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Case report

CONTRAST-ENHANCEMENT ULTRASOUND WITH MICROBUBBLES FOR SENTINEL NODE IDENTIFICATION: A CASE REPORT

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ABSTRACT

Lymph node (LN) stage remains the primary prognostic discriminant in breast cancer. Lymphatic mapping with sentinel LN (SLN) represents the gold standard for axillary staging in early breast cancer (EBC), thus identification of a new contrast agent could provide clinicians with an alternative to blue dye. AX-CES 1.2020, a prospective non-inferiority phase III trial designed to evaluate the use of Sonovue (microbubbles with sulphur hexafluoride) under contrast enhanced ultrasound (CEUS) as a SLN contrast agent. We herein present the first patient enrolled in the AX-CES 1.2020 trial. In the present clinical report, CEUS-SLN was a safe and feasible technique that enhanced the same LN identified by ^{m99}Tc. Larger series are needed in order to investigate the role of CEUS-SLN in EBC and further studies could evaluate the combination of the pathological and ultrasonographic features of CEUS-SLN to predict axillary involvement.

1. Introduction

Even though the role of molecular biomarkers in oncology is now widely recognized (1,2), nodal status remains the primary prognostic discriminant in breast cancer and axillary involvement and is still evaluated through a surgical procedure (3).
Despite their pivotal role in oncological treatment, surgical procedures are a significant source of complications (4). Several ongoing studies are currently investigating the role of mini-invasive techniques as radio-immuno-guided surgery(5), percutaneous procedures (6) or new prosthetic material(7) in reducing surgical extent and postoperative stress (8).
As for the primary tumor, several ongoing studies are evaluating the role of non-invasive axillary staging in breast cancer contrast-enhanced ultrasound (CEUS)-guided biopsy of the sentinel lymph node (SLN) (9).

CEUS-SLN is a promising innovative technique described by Sever *et Al.* for SLN individuation without the use of the radioisotope Technetium-99 (^{m99}Tc) (9).
CEUS-SLN is performed with periareolar intradermic injection of phospholipid stabilized microbubbles with sulphur hexafluoride gas and subsequent axillary ultrasound (US). The non-inferior phase 3 Axillary Contrast-Enhancement UltraSound evaluation 1.2020 study (AX-CES 1.2020 study) was designed in order to evaluate the safety of the contrast agent, the feasibility of the technique and the concordance rate with the radioisotope procedure. In January 2020 the local institutional review board of Fondazione Policlinico Tor Vergata approved AX-CES 1.2020 study. Herein, we report the first case of the CEUS-SLN procedure performed at our institution.

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2. Case report

A 65-years-old post-menopausal woman, a smoker of 5 packs/years, was referred to our department after diagnosis of infiltrative ductal carcinoma of the left breast on January 15, 2020. Patient family history was negative for oncological or cardiovascular diseases, and personal history revealed essential hypertension and moderate psoriasis treated with Tofacinib (10). Physical examination revealed a left retroareolar palpable firm lump with nipple retraction without any clinically suspicious axillary lymph nodes.

The patient underwent bilateral mammography on January 20, 2020, that revealed an architectural deformity in the left retro areolar breast tissue. On February 1, 2020, the patient underwent a second US that confirmed a 5x13 mm BI-RADS V breast nodule in the retro areolar left breast. Therefore, US-guided Tru-cut biopsy was performed and pathological examination revealed invasive ductal carcinoma (B5b). The case was discussed at the breast cancer multidisciplinary meeting and up-front surgery was planned (left batwing quadrantectomy and sentinel lymph node biopsy). The patient signed the written consent during an outpatient visit in which the patient was fully informed regarding the risk, pros and cons of the study.

Following the enrollment, the patient was admitted one day prior to the surgery to perform lymphoscintigraphy with intradermal periareolar injection of 74 Mq ^{m99}Tc-labeled macroaggregated albumin. The procedure revealed one SLN. Eventually, the patient underwent a CEUS-SLN just before surgery and under general anesthesia in the surgical theater.

3. Description of the technique

CEUS-SLN was performed according to a modified *Sever's* technique(9). Figure 1 shows the materials used in the procedure. The chosen Microbubble contrast agent was Sonovue® (Bracco imaging, Milan, Italy), composed of phospholipid stabilized microbubbles with sulphur hexafluoride gas. The contrast agent was prepared with 2 ml of sterile saline solution. Following an injection of 5 ml of 2% Lidocaine solution in the periareolar region, 0.2-0.4 ml of contrast agents were injected in the periareolar region. The contrast agent injection could be repeated up to three times (Fig.2a). The injection site was massaged to enhance the drainage of the contrast agent by the lymphatic vessel.

Axillary CEUS was performed with Esaote scanner (MyLab Twice, Esaote, Genoa, Italy) with a linear-probe (Figure 2b). Esaote contrast-specific software package was used to enhance the microbubble-specific scanning. US mechanical index (MI) was maintained between 0.3-0.7 and linear-array transducer at 7 MHz. CEUS-SLN was performed by a breast surgeon with more than 10 years of experience in breast US. After 15 seconds, the injection enhanced a LN for 65 seconds, localized in the left axilla, as shown in the Figure 3. Once localized, blue dye was used as a marker of the enhanced region (Figure 4a). Grey scale US revealed a lymph node without any suspicious features of metastasis. At the end of the CEUS-SLN, the surgeon who performed the procedure left the surgical theatre.

Subsequently, a surgical procedure was carried out by a second breast surgeon with more than 20 years of experience in breast and axillary surgery (Figure 4b).

The second surgeon was completely unaware of the CEUS-SLNB technique and the blue dye injection. Sentinel lymph node biopsy was eventually performed with Neoprobe (Mammotome, Johnson & Johnson Corp., New Brunswick, NJ). At the end of the procedure, one lymph node with blue dye marker was isolated as a SLN (Figure 4c).

The lymph node surgical specimen was evaluated during surgery through a frozen section that revealed the absence of macrometastasis. Definitive staining confirmed the absence of breast cancer cells in the specimen. The postoperative course was regular, and the patient was discharged on the second postoperative day, as is our customary clinical practice. No side effects or complications were reported during the follow up visit at 30 days.

Figure 1. CEUS-SLN materials. a) SonoVue® package b) Lidocaine 2% 20 mg/ml 10 ml which were used for local anesthesia c) 26 G needles and a 1 ml tuberculin syringe used for microbubble suspension d) 26 and 21 G needles and a 10 ml syringe for local anesthesia injection.

Figure 2. CEUS-SLN procedure: a) contrast agent injection and b) Axillary US. On the left breast is displayed the preoperative design (left batwing quadrantectomy) and in the left axilla is shown the cutaneous projection of SLN located with ^{m99}Tc.

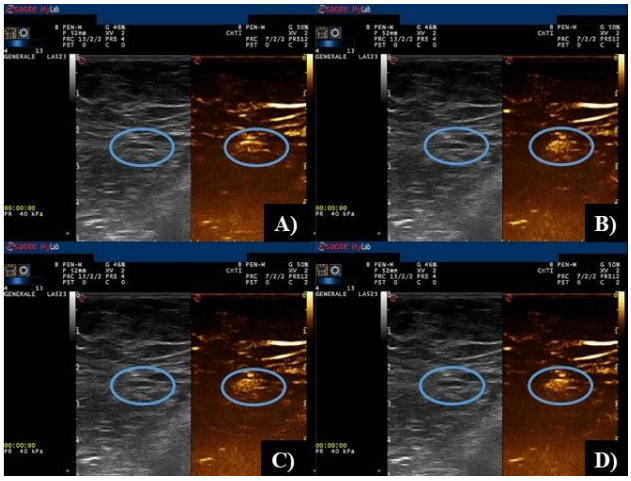

Figure 3. Axillary CEUS enhanced node in the pale blue circle. a) 15 b) 25 c) 35 and d) 45 seconds after 0.2 ml injection of CEUS in the left periareolar space. Dual mode visualization.

Figure 4. Surgical procedure: a) Blue dye injection in the enhanced lymph node by CEUS-SLN b) SNL identification with ^{m99}Tc. Ex-vivo SLN evaluation c) SLN surgical specimen.

4. Discussion

Non-invasive methods for axillary involvement evaluation could reduce the rate of axillary surgery, thereby preventing complications(4). However, lymphatic mapping with SLN represents the gold standard of axillary staging in early breast cancer, thus identification of a new contrast agent could provide clinicians with an alternative to ^{m99}Tc (4,8).

AX-CES 1.2020 study was designed to evaluate the role of microbubbles with sulphur hexafluoride as a sentinel lymph node tracer, alone or in association with other contrast agents (e.g. blue dye or ^{m99}Tc-labeled macroaggregated albumin). In the present case, CEUS-SLN was a feasible technique and indeed enhanced the same lymph node identified by ^{m99}Tc. Moreover, as reported by Sever *at Al.* in larger series, no side effects were reported(9).

Furthermore, CEUS-SLN could combine pathological and ultrasonographic features. Despite reports by several papers regarding the limitation of greyscale US(9), axillary preoperative ultrasound is routinely performed to predict axillary status(4) and to guide percutaneous procedures (6). On the other hand, Sever *et Al* reported that in up to 40% of the cases the presumed SLN was not visible on greyscale US due to the thin cortex, the fatty hilum, deep location or because it was obscured by the surrounding axillary fat and CEUS-SLN technique enhanced the LN echogenicity (9).

5. Conclusion

In the present case, CEUS-SLN represents a safe and feasible technique that could be performed by surgeons to identify SLN. Larger series are required in order to investigate the role of CEUS-SLN in early breast cancer. Further studies could evaluate the combination of pathological and ultrasonographic features on CEUS-SLN in predicting axillary involvement.

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