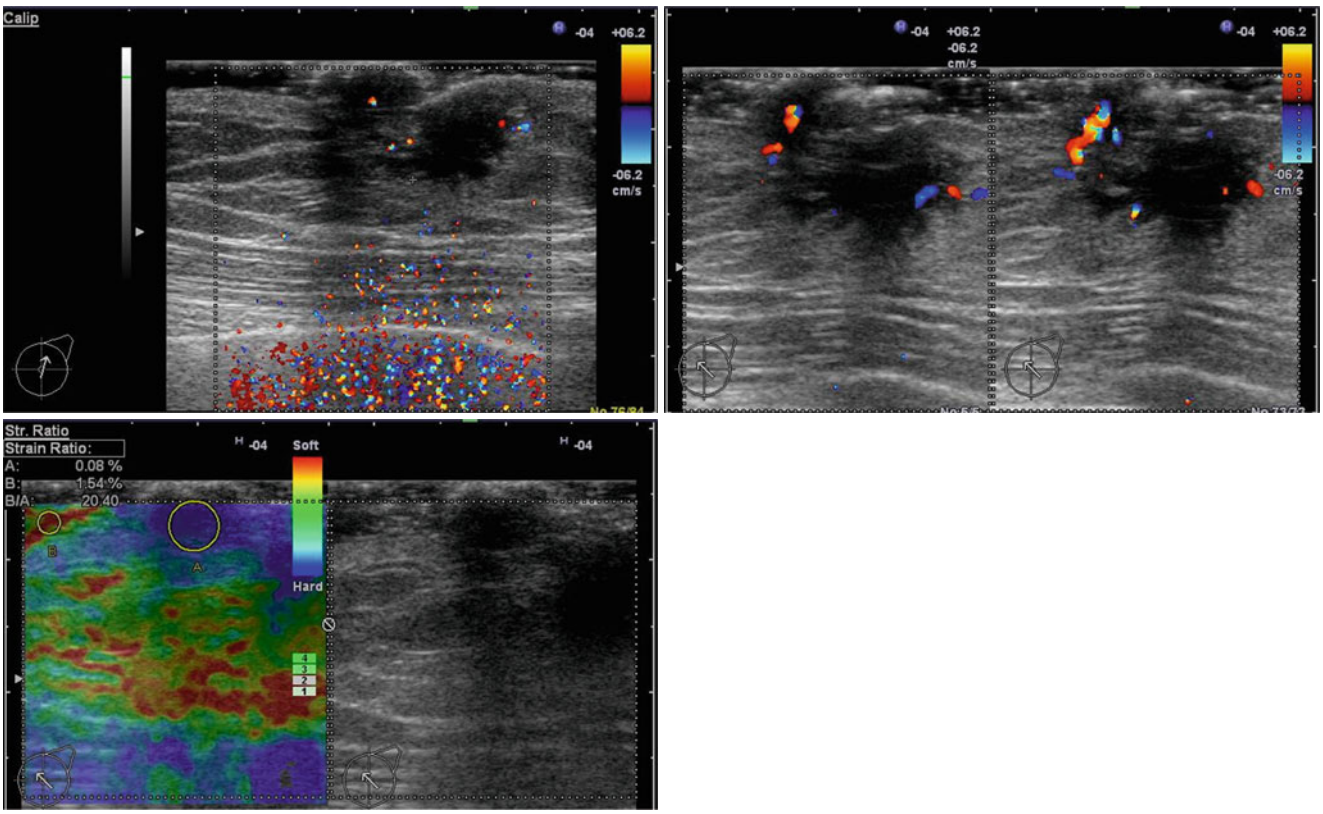


**Fig. 10.23** L 5:00 central breast cancer in a 69-year-old male: FBU demonstrates the pathological mass with malignant features based on Stavros, connected to the nipple, with new formation vasculature and increased stiffness of the whole assembly tumor-connecting ducts-nipple

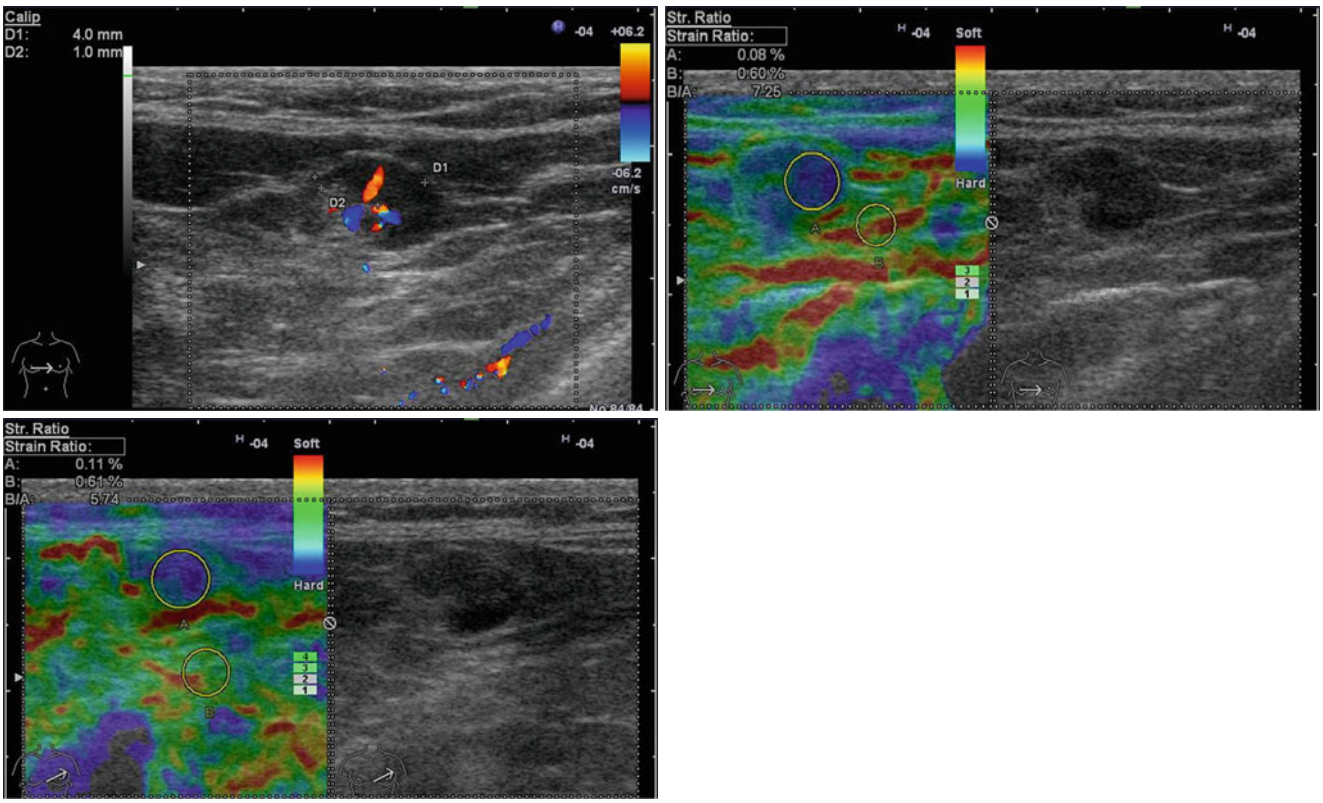


**Fig. 10.24** The same case: suspected findings of intramammary lymph node in the lower-inner quadrant (*upper and middle images*) and left axillary lymph node (*bottom image*)

A study published in 2002 tested whether men with gynecomastia were at greater risk of developing cancer elsewhere [26]: a cohort of 446 men having a histopathologic diagnosis of gynecomastia following an operation for either unilateral or bilateral breast enlargement, between 1970 and 1979, was evaluated during a 20-year period, and at the end, the cohort constituted a significant value of 8375.2 person-years of follow-up time. The authors concluded there was a significant increased risk of testicular cancer and squamous cell carcinoma of the skin after more than 2-year interval in men which have been operated on for gynecomastia. In this cohort, there were 2 persons with initial breast carcinoma, but no new cases of male breast cancer were observed, with the explanation that diagnostic operations for gynecomastia may substantially have reduced this risk. We can observe the large proportion of unnecessary breast surgery (just 2 breast cancers from 446 cases, 0.44 %), which was justified as the main method of diagnosis in that period of time, as compared with the advanced developments in US available nowadays that offer a most accurate noninvasive diagnosis. The authors could not explain the risk of skin cancer, but they concluded that no improvement in prostatic cancer evolution was observed after estrogen therapy, which was responsible for gynecomastia.

For the differential diagnosis of male breast lesions, there are many classifications based on their risk of developing in male; a very useful classification based on the occurrence criterion was proposed by Olsson and col. [26]:

I. *Lesions that do occur in man* [26]
   A. Gynecomastia with parenchymal secondary lesions:
      - Ductal hyperplasia
      - Ductal ectasia (galactorrhea)
      - Papilloma
      - Adenoma
      - Fibrocystic changes
      - Diabetic mastopathy
      - Paget disease (more frequent as in women)
      - Breast cancer
   B. Non-gynecomastia
      - Pseudo-gynecomastia
      - Myofibroblastoma
      - Granular cell tumor (neural origin)
      - Epidermal inclusion cyst
      - Cystic lymphangioma
      - Varix
      - Leiomyoma
      - Lipoma
      - Pleomorphic hyalinizing angioectatic tumor of soft tissues
II. *Lesions that do not occur in man or are extremely rare* (rare cases with presence of the Lobules, as Precursory Lesions):
   - Fibroepithelial lesions:
     – *Fibroadenoma*
     – *Phyllodes tumor*
     – *Carcinosarcoma*
   - Lobular carcinomas

This classification does not include accidentally breast infections, from folliculitis to abscess, because the history and the clinical examination are usually concluding and the imaging diagnosis are not justified.

## 10.3 Endocrine and Imaging-Pathological Correlations in Gynecomastia

Because benign gynecomastia represents the most part of pathological male breast enlargement and the dishormonal etiology is the most frequent, DE is the method of choice before any interventional procedure, because the anatomical analysis offers the positive and differential diagnosis of gynecomastia and could characterize its subtypes (acute/florid, chronic, with or without additional masses), with recommendation for targeted hormonal tests and complementary imaging exams, reducing the time and the costs of the overall diagnosis [16].

The most important dishormonal changes implying gynecomastia were signaled:

- *Infertility:* A report of a positive correlation between E2 and FSH ($r=0.67$, $p<0.0001$) in a group of 106 infertile men [3] confirms the correlation of hyperestrogenism (gynecomastia) with infertility (hypogonadism). Based on that result, gynecomastia should be interpreted as a symptom, but also as a marker of treatment response in infertile man.
- *Goiter and pituitary pathology:* In daily practice, there are many cases with gynecomastia and goiter, with or without hormonal changes, and rarely may be associated hyperprolactinemia. Most cases are acquired diseases with expression predominantly in adulthood, with various etiologies, but a report of Benvenga and col. (2000) presented a 10-year-old boy with congenital adrenal hyperplasia and associated hyperplastic testicular adrenal rests, which had high serum concentrations of 17-OH progesterone (17-OHP), estradiol (E2), testosterone (T), and basal and TRH-stimulated TSH and PRL, but normal thyroid hormones (T3, T4, FT3, FT4) and thyroxin-binding globulin (TBG). This case suggests that E2 stimulates the secretion of basal and TRH-elicited TSH and PRL [6]. The importance of this study is the illustration of the pathogenic relation between E2 (gynecomastia) and TSH and PRL and also the possibility of the presence of a goiter with normal T3 and T4.

- *Hyperprolactinemia* in man has multiple etiologies [13], and the serum levels are generally correlated, in women and men, with the FBU aspect: the illustration of ductal ectasia with diffuse increased vasculature is correlated with high hormonal activity, while the low Doppler mapping is always correlated with normal prolactinemia, whether an associated chronic galactophoritis could be present [27]. Doppler DE could be a good follow-up examination for hyperprolactinemia, less expansive, and time-consuming than the serologic hormonal tests.
- *Hyperestrogenemia* may be related to the coronary thrombosis in man [28], similar to the menopausal hormonal substitution treatment. Inversely, if florid gynecomastia or ductal-lobular hyperplasia in men is demonstrated on DE, the serum concentration of E2 must be evaluated as a risk factor for thrombosis.
- Hyperestrogenemia in elderly should be firstly considered as pathological, and after exclusion of any associated etiology, it could be assumed as "physiological." Some cases could have complex etiology, with hyperestrogenemia masked by other symptoms and pathological markers. A report of a 71-year-old man with clinical signs of Kennedy disease, including dysarthria, dysphagia, palatal and oral mandibular fasciculations, lower-extremity weakness, gynecomastia, and testicular atrophy, proved the correlation with an increased estrogen level of 180–220 pg/mL [29]. This paper demonstrates the importance of gynecomastia as a symptom in elderly man.
- *Male breast cancer* coexists with gynecomastia, but there are confusions in the management of these diseases, while the classical methods of diagnosis could not demonstrate the benign mammary buds and ducts.

Gynecomastia in the general assumption is either a benign disease or a physiological breast development in male; however, 50 % of cases with gynecomastia are selected for mammography [10]. In elderly males, gynecomastia makes up 65 % of all breast lesions; 25 % is carcinoma and 10 % are other lesions. In fact, estrogen receptors are more commonly present in males with breast cancer than in women, occurring in 75–94 % of males with cancer [2].

Because the breast tissue in males responds to the hormonal stimulation, with growth of ducts and connective tissue resulting in gynecomastia, the overwhelming histological subtype of breast carcinoma in men is ductal or unclassified (93.7 %), followed by papillary (2.6 %). Infiltrating lobular carcinoma is rare in males, likely because of the rarity of terminal lobules in the male breast. The value of the FBU examination consists in the diagnosis of both gynecomastia and cancer, with visualization of nonpalpable infracentimetric tumors. In our experience, florid gynecomastia with salient new vasculature or the type with ductal hyperplasias are correlated with hyperestrogenemia at the time of the examination, while chronic gynecomastia with less vasculature may be associated with normal values of the steroid tests (Figs. 10.3, 10.4, 10.5, 10.6, 10.7, 10.8, 10.9, 10.10, 10.11, 10.12, and 10.13).

Doppler DE demonstrated large central ductal-ampullary ectasia up to 3–4 mm in diameter, peripheral thickened lobules connected to the ending ducts, and increased vascular Doppler signal with arterial and venous flow, similar to the lactating breast. Previous surgical treatment had proven milky ducts in the right breast (based on [1]) (Figs. 10.14, 10.15, and 10.16).

MRI examination demonstrated a right adrenal mass with heterogeneous hypersignal in axial T1WI and T2WI, with mark on the right kidney. WFT1 WI changes the character of the tumor in a heterogeneous hyposignal, demonstrating the lipid component of the tumor, almost pathognomonic for the benign adrenal adenoma (the "chemical shift sign") (based on [16]) (Figs. 10.17, 10.18, 10.19, 10.20, 10.21, 10.22, 10.23, and 10.24).

## 10.4 Pediatric Breast Disorders

The breast develops from the mammary bud that is formed in the first 6 weeks of life in utero. At birth, neonatal bud breast usually presents a small ductal branching with swelling, tenderness, and sometimes a minimal nipple surge, the so-called witch's milk, considered as physiological due to the maternal hormonal transplacental transfer. Further normal breast development does not occur until puberty, which usually occurs after 9 years old (Fig. 10.25).

Precocious breast development in girls represents precocious/premature thelarche and occurs before 8 years old. Developing breast bud mistaken for a mass could determine unsuitable surgical treatment finalized with amastia. The premature thelarche must be differentiated in the isolated form, considered as "benign," slowly progressive, from the premature puberty that refers to the appearance of physical and hormonal signs of puberty earlier than 8 years in girls and 9 years for boys. The precocious puberty is associated with pubarche (appearance of pubic hair in girls or boys younger than 7–8 years) and hormonal changes, as resulting risks of emotional distress, short stature because of rapid closure of the growing cartilages, presence of menses in girls, and increased libido in boys. In girls, US examinations may illustrate the development of the uterine body, with reversal of the index body/cervix >1 (in the prepubertal age, the index cervix/uterine body >2) and the development of multiple ovarian antral follicles (Figs. 10.25, 10.26, 10.27, 10.28, and 10.29).

Asymmetric development of breasts is usual, and it could be mistaken for a unilateral breast mass at clinical examination both in children and men and frequently is followed by biopsy and eventually surgical treatment. Breast biopsy in children must be carefully decided, because the secondary

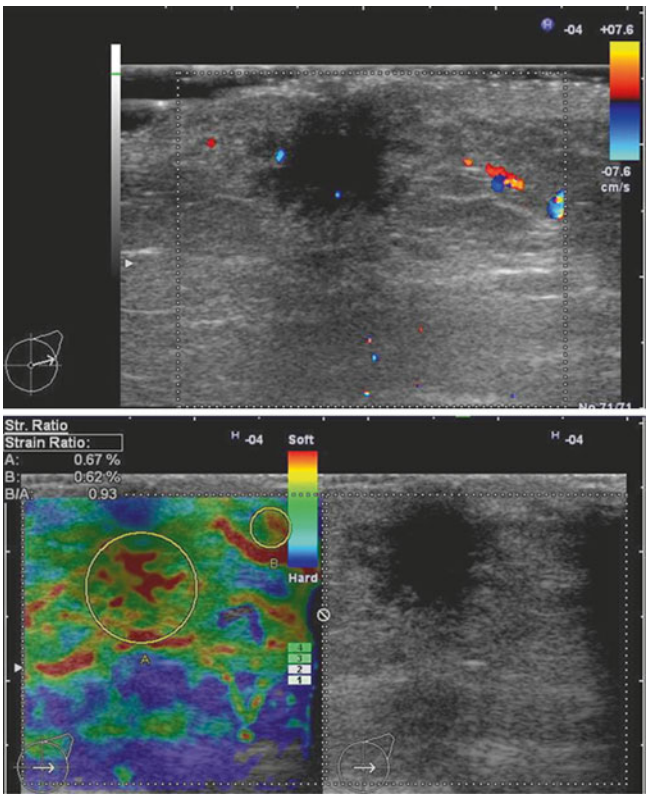


**Fig. 10.25** FBU in a 10-year-old girl, normal thelarche: the mammary bud with peripheral branching ducts, surrounded by few amount of hyperechoic specific glandular stroma, containing many branches of new formation periareolary vasculature

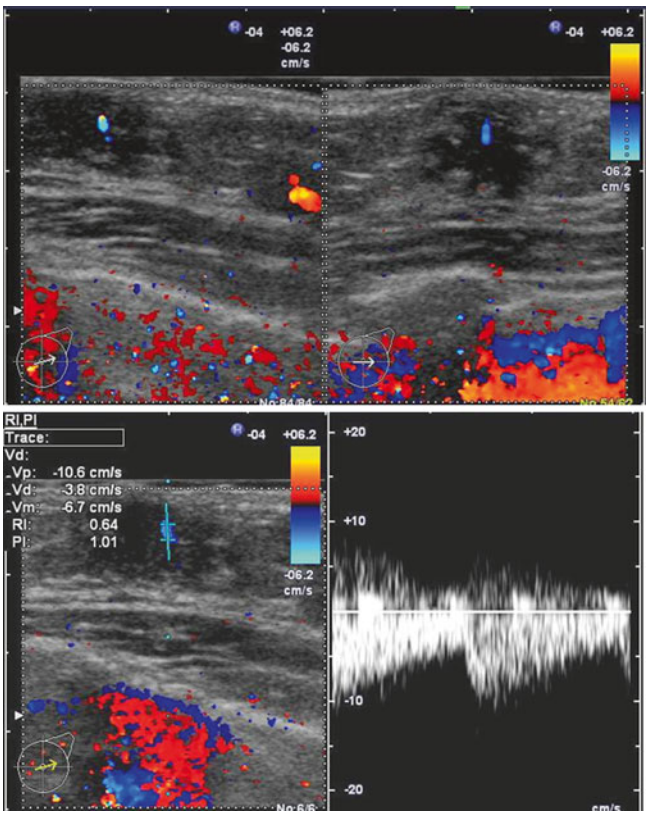


**Fig. 10.26** Precocious thelarche in a 1-year-old girl, with similar Doppler US appearances with recent development

effects may be more important than in adults, due to the risk of hematomas [14] and to the effects of scar formation in a developing breast.

The premature thelarche has multiple etiologies, the most important being related to the precocious puberty that is determined by the secretion of high-amplitude pulses of gonadotropin-releasing hormone (GnRH) by hypothalamus.

Most cases of simple, isolated premature thelarche have no further complications, with most of these girls having normal puberty at a normal age.

The importance of the diagnosis of the true premature thelarche is the selection of the cases with risk of premature puberty, which must be further investigated for central nervous system abnormalities (tumors, inflammations, trauma, surgery, and congenital anomalies) [30]. Other causes seem to be familial inheritance, an increased body mass index, and an exposure to exogenous sex hormones (estrogens in poultry, phytoestrogens in soy products, environmental estrogen like agents such as pesticides and phthalates) [31]. To optimize visualization of the breast tissue, a linear-array high-MHz transducer should be used. For the evaluation of superficial lesions, using of a standoff pad or a generous mound of acoustic coupling gel to substitute for a standoff pad is helpful.

Normal US findings in children prior to thelarche were described in Chap. 3; there is the small hypoechoic mammary bud surrounded by the subcutaneous fatty tissue and with linear fibers of the pectoralis muscle located posteriorly. Subcutaneous fat demonstrates heterogeneous echotexture in a healthy infant. The ribs may also be seen as hypoechoic masses with associated shadowing, but they should not be mistaken for breast masses because they lie posterior to the pectoralis muscle; the cartilaginous parasternal rib segments may appear as hypoechoic well-shaped ovalar masses with posterior acoustic enhancement and marginal shadows (Kobayashi signs), mimicking benign lesions, but they are located posteriorly to the pectoral muscles, and no connection with the mammary bud can be demonstrated. When breast development starts, the breast bud appears as retroareolar pyramidal hypoechoic tissue that has small branches usually asymmetrically extended, mostly towards the upper-outer quadrant. The presence of the hyperechoic mammary stroma is always detected with new vasculature more or less salient, always beginning in the periareolary vascular circle, and with uniform distribution in the mammary quadrants (Figs. 10.28, 10.29, 10.30, 10.31, and 10.32).

In the pediatric and adolescent population, the literature and our results show that benign findings are the most

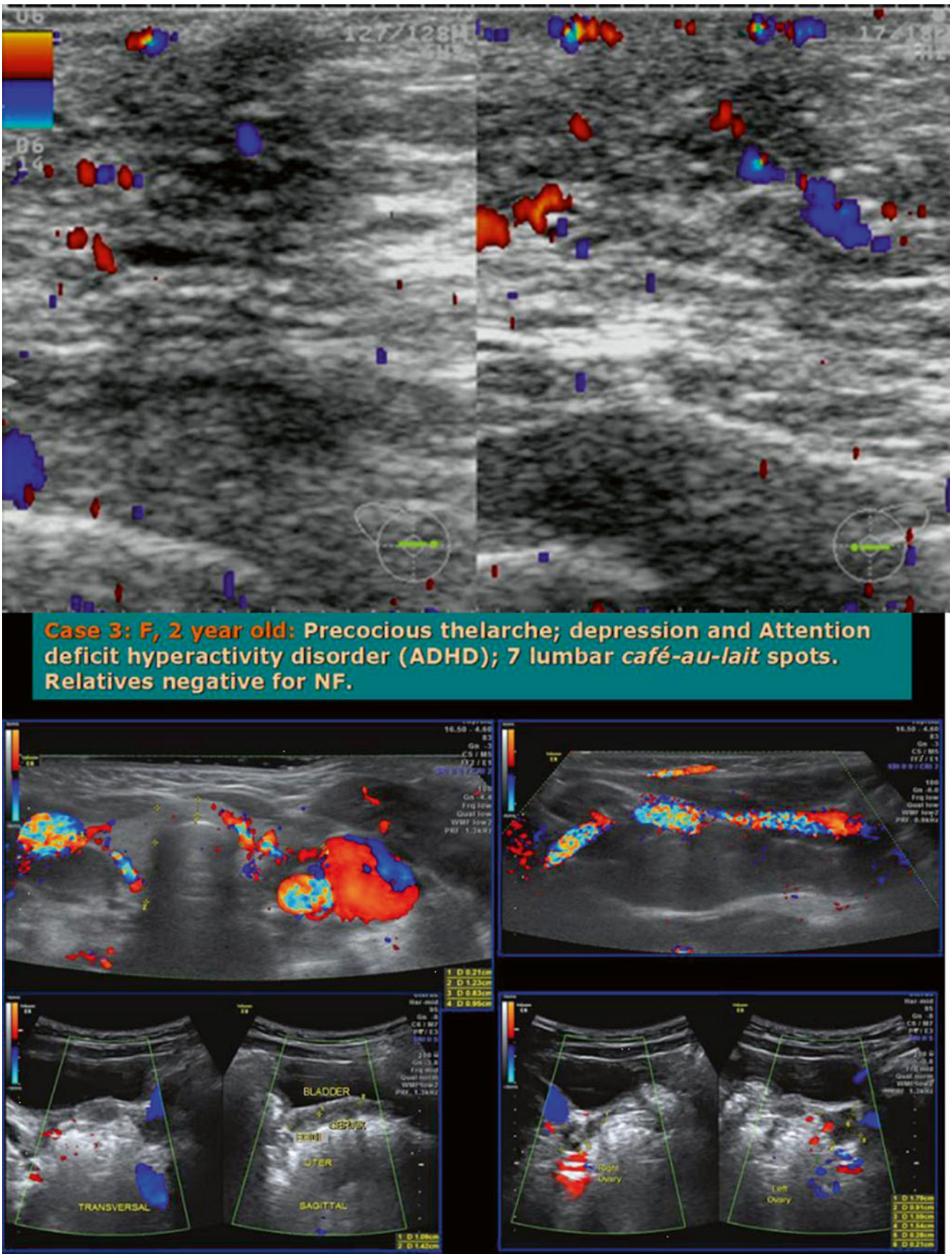


**Fig. 10.27** Precocious puberty with precocious thelarche in a 2-year-old girl with neurofibromatosis 1 (the von Recklinghausen disease); the deep right cervical plexiform neurofibroma is displacing the right common carotid artery (based on [30])

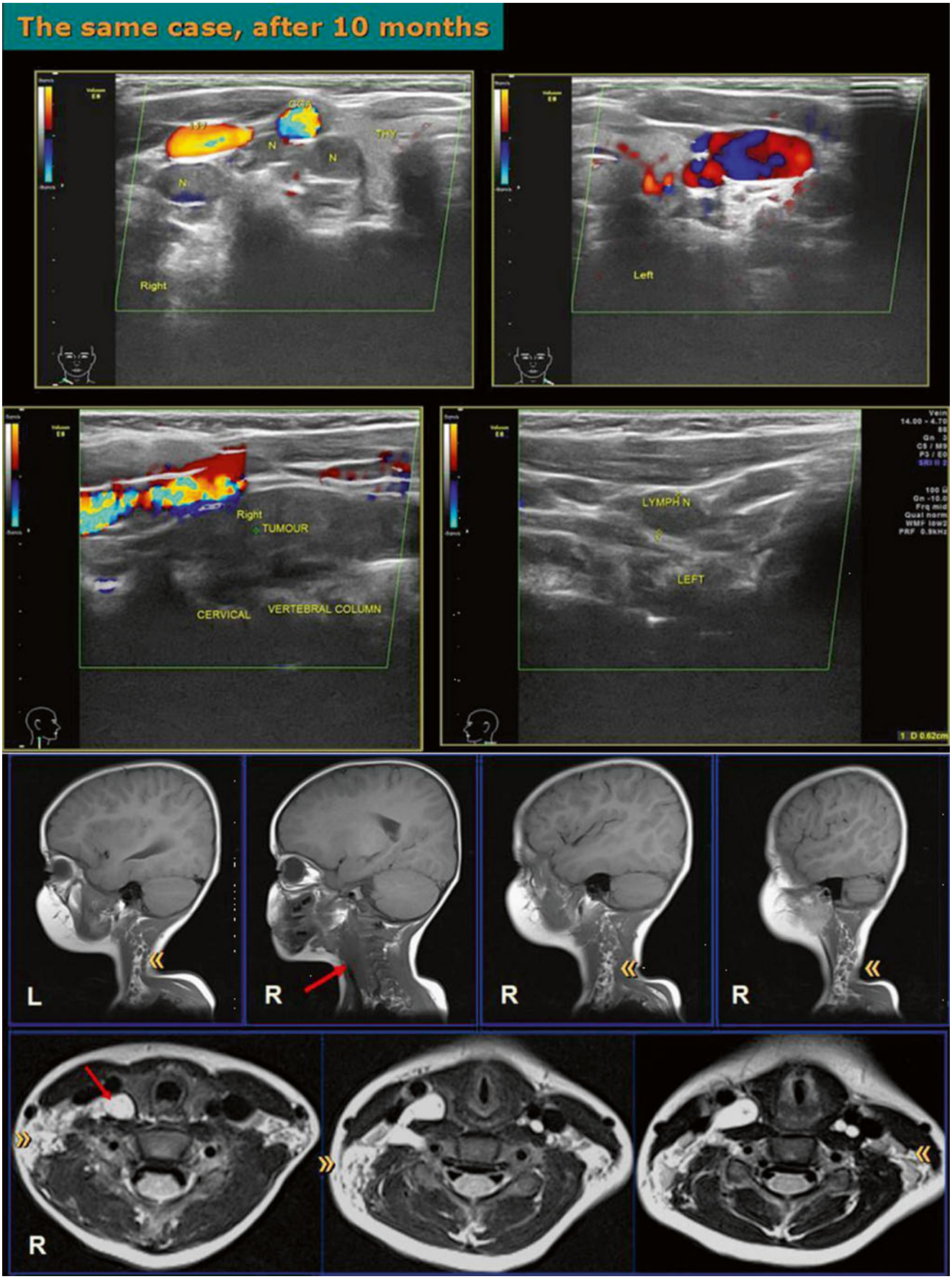


**Fig. 10.28** Precocious puberty associated to neurofibromatosis 1, the same case: sagittal US scans illustrate the right plexiform neurofibroma and the left nodular tumors, similar to the sagittal T1WI and axial T2WI MRI scans; no evolution in the first 10 months (based on [30])

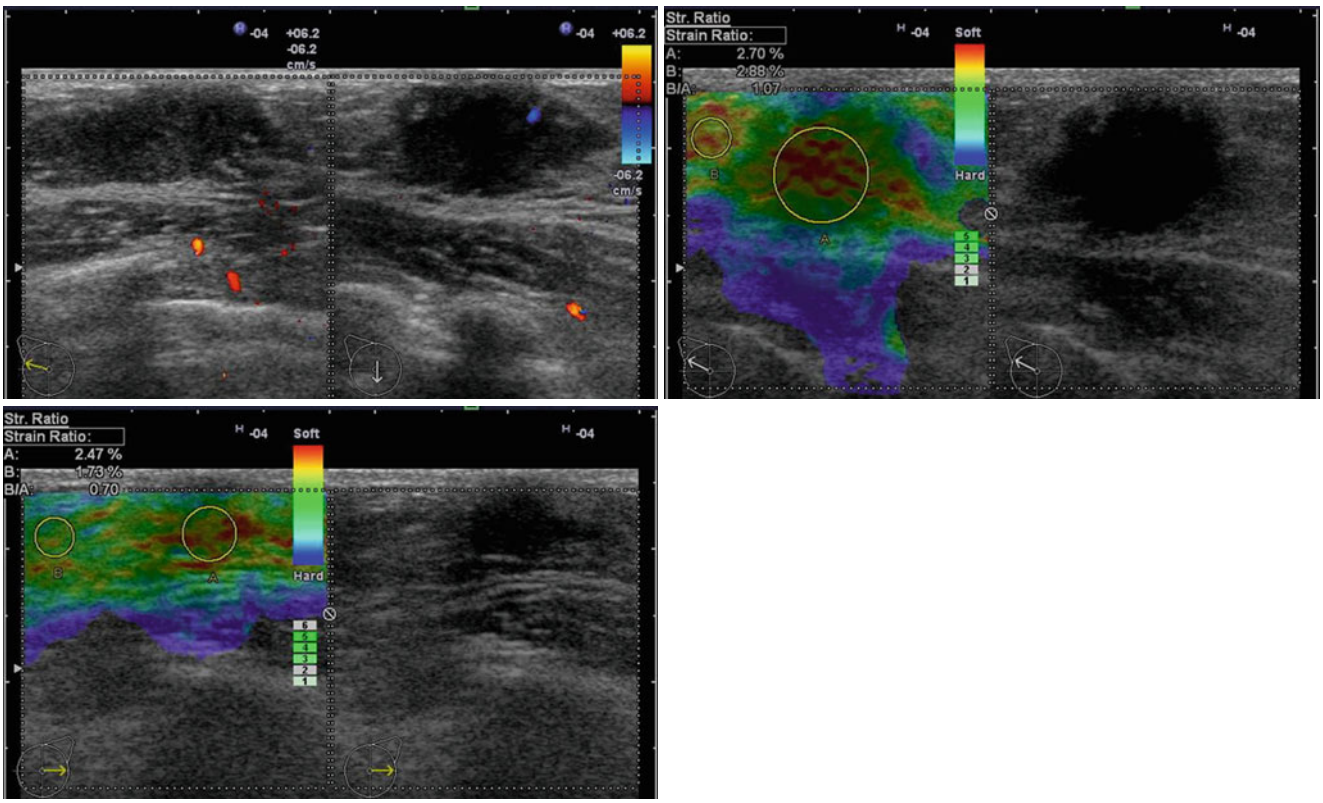


**Fig. 10.29** Precocious thelarche in a 5-year-old girl, with asymmetrical development and pseudotumoral features; however, the peripheral ducts emerging from the hypoechoic mammary bud, which has benign posterior effects based on Kobayashi, are concordant with the benign score on sonoelastography

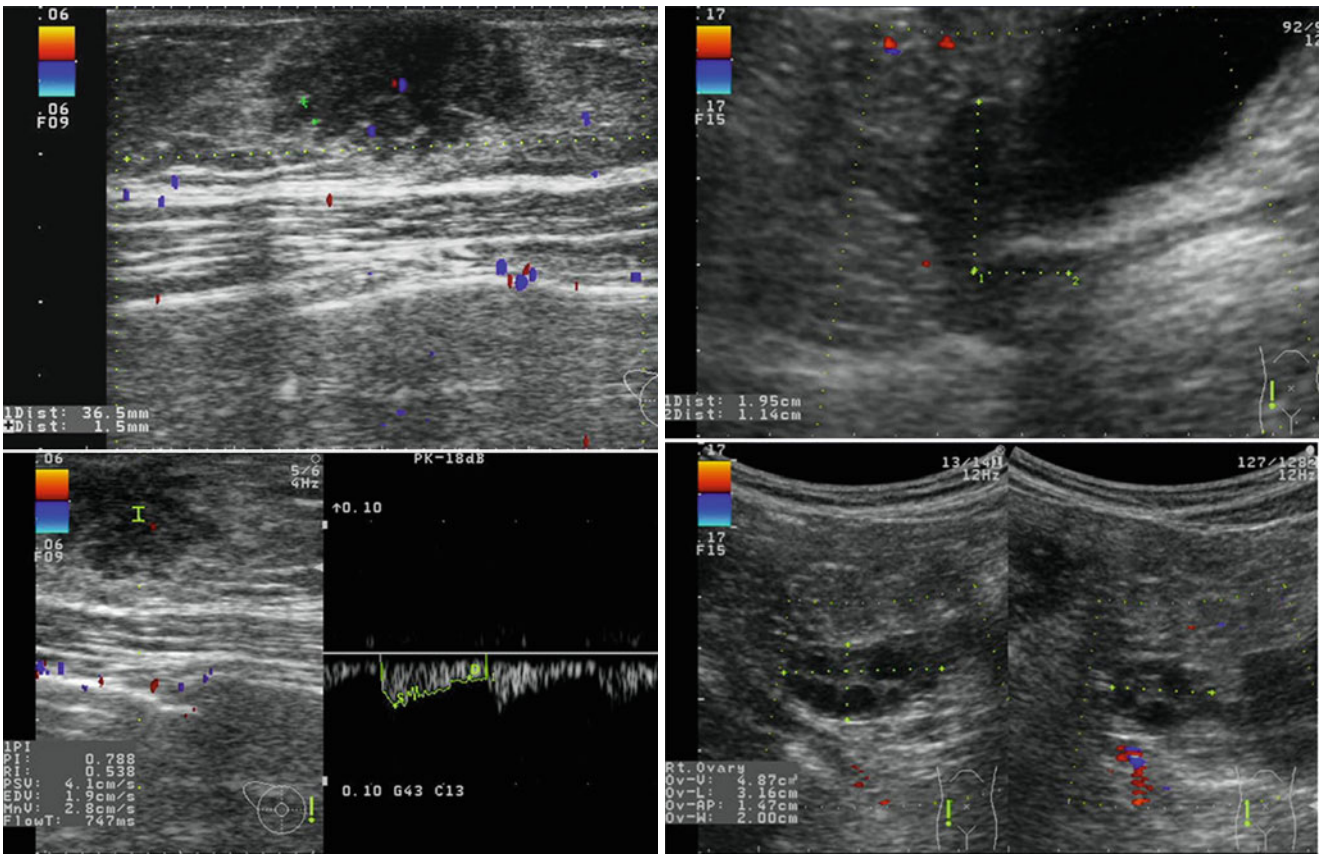


**Fig. 10.30** Physiological thelarche in a 9-year-old girl, with uterine and ovarian simultaneous changes

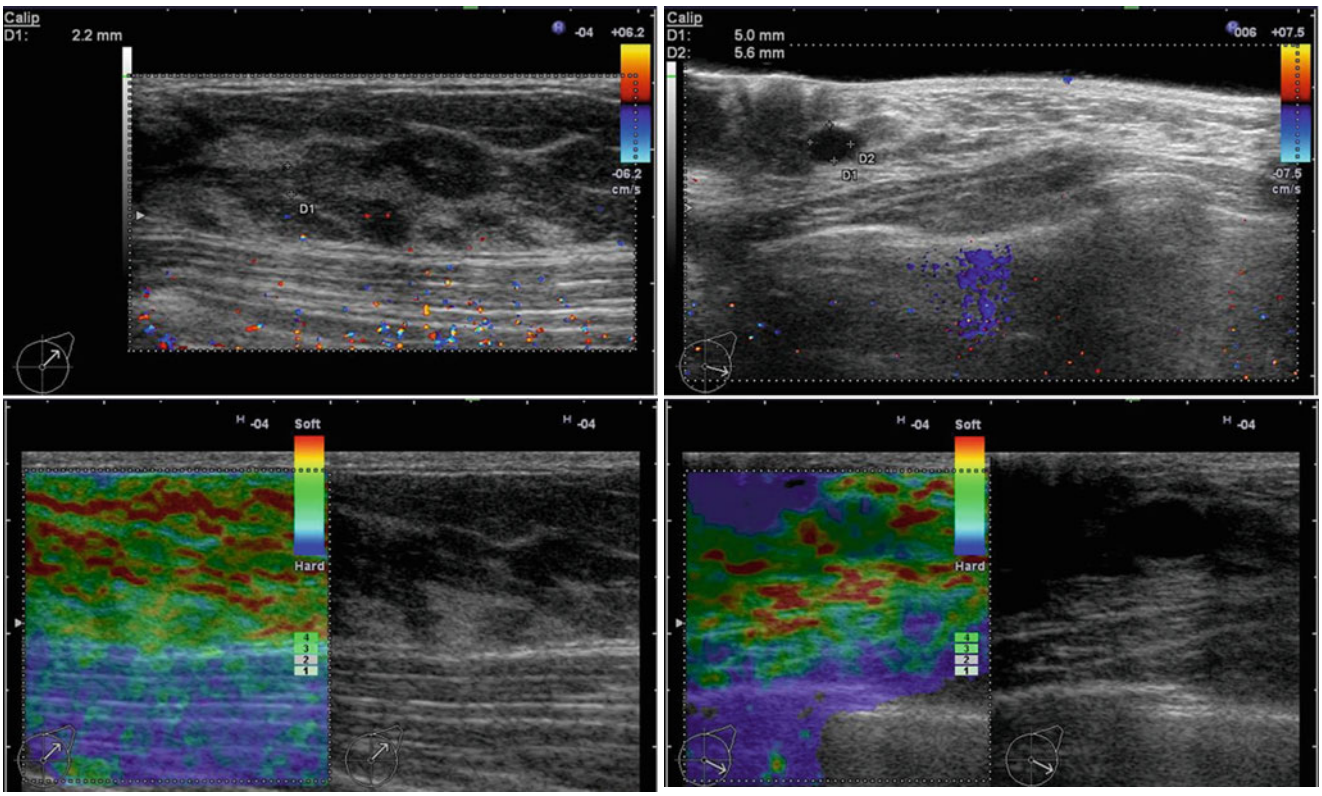


**Fig. 10.31** Normal young pubertal breast in a 15-year-old: branching ducts and a remnant of the bud, with new vessels. RTSE shows high elasticity of the breast parenchyma

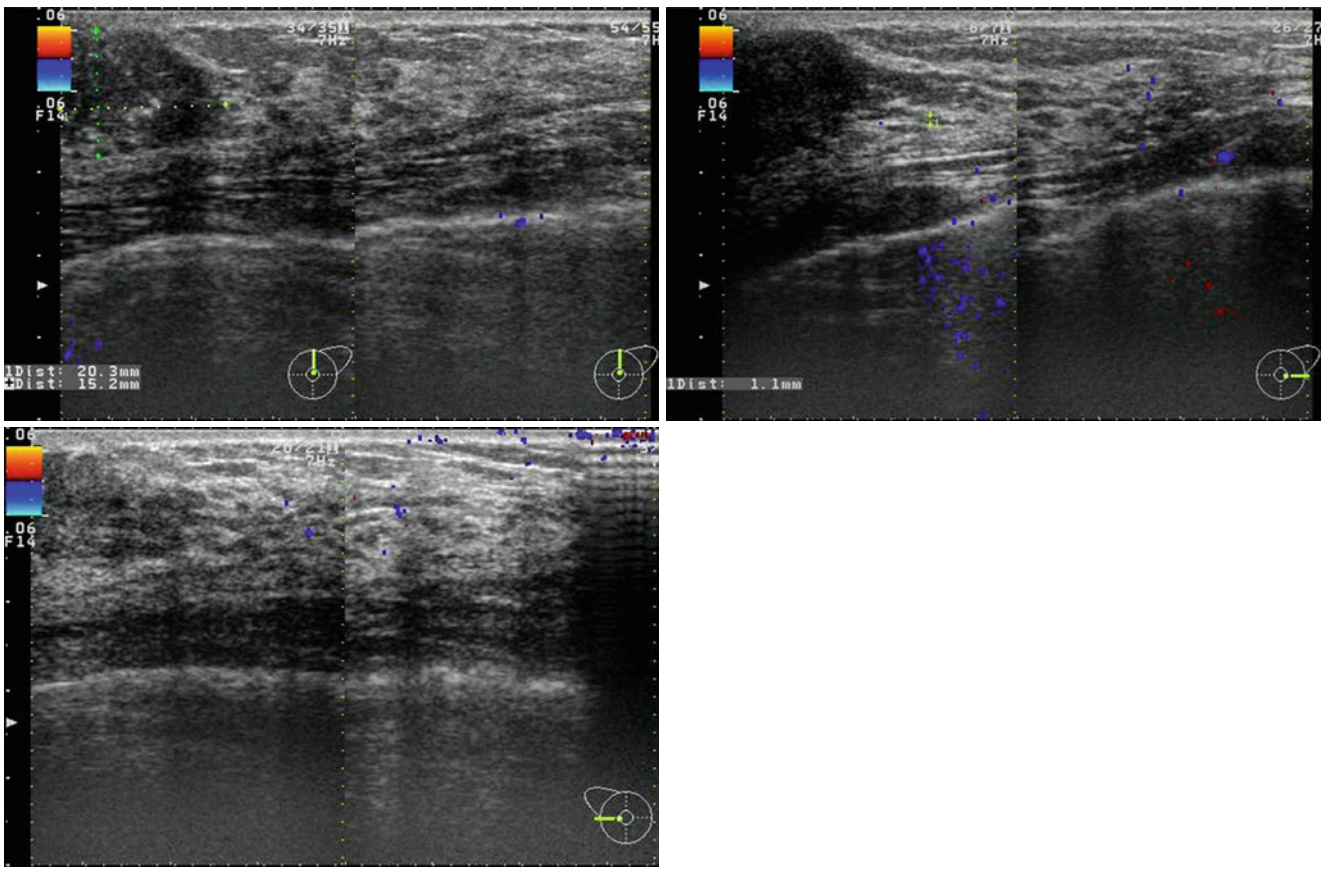


**Fig. 10.32** Physiological thelarche: advanced stage of branching ducts in healthy 17-year-old patient; the remnant mammary bud has a pseudonodular aspect due to less developed mammary stroma in the retroareolar space, specific to the young breast type

common cause of symptomatic breast abnormalities. A careful physical examination with clinical follow-up and US helps in the evaluation of patient symptoms. Fibroadenomas are the most common solid breast masses excised in the pediatric and adolescent population, but the precise moment of the surgical treatment is unclear; we think that if the solid mass has no significant new vasculature and the size and growing evolution are not increased, then a conservative expectative treatment should be preferred in children and puberty, because of the possibility of spontaneous remission of the small lesions during breast development; moreover, fibroadenomas in young people are usually multicentric and multifocal, with asynchronous evolution, and each surgical treatment may increase the number of scars and may involve the breast growing process.

However, in the classical literature it is recommended in cases with US scans negative to base on the level of the clinical concern. Given the overwhelmingly benign causes, surgery should be the last resort and reserved only for lesions that are enlarged or have highly suspected features.

In the last years, given the development of the ultrasonographic machines, the knowledge of the sonographic appearance of physiological breast development and specific lesions in children and the young has acquired new acquisitions; as a consequence, breast sonography is nowadays most helpful in identifying and characterizing abnormalities and guiding further investigation.

A study of Aruna Vade and col. [32], concerning 20 adolescent girls between 13 and 19 years old who presented with palpable breast masses found to be solid at breast US, concluded that the classical US was not useful for predicting the histological diagnosis of all solid benign breast masses in adolescent patients. The Stavros sonographic criteria [33], however, were useful for predicting benignity in 65% of the breast masses on which histopathologic examination was performed. We think not all benign findings in children must be surgically removed, especially when there are multiple nodular hyperplasias, because of inaesthetical risk of scars, risk of recurrence, and risk of damage relative to the finalizing of the developing breast. Moreover, this study is in accord with the specific literature and demonstrates the low specificity of the Stavros criteria in young breast when the glandular anatomy is neglected, the ductal connection is unknown, and the Doppler value is underestimated.

A detailed classification of the lesions found in 62 patients between 8 weeks and 20 years of age [34] after clinical and classical sonographic evaluation established four main groups of diagnoses: benign tumors (15), developmental disturbances (14), cystic changes (11), and inherent defects (7). In the remaining cases, the findings were no abnormality (9), nipple discharge without evidence of pathological or morphological correlates (3), abscesses (2), and epidermoid cyst (1). This study is significant because it demonstrates the absence of the malignancy, but it does not prove the accuracy of US in the differential diagnosis of benign findings; moreover, this study based on the classical US does not define the "developmental disturbances" or the "inherent defects" and cannot explain the nipple discharge, these limits being imposed by the nonanatomical sonographic examination.

Classical US is particularly helpful in characterizing cystic, inflammatory, and neoplastic lesions in children. Although most masses that occur in the pediatric breast are benign, *phyllodes tumor* may be benign or malignant. In adolescents, cystosarcoma phyllodes is rare, but it rests still as the most common malignant breast tumors. Phyllodes tumor is presented in the classical US as well-circumscribed, oval, or lobulated tumor with rapid grows; it develops from the periductal stroma, and it has a fibroepithelial structure, sometimes containing cystic areas.

After using US to evaluate breast masses in pediatric and adolescent patients, Weinstein and col. [34] reported the following findings: gynecomastia, cyst, fibroadenoma, lymph node, galactocele, ductal ectasia, and infection. They had no patients with malignancy, but citing Kronemer and col., they cautioned that, in rare cases, rhabdomyosarcoma, non-Hodgkin lymphoma, and leukemia may metastasize to the breast in children and adolescents [35].

Generally, most studies presented the occurrence especially of the solid masses and of no focal abnormality in symptomatic breasts for this group of age, while the cysts are more rare [34]; contrarily, as the women are aging, the incidence of simple cysts or fibrocystic dysplasia and of ductal ectasia is increasing. This aspect was not yet explained, but it is in contradiction with the occurrence of the cystic dysplasia based on *the sick lobe theory* that assumes the embryonic period [36].

The absence of the anatomical examination and interpretation of the breast in children determines the misdiagnosing of the classical US, which describes, for instance, in adolescents *glandular tissue, which is echogenic and surrounded by hypoechoic fat*, or *the glandular tissue is echogenic relative to the hypoechoic fat; this appearance mimics the breast tissue in an adult.* In fact, the specific *glandular tissue* in the breast is hypoechoic and represents the glandular parenchyma as in adulthood, which in children contains the mammary bud with branching galactophorous ducts, and lately completed at the end of the TDLUs with the glandular lobules. The glandular parenchyma is surrounded by the glandular stroma, which is itself well defined from the fatty tissue at the periphery and the glandular parenchyma in the central mammary area; the glandular stroma is hyperechoic due to the various components of the connective tissue and is similar in the developing breast with those of an adult breast. The glandular stroma is thicker than the stroma of the fatty tissue, represented by thin, linear hyperechoic *septa*, some with vascular signals on Doppler (Figs. 10.33, 10.34, 10.35, 10.36, 10.37, 10.38, 10.39, and 10.40).

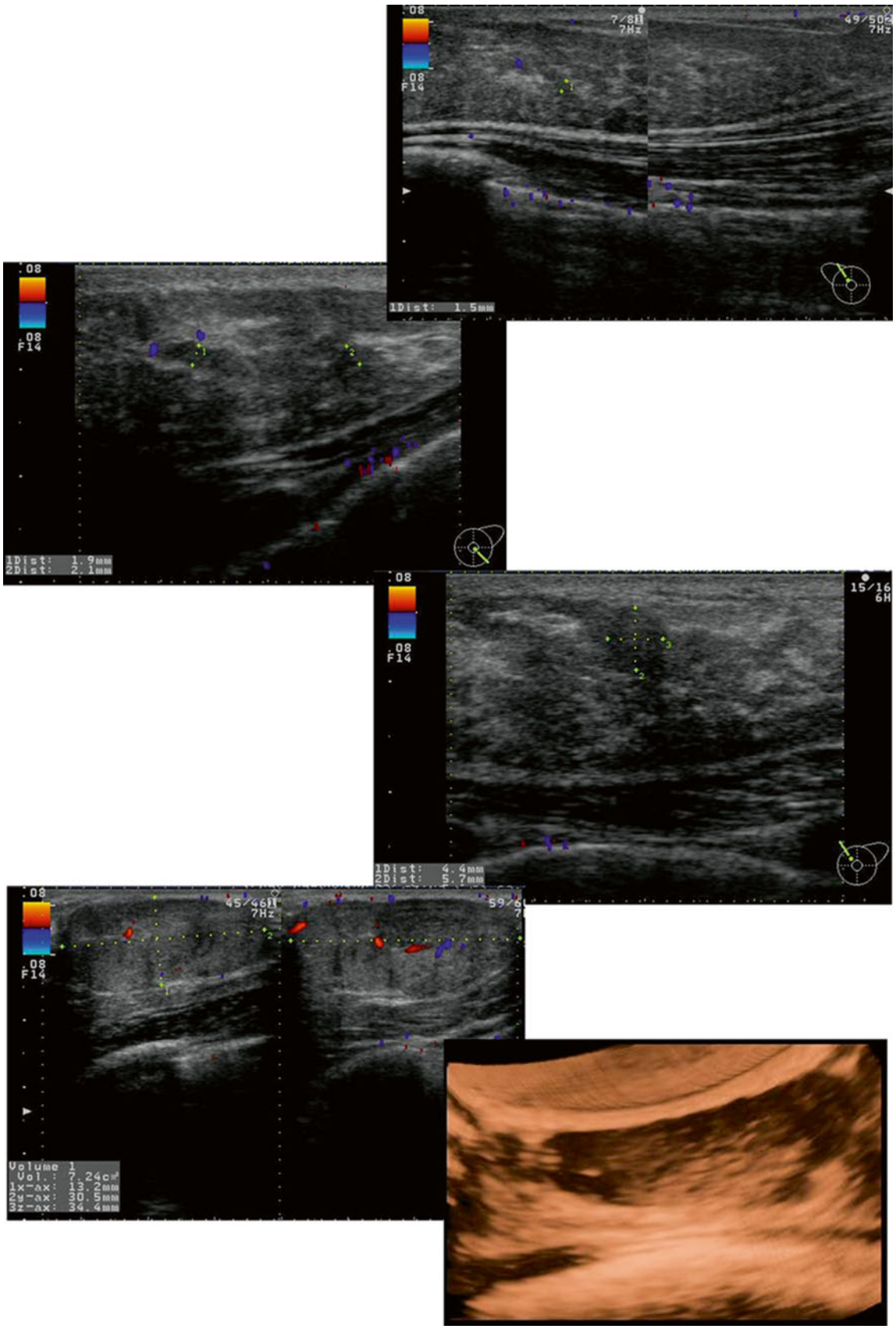


**Fig. 10.33** A 15-year-old patient: dense young breast, with multiple fibroadenomas, on Doppler 2D US and 4D US

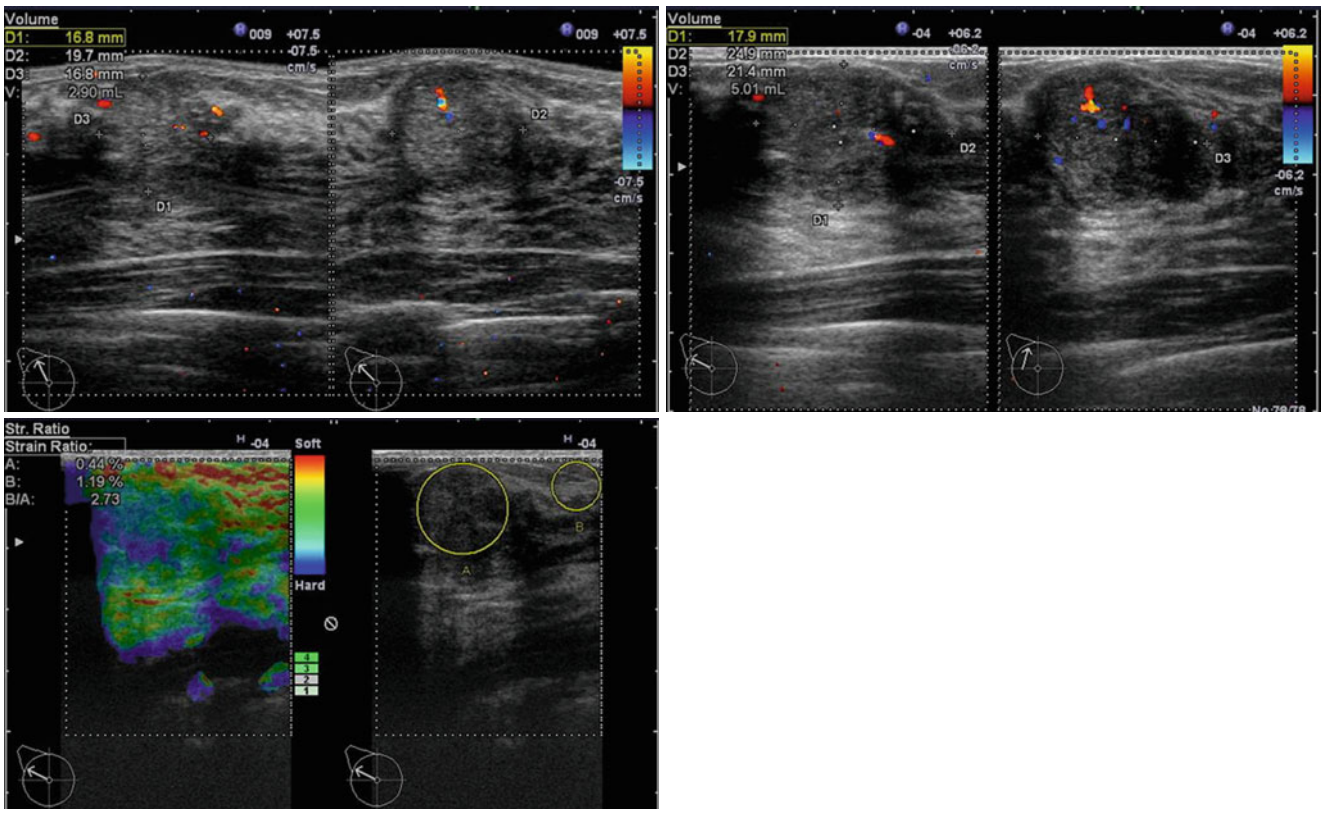


**Fig. 10.34** A 15-year-old patient, the same case: R 11:00 normal developing breast, whereas at R 9:30, a solid nodule with 2D, color Doppler, and RTSE aspect of a benign lesion suggesting fibroadenoma

## 10.5 Malignancy of the Pediatric and Adolescent Breast

It is worldwide accepted that malignancies in the pediatric and adolescent populations are extremely rare. Potential malignancies in such patients may be either primary breast cancers or metastatic disease from other primary lesions. Primary breast cancer in patients younger than 20 years is exceedingly rare. Metastatic disease to the young breast occurs late in the course of a malignancy, because of the reduced vascularity in this period of life. Rhabdomyosarcoma, non-Hodgkin lymphoma, and leukemia are the most common primary tumors to metastasize to the breast in young patients [37]. When malignant breast mass occurs in this age group, it is more likely to be metastatic from a non-breast origin than a primary breast cancer [38].

The malignant findings of a mass have the same characters as in the adult population:

- *Irregular, angular, or microlobulated margins.*
- *Posterior acoustic shadowing.*
- *Exhibit vertical growth that is greater than horizontal growth.*
- *A rapidly enlarging mass should also be clinically suspected, although benign masses such as fibroadenomas may also grow over time.*

In a child or adolescent, especially those with a known history of a primary malignancy other than breast cancer, enlargement of even a circumscribed solid mass should be viewed with caution because it can be a metastasis to the breast; the differential diagnosis with precocious thelarche or gynecomastia may be clinical resolute by the absence of the breast pain. Chateil et al. [37] describe a variety of appearances for metastatic disease. In the classical US, some lesions are well circumscribed, but others exhibit more suspect features, such as posterior acoustic shadowing and vertical growth greater than horizontal growth. Among metastatic lesions, the most common US feature is heterogeneous echotexture.

None of the patients in our population had a malignant mass, but metastases from distant cancers are possible; moreover, axillary adenopathy may have extramammary

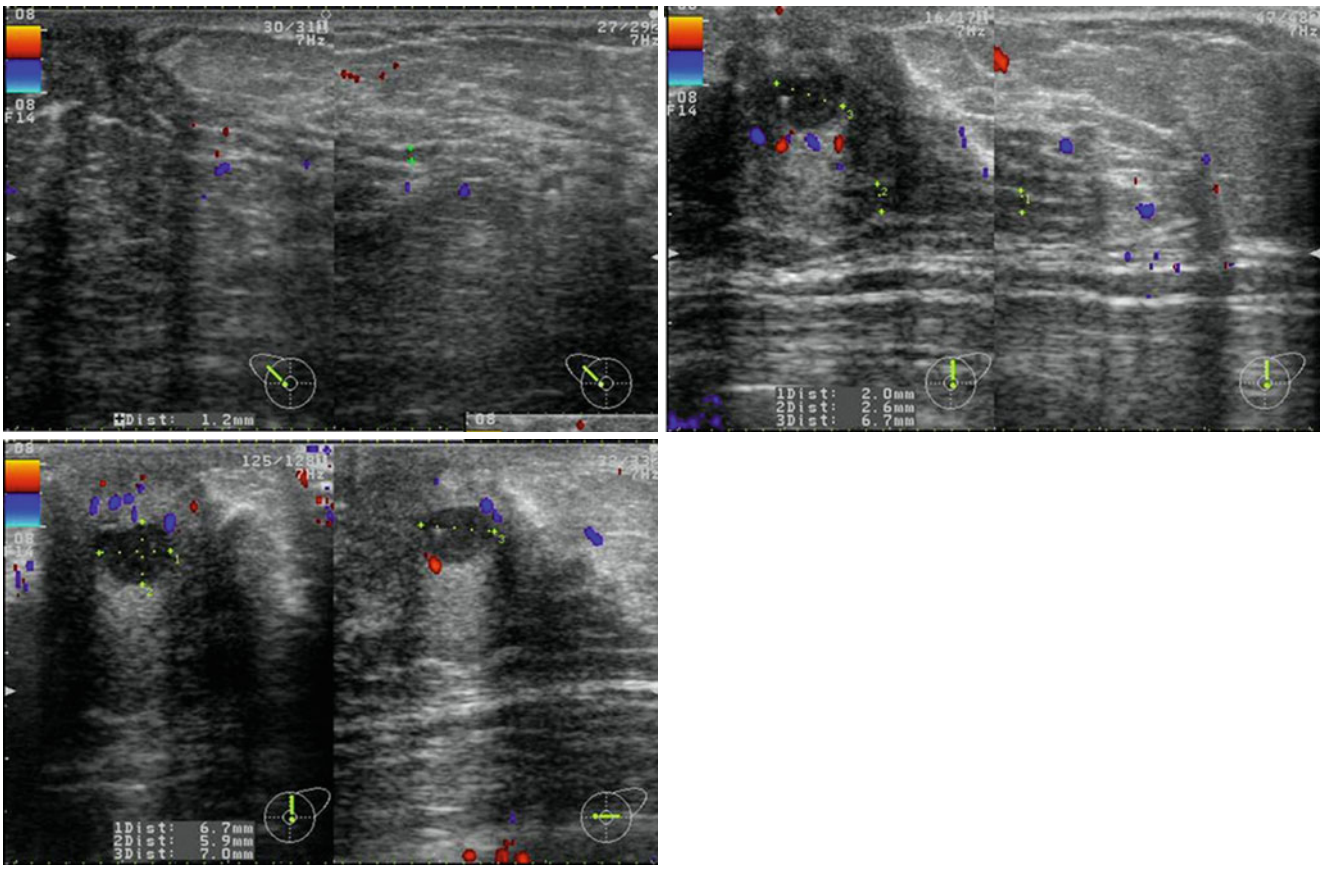


**Fig. 10.35** Pathological thelarche in a 14-year-old girl: a 7 mm retroareolar fibroadenoma, located inside the mammary bud, hypoechoic with benign Kobayashi posterior effects, surrounded by new formation vessels. The ducts are distinct in the periphery, where the stroma is more developed than in the central region of the breast, typically for the thelarche

origins, and the breast involvement can be excluded after normal FBU. Despite the proved value in the assessment of the tissue strain in adults, sonoelastography is less applied in the pediatric investigation, mainly for the assessment of liver fibrosis, of the muscles in spastic neuropathy, of the thyroid, or of the peripheral lymph nodes. Further researchers will allow the use of sonoelastography in the diagnosis and therapeutic response monitoring of the soft tissue malignancies in pediatric breast included.

The connection with the ducts is proved by DE, and the developing process by accretion (new vessels) and concretion (fusion of the surrounding hypertrophic lobules) is obvious.

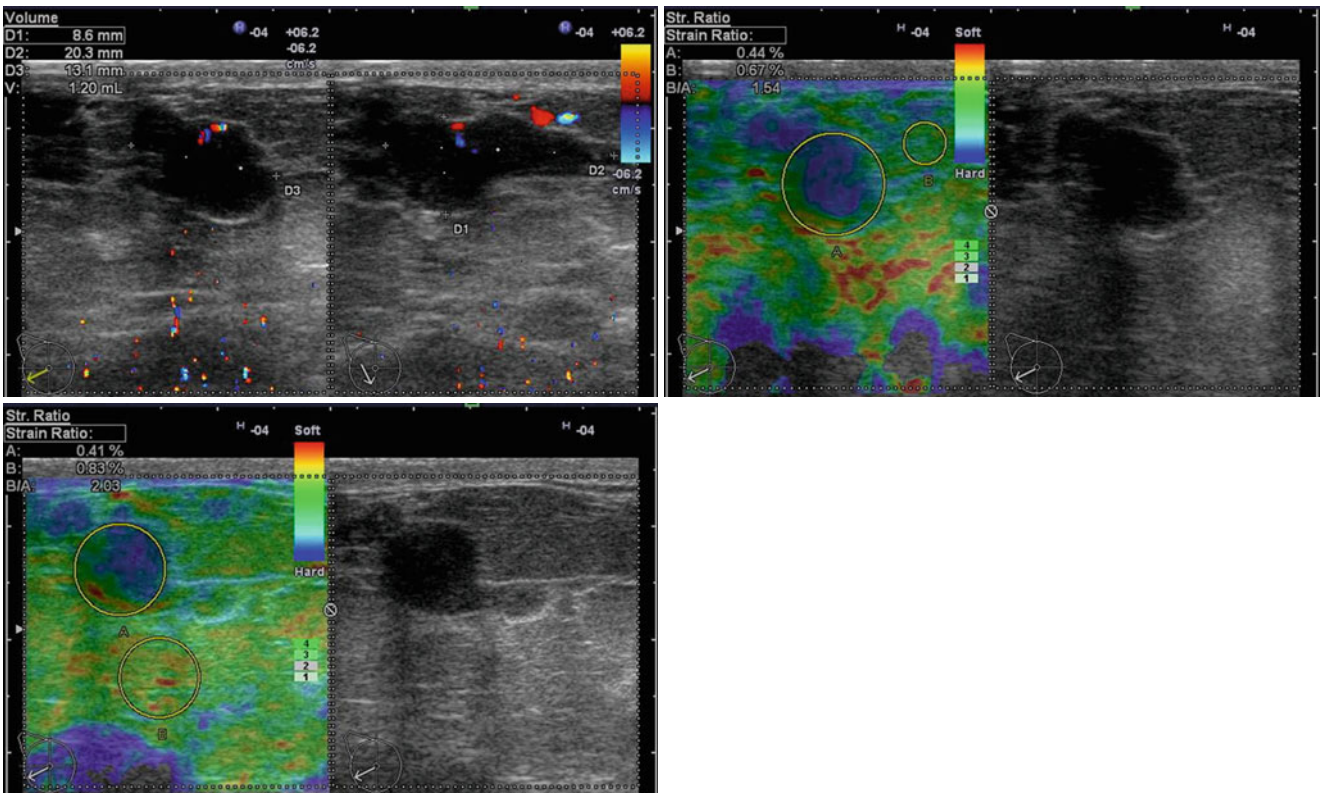


**Fig. 10.36** Pathological thelarche in a 14-year-old girl: FBU illustrates at R 8:00 an enlargement of a ductal-ampullary segment, with ductal wall thickening with Doppler signal and fluid content; the BGR score based on Ueno and the low FLR are argued for benign findings with recommendation for a conservative treatment

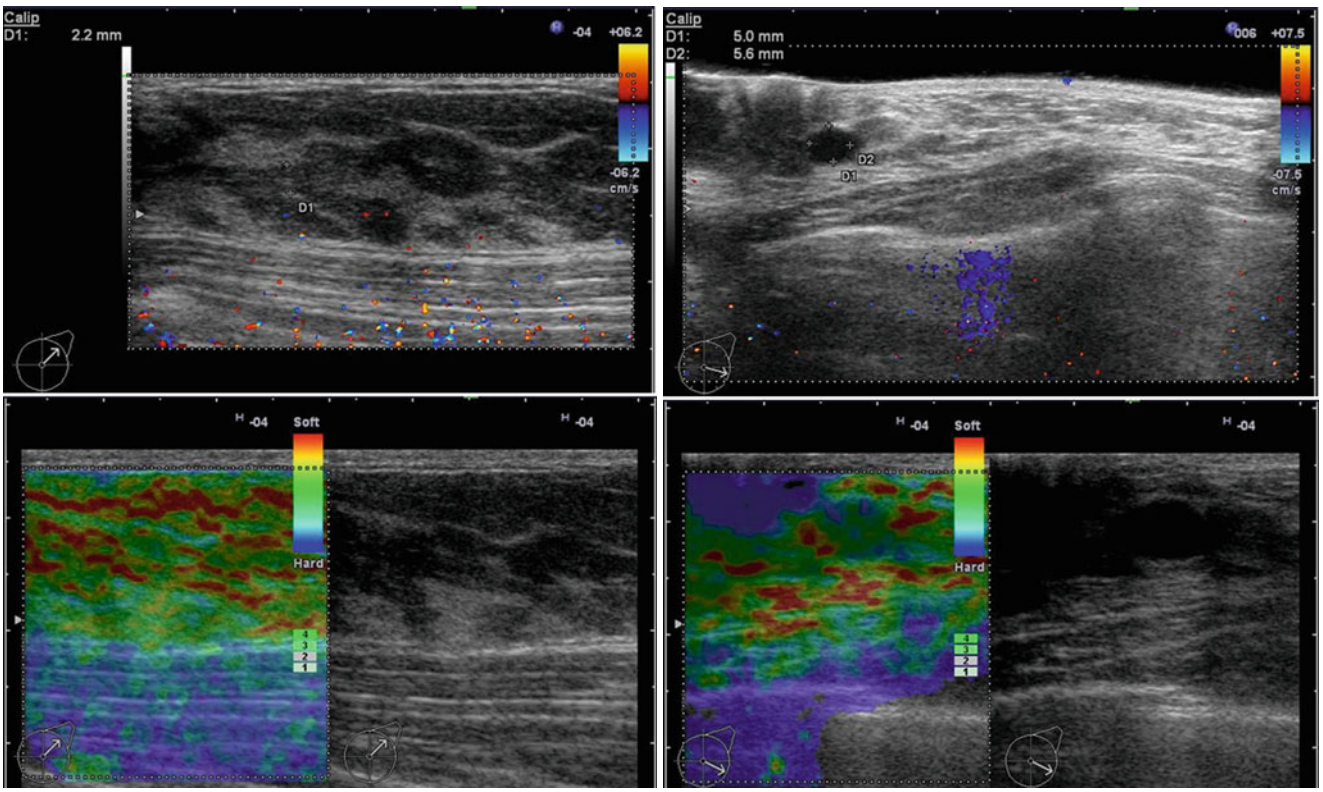


**Fig. 10.37** Pathological thelarche in a 15-year-old girl: small cyst in the retroareolar region between the emerging ducts

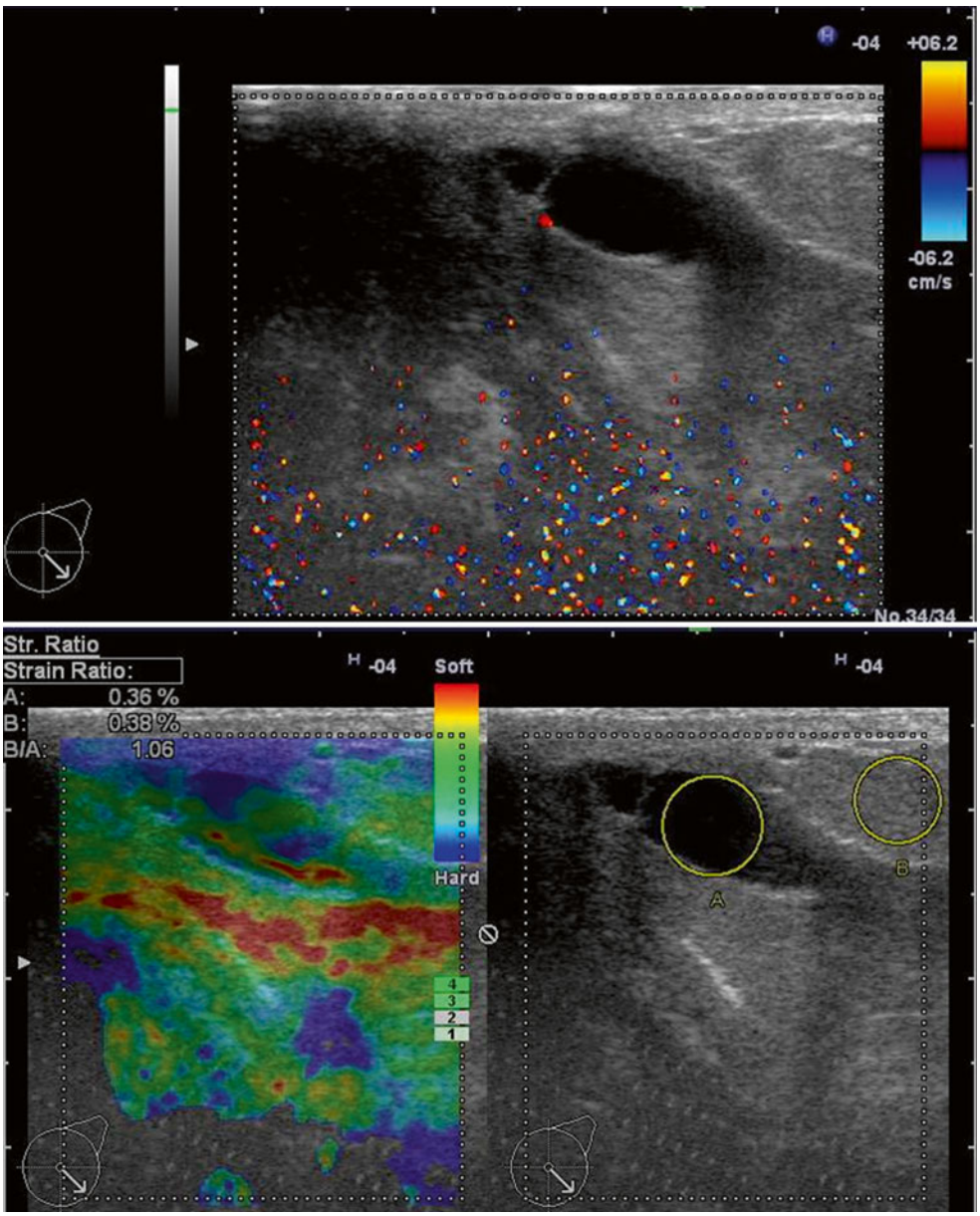


**Fig. 10.38** Pathological thelarche in a 14-year-old patient: a couple of periareolary cysts with transonic content and thin walls in the L 5:00 radius, at the periphery of the mammary branching bud, with BGR score; the normal bud with intense hypoechogeneicity has high elasticity scored 1 Ueno

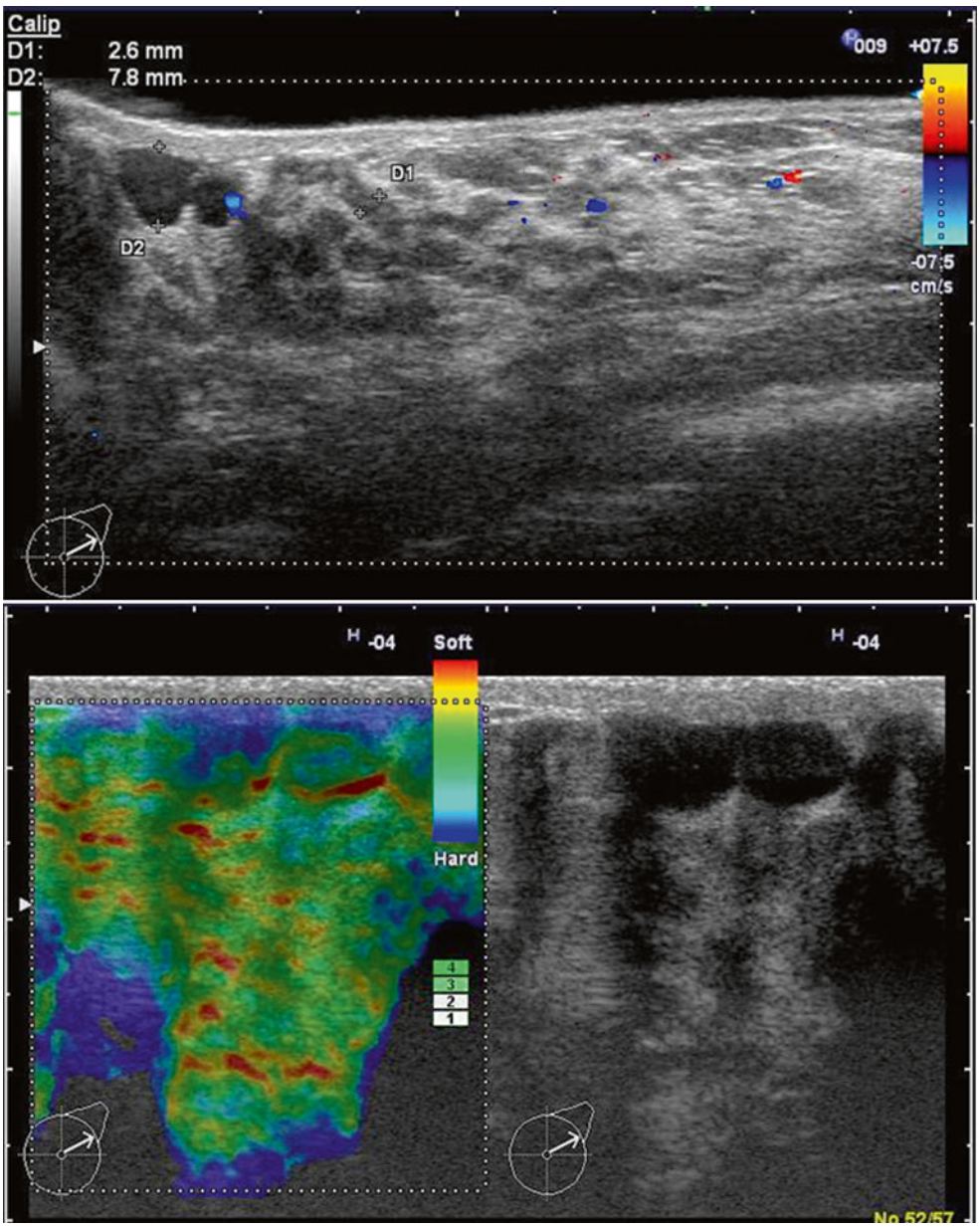


**Fig. 10.39** Pathological thelarche in a 16-year-old girl: FBU illustrates at L 2:00 a young-dense type of mammary breast with thick ducts and large amount of glandular stroma and a periareolary couple of communicant cysts with fluid/debris level and BGR score

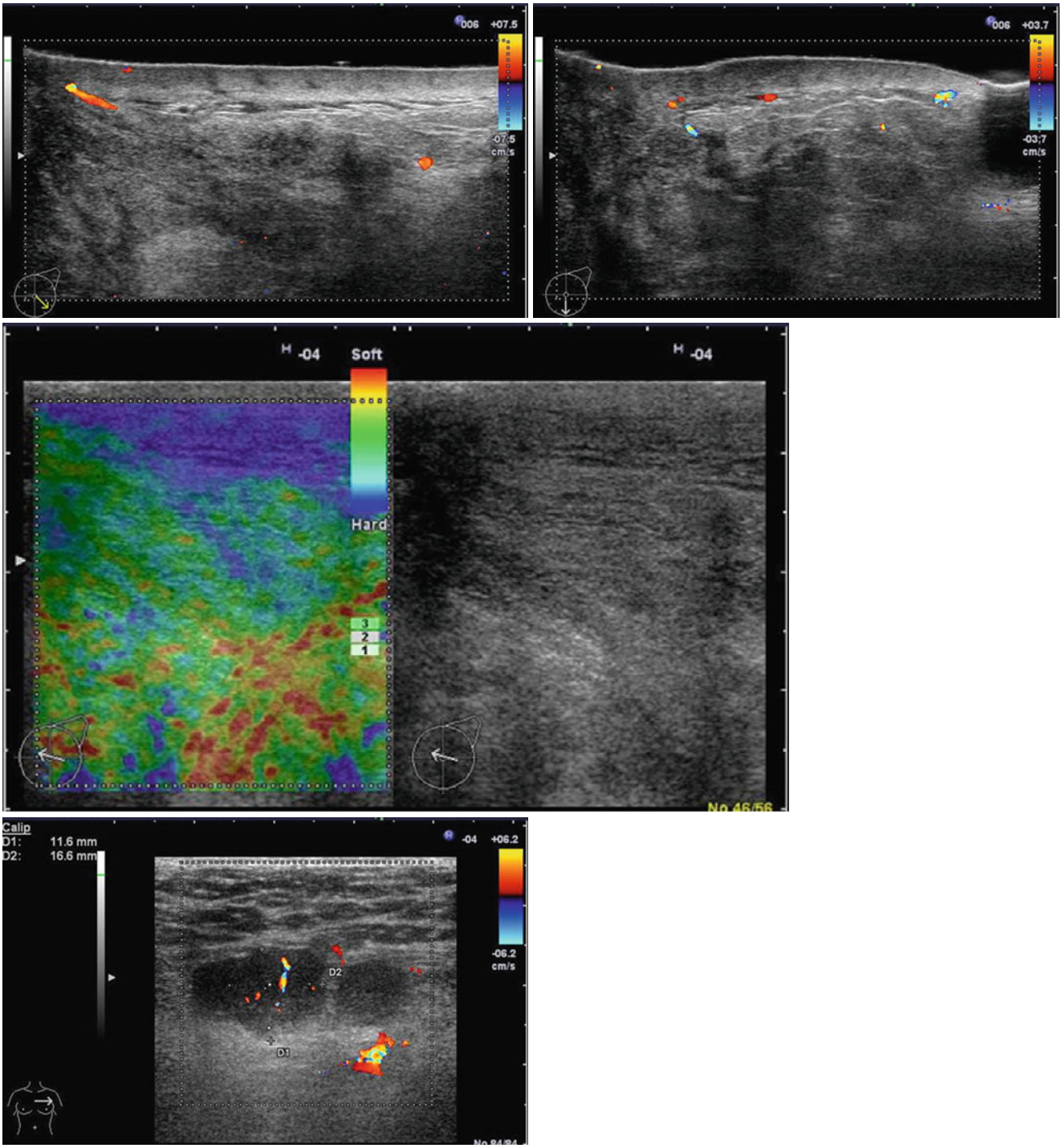


**Fig. 10.40** Pathological thelarche in a 17-year-old patient with diffuse nonpuerperal mastitis: FBU illustrates the edema with thickening of the skin and lymphatic vessels in the premammary fatty tissue, an increase echogenicity of the glandular structures, salient diffuse vasculature, high stiffness of the superficial tissues (skin and fat), and a normal elasticity of the glandular region (ducts in *green*). The satellite axillary lymph nodes present reactive changes

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