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The diagnosis of gynecomastia by Doppler Ductal Ultrasonography. Etio-pathogenic, endocrine and imaging correlations – partial data

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Abstract

Aims: We evaluated the utility of Doppler Ductal Ultrasonography (DDUS) in the positive and differential diagnosis of the gynecomastia and distinguishing, for the first time in the literature, various endocrine aetiologies.

Patients and method*:* A retrospective analysis of 47 cases with unilateral/bilateral "true" gynecomastia, aged between 8 month - 67 year old was performed. The cases were randomly selected from 65 males examined during January 2007- May 2009. DDUS is a new term for the radial breast scanning upon a Teboul-Amy standardized technique, using both a long, linear, water-bag probe and a short, higher frequency probe for detailed characterization. The DDUS findings were compared with the hormonal tests and Sono-elastographic aspects.

Results*:* DDUS defined three essential histological elements of diagnosis of gynecomastia. *Parenchyma* was represented by *the retroareolar bud*, branching in *lactiferous ducts,* in rare cases ending with small *lobules*. Five cases presented ductal ectasias, correlated with *hyperprolactinemia*. Among these, 1 case with milk secretions due to a microprolactinoma was found. Seven cases with ductal-lobular thickening up to 3 mm diameter, presumed as hyperplasia, were correlated with hyperestrogenemia: one case presented an adrenal adenoma, 3 cases had diffuse adrenal hyperplasia and 3 cases were interpreted as dietary hormonal changes. *Stroma* surrounding the parenchyma was essential in the differential diagnosis with pseudo-gynecomastia. The *formation* of *new* vessels was the third element, proportional with the painful developing gynecomastia and the malignancy.

Conclusions: The high accuracy of DDUS completed with Sono-elastography offers the possibility of avoiding unnecessary biopsies or surgical approaches and suggests endocrine types of pathology in gynecomastia.

Key words: gynecomastia, ductal ultrasonography, Sono-elastography, lactiferous ducts.

Rezumat

Scop: Am evaluat utilitatea ecografiei Doppler ductale (DDUS) în diagnosticul pozitiv şi diferenţial al ginecomastiei, descriind, pentru prima dată în literatură, variate etiologii endocrine ale acesteia

Pacienţi şi metodă: S-a realizat analiza retrospectivă a 47 de cazuri cu ginecomastie "reală" uni- sau bilaterală alese la întâmplare dintre cele 65 de cazuri examinate în perioada ianuarie 2007-mai 2009. Vârsta cazurilor a fost cuprinsă între 8 luni-67 ani. DDUS este un termen nou utilizat pentru ecografia radială a sânului după tehnica standardizată a lui Teboul şi Amy, utilizând atât un transductor liniar lung, cu punga de apă cât şi un transductor liniar scurt, de frecvenţă înaltă pentru caracterizarea în detaliu. Constatările la DDUS au fost comparate cu testele hormonale şi aspectul elastografic.

Rezultate: Examinarea DDUS a permis caracterizarea a 3 elemente histologice esenţiale pentru diagnosticul ginecomastiei. *Parenchimul* a fost reprezentat de către mugurele retroalveolar ramificat în ductele galactofore, în cazuri rare terminîndu-se în mici lobuli. Cinci cazuri au avut ectazii ductale care au fost corelate cu hiperprolactinemia. Dintre acestea a fost identificat un caz cu secreţie lactată datorită unui microprolactinom. Şapte cazuri cu îngroşare ducto-lobulară peste 3 mm diametru, suspicionate ca fiind hiperplazice, au fost corelate cu hiperestrogenemia (un caz cu adenom suprarenalian, 3 cu hiperplazie adrenală difuză iar 3 cazuri interpretate ca modificări ale conţinutului hormonal al dietei. *Stroma* ce înconjoară parenchimul a fost esenţială pentru diagnosticul diferenţial al pseudoginecomastiei. *Formarea de vase noi*, al treilea element, a fost proporţională cu ginecomastia dureroasă în dezvolatare şi malignitatea.

Concluzii: Acurateţea înaltă a DDUS completată cu elastografia oferă posibilitatea evitării biopsiilor inutile sau a intervenţiilor chirurgicale, sugerând tipurile de patologie endocrină ale ginecomastiei.

Cuvinte cheie: ginecomastie, ecografie ductală, elastografie, duct galactofor.

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Introduction:

There are few imaging presentations of male breast pathology in the literature, despite the "classical" aspect on Ultrasonography (US) that is intended rather to make

the differential diagnosis of the malignant from the benign conditions and gynecomastia, than to describe gynecomastia itself. Many believe that the addition of US to mammography increases the diagnostic accuracy. However, it was proved that classical US findings of malignancy in the male breast may be subtle, and the appearances of benign and malignant disease overlap.

Gynecomastia represents the development of the mammary bud in true mammary glandular structures in men. The disease is believed to have peak frequencies at three periods during the lifetime [1]: in the neonatal period, gynecomastia is due to influences from maternal estrogens across the placenta, with a spontaneous resolution in 2-3 months; on puberty, with peak frequency at 13–14 years, when about 60% of male adolescents are affected and typically resolves within months to 2 years; in elderly men with various etiology. In fact, we can differentiate physiological gynecomastia that includes the neonatal period and the adolescence, and the pathological gynecomastia in other periods of life, including childhood, teenagers or adults. It is admitted that estrogen, acting through its ER a receptor, promotes duct growth, while progesterone, also acting through its receptor PR, supports alveolar development [2]. It is not the aim of this paper to present the full etiology of this disease, but we shall illustrate the typical aspects of pathological gynecomastia usually referred to on account of abnormal clinical findings.

The clinical appearance as a retro-areolary painful lump has usually an asymmetrical development, but rarely is found unilateral. Breast glands under estrogenic stimulation tend to grow, to be sensitive, tender, and are painful. Under enough prolactine stimulation, milk production will occur. Usually, the diagnosis of gynecomastia is made by the physician through simple observation and the presenting history. The breast is always palpated to ensure there are no hard masses present. A mammogram has no role in the evaluation of breast mass in males, because a mammogram requires fairly decent sized breasts to be placed between two compressive plates, and it is difficult to differentiate the eventual opacity in simple gynecomastia or tumoral lesion. In addition, mammography can not be used in children. **The classical US** has been usually recommended for the identification of cysts, other fluids or solid masses [3], but it is not possible to analyze the types of benign gynecomastia, and being operator dependent, it is not a reproducible, accurate method of diagnosis [4].

Doppler Ductal Ultrasonography (DDUS) is a recent technique developed by Teboul [5,6] followed by Amy [7] and represents a unique imaging method that allows the visualization of the breast *glandular parenchyma*, which is represented by branching ducts and lobules emerging from the parenchymatous retro-areolar bud, surrounded by the normal stroma, the supportive framework of any organ.

This paper is devoted to the evaluation of the utility of DDUS in the positive and differential diagnosis of gynecomastia, and, for the first time in the literature, in the distinguishing, of various aspects of gynecomastia, in order to establish the etiological diagnosis.

Patients and method

We made a retrospective analysis of 47 cases of males with unilateral/bilateral "true" gynecomastia, aged 8 months – 67 years old, selected from 65 males examined by DDUS during January 2007/ May 2009. The rest of 18 patients with breast area enlargement were grouped with the diagnosis of pseudo-gynecomastia The patients presented subacute (few months) or chronic (more than 6 months), usually painful thickening of the mammary soft tissues. The DDUS findings were compared with the paraclinical hormonal tests and in specific cases endocrine selective imaging were performed (US and MRI of the adrenal glands, MRI of the hypophyse). We performed a radial breast scanning upon Teboul-Amy standardized technique, with double probes (transducers). First, the water-bag probe an as-long-as-possible with as-high-as-possible frequency was used, with a water-bag adaptor, useful for the global evaluation of the skin, subcutaneous fatty tissue and mammary structures. This global approach offers the image of a mammary lobe with ducts and stroma; secondly, the highest frequency usually shorter probe, allows a better resolution, better analysis of the mammary bud, ducts, eventually glandular lobules, blood vessels and pathological findings. We used thus a 7-9 MHz water-bag long-linear probe of 9 cm length and a 9-12 MHz short-linear probe of 4 cm length, with good magnifying sections that offered good anatomical images. As a conventional standardization introduced by Teboul, all the sections present the nipple in the upper-left corner and the periphery of the mammary lobe on the right side of the screen, the level of the section represented by the scanning radius being noted on the image and codified with the sign R or L for the right or the left side, followed by the clockwise number representing the precise site (for example, L7:00 represents a radial scanning of the left breast at seven o'clock level, in the lower-inner quadrant). The radial scanning with a composed panoramic view by double scan in the same radius with the shortest high-frequency probe represented a trade-off between resolution and anatomy in the evaluation of the mammary lobe. The high-frequency probe is

recommended for the Sono-elastography, too, because of better characterization of the tissues. We used the Real-time-elastography and the score of Ueno/Tsukuba for the qualitative classification, completed with the *fat-to-lesion ratio / strain ratio* for the quantitative assessment.

Results and discutions

Usually, *classical US* scans performed directly over the palpable area in the breast present a "hypoechoic tissue" in the subareolar region, considered as "breast tissue", which is similar to early breast development in female adolescents. US scan of the opposite breast may present a similar appearance, although the "hypoechoic tissue" is less prominent, because almost always there is bilateral more or less symmetrical gynecomastia. The *classical US* offers a difficult differential diagnosis with the pathological masses, which usually are hypoechoic too, and most cases in adults are usually misinterpreted. No discrimination of gynecomastia types was possible with this US technique.

Otherwise, *DDUS* presented three essential histological elements of diagnosis of gynecomastia:

1. Parenchyma: represents the key functional elements of certain organ; in the breast it begins with the retro-areolar bud, hypoechoic, with pyramidal shape, the basis on the thoracic wall, with progressive peripheral branching in lactiferous ducts, more developed in the upper-outer quadrant. The initial branching was less specific, but the advanced stages presented typical "normal" ducts, isoechoic with thin walls, less 1mm diameter and with a hyperechoic central line corresponding to the virtual lumen (Fig.1.).

The ducts contained fluids in 5 cases, where ductal ectasias were seen, with the same appearance as in women. 1 case with very large ectasias in the upper quadrants misinterpreted on the classical US and mammography, had a surgical excision that proved milk secretions. Over

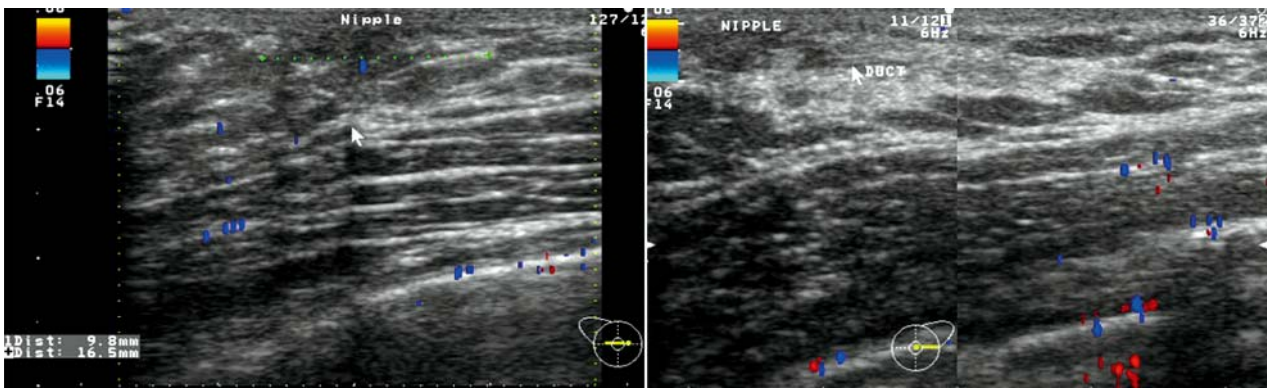


Fig 1. DI, 24-year-old man: Mammary bud on right side, as a hypoechoic retroareolar area with irregular borders, surrounded by a minimal stromal reaction; developed gynecomastia on the left side, with ducts containing the specific central hyperechoic line and a large surrounding stroma. The double scan with contiguous radial sections with high resolution probe was performed to demonstrate the whole long axis of the mammary lobe.

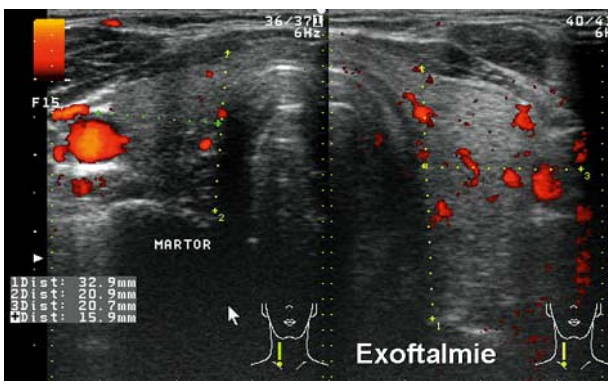


Fig 2. RN, 54-year-old man: Diffuse goiter, with hyper vasculature proved on power Doppler exam comparing with a witness image, concordant with clinical exophthalmia and neuro-vegetative syndrome.

the next 3 months ectasias developed in the lower quadrants, visualized on DDUS, as well as an associated diffuse goiter with hyper vasculature subsequently proven to illustrate Basedow disease (Fig.2); hyper prolactinemia decided a pituitary MRI that presented a microadenoma (Fig.3).

The lobules were usually not visualized in the initial stages of gynecomastia, but they may appear in the advanced stages or in relation to high hyper-estrogenemia, when we have seen lobules associated with ductal thickening up to 3mm diameter, presumed as hyperplasia; for these cases, an adrenal or testicular feminizing tumor may be responsible. We found 7 cases with ductal-lobular hyperplasia, and a US exam of the adrenal and testis was performed: in 1 case there was an adrenal adenoma, confirmed by MRI examination (Fig.4, Fig.5); 3 cases pre-

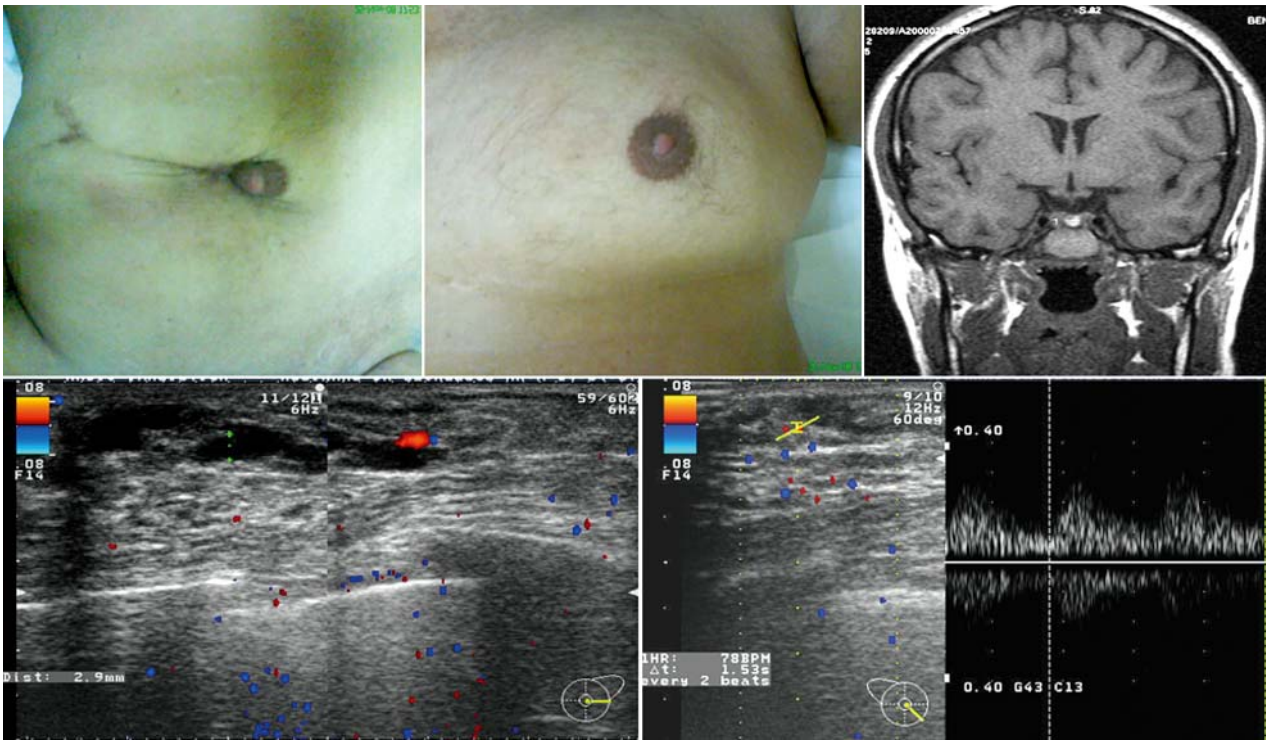


Fig 3. RN, 54-year-old man, the same case: Gynecomastia initially on right side, misdiagnosed with surgical excision of the upper-outer quadrant that proved dilated ducts with milk; local recidivate in the others quadrants and contra lateral secondary development, demonstrating ductal ectasia and active new vasculature. Hiperprolactinemia confirmed galactorea and pituitary microadenoma was detected on MRI exam.

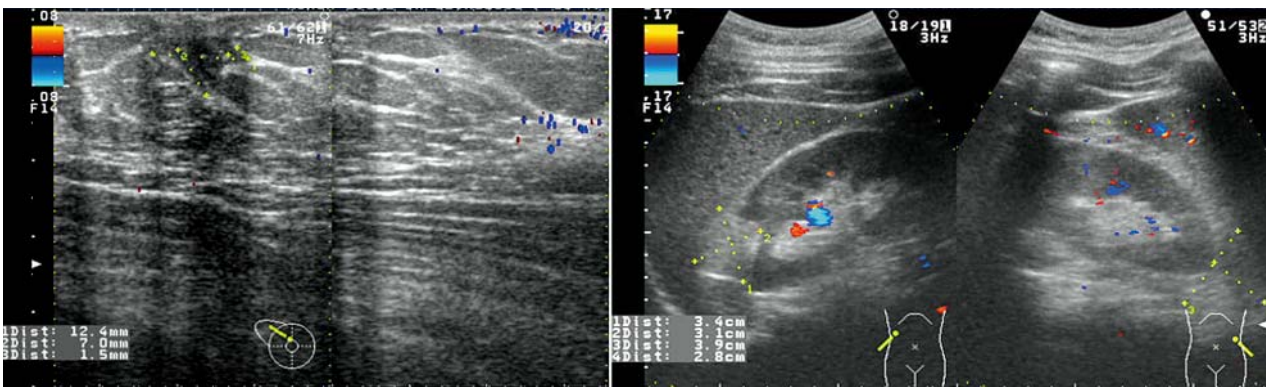


Fig 4. MG, 33-year-old man: Gynecomastia of a patient with hyper estrogenemia and Cushing syndrome confirmed by the paraclinical tests; US visualized a right adrenal hyperechoic mass, without calcifications or colour Doppler visible vasculature.

sented diffuse adrenal hyperplasia with hyper cortisolemia and hyper estrogenemia; we found no cases in this small group with testicular tumors, and the last 3 cases were interpreted as dietary hormonal changes, among them 2 boys of 8 months and respectively 4 years old and a man of 38 years. These 3 last cases were partially remitted after restrictive animal fat dietary and physical exercises.

2. Stroma was another essential element of gynecomastia visualized on DDUS; stroma represents in fact an amount of tissues containing connective cells, fibers, the arterial and venous vasculature, the lymphatic vessels, the nerves, and presents a general hyperechoic aspect. The presence of stroma surrounding the parenchymatous bud and the emerging ducts is essential to confirm a mammary glandular architecture in the "true" gynecomastia similar to the premature thelarch, while its absence is noted in pseudo-gynecomastia and in the normal fatty tissue (Fig.6). The amount of stroma was not correlated in our study with the history of the disease or with the clinical aspect (pain or volume of the mammary gland), but was

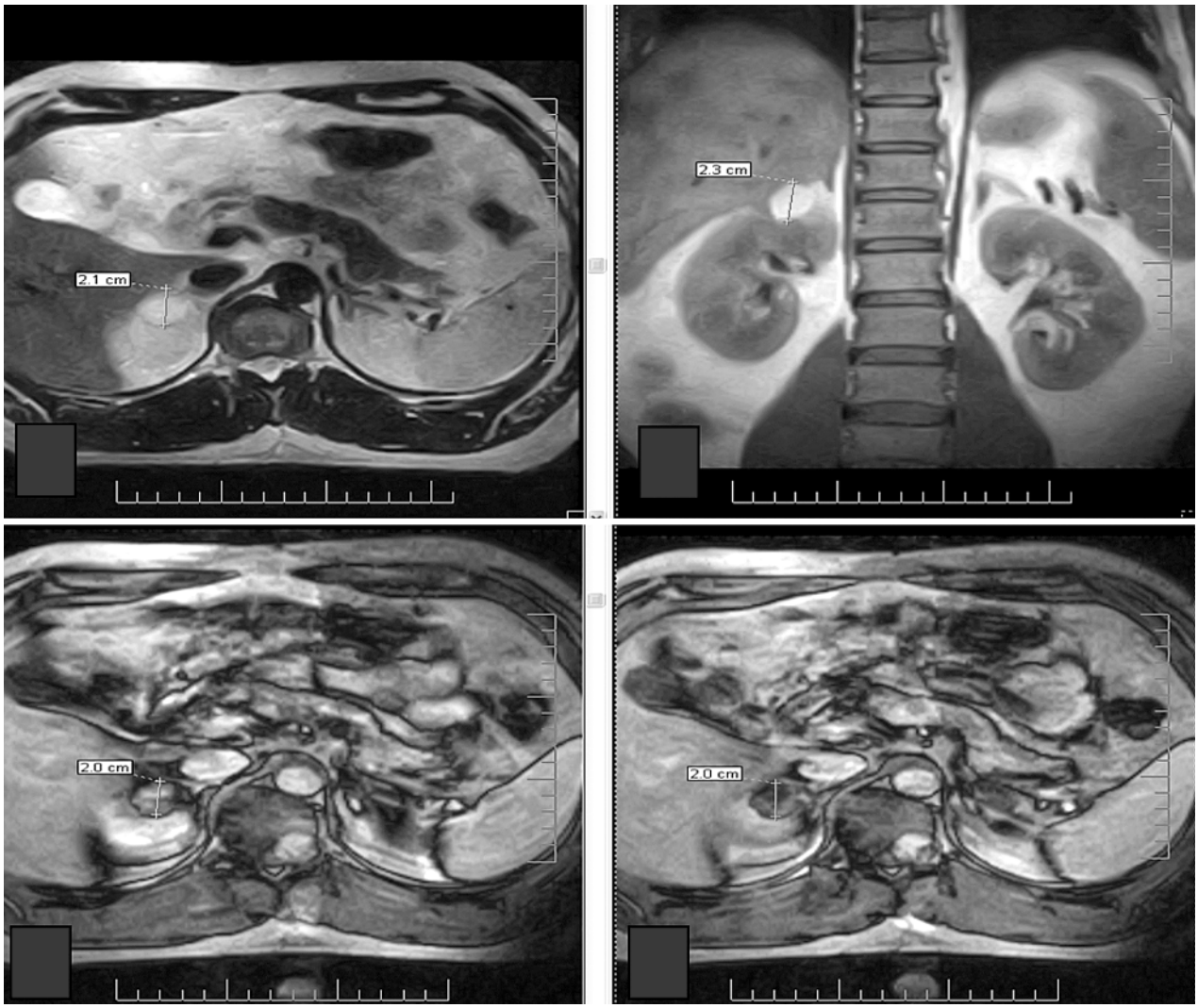


Fig 5. MG, 33-year-old man: Same case: MRI demonstrated a right adrenal well delineate mass, in hyper signal T1 and T2 WI, with a chemical shift for fat of the lesion, high suggestive for adrenal adenoma.

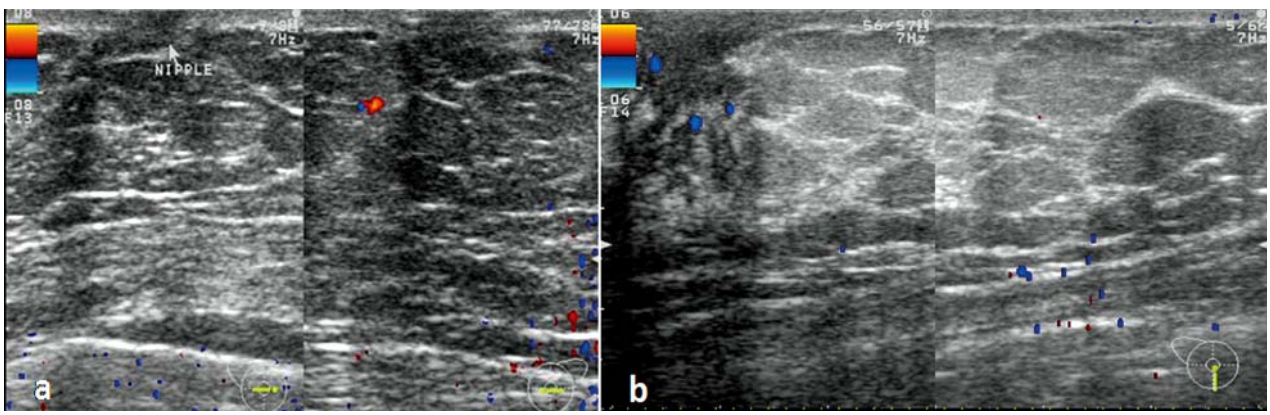


Fig.6.*a:* IM, 56-year-old man: bilateral pseudo-gynecomastia. *b:* MC, 52y: left breast 6:00 radial scan of recent gynecomastia, illustrating the mammary bud branching in ducts, all representing the *parenchyma*, surrounded by the hyperechoic *stroma* and visible *new vasculature*.

the essential element in the differential diagnosis with the pseudo-gynecomastia that presents only a hypoechoic heterogeneous mass, represented by fat with conjunctive septae, without well defined boundaries towards the subcutaneous peri-mammary fatty tissue.

3. The new-formation vasculature was essential in the developing breast, such as gynecomastia or thelarche; color and power Doppler was useful in confirming the diagnosis, the number and size of the detected vessels being proportional rather with the breast pain and the active disease, than with the size of the developing breast (Fig.7). Spectral Doppler presented arterial low resistance velocimetry flux indices, known as "central type vasculature", specific for the breast as a normal anatomical organ, but unusual for the subcutaneous fatty tissue in pseudo-gynecomastia. The follow-up DDUS exam was useful in assessing the therapeutic response or the spontaneous resolution in newborn or teenager boys, and confirmed the relationship between the vasculature and the evolution of the gynecomastia. In recent painful cas-

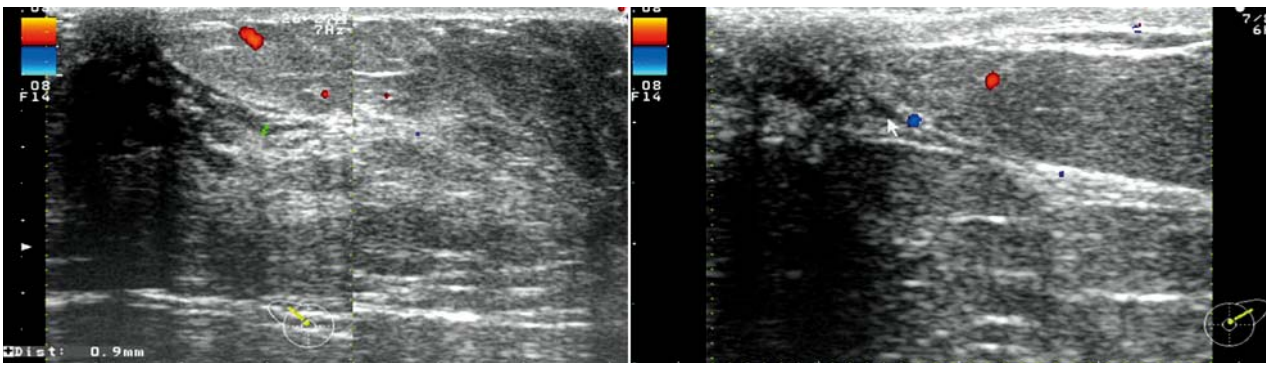


Fig 7. MD, 19-year-old man: Recent gynecomastia with bilateral asymmetrical development: the retro-areolar bud is branching in ducts, surrounded by a simultaneous developing stroma with the presence of the new vasculature. This patient is the son of the case from fig 8.

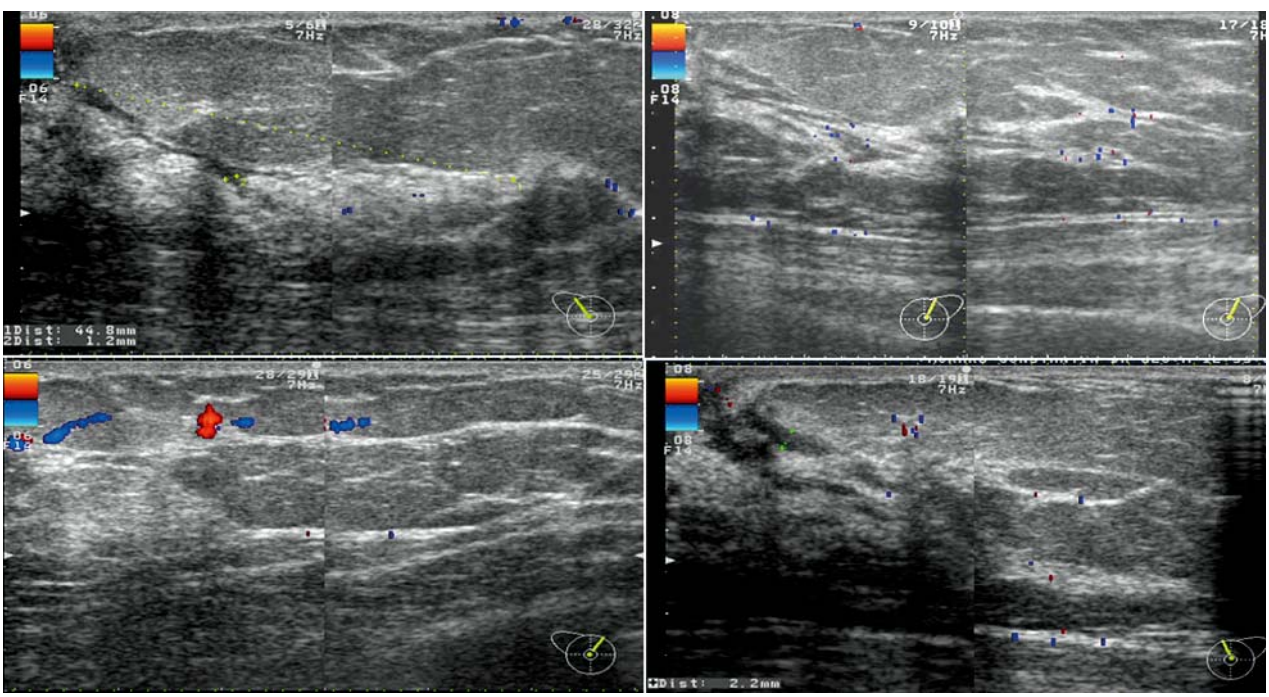


Fig 8. MC, 52-year-old man, the father: chronic gynecomastia (since 4 years), with bilateral asymmetrical development; the retro-areolar bud is no more visible, because his complete branching in ducts, surrounded by a significant amount of stroma; the presence of the new vasculature is the third element of diagnosis.

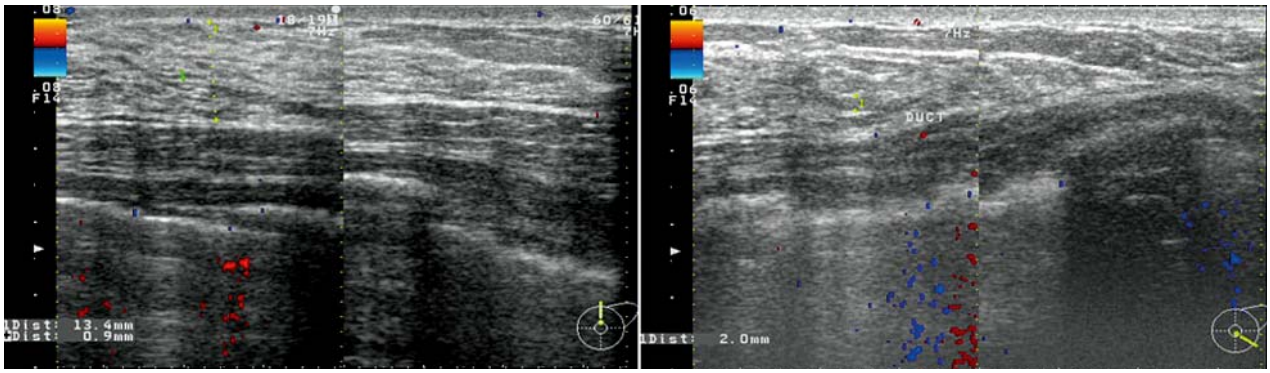


Fig 9. RD, 21-year-old man: Chronic gynecomastia on high-resolution double-scan reconstruction of the mammary lobe, with similar aspect as in adult woman; the poor vasculature was correlated with the less painful breast.

es the vasculature was evidently better illustrated than in chronic patients with less pain. (Fig.8; Fig.9).

In pseudo-gynecomastia no increasing vasculature was observed. The tumoral development of breast in male is much rarer, especially breast cancer which is less painful, presenting the classical features known as the Stavros criteria [8]. We noted the presentation of these patients was usually in advanced stages, when the local development of the tumor with malignant vasculature (increasing number, dimensions, tortuosity) was associated with satellite lymph nodes involvement and in some cases with metastatic lesions. Contrast-enhanced ultrasound is considered a better method in the evaluation of periductal angiogenesis [9], but the most high resolution probes, over 12 MHz, are useful enough in the detection of new vasculature. We encountered a male patient with breast cancer in this group, very well vascularized and misinterpreted as a furuncle, because a furuncle may begin as a tender, pinkish-red, swollen "nodule", but ultimately filled with pus. The patient had tried to open that "furuncle" and because of worsening evolution he presented with spread malignancy.

It is assumed men with gynecomastia may suffer from absolute or relative estrogen excess and their risk of different malignancies may be increased. A study published in 2002 tested whether men with gynecomastia were at a greater risk of developing cancer [10]. A cohort of 446 men having a histopathological diagnosis of gynecomastia following an operation for either uni- or bilateral breast enlargement, between 1970–1979, 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 years interval in men who had 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 operations (just 2 breast cancers from 446 cases, 0.44%), which was justified as the main method of diagnosis in that period of time, while the advanced DDUS combined with Sono-elastography are able to make the most accurate no invasive diagnosis. The authors could not explain the risk of skin cancer, but they concluded no improvement in the prostatic cancer evolution was observed after estrogen therapy, which was responsible for gynecomastia. In addition, no etiological information was offered or any discrimination of the types of gynecomastia was realised, this study being selected as an example of the usual wrong approach of this pathology.

Conclusions

DDUS can differentiate benign gynecomastia from benign pseudo-gynecomastia and malignant breast lesions, avoiding unnecessary biopsies or surgical treatment. This technique is easy to perform, if respecting the ductal/radial echography of Teboul, especially with the water-bag probe that is conceived to follow the relief of the skin and to quickly detect and localize the normal or abnormal structures. **Being the unique imaging method that allows the identification of breast parenchyma,** (neither mammography, nor breast MRI are able to visualize ducts and lobules), ductal echography allowed the differentiation of "simple" gynecomastia from ductal hyperplasia and ductal ectasias, with orientation for the etiological diagnosis (adrenal adenoma, hypophyseal prolactinoma, and so on).

The differential diagnosis of pseudo-gynecomastia was easy to perform when the three anatomical elements were demonstrated: the parenchyma (mammary bud,

more or less divided in ducts and lobules), the mammary hyperechoic stroma and the new vasculature. The analysis of the vasculature must avoid the overestimation, due to more and more performance machines, and a differential diagnosis with an inflammatory or a tumoral lesion must be considered. Thus, we must eliminate in the breast US lexicon some erroneous and vague terms such as "breast tissue", "glandular tissue".

DDUS made an easier diagnosis of the lumps because of the proven connections of the pathological masses with the ductal tree. Breast malignant lesions in men are very rare, but in suspicious cases Sono-elastography may be the choice before the biopsy [11]; the results of the method become more and more optimistic because the accuracy is increased when the qualitative Sono-elastography is completed with the quantitative estimation by using the *strain ratio*. For better results we sustain the idea that Sono-elastography itself must be used after the gray-scale is completed with the Doppler analysis of the breast. The best choice for breast US is in our experience, too, the Teboul radial technique, because it is anatomical and thus it proves, locates and analyzes the lesions following the Stavros criteria completed with Doppler research. This method is standardized, is operator independent and can be used as a breast US screening method, with similar reports such as the US BI-RADS classification. This complete investigation of the breast, in male and in female, is the real Full-Breast-Ultrasonography, a new concept, available, without side-effects, proving a high accuracy based on the anatomical "logical" approach, as well in the malignant and in the benign disorders, such as benign types of gynecomastia.

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