

The full breast ultrasonography usefulness in the diagnosis of a bicentric breast cancer – An anatomical imaging approach correlated with the pathological findings: A case report

Aristida Colan-Georges

ABSTRACT

Introduction: The classification of multiple, simultaneous, ipsilateral breast cancer after localization in arbitrarily delimited quadrants, according to BI-RADS criteria, is in disagreement with pathological and cytogenetic investigations and with the evolution of the disease. This classification is related to the non-anatomical examination in two standard mammographic projections, including tomosynthesis, and to the non-anatomical orthogonal scanning in the classical ultrasonography and magnetic resonance imaging of the breasts.

Case Report: We illustrate a case of a 69-year-old woman with multicentric breast cancer detected and characterized by a non-invasive technique of diagnosis, based on the triad: anatomical ductal radial and antiradial breast ultrasound, Doppler study and strain sonoelastography, briefly named the full breast ultrasonography.

Conclusion: The complete technique of ultrasonography has the advantages of high availability, low costs, standardization of scanning and reporting, and especially a detailed imaging illustration of the breast anatomical

normal and abnormal structures correlated with the pathological findings.

Keywords: Breast cancer, Multicentric cancer, Multifocal cancer, Strain sonoelastography, Ultrasonography

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INTRODUCTION

Concomitant multiple mass-type breast cancers (BCs) could be classified according to their location and composition into two categories: the multicentric cancers, either bilateral or ipsilateral but with different histological and cytogenetic compositions, and multifocal cancers when the masses/nodules are located in the ipsilateral breast and usually have the same composition, representing monoclonal tumors. Multifocal cancers are interpreted by some authors as intralobar dissemination of malignant cells following the lowest intraductal pressure, and could be considered intralobar metastases, with a larger tumor associated with smaller foci of decreasing size as the distance from the main tumor is enlarged. The pathologists consider there is very low probability that all independent foci happen to inactivate the same allele of the X-chromosome-linked phosphoglycerokinase (PGK) gene [1]; moreover, other pathologists found

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an association between the proximity of the foci and their likelihood that were karyotypically related [2]. In addition to the migration process, it was demonstrated that cancer cells could secrete specific factors that are sufficient to induce cancerous transformation of normal epithelial mammary cells [3], and both mechanisms are favorable to develop a multifocal cancer inside a lobar ductal-lobular tree. The BC metastases are unlikely in other mammary lobes. When a different mass with malignant descriptors is found in a distant mammary lobe, the highest probability is represented by other types of cancer, i.e., by multicentric, multiclonal malignant tumors.

The precise pretherapeutic differential diagnosis of multicentric or multifocal type is important because the extension of the disease and, consequently, the staging and the treatment are different and the long-term outlook is changed. The multifocal staging is based on the size of the largest tumors, but it is considered the risk of lymph node metastases and the risk of recurrence to be greater than for unifocal cancers. Moreover, some rare cancers have multiple subtypes within the same tumor, which complicates the diagnosis and the treatment [4].

The radiological-imaging diagnosis in the worldwide practice is standardized by the BI-RADS 5th edition (2013), and the multiple BCs are defined as multifocal if located in the same quadrant, and multicentric if the lesions are located in different quadrants [5]. This arbitrary assessment is illogical and inaccurate, simplified because of the mammographic standard views and of the orthogonal scanning in the classical breast ultrasonography (US) and magnetic resonance imaging (MRI) practice, but there is not a correlation with the breast anatomy, or with the pathological reports.

The incidence of the multiple BCs has a wide variation among the clinical studies because of lack of standardization [6]. Magnetic resonance imaging is considered the best technique of diagnosis of multiple BCs, which was detected in 14–30% cases [6]. However, multiple cancers were found in 40% cases diagnosed by full breast ultrasonography (FBU) of a series of 1841 examinations in 1333 patients, confirmed by other imaging techniques or after surgical treatment with histopathological examination [7]. This result is according with a pathological report of a series of 1000 cases, examined by the use of the large-pathological sections, which established by combining in situ and invasive breast tumors, three “aggregate growth patterns”: unifocal (36%), multifocal (35%), and diffuse (28%) [8].

The value of the FBU is represented by the high resolution of the radial scanning examination of the whole breast volume, following the ductal-lobular tree of the mammary lobes that are disposed radially around the nipple; this technique offers a sensitivity close to 100%, and a specificity over 95–98% [7], as a result of combining 2D ultrasound data (that illustrates both the descriptors specified by the US BI-RADS system and the intralobar ductal connection), with Doppler analysis

of the salient vasculature and strain sonoelastography (SSE) [9]. The normal galactophorous ducts may be detected using actual transducers from a thin diameter of 0.4 mm, representing the atrophied ducts, up to 3.0 mm in young women or at puberty; the normal lobules have a comparable size. Thus, FBU can illustrate any abnormal ductal-lobular changes that except the aspect of the background parenchyma, and the suspect findings could be detected in their first 5 mm size.

CASE REPORT

We present a case of a 69-year-old woman who was referred in March 2020 for diagnosis of a new painless nodule located in the upper outer quadrant of the right breast, detected by self-palpation. The patient had a history of another benign nodule in her left breast, detected for the first time 23 years earlier, that was stationary at control examinations.

We applied a FBU using an ultrasound platform E8 Expert (GE Healthcare, Tiefenbach, Austria), provided with 3D/4D, Doppler color, power and spectral, and real-time SSE. The linear transducer ML 6–13 MHz had an intermediary length of 5 cm, but with a virtual convex-trapezoid view useful for the radial scanning especially in large breasts. The Doppler sensitivity was improved by using in addition to the menu “Breast” the “Nearfield” menu that was more sensitive for detecting the vessels of lower velocities, and we completed the US BI-RADS descriptors with the incident angle of the plunging artery upon Kujiraoka et al. [10], as the most specific descriptor for malignant masses [7]. The SSE results were classified upon the Ueno/Tsukuba scoring as a complementary technique [11].

The FBU of the whole breast volume upon the clockwise notation illustrated the breasts with predominantly fatty composition of climax-type, with proportional glandular atrophy of the stroma and parenchyma in all quadrants, with the galactophorous ducts of an average diameter below 1 mm, and the lobules involved, immeasurable. The background vascularization explored by color Doppler was physiologically reduced.

The left breast presented at 1:30 and 4 cm away from the nipple, a well-defined hypoechoic nodule, apparently developed inside a Cooper ligament which it widened, ovoid in shape, with a multi-lobulated contour, benign posterior acoustic effects, a benign peripheral vascular pole, the diameters 7.6×12.5×14.7 mm with an estimated volume 0.73 cm³, and repeated SSE score 2 and 3 Ueno within benign limits, suggesting fibroadenoma appearance (Figure 1). We identified small retroareolar ductal-ampullary ectasias within benign aspects, usually considered by pathologists as physiologic findings in postmenopausal women, with transonic appearance and sketch of summation-type blue-green-red (BGR) score. There were no other solid nodules or other suspicious lesions in the left breast. The left axillary lymph nodes

presented the transverse diameter up to 8.2 mm, normal cortex and vascularization, slight changes of reactive histiocytosis in the sinus with hypoechoic aspect and SSE of score 2 Ueno.

The right breast, with a similar background structure, presented at 10:00 peripherally, in the axillary extension of the gland (Spencer tail), corresponding to the new lump, an intense hypoechoic mass, well delimited, with a polylobulated contour, apparent transonic content with septa, benign posterior acoustic effects, of 13.5 × 24.9 × 14.0 mm size and an estimated volume of 2.5 cm³. The peripheral and internal multipolar vasculature demonstrated an incident angle of malignant type and the SSE scoring was 3–4 Ueno with some BGR areas, aspect suggesting a rare type of breast carcinoma, including a mucinous-type, an aggressive cancer with internal necrosis and without peripheral stromal reaction or an intra-cystic carcinoma. In addition, tumor vasculature with aliasing and high-resistance flow strengthened the suspicion of malignant breast lesion (Figure 2).

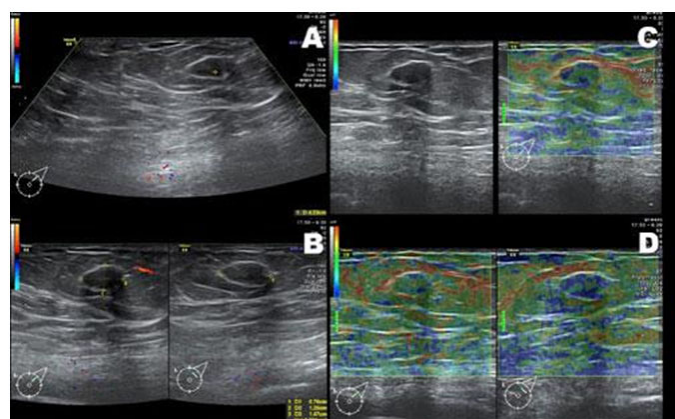


Figure 1: FBU of the left breast: Radial scan at L 1:30 (nipple in the upper-left corner) illustrates a benign mass upon US BI-RADS assessment (A, B), with benign-type vasculature (B) and SSE score 2 and 3 Ueno (C, D).

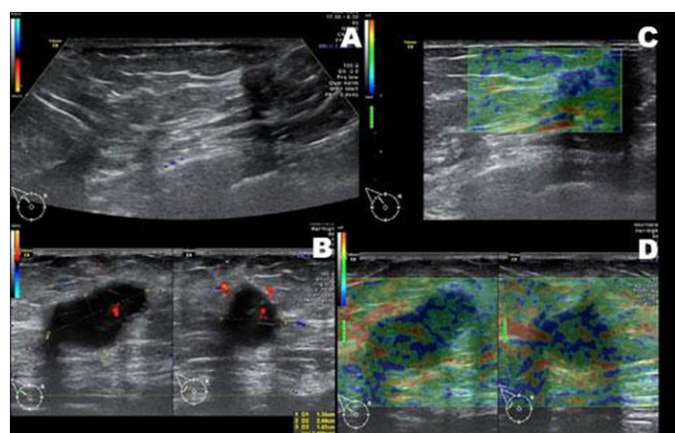


Figure 2: FBU aspect of the R 10:00 complex cystic mass, with combined benign and malignant descriptors upon the US BI-RADS (A, B), the SSE of borderline type (C, D) but the vasculature presenting the most suspicious features (B) after Kujiraoka et al. [10].

At 5:30 in the sub-mammary sulcus it was identified other unexpected, “silent” hypoechoic mass, impalpable with angular margins, located along a Cooper ligament, with acoustic shadowing, inhomogeneous, sized 6.0 × 8.4 × 7.8 mm with an estimated volume of 0.21 cm³, SSE of score 5 Ueno, and peripheral tripolar vessels with incident angle, with the appearance of a typical malignant nodule (Figure 3). The right axillary lymph nodes had transverse diameter up to 10.4 mm, with normal cortex and vasculature in hilum, associated with changes of reactive histiocytosis in the sinus and scored 2 Ueno, within benign limits. There were no lymphadenopathies along the right external thoracic artery, internal mammary arteries, and supra- or sub-clavicular fossae.

The conclusion of the examination was: “Right multicentric breast cancer with a first mass at 10:00 peripheral, of rare carcinoma type with 2.5 cm diameter and a second nodule in the sub-mammary sulcus at 5:30 of 0.8 cm diameter, with the appearance of invasive ductal carcinoma (IDC). No satellite lymphadenopathy detected, US BI-RADS assessment 5 category.”

The recommendation for oncological examination with targeted tru-cut biopsies was followed by a pathological and immunohistochemical report, which described two different types of malignancies:

- the R 10:00 mass had the diagnosis of moderate differentiate IDC (G2), ER+ over 85%, PR+ 70–75%, Her2-;
- the mass of the sub-mammary sulcus at 5:30 represented a low differentiated IDC (G3), with medullary component, ER+ 5–6%, PR-, Her2-.

The neoadjuvant chemotherapy and hormonal therapy were followed by the modified radical mastectomy type Madden after a month. The biological tests and a preoperative multidetector contrast computed tomography (CT) had not significant pathological results, except for the cancer antigen CA 15-3, in slight

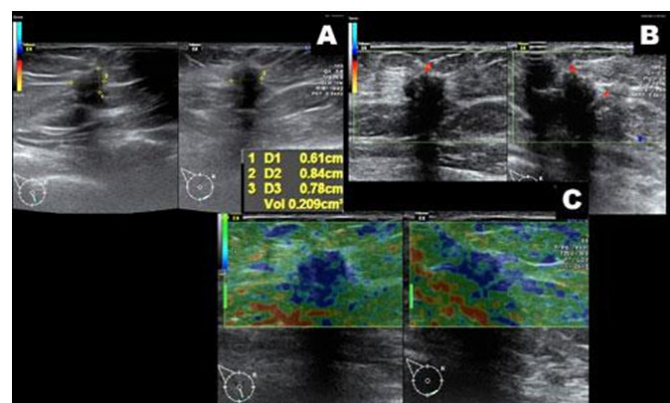


Figure 3: FBU at R 5:30 illustrates in the sub-mammary sulcus the infracentimetric mass with the most malignant descriptors upon US BI-RADS (A) and with malignant-type vasculature presenting an incident angle of the plunging artery (B), and strain with score 5 Ueno (C), suggestive for an invasive carcinoma with stromal reaction.

progression, but considered within benign limits after a surgical approach: 18.63 U/mL before the surgical treatment and 39.05 U/mL one month after mastectomy (the reference range was less 30 U/mL).

The postoperative evolution had a slow healing, marked by inflammatory phenomena and the formation of a hematoma in the area of the surgical bed, demonstrated by targeted classical US in the same surgical service. The heterogeneous collection was recurrent after puncture and drainage (insufficient) and under anti-inflammatory and antibiotic therapy. The FBU follow-up examination in our service of 6 months post-mastectomy was recommended for persistent skin redness, tenderness, and edema. The FBU illustrated a status post incomplete right mastectomy with peripheral remnant glandular tissue with specific stroma and atrophied galactophorous ducts, skin thickening around the surgical scar up to 3.6 mm (normal skin areas thickness of 2 mm), edema of the subcutaneous fatty tissue with a hyperechoic aspect as compared with the normal areas, and a chronic retro-pectoral hematoma of 24.65 cm³, unexpected, probably produced after incorrect insertion of the initial surgical drainage tube by counter-incision (a usual—and illogical!—insertion of a drain for a non-anatomical pre-existing cavity, but in the surgical practice for both conservative breast resection and radical mastectomy) (Figure 4). Due to apparent reduced initial drainage, the (inefficient) tube was early removed, with further local inflammatory changes.

The control multidetector contrast CT scan confirmed the location under the great pectoral muscle of the heterogeneous hypodense mass, without contrast enhancement, which could justify the slow healing (Figure 5). No remnant tumor was identified in both FBU and CT and no distant metastases were radiologically detected. The evolution was finally favorable under correct surgical drainage and anti-inflammatory treatment, in addition to chemotherapy and adjuvant hormone therapy.

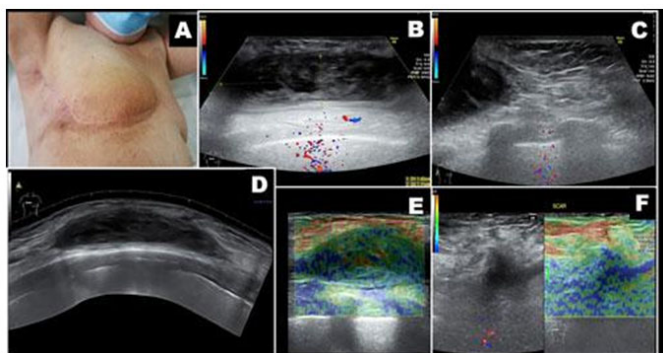


Figure 4: FBU at six-months follow-up: note the inflammatory changes of the superficial small parts in the right-anterior thoracic area (A), and the retro-pectoral heterogeneous fluid collection in real-time US (B, C) and panoramic view (D), with benign aspect of Doppler and SSE (E, F).

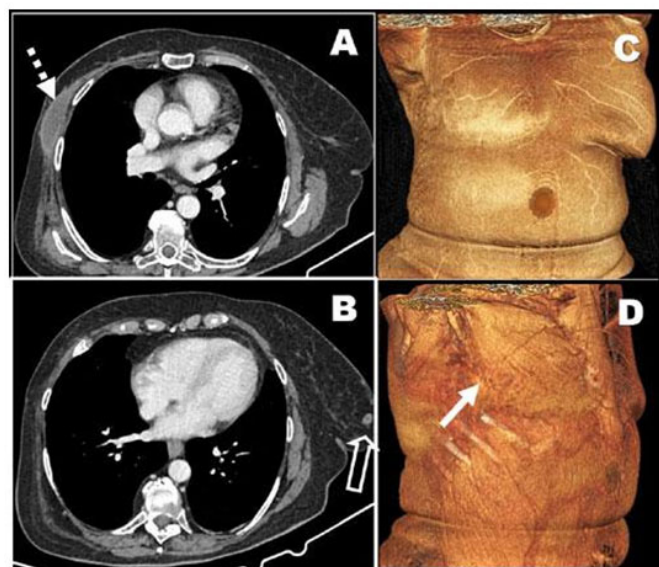


Figure 5: Multidetector contrast CT illustrated the same retro-pectoral fluid collection (A, dashed arrow), without any forgotten/recidivate local or distant malignancy. The small nodule of the left breast was salient in the predominant fatty composition (B, open arrow). The volume rendering technique (VR) illustrates the local swelling (C) similar to the clinical aspect in Figure 4A, and the distortion of the lower-outer fibers of the great pectoral muscle (D, arrow).

DISCUSSION

This case presented falls within the BI-RADS definition of multicentric cancer, the two lesions being located in different quadrants. However, the definition is arbitrary, because the breast glandular architecture is based on mammary lobes oriented radially around the nipple, which are morphological-functional mammary units and do not communicate (with rare exceptions) but may overlap, as demonstrated the anatomist Cooper since 1840 [12]. They are of unequal size and may be located inside a quadrant or may exceed its limits by extension into two adjacent quadrants. The actual surgical techniques in worldwide use, either conservative or radical, do not respect the lobar anatomy. The conservative techniques of multifocal cancers are simultaneous overtreatment with incomplete excision, because some segments of the healthy adjacent mammary lobes are excised and other segments of the “sick” lobe are preserved following the rule of the surgical safety margins, with high risk of recurrent malignancies. Similarly, in the radical mastectomy for the false considered multicentric breast cancers in adjacent quadrants represents an overtreatment with unnecessary mutilation and risk of surgical complications.

The usual pathological sections are small, centered on the lesion and their limits and do not allow the research of the lobar pathology, nor the relationship between the malignant foci. By consequence, the pathological

reports of the multiple foci do not precise the multifocal or multicentric lesions, the extension of the disease is controversial and the interpretation of the resemblances between tumoral clones is ambiguous and with inter-authors disagreements [13]. By contrarily, the “theory of the sick lobe” (the whole lobe presents a genetic defect with benign or malignant risk) of Tot [14] and the pathological analysis of the large radial histological section (“gross section”) [15] are useful for the discrimination of the multifocal cancer (with ductal connection), from the multicentric cancer. There were large-format histological sections that detected 26% of unexpected malignancies otherwise neglected by conventional histology [16].

The best pre-surgical diagnostic technique for simultaneous multiple breast cancer is considered MRI, but it has low availability, high costs, and involves the use of gadolinium-based contrast agents that have a restricted recommendation due to their side-effects, so these contrast agents could not be used in an unlimited screening examination. However, despite the MRI sensitivity (around 81%) is higher than of mammography (60–66%) in detecting the multiple ipsilateral breast cancers, the positive predictive value is low for both techniques, around 70–80% [17], and no specific descriptors could discriminate between multifocal and multicentric cancers. Another technique proposed was the US of the whole breasts upon the classical scanning, which proved significantly increased sensitivity compared with a targeted US, but a low sensitivity of less than 60% reported to the final pathological diagnosis [18].

The radial and antiradial scanning in FBU reassures the non-invasive research of the whole breast anatomy, which includes the age, gender, physiological condition, breast implant, or other previous surgery. The findings are described in anatomical terms, the high resolution allowing a magnification of 3× that could be interpreted according to the “gross pathological section” mentioned above. As a consequence, some conservative surgical techniques were developed, based on the armpit (sentinel) node(s) excision followed by a “précised mammary lobectomy” [19], with esthetical best results, without any mandatory drainage and with reduced risk of tumor recurrences, reported as 0.3% [20], while the 10-years recurrence rate after conservative surgery in early stages of invasive BC is described up to 10–20% [21].

In this case report, post-surgical FBU précised the size and the unexpected location of the heterogeneous collection behind the great pectoral muscle, allowing a correct drainage. In other cases, the FBU technique detected other various post-surgical complications, such as seromas, suture granulomas, remnant breast tumors or remnant normal or pathological axillary lymph nodes, or even a drain tube “forgotten” and partially migrated behind the great pectoral muscle, probably related to its insertion by counter-incision (Figure 6).

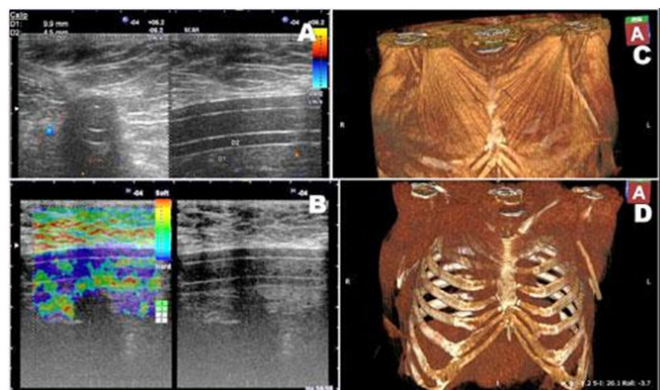


Figure 6: Other case, 60-year-old patient, 5 years after the radical modified mastectomy Madden for BC: FBU depicted a “forgotten” drain tube with the upper pole under the great pectoral muscle, persistent after oncological treatment and radiotherapy, with local tissue tolerance, but a slight functional muscular disturbance of the ipsilateral upper limb (A, B); the multidetector CT with VR confirmed the diagnosis (C, D).

CONCLUSION

The importance of this case report is to illustrate the usefulness of the non-invasive but anatomical FBU in the detection and characterization of multiple ipsilateral breast cancer that presented different descriptors correlated with the grade of cellular differentiation. The late initial presentation of the patient was favored by the absence of an official national screening program of breast cancer in our country, and by the evolution of the case during the first year of Covid-19 pandemic, which disturbed the medical system in most countries. The relatively new method of diagnosis represented by FBU, with high availability in any medical situation, could be helpful as first screening technique for the countries or any population with reduced resources.

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Author Contributions

Aristida Colan-Georges – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Guarantor of Submission

The corresponding author is the guarantor of submission.

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Consent Statement

Written informed consent was obtained from the patient for publication of this article.

Conflict of Interest

Author declares no conflict of interest.

Data Availability

All relevant data are within the paper and its Supporting Information files.

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