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Case Report

Bilateral breast metastases as the first manifestation of an occult pancreatic neuroendocrine tumor ☆

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ABSTRACT

Breast metastases are uncommon findings compared to primary breast cancer and in particular bilateral secondary breast lesions from neuroendocrine tumor (NET)s are extremely rare with just less over 13 cases described in literature. We reported herewith the case of a 54-year-old woman who presented to our Breast Unit after noticing multiple, mobile, bilateral breast lumps. Imaging studies confirmed the presence of multiple, circumscribed, bilateral breast masses with slightly spiculated margins, classified as suspicious for malignancy (BI-RADS 4). A tru-cut biopsy was carried out on the largest lesion of each side and histopathologic and immunohistochemistry examination was consistent with metastases from pancreatic neuroendocrine tumor (PNET). Total-body CT revealed the presence of a mass located in the pancreatic body - tail with associated abdominal lymphadenopathies and multiple secondary nodules in bilateral breast and in the liver. Stage IV disease was diagnosed, patient did not undergo surgery and started LAR – octreotide therapy. Although rare, breast metastases from NETs represent an important diagnostic challenge for practitioners because of the difficulty to differentiate from a primary breast carcinoma or even from benign breast lesions. Clinicians should be aware of the possibility of bilateral breast metastases in differential diagnosis of breast lesions in order to ensure the correct diagnosis and the most appropriate management of these patients.

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Introduction

Breast metastases are rare findings compared to primary breast cancers, accounting for around 0.5%–2% of all breast carcinomas [1]. They generally originate from the contralateral breast or hematopoietic malignancies; other tumors that have been reported to metastasize to the breast are melanoma, lymphomas, sarcomas, neuroendocrine tumors (NET)s, ovarian and lung cancer [2-6]. If hematologic malignancies are also excluded, the number of non-mammary metastases to the breast drops to well below 1%. However, in up to 50% of cases, the breast lesion may be the first manifestation of the disease [7].

Although recent data suggests that, probably, breast metastases from NETs are more frequent than what was thought, they remain a rare phenomenon with no more than 200 cases published in literature [8,9-19]. The most common primary site of metastatic NET breast lesions is represented by the ileum, followed by appendix, duodenum, pancreas, lung and ovary [8,20-27]. With regard to cases of bilateral breast metastases from a distant primary NET, there are less than 15 cases reported in literature and, in particular, to the best of our knowledge, only two cases originating from a pancreatic neuroendocrine tumor (PNET) are reported [8,20].

Metastases from extra-mammary primary represent a diagnostic challenge, since they may mimic primary benign and malignant mammary lesions [4]. An accurate diagnosis is essential, owing to different clinical management and prognosis [2-4,28].

We reported the case of a 54-year-old woman presenting with multiple, bilateral breast nodules as the first presentation of an occult primary PNET.

Case report

A 54-year-old woman presented to our Breast Unit after noticing bilateral breast lumps. She had no previous medical problems and no family history of malignancy. Screening mammography performed 10 months prior to the development of symptoms was negative.

Mammography completed with tomosynthesis revealed the presence of multiple bilateral, round and circumscribed masses with slightly spiculated margins and without calcifications ranging in size from 3 mm to 10 mm in the lower-outer quadrant (Fig. 1); at ultrasound scan the lesions had a maximum diameter of 11 mm, were hypoechoic with indistinct margins and characterized by mild rim vascularity on Color Doppler (Fig. 2). No involvement of axillary lymph nodes was observed. For further evaluation we performed a Magnetic Resonance Imaging (MRI) that confirmed the findings; in particular the examination showed bilateral irregular masses, with a maximum diameter of 10 mm, characterized by heterogeneous enhancement and washout kinetic curve (type 3) without enlargement of loco-regional lymph nodes (Fig. 3). The findings were classified as suspicious for malignancy (BI-RADS 4). A tru-cut biopsy was then carried out on the largest lesion of each side. Microscopically the tumor cells were arranged in nests or sheets of uniform cell populations with abundant eosinophilic cytoplasm and round nuclei and they were surrounded by capillary vessels (Fig. 4). Ki-67 index was 2% and mitotic index 0 x HPF. No ductal carcinoma in situ was observed. Breast markers including estrogen receptor (ER), progesterone receptor (PgR) and C-erbB-2 (HER2) were negative. Synaptophysin and chromogranin were diffusely positive in the tumor cells, supportive of neuroendocrine origin. Immunohistochemistry was negative for TTF-1 and CDX-2 and positive for PDX-1 suggesting the possibility of a PNET (G1).

Complete blood count was in normal range. Tumor markers of pancreatic carcinoma CA15.3 (90.2 U/mL) and CA19.9 (118.3 U/mL) were significantly increased, whereas CEA (3.7 ng/mL) was within normal limits.

Subsequently we performed a total-body CT to stage the disease. The examination revealed the presence of a heterogeneous mass (5,4 × 4,8 × 5,2cm) of the pancreatic body-tail with associated peripancreatic, hepatic hilar, retrocrural, paraaortic, interaortocaval and paracaval lymphadenopathy. In addition, contrast-enhanced CT scan confirmed bilateral breast nodules and showed multiple hypovascular liver metastases on portal phase, the largest measured 5 cm in diameter (Fig. 5). Nor involvement of other lymph nodes or other distant metastases were observed. Gallium-68-DOTA-NOC PET/CT confirmed the extension of the disease.

With these findings, stage IV disease was diagnosed. Then the patient did not undergo surgery and started LAR - octreotide therapy.

Discussion

Breast cancer is 1 of the most common primary malignancies in women, but breast metastases from extra-mammary malignancies are rare and usually associated to poor prognosis [4].

In particular, bilateral breast metastases from a distant NET represent an extremely rare manifestation with just less over 13 cases described in literature and only two cases originating from PNET are described [8,20].

NETs are heterogeneous group of uncommon malignancies originating from the diffuse endocrine system. While poorly differentiated NETs have an aggressive behavior with a poor prognosis, well-differentiated NETs are usually slow progressing even though they can give metastatic spread to distant sites, mainly to the liver. In 2010, the WHO published the new classification of gastroenteropancreatic (GEP) NETs based on proliferation index (Ki-67) and/or mitotic index (MI), aiming to differentiate between tumor (NETs) and carcinoma (NECs). In particular well-differentiated NETs generally present low mitotic and Ki-67 labelling indices and include grade 1 (Ki67 $<$ 2% and/or MI $<$2/10 high power field) and grade 2 (3% $<$ Ki67 $<$ 20% and/or 3$<$MI$<$20 high power field) NETs; in contrast NETs with high-grade nuclear atypia, diffuse growth pattern, necrosis and high cellular proliferative activity (Ki67 $>$ 20% and/or MI $>$ 20 high power field) are referred to the grade

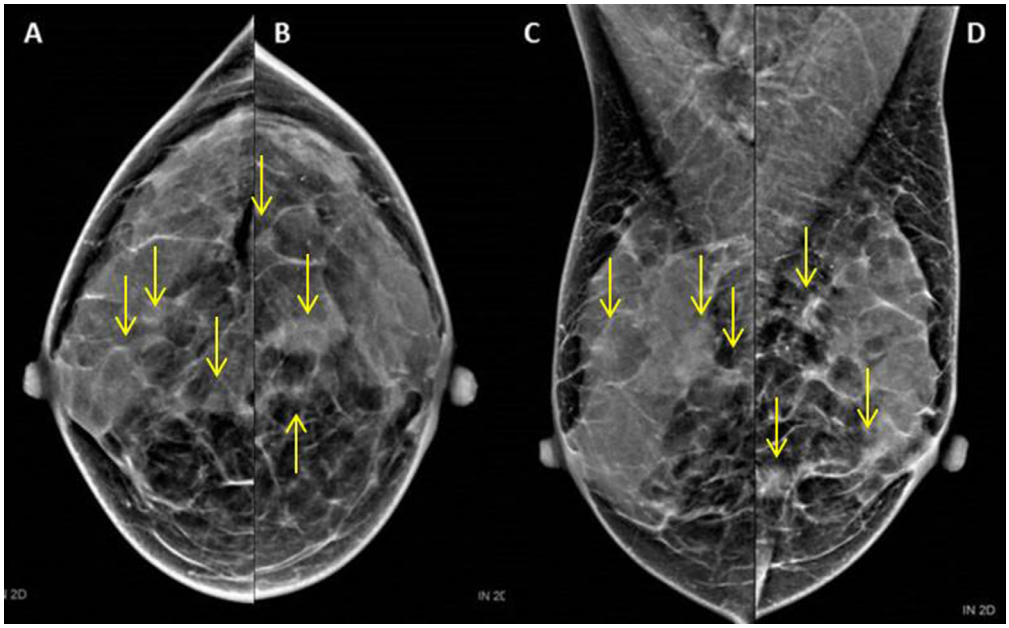

Fig. 1 – Craniocaudal (A,B) and mediolateral oblique (C,D) mammograms showed multiple, bilateral, round masses with slightly spiculated margins (arrows). Microcalcifications or spiculations were not found

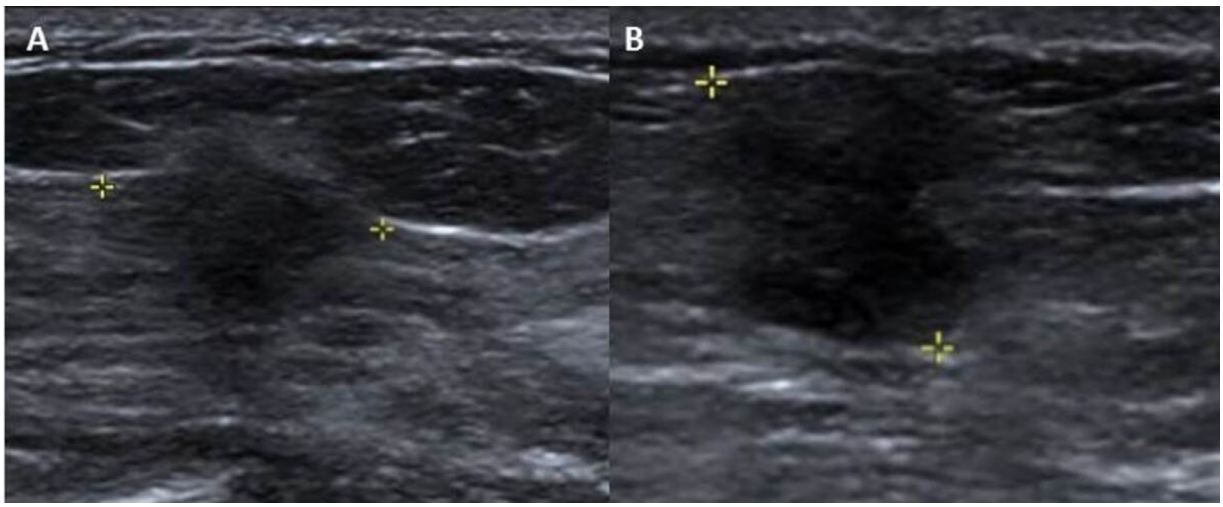

Fig. 2 – Breast ultrasound (A and B) revealed well circumscribed, hypoechoic lesions with indistinct margin in superficial area of bilateral breast. No involvement of axillary lymph nodes was observed

3 or as poorly differentiated neuroendocrine carcinomas (NEC) [29,30].

This grading is strong predictor of prognosis. In fact, in the well to moderately differentiated NETs survival at 5 years reaches 35%, whereas in the poorly differentiated NECs it is less than 5% [28].

NETs can develop in any part of the body, most commonly in the gastrointestinal tract. The ileum was found to be the most common primary site of metastatic breast NETs. The appendix, duodenum, pancreas, lungs and ovaries were the other primary sites from where NETs metastasize to the breast [4,5,12,13].

The mean age of presentation for metastatic breast NETs is considered to be 56 years, which is by 10 years younger than the patients presenting with primary NETs of the breast, usually in their sixth and seventh decade of life [1].

PNET are mostly diagnosed incidentally during workup of pain abdomen or intestinal obstruction due to pressure effect. Carcinoid syndrome, characterized by flushing, diarrhea and bronchospasm is present only in 5%–10% of PNET [20]. However, none of these features were seen in our patient. Breast lump can also be the first manifestation of occult primary tumor in some patients, as in our case [12].

Breast metastases from NETs represent an important diagnostic challenge for practitioners because of the difficulty to

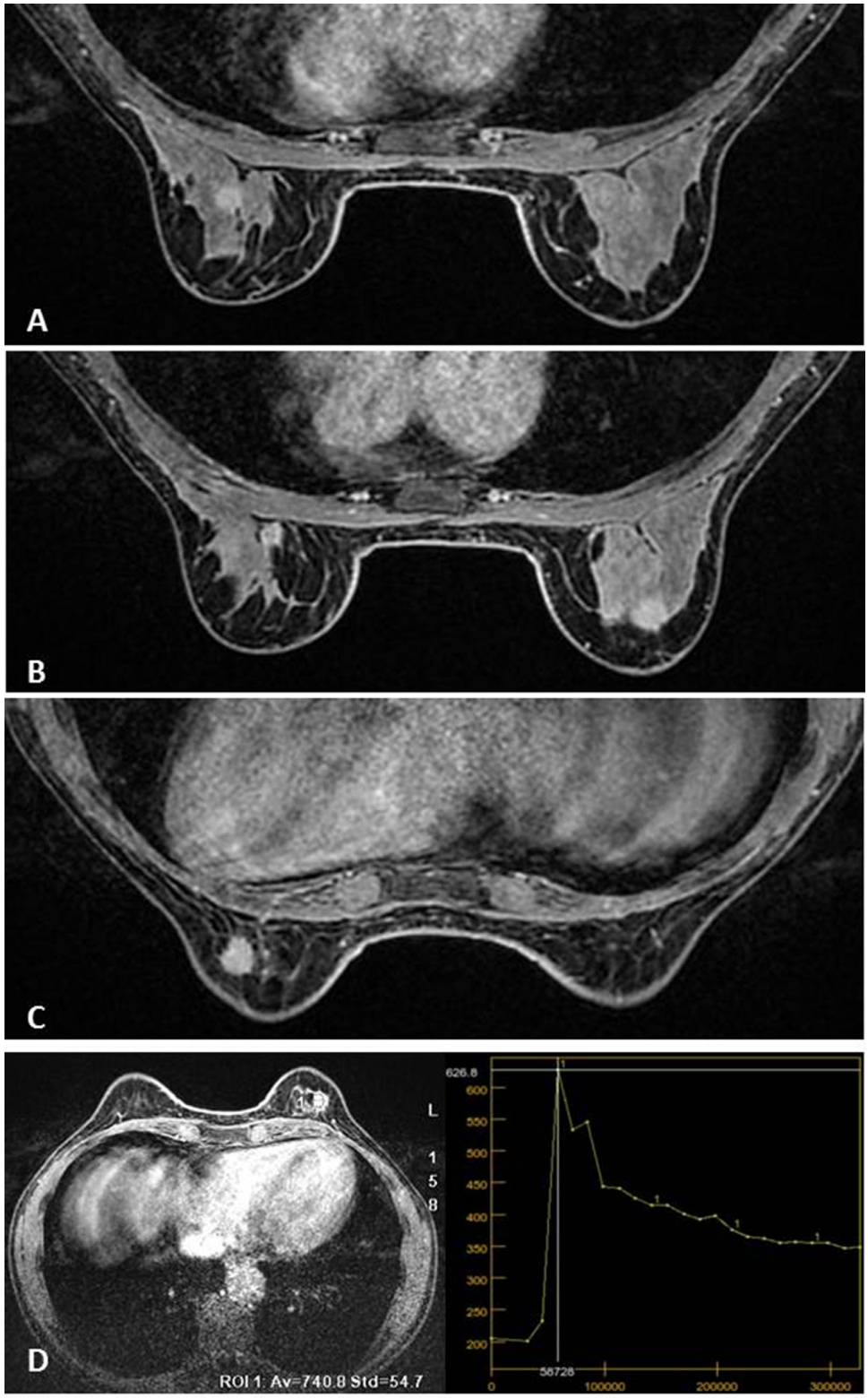

Fig. 3 – MRI confirmed the presence of multiple, bilateral and round masses with slightly spiculated margins and heterogeneous contrast – enhancement without enlargement of loco-regional lymph nodes. (A, B and C). The lesions are characterized by type 3 enhancement pattern with an initial increase and subsequent decrease in signal intensity (D)

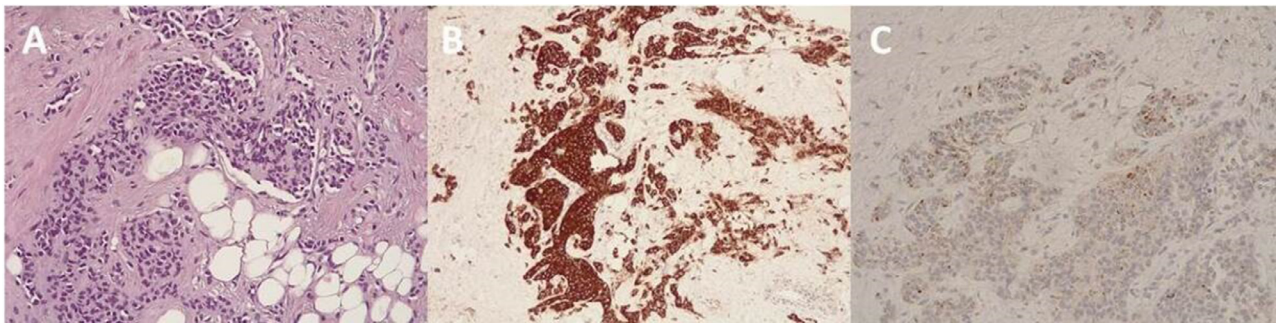

Fig. 4 – Microscopically the histologic appearance is that of a solid nesting architecture; the tumor cells are round to ovoid with eosinophilic, slightly granular cytoplasm and dispersed nuclear chromatin resembling "salt and pepper" (A). Immunohistochemistry showed cytoplasmic positivity for synaptophysin (B) and chromogranin (C)

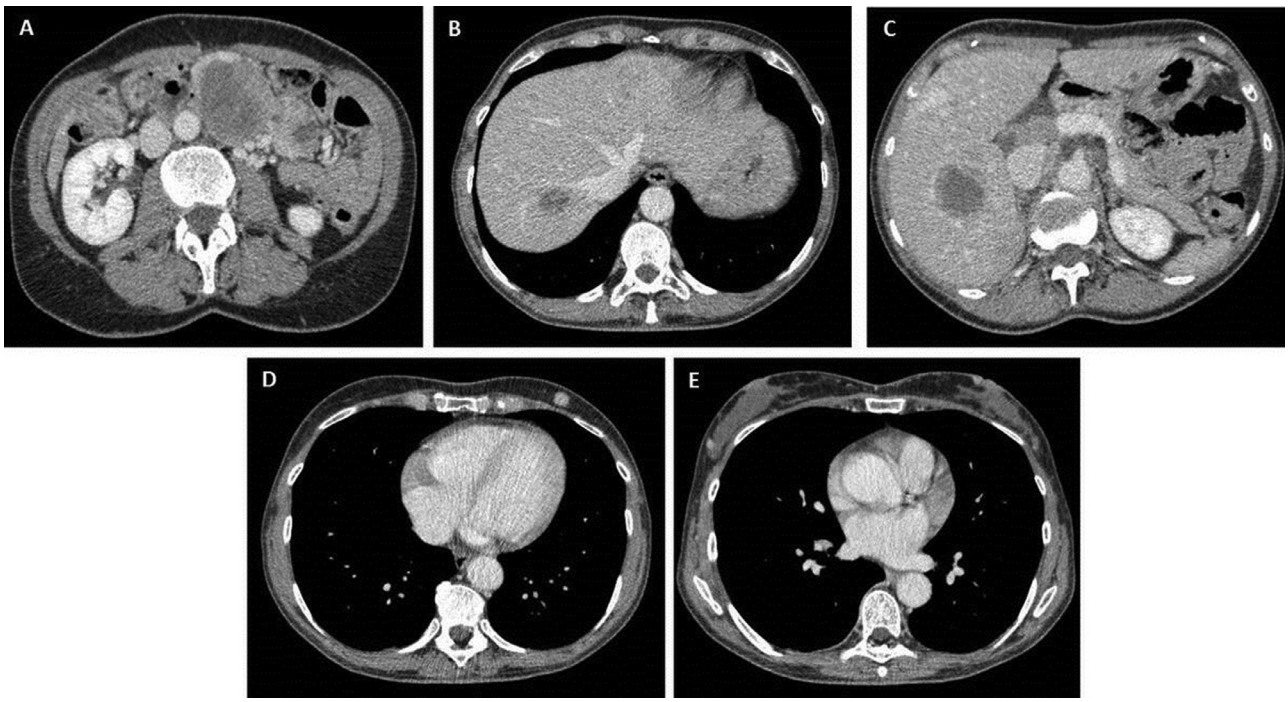

Fig. 5 – CT showed the presence of a mass located in the pancreatic body-tail (A) with associated peripancreatic (A) and hepatic hilar (B) lymphadenopathies. In addition, CT scan revealed the presence of multiple hypovascular liver metastases on portal phase (C) and confirmed bilateral breast nodules (D and E).

differentiate from a primary breast carcinoma or even from benign breast lesions [8].

The form of presentation of the metastatic lesion in the breast depends on the path of dissemination of the neoplasia, whether haematogenous or lymphatic [4].

Usually haematogenous disseminated lesions present as circumscribed masses, sometimes with cystic areas and calcifications and may mimic benign or circumscribed malignant tumors (ie medullary, mucinous or papillary carcinoma). Lymphatic dissemination may lead to diffuse findings in the breast, such as oedema, trabecular thickening and skin thickening, which may mimic inflammatory processes such as mastitis or inflammatory carcinoma [4,5].

While a solitary breast nodule may often be the first and only manifestation of the disease and can mimic a primary breast carcinoma, our patient presented with multiple bilateral mobile lumps which can be confused with fibroadenoma, mucinous carcinoma or medullary carcinoma clinically [4].

From a radiological point of view, breast metastases, included the ones from NETs, could be identified in mammogram as round and circumscribed masses, generally without spiculated margins or with slightly irregular and microspiculated margins and without skin or nipple retraction because of the absence of desmoplastic reaction, often mimicking benign tumors. Margins could also be microlobulated or indistinct. Calcifications are not usually present and occur generally in

patients with ovarian cancer due to the presence of psammomatous bodies [4,5,31].

At ultrasound examination, as in mammography, most metastatic lesions appeared as round or oval masses, with circumscribed, indistinct or microlobulated margins. These lesions are frequently located superficially in the subcutaneous tissue or immediately adjacent to the breast parenchyma, due to the rich blood supply [3]. Furthermore, lesions are often hypoechoic but they could also be heterogeneous with anechoic or hyperechoic area, frequently associated with posterior enhancement. The Doppler study may be useful mainly in differential diagnosis with benign lesions, such as fibroadenomas and cysts [5]. Calcification, architectural distortion, and posterior acoustic shadow are not commonly observed in metastatic lesions and in addition axillary nodes involvement is less common than in primary breast cancer [4,31]. Metastases with lymphatic dissemination usually present with diffuse and heterogeneously increased echogenicity of subcutaneous fat and glandular tissue, with skin thickening, lymphedema and enlarged lymph nodes; this presentation makes very difficult differential diagnosis with inflammatory carcinoma [4,31].

At MRI, generally breast metastases show intermediate signal on T2 weighted sequences and low signal on T1 weighted sequences, with the exception of melanoma metastases, which may have high signal on T1 weighted images. After administration of paramagnetic contrast, intense and homogenous enhancement is usually observed [4].

However, imaging characteristics alone are not sufficient for a definitive diagnosis; fine needle aspiration or core needle biopsy is necessary to confirm or exclude suspicion [3,5,31].

A recent study showed that 68Ga PET/CT-DOTATEC in patients with NET enables detection of cardiac and breast metastases from NETs, as well as other sites [32].

Histology and immunohistochemistry (IHC) play a pivotal role not only in diagnosis but also in determining therapeutic strategy of the patients [8]. The histopathological features of NETs are characteristics in the great majority of cases. Neuroendocrine tumors typically form nests or sheets of uniform cell populations with abundant eosinophilic cytoplasm and round nuclei. The tumor nests are surrounded by thin vascular stroma; perivascular pseudorosette arrangements are considered highly specific in NETs [33].

The neuroendocrine differentiation of the tumor is confirmed by the expression of ChA and/or SYN [30]. Several markers are useful in the identification of a primary organ of NETs metastatic lesions and in particular PDX-1 is highly specific, with very good overall diagnostic accuracy for PNET and is useful in distinguishing them from NETs with a gastrointestinal or bronchopulmonary origin [29,30,33].

In our case tumor cells are negative for cytokeratin 7, whereas breast carcinoma strongly express cytokeratin 7. The SSTR expression is usually negative in breast carcinoma unlike NETs (even though in some cases NETs may lack expression of SSTR expression). Oestrogen and progesterone hormone receptors do not help to differentiate breast carcinoma from primary breast NET, as may be positive in both cases, whereas metastatic NETs are typically negative for hormone receptors and Her-2 [30,33].

There are no clear recommendations about the surgical approach of these tumors. With regard to patients with breast metastases from NET, a lumpectomy alone is recommended, whereas mastectomy is advisable only if there are numerous large metastatic NETs to the breast. Multiple resection would be recommended in the presence of more than 1 lesion, aiming to locally control the disease and preserve the breast [1,34]. Debulking of metastases often offer better survival compared to no resection. If palpable adenopathy is absent, axillary lymph node dissection is not deemed necessary [34]. In addition to surgical treatments, the need for medical therapy either locally or more frequently systemic arises, depending on the site and extension of metastases, clinical history and symptoms [8,35].

Owing to the lack of specific clinical and radiological signs for breast metastases diagnosis, a multiple disciplinary approach is needed to differentiate these lesions from primary breast carcinoma or from benign breast lesions [4]. An accurate clinical history is crucial considering the simultaneous or previous diagnosis of extra-mammary malignancy, combined with a careful clinical examination, a radiological and anatomopathological evaluation, to ensure the correct diagnosis and the most appropriate management of these patients [4,8,20].

Conclusion

In conclusion, although rare, breast metastases could be considered in the differential diagnosis of breast lesions in the appropriate clinical setting; the knowledge of these possibilities can help the correct diagnosis of the patient and lead to more rapid and appropriate management strategies.

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Authors' contributions

LV and MF contributed to the design and implementation of the research, to the analysis of the results and to the writing of the manuscript; FGM contributed to the revision of the manuscript; GO, EA, LR and CAZ contributed to the acquisition and interpretation of the data and to revision of the manuscript and GL contributed to the revision and final edit of the manuscript.

All authors read and approved the final version of the manuscript.

Ethical considerations

Written informed consent was obtained from the patient. We confirm that this work is original and has not been published

elsewhere nor it is currently under consideration for publication elsewhere.

Data availability

The data that support the findings of this study are available from the corresponding author, [LV], upon reasonable request.

Disclaimer

The views and opinions expressed in this research article are those of the authors and do not necessarily reflect the official policy or position of any affiliated agency of the authors.

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