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REVIEW ARTICLE

Role of the contrast-enhanced spectral mammography for the diagnosis of breast metastases from extramammary neoplasms

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Summary

Purpose: *Extramammary breast tumors are quite unusual but they might represent the first semiotic sign of non negative mammography. Thus, the need for an early and accurate diagnosis is crucial, with the purpose of planning and optimize the therapeuthical strategy and consequently to improve the clinical outcome of patients.*

Methods: *Due to the intrinsic characteristics of this technique, contrast-enhanced spectral mammography (CESM) lends itself as a useful and reliable tool for a complex diagnosis, since it may simultaneously provide both the data of the mammographic semiotic and the dynamic one of an examination with a contrast medium.*

Results: *The most common radiological signs of this type of lesions are summarized through an analysis of the published literature. The article focuses on the different mammographic semeiotics in primary and secondary malignant lesions in the breast, on the different aspects of metastases deriving from blood and lymphatic spread, as well as on the common analogies between metastatic lesions and fibroadenomas. Moreover, the characteristics of a unique case of breast metastasis from pleural mesothelioma analyzed by CESM are described.*

Conclusions: *On the basis of our experience, CESM could represent an extremely valid method to address a correct diagnosis in complex cases of potentially metastatic lesions.*

Key words: *breast metastases, contrast-enhanced spectral mammography, extramammary tumors, pleural mesothelioma, radiological features*

Introduction

Cancer is one of the leading causes of death in the world. In particular, breast cancer is the most frequent tumor and the first cause of cancer-related deaths among women [1]. The stage of this disease at the time of diagnosis is important to predict mortality: patients in early stages (I-II) have a low mortality rate and often require a conservative surgical treatment, while patients in advanced stages (III-IV) need more aggressive and combined treatments, with much higher health costs and higher mortality rates [2,3].

Metastases to the breast from tumors of different origins are generally reported for aggressive and advanced cancers, although quite rare (0.3-6.6%) [4-6]. The most common breast metastases from extramammary malignancies are related to melanoma (29.8%), lung cancer (16.4%), gynecological tumors (12.7%), intestinal tumors (9.9%), hemolymphopoietic malignancies (8.4%), rhabdomyosarcoma (7.7%) and renal cell carcinoma (1.5%). Breast metastases from pleural neoplasms have been described in very few cases [7,8]. The

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rarity of breast metastasis by extramammary tumors is statistically opposed to the high number of primitive mammary tumors; the reasons of this disparity are not fully known, even though some authors have suggested a causal link with the features of the breast tissue and the hormonal status (greater in puberty, pregnancy or lactation), or with the possible diffusion by lymphatic or systemic of stem cells into breast metastases from other organs [5]. The difficulty of their diagnosis is a challenge for the radiologist at the first level imaging methods, and sometimes inconclusive even after needle sampling. Two cases diagnosed after the surgical removal are reported by Lee et al. [5], since initially in the micro-histological sampling two primary breast lesions were diagnosed rather than secondary.

The final diagnosis could be sometimes obtained thanks to the clinical history and the immunohistochemistry (often not required in the initial biopsy sampling): in some cases, this might lead to misunderstanding or a delay in the diagnosis, since in 50% of cases the secondary breast lesion represents the first sign of a still unknown extramammary tumor [6].

Our experience of an exceptional case of breast metastasis from pleural mesothelioma has highlighted the importance of the contrast-enhanced spectral mammography (CESM), useful due to the difficult differential diagnosis of rare breast neoplasms.

The aim of this article was to show and summarize the most frequent radiological characteristics of breast metastases from extramammary tumors as well as to suggest the easiest path to achieve a reliable and conclusive diagnosis, also by means of the latest generation techniques, starting from our case and through a brief literature review.

Radiological findings

Digital mammography (DM) plays a fundamental role in the early diagnosis of breast cancer and in the initial assessment of the disease extent. However, the diagnostic performances of DM are variable and dependent on some properties, such as breast density [5]. Despite these limitations, the literature data indicate in the mammographic size of lesions, as compared to the palpable dimensions, a possible differential diagnosis between primary tumors and metastatic lesions: the first ones appear larger in mammography, while the second ones have dimensions superimposable to the clinical remark. This is linked to the presence of a fibrous proliferation that often surrounds the metastasis [4,9], delimits it and is absent in the primary tumor, but clearly visible in many macroscopic preparations (Figure 1).

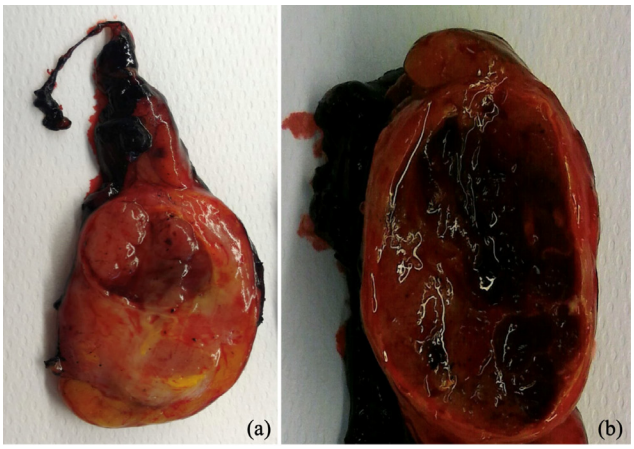

Figure 1. (a) Atypical AB thymoma metastasis, where the nodule is well-defined with a surrounding capsule. **(b)** Melanoma metastasis: in a macroscopic section, cystic areas and a fibrous and well-defined capsule are visible.

Table 1. Radiological signs of breast metastases from extramammary neoplasm according to three different imaging techniques, such as mammography [6], ultrasound [6,10], and CESM

Image technique	*Common signs*	*Rare signs*
Mammography [6]	round and circumscribed mass, high density, no desmoplastic reaction	lobulated or indistinct margins, calcifications
Ultrasound [6,10]	round and circumscribed mass, hypoechoic lesions, heterogeneous echotexture, enhancement posterior	lobulated or indistinct margins, isoechoic lesions, non mass-like with lymph nodes, edema and inflammation (lymphatic dissemination)
CESM	round and circumscribed mass, heterogeneous enhancement, neoangiogenesis	indistinct margins, non mass-like, edema and inflammation(lymphatic dissemination)

Some reports [6,9] have shown that the most frequent radiological sign of a breast metastasis is the circumscribed, round or oval nodular shape, fairly defined. These characteristics would differentiate the lesions from primary tumors, but they would pose the problem of differential diagnosis with fibroadenomas.

Distortion, spikulation of contours, microcalcifications, thickening and skin retraction are typical mammographic and clinical signs of primary breast tumors; they are not usually detected in metastases, except in ovarian tumors with microcalcifications and spikulation of contours, where they are observable. Moreover, the lesion morphology seems to depend also on the systemic diffusion: the hematogeneous lesions are well-circumscribed and nodular, while lymphatic ones often appear with a morphology not always well-identifiable (non mass-like), widespread and associated with edema and inflammatory findings. Lymph node involvement is present in approximately 25% of the cases (Table 1) [5,10].

CESM, a new imaging technique

In recent years, several developments of DM have been introduced, including CESM, an imaging technique based on the administration of an iodinated contrast medium and dual-energy exposure [11]. This method produces a low-energy image, superimposable to a 2-dimensional DM (Figures 2a and 3a), and a recombined image obtained through subtraction with a high-energy image, allowing to emphasize breast areas with greater angiogenesis (Figures 2b and 3b). These characteristics make CESM particularly interesting because it is achievable in a single step with respect to the double result of morphological data by DM and the dynamic-contrastographic data by magnetic resonance (MR) [11].

Based on the same principle of neoangiogenesis, CESM indications could be considered largely overlapping with those of MR [12,13]. Except in some particular cases, the high negative predictive value of MR excludes the presence of invasive breast cancer with a negative test. Similar results could be expected from CESM studies, although until now there are no data about the diagnostic accuracy of this technique in studies with high statistics. Indeed, the studies already published have almost always been performed on small symptomatic populations or with a high prevalence of breast tumors [13,14]. In the first studies, CESM presented a higher sensitivity than standard mammography in the detection of breast lesions and better detection and estimation of lesion size with

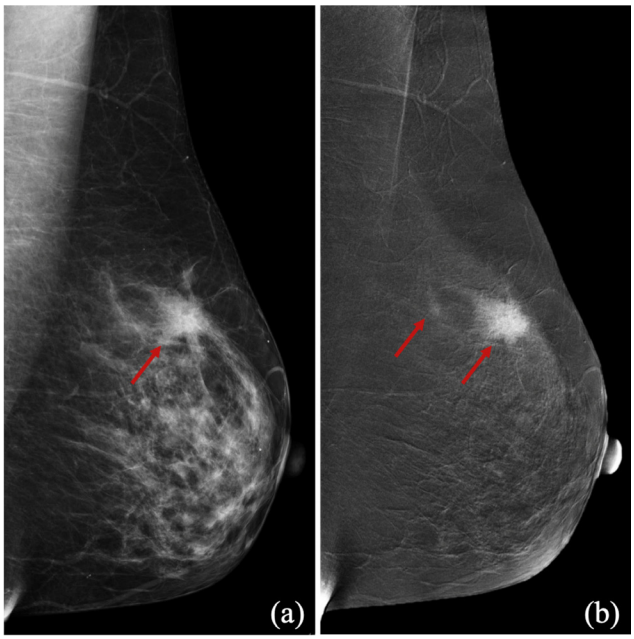

Figure 2. A case of 58-year-old woman with infiltrating ductal carcinoma. **(a)** Low-energy CESM image of the left breast, in which a nodule with spiculated margins is clearly visible in the superior external area (arrow). **(b)** Recombined CESM image of the left breast, where the neoplastic lesion by highlighting a further small posterior lesion with the same features is emphasized (arrows).

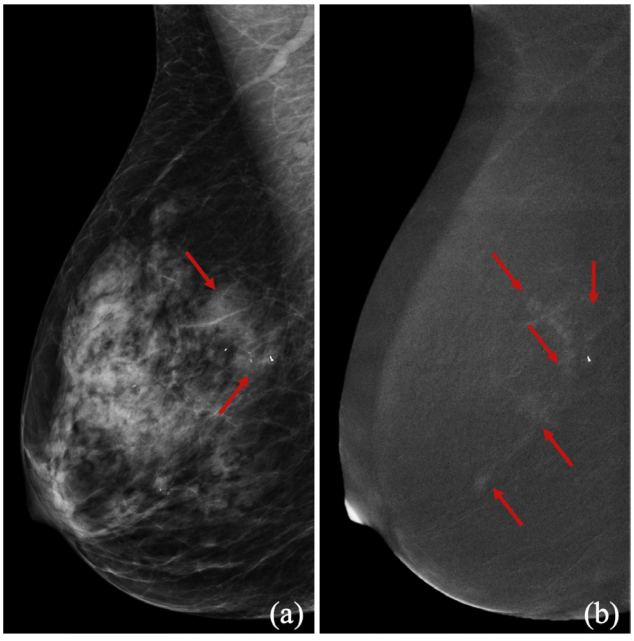

Figure 3. A case of 48-year-old woman with extended ductal carcinoma *in situ*. **(a)** Low-energy CESM image of the right breast, where irregular morphology and faded margins at the superior external quadrant area are observed with sporadic microcalcifications mixed with intra- and extra-lesions (arrows). **(b)** Recombined CESM image, showing a non mass-like area (arrows) that only partially impregnates the coarse marked opacity and branches off towards the nipple's axis, suggesting a significantly larger extent of the neoplasm with respect to the initial data.

respect to mammography comparing their postoperative histological examinations [13]. Therefore, CESM is a technique that may provide a preoperative staging and an accurate treatment program in patients affected by malignant breast lesions with an accuracy not less than MR [13]. A meta-analysis [15] confirms an average sensitivity comparable to that of MR (98%) and an average specificity lower than of MR (58%), very variable among the different examined studies and later evaluated again by other authors.

In mammography the metastatic lesions usually present high density, round and circumscribed mass similar to benign tumors; some types of tumor (ovarian, thyroid and gastric cancer) less frequently show microcalcifications and psammomatous bodies. Moreover, breast metastases do not have spiculated margins, skin or nipple retraction, desmoplastic reaction, typical features of primary breast carcinomas.

Similar characteristics are visible in ultrasound [6,10]: circumscribed and microlobulated margins, heterogeneous and hypoechoic structure, ultrasonic reinforcement on the back of the lesion makes it necessary to differentiate from benign lesions. The indistinct apparance of lesions associated with edema and inflammation is uncommon and typical of metastasis with lymphatic diffusion.

The above exposed characteristics would lead to visualize this type of lesions in CESM as well-circumscribed lesions with inhomogeneous enhancement or, less frequently, no mass-like lesions in lymphatic metastasis.

Our clinical experience

In this paper, we started from a recently published case concerning a patient with advanced pleural mesothelioma in progression with metastases to the breast [16]. Here, a 61-year-old woman with no family history of breast or ovarian cancer presented a retroareolar, hard, and fixed mass on the left breast after first-line chemotherapy. The overlying skin appeared thickened and edematous with no retractions or pathological secretions from the nipple. A homolateral axillary lymph node was also palpable and enlarged.

Mammography showed a nodular opacity of 5 cm, with a roundish shape and well-defined margins, as well as axillary lymphadenomegaly on the left breast (Figure 4a). Some sporadic, non-suspicious, and dystrophic microcalcifications were present in several bilateral quadrants.

Following these mammographic findings, ultrasound examination showed a non-homogeneously hypoechogenic round lesion and with clear

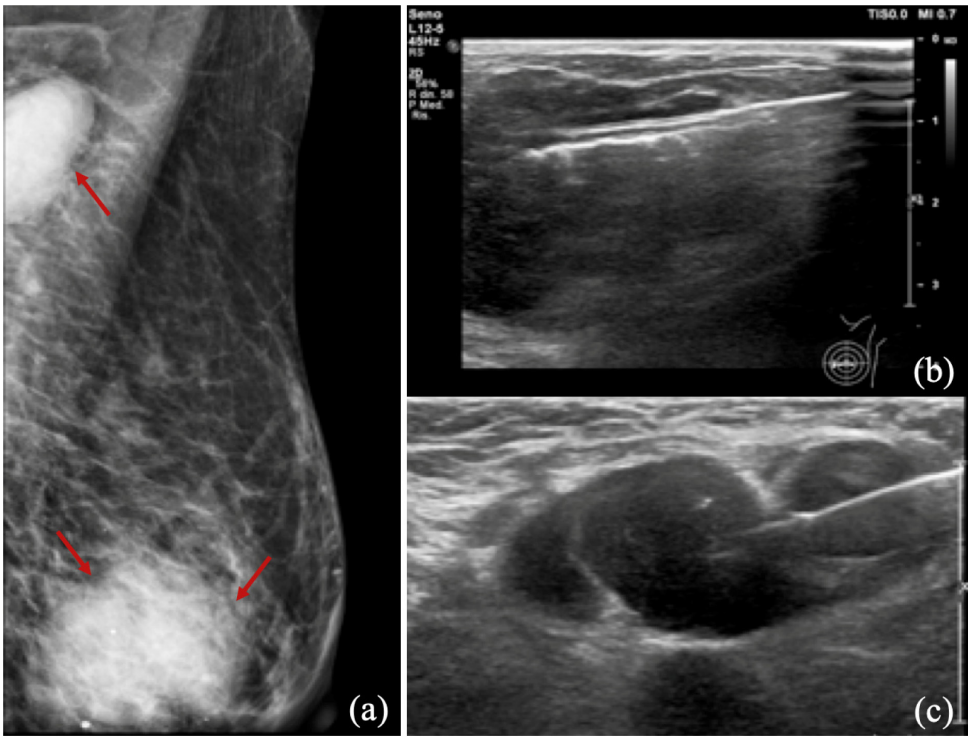

Figure 4. Breast metastasis from pleural mesothelioma. **(a)** Low-energy CESM image, where a coarse fairly well-defined roundish opacity with associated axillary lymphadenomegaly (arrows) may be observed. Ultrasound-guided biopsy performed by a 13-G VABB Elite system on the left breast lesion **(b)** and a 16-G core-biopsy on the left axillary lymphadenomegaly **(c)**.

margins (Figure 4b); moreover, two solid, sub-cm, oval and hypoechoic lesions with clear margins were found on the right breast, already known from the young age. The presence of a 4-cm lymphadenomegaly on the left axilla at level I was confirmed (Figure 4c).

Then, a locoregional staging was requested and, due to patient's clinical conditions, a CESM examination was performed since it is a procedure faster and better tolerated than the MR. The CESM images confirmed the mammographic data: a nodule was present on the left breast with a moderate and inhomogeneous predominantly peripheral impregnation, scarce in the central sectors in relation to necrosis. There were no signs of pathological enhancement (Figure 5a) on the right breast, particularly in the sites of the nodular findings described as benign in ultrasound examination. The analysis of the background parenchymal enhancement showed a clear asymmetry between the two breasts with an absent impregnation on the right breast (Figure 5a) and a strongly accentuated vascularization on the left one (Figure 5b) with numerous and coarse newborn vessels visible near the breast neoplastic lesion.

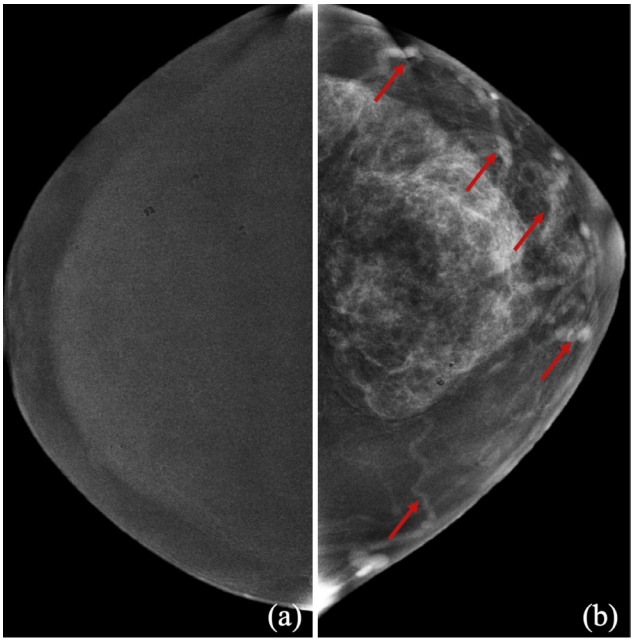

Figure 5. Breast metastasis from pleural mesothelioma. In recombined CESM images, an asymmetric vascularization between the two breasts may be observed: **(a)** on the right breast no impregnation is observed, while **(b)** on the left one numerous newborn vessels (arrows) are around the coarse retroareolar lesion, well-marked and with a moderate, heterogeneous and prevalent enhancement in the periphery.

Finally, ultrasound-guided biopsies were taken on the left breast lesion (13-G VABB Elite) and on the left axillary lymphadenomegaly (16-G core-biopsy), also requiring immunohistochemistry with final diagnosis of secondary lesion from malignant pleural mesothelioma on the left breast and axilla.

Indeed, mesotheliomas may present a diverse array of cytomorphologic features and resemble a variety of carcinomas, including breast tumors [16]. In such cases, an adequate immunohistochemical panel including calretinin, Wilms tumor 1, and podoplanin could allow for a correct differential diagnosis because Wilms tumor 1 positivity is usually absent in breast cancer, whereas it is widely detected in epithelioid mesothelioma (Figure 6).

Discussion

Pleural mesothelioma is a neoplasm generally hosted in the chest with a trend to metastasize mainly by contiguity or lymphatic way: blood-borne metastases are rare, while breast ones are considered anecdotal. The reported experience highlights many radiological features already described in the literature for breast metastases which spread by

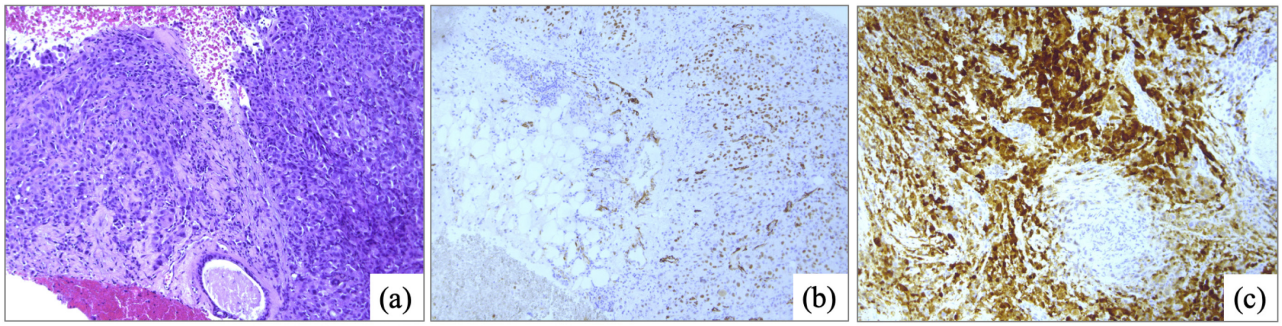

Figure 6. Histopathology examinations. **(a)** Cord-like or large solid sheets of malignant epithelioid cells having abundant eosinophilic cytoplasm, evident atypia, nuclear infiltrate of mammary parenchyma and spare few ducts. Hematoxylin and eosin staining (original magnification×100). **(b)** Immunoreactivity for Wilms tumor 1 antibody: strong nuclear staining of the neoplastic cells (original magnification×100). **(c)** Immunohistochemical preparation of a mesothelioma showing strong nuclear and cytoplasmic positivity for calretinin (original magnification×100).

hematogeneous way from primitive extramammary tumors, as roundish nodular shape metastases with axillary lymphadenopathies, although other findings, such as skin thickening and edema, are generally related to lymphatic diffusion. In our opinion, it makes this case very peculiar and interesting [10].

Despite the usual diffusion by contiguity and lymphatic way of malignant pleural mesothelioma, the diagnosis of this case was challenging, requiring a more accurate radiological technique and a histopathological confirmation. In this specific case, the asymmetry of the neovascularization with numerous and coarse newborn vessels around a lesion with rather defined margins and a non-homogeneous impregnation on CESM images (Figure 5b) has rapidly oriented the diagnosis towards a malignant neoplastic form. The secondary form was considered on the basis of the patient's oncological history and the radiological features described in the nodule of the left breast.

This case was complex due to some small oval lesions found by the ultrasound examination on the right breast, with benign features: the hypothesis of metastatic breast lesions in an advanced stage of mesothelioma needed to be excluded. However, in this case it was decided not to proceed with a biopsy on the right breast. Indeed, CESM examinations highlighted the absence of pathological impregnation on the right breast (Figure 5a) and the presence of coarse lesion with moderate and inhomogeneous impregnation with numerous newborn vessels on the left one (Figure 5b); this made possible to correctly diagnose the disease on the left breast, before any bioptic procedure.

Our experience is in agreement with a recent report [17], where a comparative study between CESM and MR on primary and secondary breast lesions showed a 100% reliability of CESM to detect secondary lesions, a higher positive predictive value and a lower number of false positives than MR.

Conclusion

CESM confirmed its usefulness as a staging method, allowing for a correct diagnosis, which was then confirmed by the micro-histology. Therefore, it could be considered the preferential non-invasive technique in the differential diagnosis between potentially metastatic and benign breast lesions in cancer patients [18].

CESM shows a sensitivity to detect malignant lesions comparable to that of breast MR [15]; moreover, it is an important method to detect additional lesions in dense mammographic patterns, where glandular density may misunderstand or underestimate the true degree of disease on mammographic images [17].

Further potential improvements in the diagnostic performance of CESM could come from radiomics studies already performed on other methods of senological imaging, especially if applied on both detection and characterization of lesions [19,20].

CESM represents a reliable tool allowing to obtain a correct diagnosis even in the case of metastatic neoplastic disease; moreover, it performs an excellent locoregional staging and provides useful data about the amount of necrosis and neoangiogenesis, so contributing to a more precise treatment and to a better clinical outcome.

Conflict of interests

The authors declare no conflict of interests.

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