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Radio-histological correlations of subtle sonography images

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Abstract  Breast lesions may, during their development, provide sonography signs can be difficult to view or are not very specific. They are called "subtle images". Proximal (ductal) lesions are differentiated from distal (ductal-lobular) lesions. Proximal lesions are mainly inflammatory or infectious, altering the duct walls that evolve into ectasia and then fibrosis with possible acute episodes of plasmocyte mastitis or bacterial mastitis. The fibrovascular stalks of the papilloma accounts for the Doppler flow. Certain secretory forms of intra-ductal carcinoma may distend the structure of the milk ducts. The sonography of lesions of the ductal-lobular units are related to the degree of fibrosis, the atrophy or cell proliferation, and the disorganisation of the architecture. The extent of the fibrosis, or the cell density of certain tumours may modify the tissue hardness in elastography.

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Sonography is currently a major tool in the diagnosis and treatment of breast diseases due to the excellent contrast between the mammary gland and most lesions. Nevertheless, some diseases are more discrete in the sonogram due to the constituents of the breast involved and their mode of development. Disorders that affect the segmentation of the milk ducts are inflammatory, infectious or tumoral and sometimes difficult to distinguish from the aspects commonly found. Disorders of the ductal-lobular unit, depending on their nature and mode of progression, will modify the echogenicity and the breast architecture. The diagnosis by sonography does depend on a good understanding of the clinical manifestations and histological modifications induced by these disorders.

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Milk duct disorders

Each breast comprises about 8 milk ducts [1]. Each of these ducts leads into the "terminal duct lobular unit" defined by Wellings. The ducts and lobules are lined with a double layer of cells, an inner layer of cylindrical epithelial cells and an outer layer of myoepithelial cells (Fig. 1). The imaging of these ducts in the retroareolar region (lactiferous sinuses) varies greatly according to the individual and their gynaecological history (pregnancies, nursing). In the sonogram, the milk ducts, when visible, appear in the form of transonic tubular structures whose diameter progressively decreases when moving to the periphery, without a focal zone of distension [2] (Fig. 2).

The most common disorders are inflammatory and infectious, with several stages ranging from simple duct ectasia, developing into a chronic form with peri-ductal mastitis or comedo mastitis, possibly complicated in the form of episodes of acute mastitis. Women between the age of 30 and 80 years are affected, predominantly in perimenopause. Outside of the acute episodes, these disorders present few symptoms, over several years, with episodes of painful tumefaction, inconstant, most often unilateral, yellowish or greenish, rarely haemorrhagic nipple discharge. In the menopausal woman, the progressive retraction of the nipple is observed.

Simple duct ectasia

Simple duct ectasia is a dilation of the duct exceeding 2 mm, and 3 mm in its ampullar portion. The pathogenesis remains controversial but seems to be related to an infectious peri-ductal inflammation that may be due to anaerobic germs [3]. The main lesion is the destruction of the peri-ductal support tissue (Fig. 3), rich in elastic fibers, that leads to the dilation of the duct [4]. This inflammation remains moderate and the beginning form is not visible on the sonogram except for duct ectasia. Duct ectasia is accompanied by intraluminal acidophilic material with amorphous debris and spumous macrophages, possibly visible in sonography as intraluminal echogenic structures that may resemble an intra-ductal papilloma (Fig. 4). Doppler analysis is very useful in confirming the caseous and non-tumoral nature of this endoluminal material.

Mammary duct ectasia

In the later forms, this inflammation becomes more pronounced and, on the sonogram, appears as a slightly hypoechoic coating surrounding the duct, and at times shrinking it, thereby creating segmental ectasia (Fig. 5). Histologically, the wall of the duct thickens with the production of a fibrosis and lympho-plasmocytic infiltration of the walls [5,6]. There is no epithelial proliferation but atrophy. This is called peri-ductal mastitis or mammary duct ectasia. In advanced forms in the elderly woman, this fibrosis has a retractile component, inducing invaginated nipple and sometimes rigidity of the ducts.

Figure 1. Description of the ductal-lobular anatomy: a: diagram of the lactiferous segmentation; b: histological correlation (×200): duct (black cross), lobule (star), double layer of cells (circle).

Figure 2. Normal lactiferous duct. Lactiferous sinus and more distal portion.

Figure 3. Simple ductal ectasia (×100). Distinct dilation of the ducts (star). Amorphous intra-ductal substance (black cross). Normal duct (circle).
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Plasmocyte mastitis

The persistent stasis of the products of intra-lactiferous duct secretion may lead to the destruction of the ducts walls, with the appearance of an intense reaction to foreign bodies at the contact with the necrotic debris and the lipid material from the duct lumen. The surrounding breast tissue is the seat of an inflammatory infiltrate rich in histiocytes, lymphocytes and plasmocytes, surrounding both the ducts and the lobules. This is plasmocyte mastitis, the evolving phase of galactophoritis [7]. The mean age for the appearance of plasmocyte mastitis is 36 years, and it often arises after a pregnancy. Clinically, there is a firm inflammatory mass that may simulate inflammatory cancer. Sonographically, the lactiferous duct tree is distended, with heterogeneous contents, associated with often hypoechogenic rearrangements of the gland, vascular in colour Doppler, heterogeneous in elastography, corresponding to inflammatory lympho-plasmocyte granuloma (Fig. 6). In the evolved forms, a retroareolar, amicrobial collection may be observed.

Figure 4. Simple ductal ectasia with intra-ductal echogenic concretions: a, b: 2D ultrasound imaging. Presence of intra-lactiferous echogenic material; c: material collected in these ectasias; d, e: echo-Doppler imaging: absence of intraluminal Doppler flow.

Papilloma

Besides these inflammatory and infectious lesions, the milk ducts may be the seat of benign tumoral disorders represented by papillomas. The papilloma is an arborescent lesion growing inside one or several large neighbouring milk ducts. The architecture may be papillary with papilla centred by a fibrovascular or adenomatous stalk with glandular tubes separated by a fibromyoid stroma. Sonographically, although some of these papilloma present with a well-circumscribed nodular mass, often surrounded by a small hypoechogenic halo corresponding to peripheral secretions [8], others may have a tubular form that may be mistaken for intra-ductal caseous secretions. The symptomatology differs from that of peri-ductal mastitis, this time the patient being totally asymptomatic, or complaining of translucent, sometimes bloody single-pore discharge. The colour Doppler analysis is fundamental in order to detect the vascular pedicle of the papilloma and assert the tumoral nature of the process (Fig. 7).
Ductal carcinoma in situ

Ductal carcinoma in situ is a proliferation of tumoral cells within the ductal-lobular junction, continuing in the milk duct tree. Although mainly diagnosed by microcalcifications on the mammography [9], it can be seen through sonography. The microcalcifications are sometimes visible in sonography, localised in the ducts (Fig. 3), or within a mass. The malignant calcifications are often better seen than the calcifications related to a benign disorder [10] and are often related to a high-grade carcinoma [11]. Sometimes the intra-ductal tumoral proliferation may only increase the thickening of the wall of the milk duct that should be considered as suspect as opposed to simple galactophoritis where the wall remains thin.

There is a rare form of intra-ductal, hypersecretory cancer, first described by Rosen and Scott in 1984 [12]. This form presents a micropapillary intra-ductal carcinomateous proliferation marked by hypersecretory activity inducing a dilation of the ducts and the production of cysts. The secretory matter seems to have a semi-gelatinous consistency [13], and appears as a homogeneous eosinophilic substance...
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**Figure 7.** Intra-lactiferous papilloma: a, b: intra-ductal tumour moulding the duct (yellow cross), with vascular pedicle; c, d: (×100) papillary proliferation (star); wall of the duct (circle); (×200) papilla: fibrovascular stalks with a double layer of epithelial cells (yellow cross).

**Figure 8.** Intra duct carcinoma: a–c: duct distension filled with a heterogeneous material with calcifications (yellow cross). Thickening of the wall (circle); d: (×100) epithelial intra-ductal proliferation (circle) and microcalcifications (yellow crosses). Distinct dilation of the duct (arrows).

Similar to the thyroid colloid substance in microscopy. Clinically, a mass is usually palpated [14], the mammography is not very informative, revealing increased density, sometimes microcalcifications. Level with the mass, the sonogram reveals ductal ectasia and multiple anechogetic cysts (Fig. 9). The diagnosis should be raised when confronted with the association of a palpable mass and multiple ductal ectasias and cysts.
Disorders of the terminal ductal lobular unit

The terminal duct lobular unit (TDLU) comprises extra- and intra-lobular canaliculi ending by the smallest epithelial structure of the lobule: the terminal canalicus or acinus [15]. This unit is the seat of a great many benign and malignant disorders that will affect its constituents to different degrees, thereby modifying its architecture.

Epitheliosis — adenosis

The benign lesions are associated with cysts, epithelial ductal or lobular hyperplasia, as well as fibrosis. Epitheliosis is a proliferation of epithelial cells that tends to fill the lumen of the extra- and intra-lobular ducts. These isolated anomalies aren’t seen on the sonogram and occasionally may be found in the expertise of clusters of microcalcifications. Adenosis induces a multiplication of lobules with hyperplasia of all of the constituents (epithelial and myoepithelial cells, palatal connective tissue). This hyperplasia may lead to a true macroscopic grainy mass, appearing as a well-circumscribed or lobular oval mass in sonography. Simple adenosis may evolve into sclerosing adenosis where the lobules are disorganised by interstitial sclerosis. This adenosis may be peri-ductal or involutive with progressive elimination of the epithelial structures, only leaving the myoepithelial contingent associated with sclerosis and calcifications. At an advanced stage, on the sonography, it is represented by an irregular mass. Before reaching this stage, it modifies the echostructure and architecture of the breast parenchyma with the appearance of slightly hypoechoic zones with focal posterior shadowing [16] whose appearance varies according to the probe orientation, sometimes with a certain degree of architectural rectitude (Fig. 10). These lesions usually do not present any suspect hardness in elastography unless that is a major sclerosing component. Microcalcifications may be seen in the sonography, both with intra- and extra-milk duct location, often within microcystic elements (Fig. 11).

Radial scar — tubular carcinoma

Besides these benign proliferative lesions directly affecting the TDLU or the afferent milk ducts, there are non-encapsulated sclerosing lesions, still called radial scars (RS) or Aschoff’s proliferative centres, corresponding to a star-shaped formation with an elastotic centre toward which converge TDLU in a radial manner [15]. The tubes inserted in the sclero-elastotic centre are very drawn out and deformed. The simple radial scar, without proliferating element, sometimes with several cysts, may be distinguished from the radial scar associated with proliferative lesions (epitheliosis, adenosis) or associated with a cancer. The association with a ductal or lobular cancer is fortuitous since these lesions originated in the TDLU and are located at the periphery of the scar. However, the tubular carcinoma, according to Linell, arises at the centre of the scar with centrifugal extension. This invasive carcinoma is greatly differentiated and the cells are regular and arranged in well-structured tubules, typically consisting of a single cell layer, surrounded by abundant fibrous stroma. In the sonogram, radial scars often appear as a more or less attenuating hypoechoic mass with poorly defined margins, not very different from an authentic invasive carcinoma (Fig. 12). Nevertheless, in case of a simple and small scar, the appearance in the sonogram may be limited to

Figure 9. Intra-ductal secretory carcinoma; a–c: multiple mammary duct ectasias and cysts; d: (×100) major duct ectasia with intra-ductal micropapillary ectasia (circle) and intraluminal mucoid substance (yellow cross).
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Figure 10. Adenosis: a, b: poorly defined hypoechogenic zone with architectural disorganisation; c, d: multiplication of the lobules (star); fibrosis (yellow crosses).

Figure 11. Adenosis accompanied by microcalcifications. Absence of significant hardness in elastography.

a simple convergent architectural anomaly without associated hypoechogenic mass [17]. The presence of cysts at the periphery of the lesion suggests a radial scar. There is no light peri-tumoral halo in RS, the masses observed appear less suspect and less attenuating than in the case of infiltrating cancer [18]. Tubular carcinoma (Fig. 13), due to the architecture very similar that of RS, does not present significant differences with the RS in sonography [19] and only a histological analysis will be able to differentiate the two entities (Fig. 14).
Lobular—ductal carcinoma

In most cases, the tumour develops at the TDLU. Therefore, the lobular carcinomas in situ is revealed by a proliferation of not closely attached tumour cells that fills and distends the intra-lobular caniculi then, at the infiltrating stage, invades the neighbouring connective tissue around the milk ducts. The stroma reaction is variable and sometimes absent, accounting for the multiple expressions of these lesions in sonography. Although most invasive lobular carcinomas (ILC) present as a poorly circumscribed or heterogeneous hypoechoic spiculated masses [15], some, depending on the intensity of the stroma reaction, are only revealed by a deformation in the gland contours (Fig. 15), or

Figure 12. Radial scar: a–c: more or less absorbent fibrous zone with radial convergence of the fibro-connective framework; d: (×100) sclero-elastosic centre (star). Convergence of TDLU (yellow cross).

Figure 13. Tubular carcinoma: irregular fibrous lesion with convergence of fibro-connective framework.
by slightly hypoechogenic zones with architectural disorganisation. These aspects are not very specific, similar to the previously mentioned mastosis lesions, since the sonography of these two entities is mainly related to the fibrous component and the disorganisation of the lobules. Elastography seems of value (Fig. 16) since the hardness is often greater than in the ILC [20].

Intra-ductal carcinoma often develops in the small milk ducts, close to the TDLU, and are characterised by an intraductal tumoral proliferation where the architecture may be massive, in comedos, papillary or cribriform [15]. There may be retrograde colonisation of the lobules, making it difficult to distinguish from lobular carcinoma, as well as an inflammatory reaction of the neighbouring connective tissue resulting in a mass (Fig. 17). In 2 to 23% of the cases, the DCIS may not contain microcalcifications, and present as an asymmetry of density in the mammography or a palpable mass, or even nipple discharge [9,21,22]. These cancers are symptomatic in over 80% of the cases [21]. The masses are most often encountered in low grade DCIS [11,23]. Sonographically (Fig. 18), the appearance varies and is not specific [24–26]. It often consists of a poorly defined, sometimes circumscribed, hypoechogenic mass with lobular margins [27].

The echostructure may sometimes be heterogeneous due to the presence of microcalcifications. A micropolycystic lesion may sometimes be seen, due to the distension of the lobular portion of the ductal-lobular units [28]. These cancers may also develop within fibro-cystic breast disease, rendering the diagnosis even more difficult. The elastography varies according to the extent of the peri-glactophoric inflammatory reaction and a normal hardness should not delay the biopsies if there are any other indications of malignancy.

Figure 14. Histological differences between radial scar (a) and tubular carcinoma (b): a (×200) dense fibrosis (yellow cross); atrophy of the lobules (circle); b (×200) cellularity of the stroma (yellow cross), stiffening of the tubes with disappearance of the myoepithelial layer in the tubular cancer (circle).

Figure 15. Infiltrating lobular carcinoma: a, b: simple deformation of the glandular margins with, in the histology (×200) a monomorphous epithelial tumoral proliferation creeping in between the adipocytes, without stromal reaction (star); c, d: poorly defined, slightly mitigating fibrous zone with fibrous stromal reaction combined with the epithelial tumoral proliferation in single file (yellow cross).
Figure 16. Infiltrating lobular carcinoma. Considerable hardness in elastography.

Figure 17. Ductal carcinoma in situ: a: (×100) intra-ductal proliferation (circle), fibrosis (cruciform arrow), calcifications (star) and peri-ductal inflammatory reaction (yellow cross); b: (×200) retrograde colonisation of the lobules (yellow cross).

Figure 18. Ductal carcinoma in situ. More or less circumscribed mass, slightly echogenic, sometimes accompanied by microcalcifications, associated by microcystic zones.
Granulomatous mastitis

TDLU may be the seat of acute inflammation characterised by the association of epithelioid and gigantocellular granulomas and abscesses. This is granulomatous mastitis. It appears in young woman within 5 years of childbirth, at a distant time after nursing. It may clinically simulate a carcinoma and should be distinguished from other inflammatory disorders, tuberculosis, sarcoidosis, and plasmocyt mastitis. The two disorders are very similar since both involve the formation of an inflammatory granuloma, although the topography differs. Plasmocytic mastitis is more specifically related to the dilation of the milk ducts, and granulomatous mastitis is due to a lobular dilation (absence of ductal ectasia) with accumulation of secretion products in the acini, then rupture of the inflammatory granuloma. The histology reveals a granulomatous process with inflammatory infiltrate of essentially lobular distribution, inflammatory cells extending beyond the limits of the lobule [29]. The infiltrate consists of histiocytes, several polymorphs, and giant multinucleate cells [30]. The formation of abscesses may be observed although they are generally small or may sometimes involve the entire lobule. In the sonogram, the lobular distension with inflammatory granuloma is revealed by a polycyclical echogenic mass, with several focal attenuations of the acoustic wave and often, considerable hardness in elastography (Fig. 19). Hypoechoic tubular structures appear later and are not galactophoric but related to the confluence of centro-lobular granulomas that have evolved towards suppuration and necrosis. The discovery of multiple, more or less circumscribed, heterogeneous lesions, with a tubular configuration therefore suggests granulomatous mastitis [31].

Bacterial mastitis

It may occur at any age, favoured by local factors (mammary duct ectasia, etc.) and general factors (smoking, diabetes, etc.). Their aetiopathogenicity is debated, related to a ductal superinfection, or due to the diffusion of an infection by haematogenic route. The germs responsible are Staphylococcus aureus or other anaerobic germs. They differ from other mastitis by local infectious signs with redness, heat, pain, in addition to the palpated mass [7]. The general signs are more rare. Histologically, there is a global oedema of the gland with disorganisation of the connective-glandular tract as well as a distension of the ductal-lobular units and ducts by purulent secretions. Sonographically (Fig. 20), this is represented by an architectural disorganisation with global distension of the mammary duct structures that seem to be filled with an echogenic material [32]. It may evolve into the formation of a collected abscess.

Figure 19. Granulomatous mastitis: a: polycyclical mass related to the distension of the lobules and granulomatous reaction; b: evolution to necrosis and suppuration creating pseudo-tubular hypoechoic images; c: (×100) disappearance of the TDLU replaced by an inflammatory granuloma (circle), accompanied by patches of necrosis (yellow crosses); d: (×200) abundant cellularity rich in histiocytes and giant cells, evolving towards necrosis.
Subtle lesions may be multiple, infectious, inflammatory or tumoral. A good knowledge of the histological substratum of the lesions helps us to better understand their echogenicity. However, characteristic lesions are rare and most of the anomalies observed in sonography are related to their fibrotic content, to the histiocytary and plasmocytary inflammatory reactions, and to any tumoral proliferations. Therefore, the images aren’t always specific, especially since the disorders may be intricate, and should be interpreted within the clinical context. The histological samples remain fundamental and help better understand the aspects encountered.

**TAKE-HOME MESSAGES**

- Simple ductal ectasia is a dilation of over 2 mm of the duct related to the destruction of the periductal support tissue, and may be accompanied by an echogenic intraluminal acidophilic material.
- The following stage corresponds to peri-ductal mastitis or mammary duct ectasia, with the appearance of a peri-ductal fibrosis and lymphoplasmocytary infiltration reducing the ductal ectasia in places, creating a moniliform duct with slightly hypoechogenic peri-ductal coating.
- Plasmocytary mastitis is the ultimate stage. The stasis of the intra-galactophoric secretions induces the destruction of the walls of the ducts, at the origin of a reaction to foreign bodies (with inflammatory infiltrate rich in histiocytes, lymphocytes and especially plasmocytes). Clinically, there is a firm inflammatory mass that may simulate an inflammatory cancer, sometimes an amicrobial retroareolar collection on the sonography.
- The papilloma is a benign arborescent tumoral lesion whose architecture is papillary or adenomatous, asymptomatic or at the origin of a translucent single-pore, sometimes bloody, discharge. It presents in the form of a well-circumscribed nodular mass, often surrounded by a small hypoechogenic halo (peripheral secretions) or in tubular form. The colour Doppler analysis if fundamental to reveal the vascular pedicle of the papilloma.
- Ductal carcinoma in situ may also provide a ductal dilation with intra-ductal mass, generally comprising microcalcifications, or reduce to a simple thickening of the wall. The microcalcifications are more visible in high grade DCIS than in mastosis lesions.
- The diagnosis of hypersecretory intra-ductal cancer should be considered when confronted with the association of a palpable mass and multiple ductal ectasias and cysts.
- Benign lesions such as epitheliosis, adenosis associates cysts, ductal or lobular epithelial hyperplasia, as well as fibrosis.
- Epitheliosis is a proliferation of epithelial cells, and most often is not revealed by sonography (occasionally clusters of microcalcifications are visible).

**Conclusion**

Figure 20. Bacterial mastitis at the acute stage. Global oedema, distension of the lobules and ducts by purulent secretions (a, b). Purulent material rich in granulocytes (c, d).
• Adenosis is a multiplication of lobules with hyperplasia of all of the constituents (epithelial and myoepithelial cells, palaeal connective tissue), at the origin of a well-defined or lobular oval mass.
• Sclerosing adenosis presents a disorganisation of lobules with interstitial sclerosis, and may be revealed by hypoechoic areas or even an irregular mass usually without suspect hardness in elastography. Microcalcifications may be seen, both with intra and extra galactophoric location, often within microcystic elements.
• The radial scar (RS) or Asschoff’s proliferative centre corresponds to a star-shaped formation with an elastosic centre towards which converge TDLU in a radial manner.
• The association with a ductal or lobular cancer is rather fortuitous, related to the disorder of the proximal TDLU. However, the tubular carcinoma, extremely differentiated invasive carcinoma arises at the centre of the scar with centrifugal extension.
• RS often presents as a more or less attenuating hypoechoic mass, poorly defined and little different from an infiltrating carcinoma. As opposed to the cancer, it does not present a hyperechogenic halo.
• Simple and small RS may appear in the form of a simple convergent architectural anomaly without associated hypoechoic mass.
• The presence of peripheral cysts is more often found in RS than in the cancers.
• The tumoral disease develops in most cases at the de TDLU.
• Invasive lobular carcinoma (ILC) manifests itself in weakly hypoechoic zones with architectural disorganisation, and considerable hardness (value of the elasto-sonography).
• Ductal carcinomas in situ may appears as hypoechoic tissue mass, sometimes accompanied by microcalcifications and microcysts.
• In granulomatous mastitis, affecting the young woman, the TDLU is the seat of an acute inflammation characterised by the association of epitheloid and gigantocellular granulomas. It may clinically simulate a carcinoma, and should be distinguished from other inflammatory disorders, tuberculosis, sarcoidosis and, above all, plasmocyte mastitis.
• Bacterial mastitis occurs at any age, favoured by local factors (mammary duct ectasia, etc.) and general factors (smoking, diabetes, etc.) (Fig. 20). The germs responsible are Staphylococcus aureus or other anaerobic germs.

Case report
A 52-year-old woman just presented an episode of acute mastitis of the left breast, suggesting bacterial mastitis.

Antibiotic and anti-inflammatory treatment was prescribed but it only improved the symptomatology slightly. Today, firm adherent swelling of the lower quadrants of the left breast persists, as well as inverted nipples.

A mammography and sonography were prescribed (Figs. 21 and 22).

Questions
1. What do you deduce from the mammography?
2. How do you interpret the sonogram?
3. What are your diagnostic hypotheses?
4. What do you recommend?

Answers
1. The mammography specifies a vast lower left mass with poorly defined contours, accompanied by nipple retraction and thickening of the skin surface.
2. In addition, the sonography points to a glandular oedema and thickening of the skin surface, a polycyclic echogenic mass suggesting a distension of the lobules and ducts, with a non-expansive hypoechoic zone in the periphery compatible with beginning necrosis.
3. The clinical aspect with a mass, and the inflammatory signs suggest carcinomatous mastitis. Nevertheless, the sonogram does not reveal a real compact fibrous mass or spiculated contours or microcalcifications. The polycyclic contours and echogenic nature of the mass with a pseudo-necrotic component indicate granulomatous mastitis, which may account for the lack of efficacy of the antibiotics.
4. The required procedure consists of taking biopsies. The result confirmed the diagnosis of granulomatous mastitis. The patient was put under corticotherapy and the clinical evolution was satisfactory. The sonography control 6 weeks later showed that the initial lesions disappeared (Fig. 23).
Figure 22. Sonography; left breast (a–c) and left axilla (d).

Figure 23. Sonographic control 6 weeks after treatment.

Disclosure of interest
The authors declare that they have no conflicts of interest concerning this article.

References


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