Breast Microcalcifications as the Only Imaging Manifestation of Metastatic Serous Peritoneal Adenocarcinoma in the Breast

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ABSTRACT

We present a case of a 65 year old female with newly diagnosed primary peritoneal serous carcinoma who was found to have indeterminate segmental microcalcifications in the right upper outer quadrant with a mildly enlarged right axillary node on mammogram. There was no associated breast mass on ultrasound. Core biopsy of the right axillary lymph node and right upper outer quadrant breast microcalcifications confirmed the presence of breast metastases at both sites from primary peritoneal serous carcinoma. This case highlights the importance of histopathological correlation of any breast and axillary abnormalities in patient with primary extramammary malignancy. Imaging features of metastatic lesions to the breast are also reviewed.

CASE REPORT

CASE REPORT

A 65 year old female patient of Malay descent presented with three month history of abdominal distension. Computed Tomography (CT) of the abdomen and pelvis was performed. This demonstrated presence of marked ascites with diffuse carcinomatosis peritonei (Figure 1). No ovarian or uterine mass was present. No solid organ, nodal, pulmonary or distant metastasis was seen. The right breast was not fully included in the thoracic CT; however no abnormal breast parenchymal enhancement was visible.

Cytology was obtained from the drained ascites fluid, which demonstrated malignant cells in papillary like groups, positive for WT-1 and BerEP4 and negative for GATA 3, mammoglobin and calretenin consistent with metastatic serous carcinoma (Figure 2). The diagnosis of primary peritoneal serous carcinoma (PPSC) was established.

During her admission, bilateral mammogram and breast ultrasound examinations were performed. There was no previous mammogram available for comparison. In the right upper outer quadrant, there were multiple suspicious amorphous, fine pleomorphic and fine linear branching microcalcifications present in a segmental distribution over a large area measuring up to 8.5 cm (Figure 3). There were no other associated mammographic abnormalities. A mildly enlarged and dense node was present in the right axilla on the mammogram. There was otherwise no underlying mammographic opacity or stromal distortion in the right

breast. The left breast mammogram was normal. The abnormal right axillary node corresponded to a slightly prominent 1.2 cm node with cortical thickening of 0.6cm on ultrasound (Figure 4). Subtle echogenic foci were present in the upper outer aspect of the right breast which may correspond to the calcification seen in the mammogram. However no focal mass or prominent duct was visualized (Figure 5). The breast imaging findings raised the possibility of a synchronous primary breast cancer, possibly ductal carcinoma in-situ (DCIS), with metastatic axillary nodal involvement.

The patient underwent ultrasound-guided core needle biopsy of the right axillary lymph node as well as mammographic-guided stereotactic vacuum-assisted biopsy of the right upper outer quadrant microcalcifications. Histopathology of the right axillary node revealed metastatic high grade serous adenocarcinoma, likely of ovarian or peritoneal origin (Figure 6). Histopathology of the right upper outer quadrant segmental microcalcifications revealed micropapillary-like clusters of high grade metastatic serous carcinomatous cells only within the lymphovascular spaces associated with Psammoma bodies. Immunohistochemistry was performed, showing positivity for WT-1, p53 and PAX 8 stains and negativity for GATA 3, GCDFP-15 and Mammaglobin stains within the tumor nests, similar to the malignant cells from the enlarged right axillary node (Figure 7). The adjacent breast tissues showed fibrosis and benign breast ducts with no evidence of any in-situ or invasive malignancy.

The patient was eventually diagnosed with PPSC with metastases to the breast and axillary lymph node. She is currently undergoing neoadjuvant chemotherapy.

DISCUSSION

Etiology & Demographics:

Metastatic involvement of breast from an extra-mammary malignancy is rare, accounting for only 1-2% of all breast malignancies [1]. The most frequent primary malignancy to metastasis to the breast is melanoma; other primary malignancies include hematological malignancies (leukemia and lymphoma), lung and ovarian cancers [1]. Of these, breast metastasis from primary peritoneal serous carcinoma (PPSC) or ovarian carcinoma forms a subset, accounting for only 0.03-0.6% of all breast malignancies [2]. In patient with ovarian cancer, breast metastasis at the time of initial presentation may occur in up to 24% of patients. In these patients with breast metastasis, more than 60% may have concurrent axillary nodal involvement [2].

PPSC is a rare malignancy amongst the malignancies of the female genital tract classified in the 2014 FIGO staging [3], with a reported incidence of 6.78 cases per one million patients in United States of America [4]. It is of unclear etiology and was originally thought to represent multifocal malignancy arising from the peritoneum. However, a fallopian tube fimbrial origin of malignancy has been proposed recently [5]. Currently PPSC is considered a descriptive term describing a clinical syndrome of high grade serous carcinoma presenting as primary peritoneal carcinoma with no associated ovarian or uterine primary. It is often confined to the peritoneal cavity and distant metastasis is unusual, even as the disease progresses [2]. When distant metastasis is present, liver, lung and pleura are most commonly involved [2]. Thus, unlike primary ovarian malignancy, breast metastasis from PPSC, such as in our case, is a rare occurrence. If present, it occurs in advanced stage of primary disease and thus indicates poor prognosis [1]. It is also unclear from the literature if PPSC is associated with increased risk of breast cancer. On a case-control analysis, Jordan et al reported an increased risk of PPSC with family history of breast cancer [6]. However Grant et al found no association between PPSC and family history of breast cancer. [7] As it is a rare malignancy, further research would be needed to establish this.

The mode of metastatic spread to the breast is via hematogenous and lymphatic channels, with the upper outer quadrant predominantly affected [1]. This was also demonstrated in our case.

Clinical & Imaging Findings:

Extra-mammary metastasis to the breast most commonly presents clinically as a palpable, painless, and rapidly enlarging breast mass [8]. Involvement may be unilateral or bilateral; a retrospective review of 51 cases of extra-mammary breast metastasis by Surov et. al. reported that in up to 59% of patients, breast metastasis were bilateral [8].

On mammogram, extra-mammary metastasis corresponds to a well-defined opacity. Ultrasound features include a hypoechoic mass with microlobulated or circumscribed margins [8]. Associated calcifications are rare, most commonly seen in mucinous ovarian carcinoma. Other malignancies, such as gastric and hepatocellular and medullary thyroid carcinomas can also develop calcification [8]. In a retrospective study of 18 cases with serous carcinoma of the ovary and peritoneum who had breast and axillary lymph node involvement over a 14-year period (1990-2003), Recine et al reported that only 3 patients were noted to have associated microcalcifications on the mammogram. In our patient, the mammographic finding of microcalcifications of suspicious morphology in a segmental distribution mimicked a possible primary breast carcinoma. As there was no associated sonographic correlate, the working diagnosis was that of a synchronous ductal carcinoma in-situ. To our knowledge, PPSC metastasis to the breast presenting as microcalcification with no other associated findings in breast imaging has not been reported previously.

Extra-mammary metastasis to the breast is seen in CT as a well defined oval mass with enhancement. These may show increased 18-F-fluoro-deoxyglucose (FDG) uptake on positron emission tomography (PET) [1]. Magnetic resonance imaging (MRI) usually demonstrates a round or well-circumscribed homogeneously enhancing mass with a rapid initial phase and variable delayed phase enhancement kinetics [1]. No

parenchymal enhancement or mass was detected on the included CT sections through the breast in our case.

The characteristic features seen in histology and cytology of PPSC metastasis to the breast are the papillary clusters of epithelial cells with nuclear atypia in the endovascular space with absence of adjoining in-situ component [2]. Certain immunohistochemistry stains are required for diagnosis. WT-1, p53 and PAX-8 are positive in PPSC and are thus helpful in differentiating between metastatic involvement of breast from PPSC and primary breast malignancy [9]. WT-1 is a tumor suppressor gene located on chromosome 11 expressed in high grade serous carcinomas, and PAX-8 is a transcription factor expressed in tumors from the female genital tract. The tumor cells are negative for stains indicative of primary breast malignancy, such as GATA 3, Mammaglobin and GCDFP-15 [10].

Differential Diagnosis:

Up to 90% of patients with DCIS are diagnosed by abnormal microcalcifications detected on mammography alone. These microcalcifications demonstrate amorphous, coarse heterogeneous, fine pleomorphic or fine linear morphology, and occur in clusters, linear or segmental distribution. In about 10% of cases, DCIS may present as a dominant mass [11]. On ultrasound, DCIS may appear as an ill-defined irregular hypoechoic lesion associated with altered echotexture of the surrounding breast parenchyma.

In our patient, the presence of microcalcifications of suspicious morphology in a segmental distribution and no underlying sonographic correlate raised the suspicion of a synchronous primary breast malignancy, possibly DCIS. As a result, the patient underwent a mammographic-guided stereotactic vacuum assisted biopsy of the microcalcifications. The abnormal right axillary node underwent an ultrasound-guided core biopsy.

MRI is very sensitive for the detection of DCIS, especially the high- and intermediate grade subtypes. The majority of DCIS lesions appear as non-mass enhancement on MRI, for which enhancement kinetics may not be helpful. Morphology should be assessed; clustered ring enhancement pattern has shown strong association with DCIS, as well as clumped pattern of enhancement [11]. CT is not routinely used for evaluation of DCIS. When visible, it may present as non-mass enhancement, however is inferior to that of MRI [11].

Breast malignancy is a heterogeneous disease which can be detected by various imaging modalities. Early in-situ breast malignancy is often detected on mammogram as abnormal microcalcifications. When in-situ disease progresses to become an invasive malignancy, an opacity, with or without microcalcifications, may be seen on mammogram. Ultrasound typically demonstrates an irregularly shaped mass without circumscribed margins. CT shows an irregularly shaped breast mass and has the added benefit of assessment for any distant metastasis. Dedicated breast MRI is the most sensitive imaging modality for the detection of an underlying breast malignancy, which can present as an enhancing mass with rapid uptake of intravenous contrast and washout, or abnormal non-mass enhancement.

Treatment & Prognosis:

For patients with extra-mammary metastasis to the breast, the treatment is to treat the primary tumor. In this case, treatment consists of neoadjuvant chemotherapy followed by cytoreductive surgery if possible [5]

Disease metastasis at presentation represents poorer prognosis. Reported survival after diagnosis of breast metastasis in patients with serous carcinoma of ovary/peritoneum ranges from 13 days to 52 months, with average 16 months [2].

TEACHING POINT

Breast calcification is a common mammographic presentation of primary breast cancer, especially ductal carcinoma in-situ. It is however a rare presentation of extra-mammary breast metastasis. To our knowledge, no case of metastatic primary peritoneal serous carcinoma with abnormal breast microcalcifications as the only imaging finding has been reported previously. In patients with newly diagnosed ovarian or peritoneal cancer, breast metastasis is not an uncommon finding. This case highlights the importance of radiological evaluation of the breast and axillae in these patients, and histopathology correlation of any abnormal breast microcalcifications or axillary lymph nodes.

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FIGURES

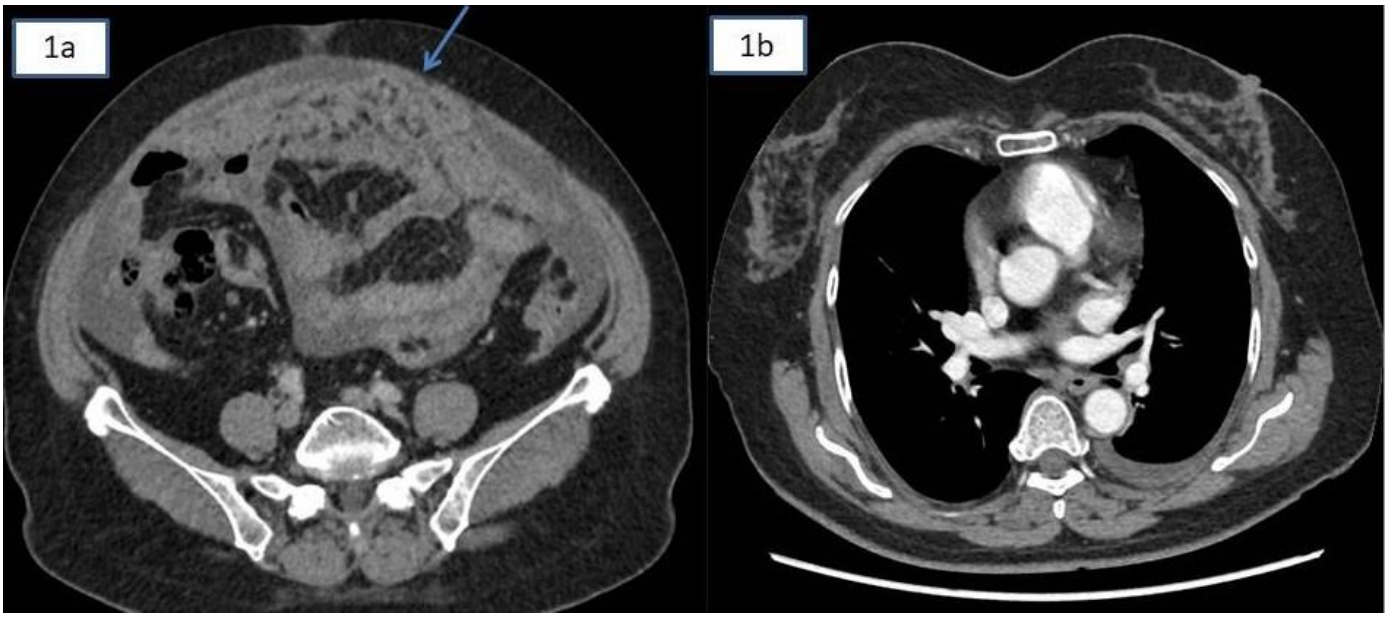

Figure 1: 65 year old female with primary peritoneal serous carcinoma with metastasis to breast and axillary lymph node

Findings: Post intravenous contrast CT abdomen and pelvis in axial plane shows; 1a: omental caking with ascites (blue arrow); no adnexal mass or lymph nodes in the abdomen and pelvis are present. 1b: no evidence of breast mass in the imaged portion of breasts seen in axial CT.

Technique: GE Revolution CT, axial plane, 140kV, 2mA: 3mm thickness; 70 ml of Omnipaque 350mg/ml

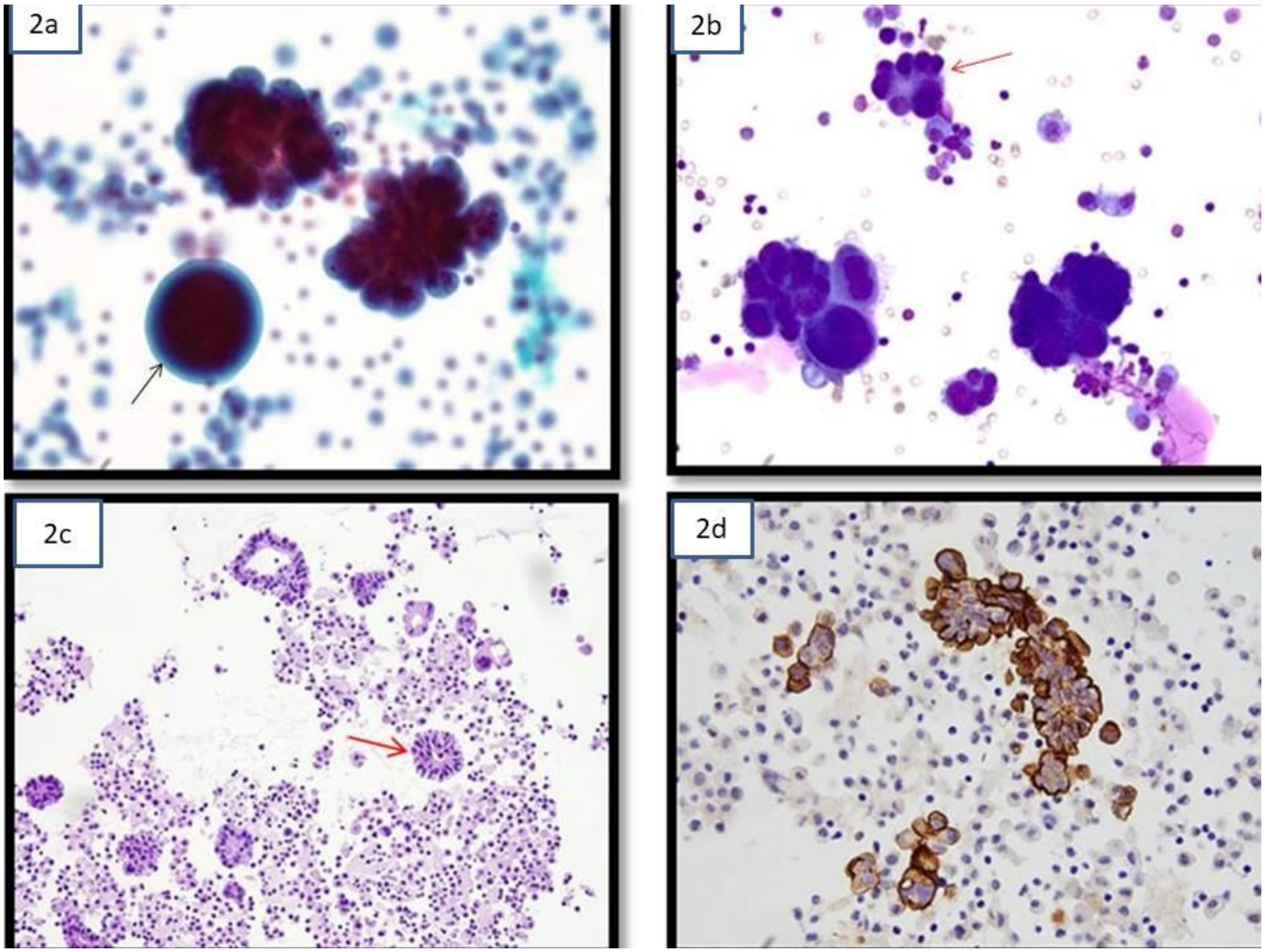

Figure 2: 65 year old female with primary peritoneal serous carcinoma with metastasis to breast and axillary lymph node

Specimen: Peritoneal fluid:
Findings: 2a: Papaniculao stained smear (PAP, 400x); 2b: May-Grunwald Giemsa (MGG) stained smear (400x) showing micropapillary clusters of malignant cells (yellow arrow) and psammomatous microcalcification (yellow arrow); 2c. Cell block: Hematoxylin and Eosin Stain (H&E stain; 200X); 2d: Immunostaining for BerEP4 showing positive brown membranous staining confirming metastatic adenocarcinoma (200x)

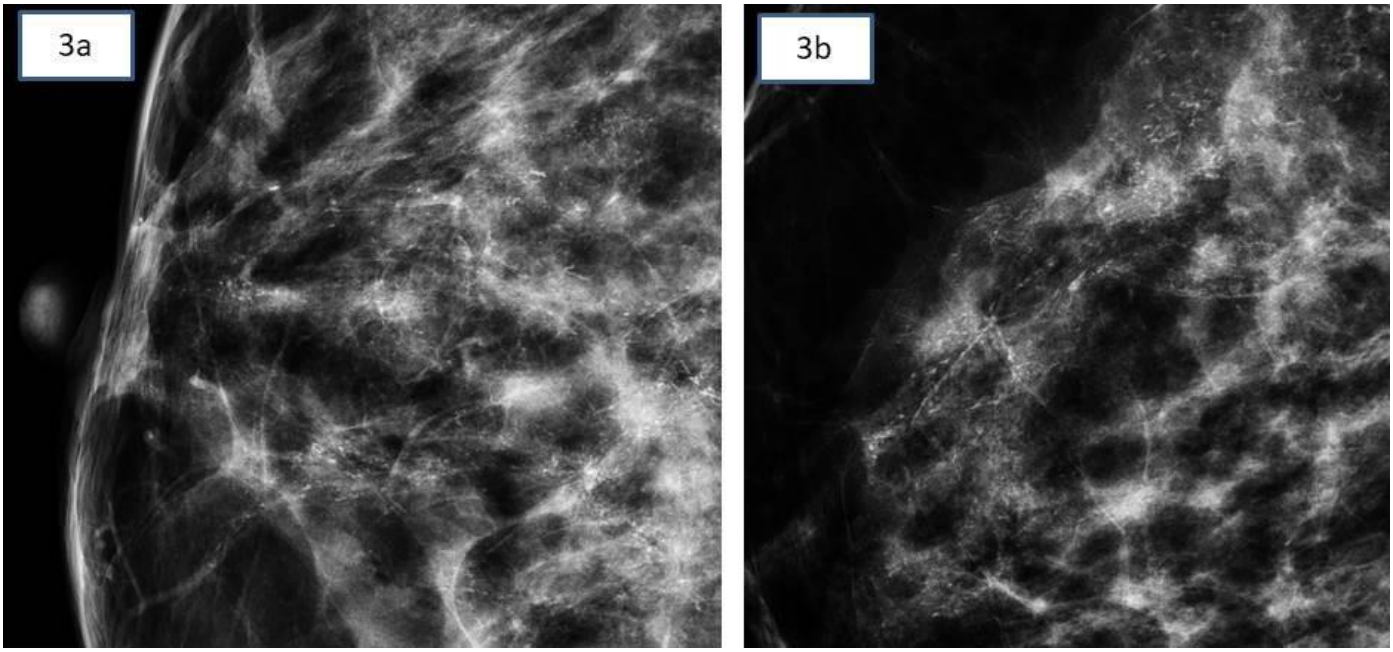

Figure 3: 65 year old female with primary peritoneal serous carcinoma with metastasis to breast and axillary lymph node

Findings: Craniocaudal magnification view (3a) and lateral magnification view (3b) demonstrate amorphous, fine pleomorphic and fine linear branching microcalcifications. 3a: mainly in the outer aspect seen in the craniocaudal view and 3b: upper aspect of the right breast in the lateral projection. It is in segmental distribution in the right upper outer quadrant. These microcalcification appear suspicious. No dominant opacity or architectural distortion was seen.

Technique: GE Senographe Essential, Rhodium filter. 3a: Craniocaudal view: kVp: 28.00, 45mA, 1.8 x magnification with spot magnification, Angle 0:00º, 45mm breast thickness 3b: Lateromedial magnification view: kVp: 30.00, 64mA, 1.8 x magnification with spot magnification, Angle: -90.00º, 58mm breast thickness.

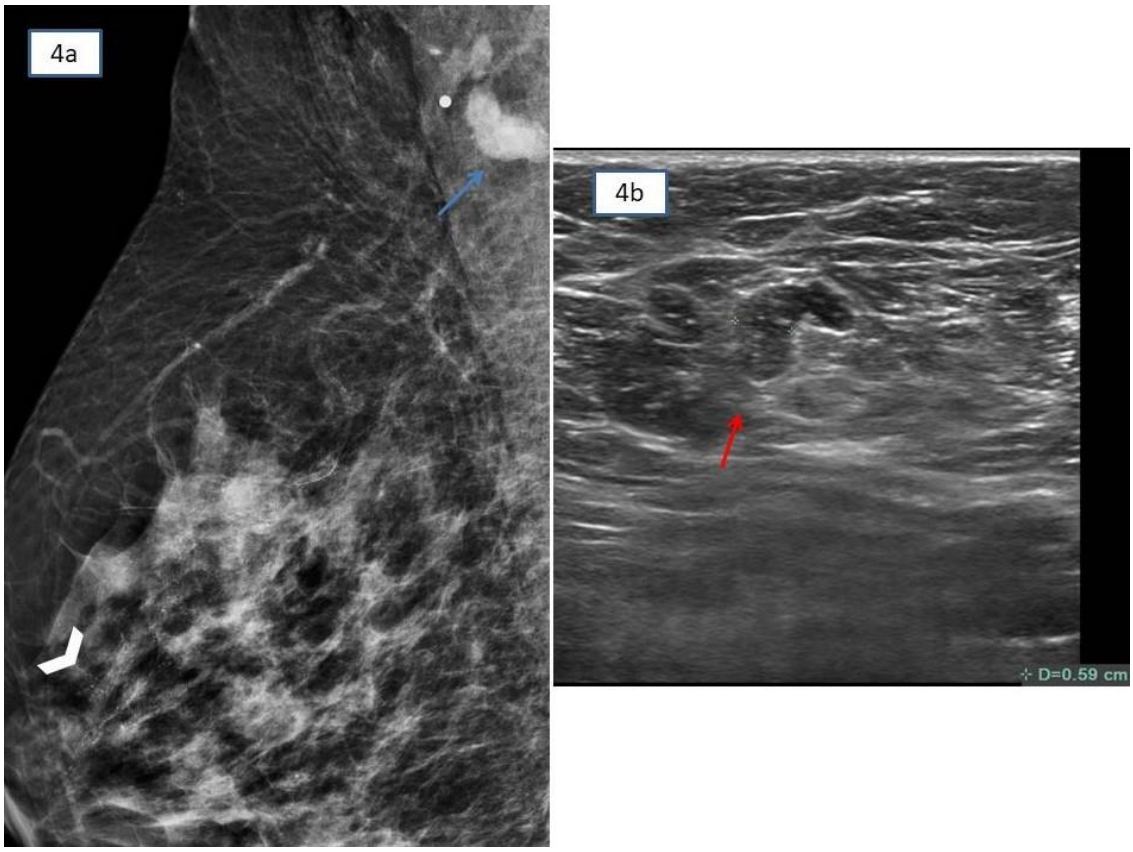

Figure 4: 65 year old female with primary peritoneal serous carcinoma with metastasis to breast and axillary lymph node

Findings: 4a: Mediolateral oblique (MLO) mammogram of the right breast showed a dense axillary lymph node (blue arrow). This corresponded to an indeterminate lymph node in the right axilla on (4b) ultrasound (red arrow), with uniform cortical thickening measuring 0.6cm. The mammogram (4a) demonstrated presence of suspicious microcalcification (arrowhead) with no evidence of dominant opacity, asymmetric density or architectural distortion.

Technique: 4a: Mediolateral oblique view, GE Senographe Essential, Rhodium filter, kVp: 31.00, 55mA, Angle: 48.00º, 64mm breast thickness; 4b: ultrasound: Siemens Acuson S2000 VE10, 18L6 probe, 10.00MHz

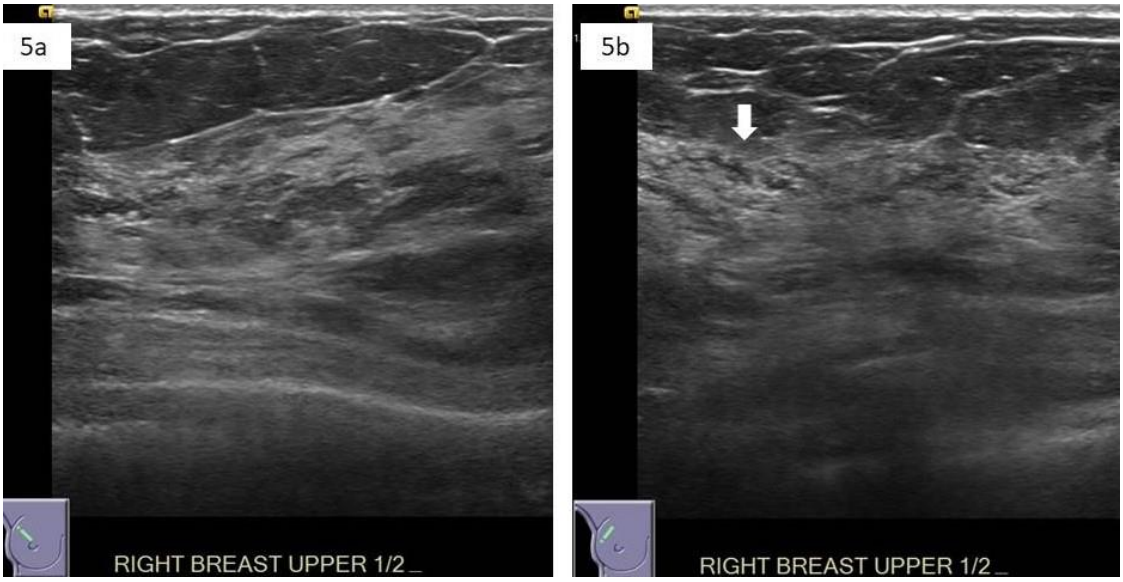

Figure 5: 65 year old female with primary peritoneal serous carcinoma with metastasis to breast and axillary lymph node

Findings: No discrete solid lesion is seen. Some echogenic foci are present (arrow), which may represent the microcalcification seen in the mammogram. No dilated ducts or evidence of architectural distortion was noted.

Technique: Siemens Acuson S2000 VE10, 18L6 probe, 10.00MHz

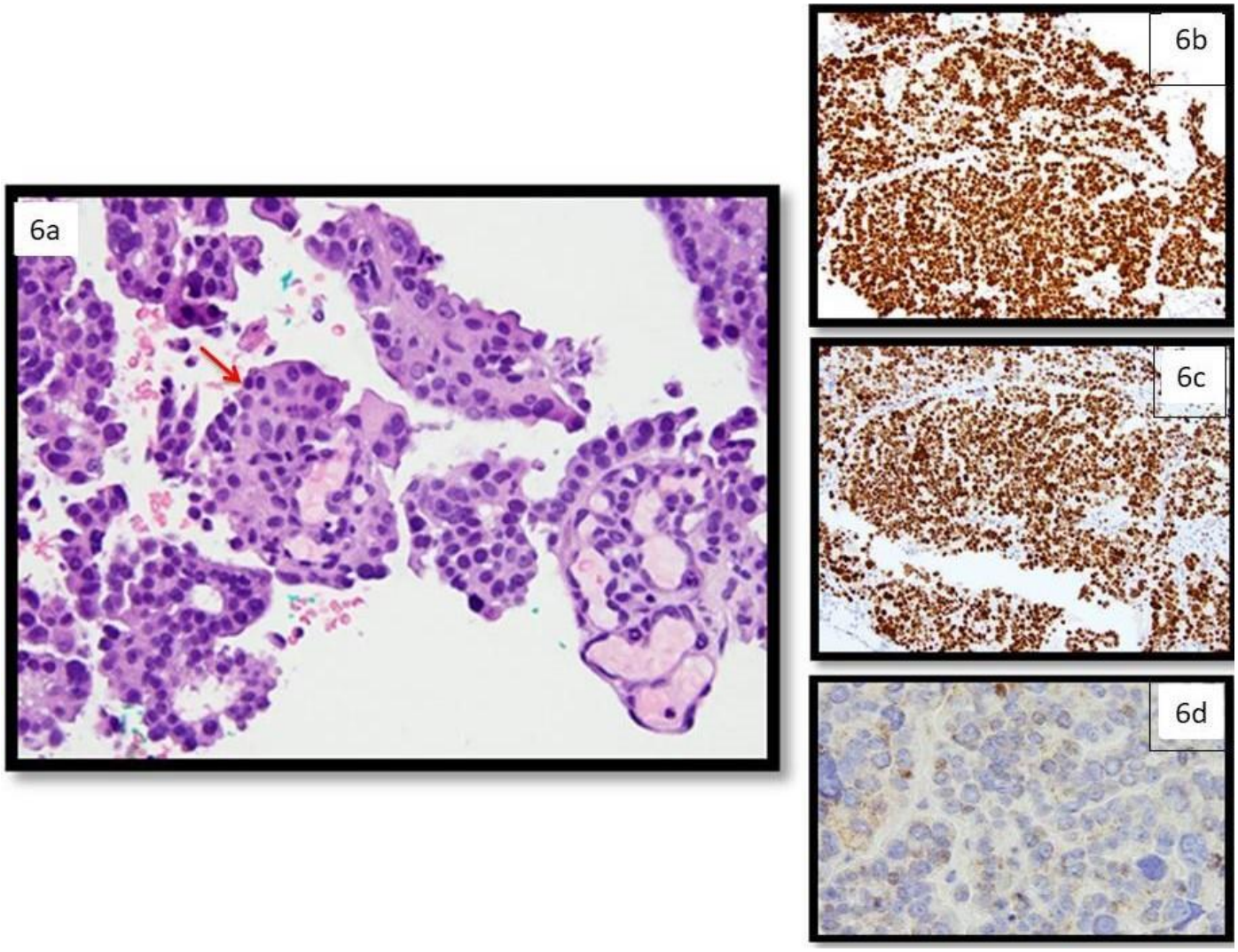

Figure 6: 65 year old female with primary peritoneal serous carcinoma with metastasis to breast and axillary lymph node

Specimen: Right axillary lymph node core needle biopsy.

Findings: 6a. H&E stain (200x); tumor cells similar in appearance to that seen in 1 and 2 exhibiting a micropapillary architecture (red arrow). 6 (b-d): Immunostains; (200x). 6b: PAX8; 6c: p53; 6d: GATA3. The tumor cells are strongly positive for PAX 8 and p53 but negative for GATA3 confirming metastatic high grade serous carcinoma (PPSC)

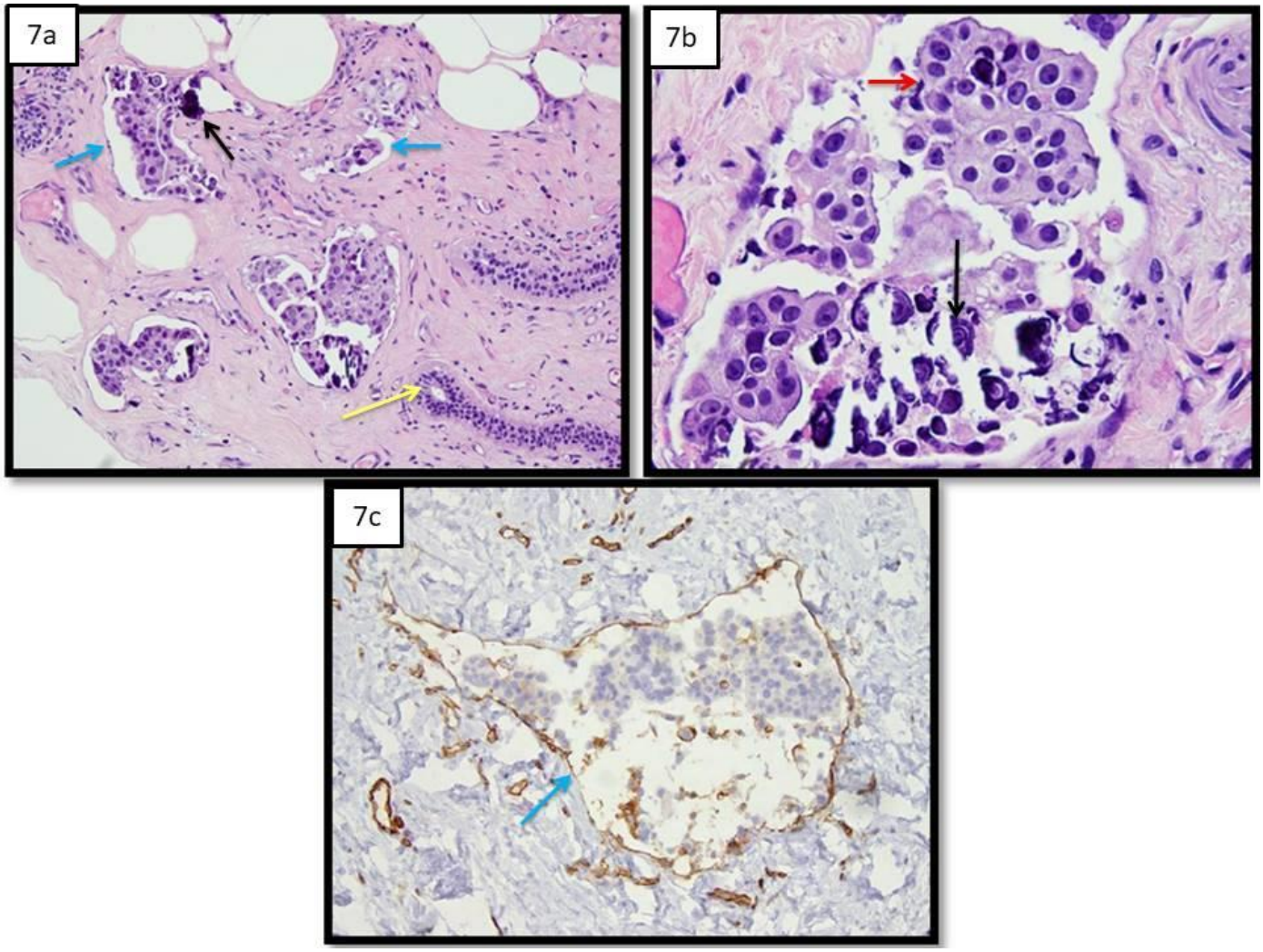

Figure 7: 65 year old female with primary peritoneal serous carcinoma with metastasis to breast and axillary lymph node

Specimen: Stereotactic guided breast core biopsy

Findings: 7a: H&E (200x); tumor cells similar in appearance to that seen in Figure 2 seen within vessels (blue arrow) exhibiting a micropapillary architecture (red arrow) and with associated psammomatous micro calcification (black arrow). 7b: Tumor emboli within vascular space; (H&E 100x); adjoining benign breast ducts with no in-situ component (yellow arrow). 7c: Immunostaining for CD31 (200x); highlighting tumor emboli within a vascular space (blue arrow). The endothelium being highlighted in brown

Etiology	Lymphovascular spread of the primary malignancy
Incidence	1-2% of breast malignancy 0.03-0.6% of breast malignancy may be due to breast metastasis from primary peritoneal or ovarian carcinoma
Treatment	Treatment of primary malignancy. For PPSC, neoadjuvant chemotherapy with optimal debulking surgery
Prognosis	Varies depending on the primary. Average 16 months for PPSC with breast metastasis
Imaging	Mammogram: well defined opacity Ultrasound: hypoechoic well-defined mass, corresponding to clinically palpable lump. Associated axillary lymph node enlargement may be present CT: well defined lesion with homogeneous enhancement MRI: well defined, oval lesion with rapid initial uptake and variable washout

Table 1: Summary table for Metastatic Breast Involvement from an Extra-mammary Malignancy

	DCIS	Primary breast malignancy	Metastatic involvement of breast from extra-mammary malignancy
Mammogram	• Pleomorphic or amorphous microcalcifications in tight cluster or segmental distribution • May be associated with associated mass	• Spiculated mass • Stromal distortion • May be associated with microcalcifications • Overlying skin changes, nipple retraction	• Well defined opacity
Ultrasound	• Unusual. • If present, hypoechoic, ill defined	• Hypoechoic, ill defined, irregular lesion. • Associated stromal distortion	• Hypoechoic well-defined mass. • Associated axillary lymph node enlargement may be present
CT	• Non mass enhancement. • Inferior to MRI for detection of breast abnormality	• Ill-defined or irregular mass with enhancement.	• Well-defined lesion with homogeneous enhancement
MRI	• Most commonly non mass enhancement of clumped pattern. Clustered ring enhancement	• Irregular mass with initial rapid uptake and washout • Most sensitive imaging modality	• Well defined, oval lesion with rapid initial uptake and variable washout

Table 2: Differential diagnosis table for Metastatic Breast Involvement from an Extra-mammary Malignancy

ABBREVIATIONS

CT = Computed Tomography
DCIS = Ductal Carcinoma In Situ
FDG = 18F-Fluoro-deoxyglucose
H&E = Hematoxylin and Eosin stain
MRI = Magnetic Resonance Imaging
PET = Positron Emission Tomography
PPSC = Primary Peritoneal Serous Carcinoma

KEYWORDS

Extramammary metastasis; Breast malignancy; Primary peritoneal serous carcinoma; Breast microcalcification; Breast disease