

Isolated Bilateral Ovarian Metastasis from Recurrent Mucinous Breast Cancer: Imaging and Histopathologic Challenges

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AUTHORSHIP CONTRIBUTIONS

All authors have read and approved the final version of this case report. Individual contributions are detailed below:

1. Nour Marroun

- Primary author and corresponding contributor.
- Collected and compiled the patient's clinical and radiological data.
- Wrote the initial draft of the manuscript, including the case report and discussion.
- Integrated co-authors' revisions and prepared the final version for submission.

2. Luc Baeyens

- Treating gynecologist and clinical contributor.
- Provided detailed clinical history, treatment details, and follow-up data.
- Reviewed and revised the clinical and therapeutic sections of the manuscript for accuracy.

3. Sophie L. Lecomte

- Anatomopathologist in charge of histopathological analysis.
- Provided and interpreted histopathological slides (HES staining).
- Wrote and validated the histopathology portion of the manuscript.
- Prepared and described pathological images and legends.

4. Eléna F. D'hondt

- Literature and references coordinator.
- Conducted comprehensive literature review and reference management.
- Drafted and finalized the abstract.

5. Nathalie A. Hottat

- Senior radiologist and project supervisor.
- Selected and interpreted all radiological studies (MRI, mammography, PET).
- Supervised the manuscript structure, provided critical revisions, and approved the final version.
- Ensured diagnostic accuracy and radiological-pathological correlation.

CONFLICT OF INTEREST / DISCLOSURE STATEMENT

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this case report.

ETHICAL STATEMENT / HUMAN AND ANIMAL RIGHTS

This case report was prepared in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from the patient for publication of this case report and any accompanying images.

ABSTRACT

Background: Ovarian metastases from mucinous breast cancer are rare and can mimic primary ovarian neoplasms. We report a case of isolated ovarian metastasis from recurrent mucinous breast carcinoma, highlighting imaging-pathology correlations.

Case Report: A 46-year-old woman, treated in 2016 for left mucinous breast cancer (pT2N2M0; mastectomy, adjuvant chemo-radiotherapy, hormonotherapy), achieved remission. In 2021, rising carcinoma antigen CA 15-3 prompted evaluation. PET-CT and pelvic MRI revealed a large enhancing right ovarian mass with solid and cystic component (O-RADS 5); histopathology after bilateral oophorectomy confirmed bilateral metastatic mucinous carcinoma concordant with primary tumor.

Conclusion: This case highlights the need to consider metastatic disease in ovarian masses, particularly if there is a history of mucinous breast cancer. Multimodality imaging and immunohistochemistry are essential to differentiate a primary ovarian malignancy from a metastasis.

CASE REPORT

CASE REPORT

Patient History

A 46-year-old premenopausal woman (Gravida 2 Para 2) with a family history of breast cancer (paternal grandmother and aunt) presented in 2016 with a palpable left axillary mass. Breast workup revealed multicentric left breast lesions and axillary lymphadenopathy, diagnosed as mucinous carcinoma (pT2N2M0). The patient underwent mastectomy, axillary lymph node dissection, adjuvant chemo-radiotherapy, and hormonotherapy, achieving remission. In 2021, follow-up detected elevated CA 15-3 levels and a right possibly malignant ovarian mass at MRI, confirmed as bilateral metastatic mucinous carcinoma after salpingo-oophorectomy. Genetic testing was negative for BRCA1/BRCA2 mutations.

*Imaging Findings***Initial Breast Workup (2016)**

Mammography (Figure 1) revealed multiple circumscribed lobulated masses of heterogeneous moderated density in the left breast with an axillary lymphadenopathy, classified as BI-RADS ACR IV. Targeted ultrasound (Figure 2) confirmed three hypoechoic, heterogeneous, ill-defined solid masses (1.5–1.9 cm) at the 9, 3 o'clock and retro areolar positions, alongside multiple enlarged axillary lymph nodes. Ultrasound-guided core-biopsies of the breast masses and fine-needle aspiration of the lymph nodes were performed. Subsequent breast MRI (Figure 3) demonstrated a multicentric disease, with masses exhibiting early intense progressive and plateau enhancement patterns (type I and II kinetic curves respectively).

Ovarian Metastasis Workup (2021)

Following an elevated CA 15-3 level (Figure 4), positron emission tomography (PET-CT) (Figure 5) identified a solitary hypermetabolic para-uterine mass. Pelvic MRI (Figure 6) further characterized this as an 8 cm irregular right ovarian lesion with solid and cystic components with an early intense contrast enhancement in the solid tissue in comparison with the external myometrium (type 3 kinetic curve). Therefore, an O-RADS MR score of 5 was given (positive predictive value for malignancy of 90%). Notably, there was no evidence of

peritoneal carcinomatosis, ascites, or pelvic lymphadenopathy. The imaging differential diagnosis included primary ovarian neoplasm versus metastasis. Follow-up breast imaging and PET-CT confirmed the absence of local recurrence or additional distant metastases.

*Pathological Findings***Primary Breast Tumor (2016)**

Initial core-biopsies (Figure 7a, 7b) revealed a well-differentiated pure mucinous invasive ductal carcinoma (Nottingham Grade 1/SBR4), Luminal A. The tumor exhibited strong hormone receptor positivity (estrogen receptor [ER] 8/8, progesterone receptor [PR] 8/8, Cancer Imaging), low proliferative index (Ki-67 5%), and HER2 negativity (1+ by immunohistochemistry [IHC], confirmed non-amplified by Fluorescence In Situ Hybridization (FISH)).

Ovarian Metastasis (2021)

Bilateral salpingo-oophorectomy specimens (Figure 7c) confirmed metastatic mucinous carcinoma in both ovaries, with immunohistochemical profiles concordant with the primary breast tumor: PR: 7/8, ER: 2/8, HER2/neu: 1+ (negative by IHC), and Ki-67 of 30%. The GATA Binding Protein 3 (GATA3) was diffusely positive. This pathological correlation, alongside the imaging findings, established the ovarian lesions as metastatic rather than a primary neoplasm.

DISCUSSION

Etiology & demographics

Mucinous breast carcinoma (MBC) accounts for 1-4% of invasive breast cancers, predominantly affecting older women (mean age around 65) and demonstrating favorable prognosis (10-year survival >85%) due to low-grade histology and hormone receptor positivity (ER/PR+ in ~90%) [1]. Classified into pure (PMBC) (>90% mucinous) and mixed subtypes (MMBC) [2].

The distinction between pure and mixed MBC is clinically important, as the pure type demonstrates less aggressive behavior and a more favorable prognosis [3].

Ovarian metastases (OM) from breast cancer are rare. In patients with a history of breast carcinoma, a primary ovarian carcinoma (POC) is 3 to 7 times more common than an OM. However, autopsy and surgical series report OM incidences of 17-47% in women with treated breast cancer [4].

OM from PMBC are extremely rare, with no precise incidence reported in the literature. This low metastatic potential is illustrated by a large Australian study of 214,507 women, which identified 45 MBC cases. Among these, only one patient had axillary lymph node involvement, and none had distant metastasis [5].

In addition, a large contemporary series from Boston reported a distant recurrence rate of less than 3% in 111 patients with MBC [6].

Although approximately 15% of ovarian tumors are metastatic, the breast is a primary origin in 3-38% of these cases. OM are often asymptomatic, leading to delayed diagnosis [7].

Our case—a 46-year-old premenopausal woman with pure MBC (Luminal A, Ki-67 5%) developing isolated ovarian metastases 5 years post-diagnosis—defies typical patterns in both demographic (younger age) and metastatic behavior (solitary ovarian recurrence).

Imaging findings and Differential Diagnoses challenges

On mammography, pure-type MBC typically presents as a circumscribed, lobulated mass of low to moderate density, often mimicking a benign lesion. In contrast, the mixed type frequently demonstrates irregular margins and a more aggressive pattern. Microcalcifications are rarely associated with either form [3]. Ultrasound reveals hypoechoic, oval, or lobulated masses with posterior acoustic enhancement due to mucin content [3, 5].

On MRI, a high T2 signal is a hallmark of both pure and mixed mucinous tumors due to the presence of mucin. PMBC typically presents as a circumscribed mass with very high signal intensity on T2-weighted fat-saturated sequences and a Type I (persistent) kinetic curve on dynamic MRI, as seen in our case. These benign-appearing features often lead to misdiagnosis as a fibroadenoma or cyst. Consequently, histopathology remains essential for definitive diagnosis. Unlike other malignant breast tumors, mucinous tumors do not restrict diffusion, demonstrating lower DWI signal and higher ADC values [8].

The enhancement pattern of mucinous carcinoma varies with its histology: lesions with predominant mucin show no enhancement; those with cellular islands in mucin show heterogeneous enhancement; and those with tumor cells at the periphery show rim enhancement. Enhancement kinetics in pure mucinous tumors vary with cellularity: hypocellular tumors enhance gradually, whereas hypercellular tumors enhance strongly early, often mimicking mixed tumors [8].

To our knowledge, no similar cases in the literature describe the MRI features of ovarian metastases from PMBC for comparison.

Pre-operative differentiation between primary and secondary ovarian tumors remains challenging. On ultrasonography, metastatic lesions are often smaller and more solid than primary ovarian tumors [9]. Key features suggesting metastasis include bilaterality (in up to 100% of cases), a multinodular appearance, extensive extraovarian spread, and a desmoplastic reaction [10, 4].

MRI is a highly sensitive tool for the detection of ovarian neoplasms; however, it possesses low specificity for distinguishing OM from POC. OM from breast cancer is frequently present as bilateral, small, solid, and hypervascular masses. Their appearance is characterized by a heterogeneous T2 signal, avid early enhancement with rapid washout, and restricted diffusion, features that typically result in an O-RADS 5 classification. Since these findings can closely mimic those of POC, definitive diagnosis invariably relies on histopathologic confirmation [4, 9, 10, 11].

In our case, the radiological differentiation between OM and POC was challenging due to the absence of contralateral disease and overlapping malignant features. In general, the absence of peritoneal spread and bilaterality can be suggestive of metastasis but are non-definitive.

Histopathological findings and Differential Diagnoses challenges

Mucinous breast carcinoma (MBC), or colloid carcinoma, is a rare histological subtype representing approximately 4% of all breast cancers. The pure form (PMBC), which constitutes about 2% of cases, is defined by tumor cells within extracellular mucin comprising over 90% of the tumor mass. PMBC is further subclassified based on cellularity: hypocellular tumors (PMBC-A) exhibit micropapillary or cribriform patterns, while hypercellular tumors (PMBC-B) feature solid nests of cells floating in mucin pools [12].

Mucinous breast carcinoma (MBC) typically demonstrates a favorable immunoprofile, characterized by high rates of estrogen receptor (ER) and progesterone receptor (PR) positivity, alongside a low incidence of HER2 overexpression. This profile guides a therapeutic approach centered on endocrine therapy [13].

Immunohistochemistry (IHC) is essential for diagnosing and differentiating ovarian tumors. Markers such as Gross Cystic Disease Fluid Protein-15 (GCDFF-15), Mammaglobin, and GATA3 support breast cancer origin. In contrast, Wilms' Tumor Antigen-1 (WT1), Cancer Antigen 125 (CA-125), and Paired Box 8 (PAX8) are suggestive of POC. Although the hormone receptor status, ER and PR and HER2 status cannot reliably distinguish an OM from a POC, they are critical for guiding subsequent systemic therapy [12, 13].

In our patient, the ovarian metastasis showed concordant Luminal A immunoprofile (ER 2/8, PR 7/8, HER2–, GATA3+) but higher Ki-67 (30%), suggesting focal dedifferentiation despite maintained mammary origin. This contrasts with primary ovarian mucinous carcinomas, which are usually GATA3–/PAX8+ and lack hormonal receptor expression.

Treatment & Prognosis

In our patient, serial CA 15-3 monitoring post-remission proved pivotal. Levels rose from 12 KU/L (baseline post-treatment) to 103 KU/L over 6 months—a 8 to 9-fold increase exceeding the normal threshold (≤ 30 KU/L)—triggering PET/MRI that detected the 8 cm ovarian metastasis while still asymptomatic [2]. This aligns with studies showing mucinous carcinomas often produce significant CA 15-3 elevations (median 5–10 $\times$ upper limit) due to their secretory phenotype, unlike ductal subtypes [1]. While CA 15-3 lacks specificity for ovarian involvement (elevated in 20–30% of benign adnexal lesions and positive in some cases of breast carcinomas) [13], its trend correlation with tumor burden—peaking at 103 KU/L pre-resection and normalizing post-salpingo-oophorectomy—reinforces its utility in monitoring mucinous breast cancer, particularly when paired with targeted imaging.

Ovarian metastases from breast carcinoma warrant aggressive local therapy (bilateral salpingo-oophorectomy) combined with systemic treatment due to their rarity and unpredictable biology [2]. While hormone receptor-positive cases (like ours: ER/PR+) may respond to endocrine therapy, the elevated Ki-67 (30%) in our patient's metastasis suggests benefit from chemotherapy [1].

Close surveillance (CA 15-3 and pelvic MRI) is advised, as late recurrences (>5 years) occur in 20% of cases [1, 2].

The literature lacks robust prognostic data for ovarian metastatic recurrence from PMBC, a consequence of its extreme rarity. However, ovarian metastases are associated with a guarded prognosis, exhibiting a median progression-free survival of 9 to 30 months [13].

As of the last oncology follow-up in March 2025, our patient remains asymptomatic and clinically stable on maintenance therapy with palbociclib (Ibrance®) and letrozole (Femara®) since January 2022. Surveillance imaging—including pelvic MRI, CT of the chest/abdomen/pelvis, and bone scintigraphy—showed no evidence of local or metastatic disease. Serial CA 15-3 levels have stabilized at 30 KU/L (within normal limits), reflecting sustained treatment response.

TEACHING POINTS

Ovarian metastases from mucinous breast carcinoma often mimic primary ovarian neoplasms radiologically. Serial CA 15-3

monitoring is particularly valuable for detecting asymptomatic ovarian recurrences in mucinous subtypes. Definitive diagnosis requires immunohistochemical confirmation (GATA3+/PAX8–) due to significant radiological overlap with primary ovarian malignancies.

Optimal detection requires collaboration between radiologists, oncologists, and pathologists to correlate imaging, biomarkers, and histology.

QUESTIONS

Question 1: Concerning the PMBC and MMBC, what is the best answer?

- A) The prognosis of PMBC is Worse
- B) The PMBC is more aggressive
- C) MMBC contains larger amount of mucin
- D) MMBC is more associated with metastatic disease (applies)
- E) Both types have favorable prognosis

Explanation: The distinction between pure and mixed MBC is clinically important, as the pure type demonstrates less aggressive behavior and a more favorable prognosis. [Etiology & demographics section].

Question 2: Which imaging feature is MOST characteristic of mucinous breast carcinoma?

- A) T1 hyperintensity with fat suppression
- B) T2 hypo intensity with calcifications
- C) Very high T2 signal intensity (applies)
- D) Diffusion restriction only in cystic portions
- E) Avid enhancement with Type II kinetics

Explanation: On MRI, a high T2 signal is a hallmark of both pure and mixed mucinous tumors due to the presence of mucin. [Imaging Findings section]

Question 3: Which immunohistochemical marker profile confirms mammary origin of an ovarian mass?

- A) GATA3+/PAX8+
- B) GATA3–/PAX8+
- C) GATA3+/PAX8– (applies)
- D) WT-1+/ER–
- E) WT-1+/PR+

Explanation: GATA3 positivity (breast origin) and PAX8 negativity (ovary origin) are diagnostic for metastatic breast cancer [Histopathological findings section].

Question 4: Which feature suggests aggressive biology in mucinous breast cancer metastases?

- A) ER 8/8 positivity
- B) PR 7/8 positivity

- C) HER2 3+ overexpression
- D) Ki-67 $\geq 30\%$ (applies)
- E) Pure mucinous histology

Explanation: In our patient, the ovarian metastasis showed concordant Luminal A immunoprofile (ER 2/8, PR 7/8, HER2–, GATA3+) but higher Ki-67 (30%), suggesting focal dedifferentiation despite maintained mammary origin [Histopathological findings and Differential Diagnoses challenges section].

Question 5: Which biomarker is MOST useful for detecting asymptomatic ovarian recurrences in mucinous breast cancer?

- A) CEA
- B) CA 19-9
- C) AFP
- D) CA 15-3 (applies)
- E) LDH

Explanation: CA 15-3 is elevated in mucinous breast cancer and often rises before radiographic evidence of recurrence, making it critical for surveillance [Treatment & Prognosis section].

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FIGURES

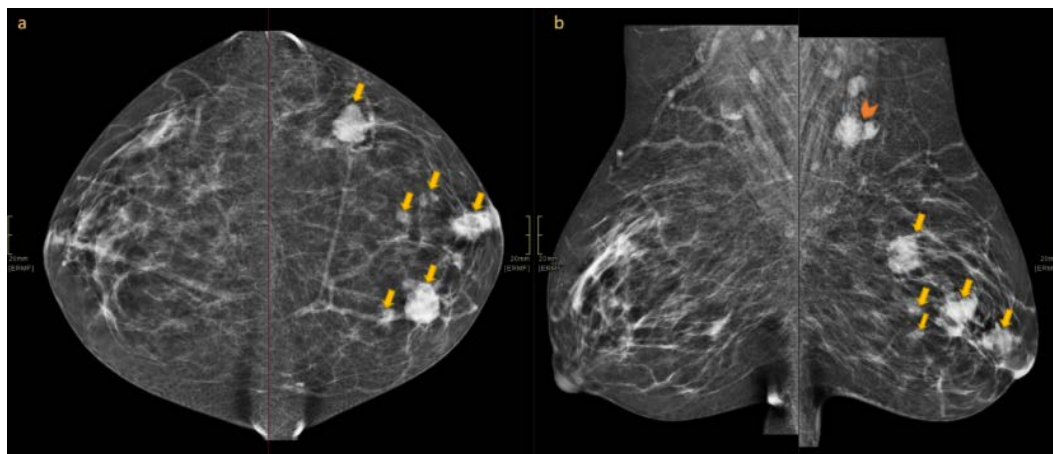


Figure 1: Mammography: (a) Craniocaudal and (b) mediolateral oblique views showed multiple circumscribed, lobulated dense masses (arrows) in the left breast with a left axillary lymphadenopathy (arrow head).

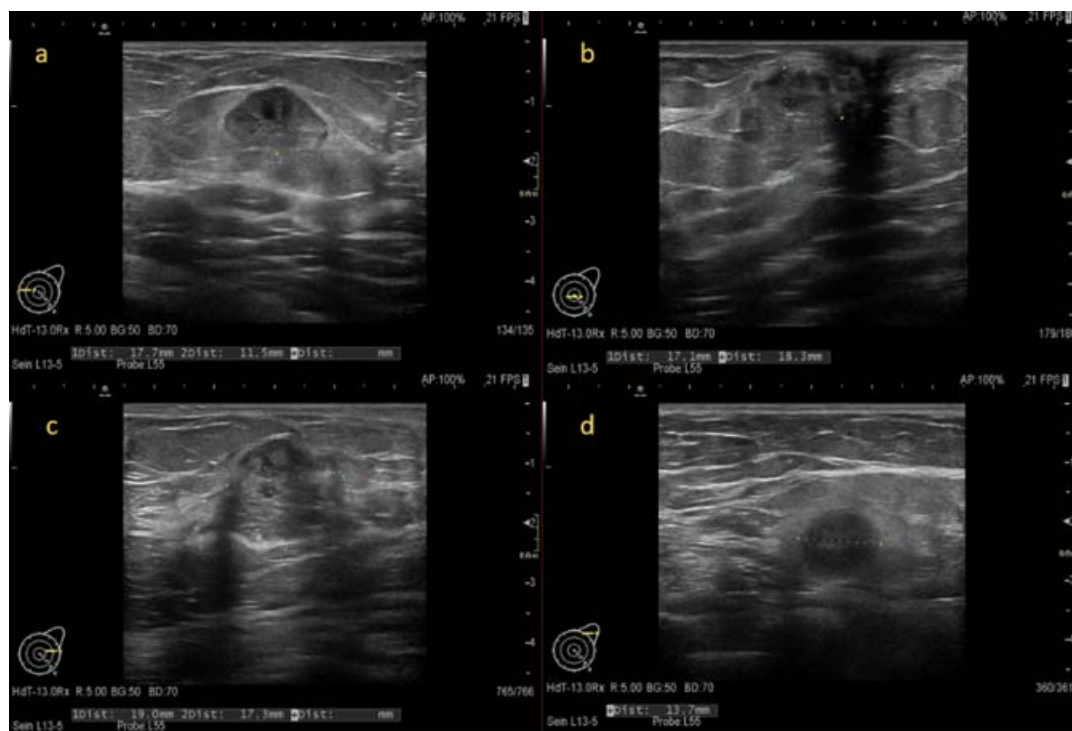
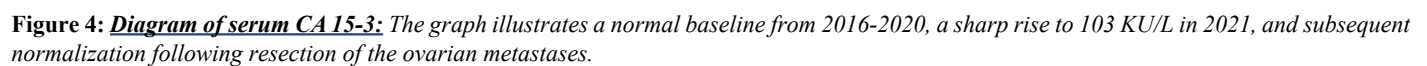


Figure 2 : Ultrasound of the left breast and axilla: (a, b and c) multiple hypoechoic, ill-defined heterogeneous solid masses (calipers) at the 9 o'clock, retro areolar and 9 o'clock respectively. (d) A round enlarged left axillary lymph node (calipers).



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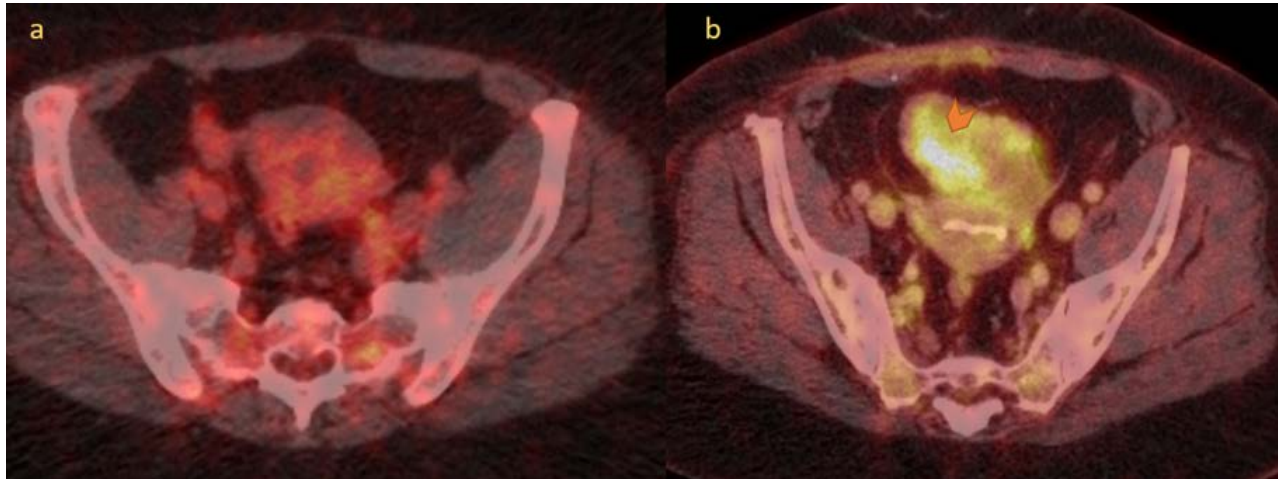


Figure 5: Positron emission tomography (PET) scanner: **(a)** A baseline scan from 2016 showed no fluorodeoxyglucose (FDG)-avid pelvic mass. **(b)** A follow-up scan from 2021 revealed a large, FDG-avid para-uterine mass (arrowhead), suspected of malignancy.

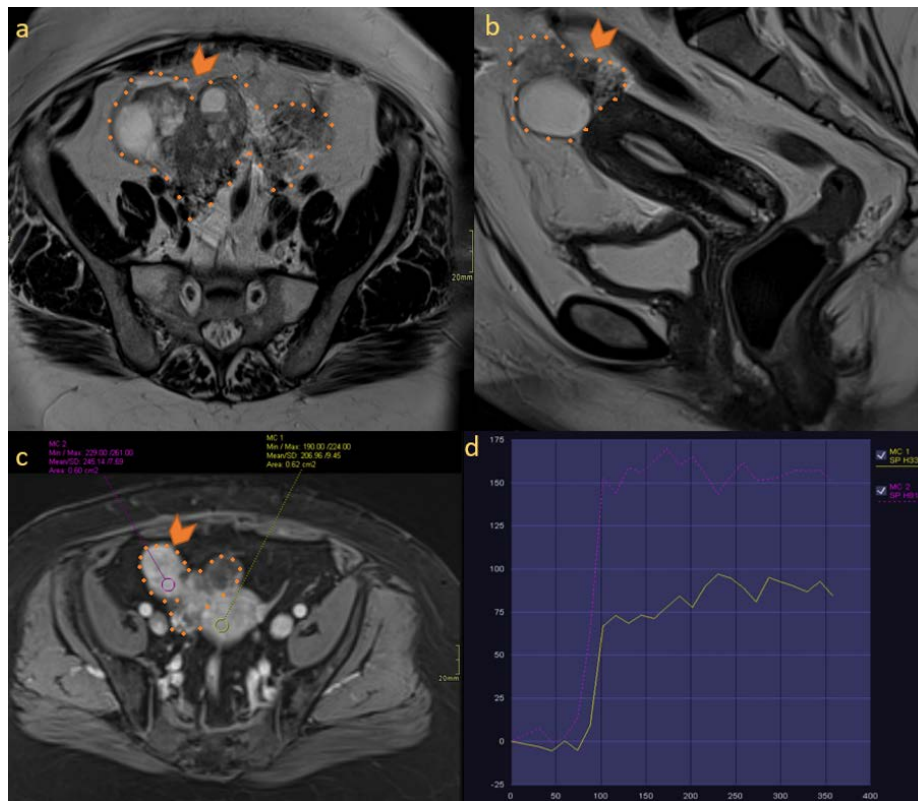


Figure 6: Pelvic MRI: **(a)** Axial and **(b)** sagittal T2-weighted images demonstrated a large irregular solid and cystic right adnexal mass (arrowhead and delineating contours). **(c)** Axial post-contrast T1-weighted image with fat suppression revealed early intense enhancement in the solid tissue. **(d)** The kinetic curve showed a rapid, intense enhancement (purple curve) in comparison with the external myometrium (yellow curve), consistent with a type 3 kinetic pattern (purple curve). An O-RADS MR score of 5 was given.

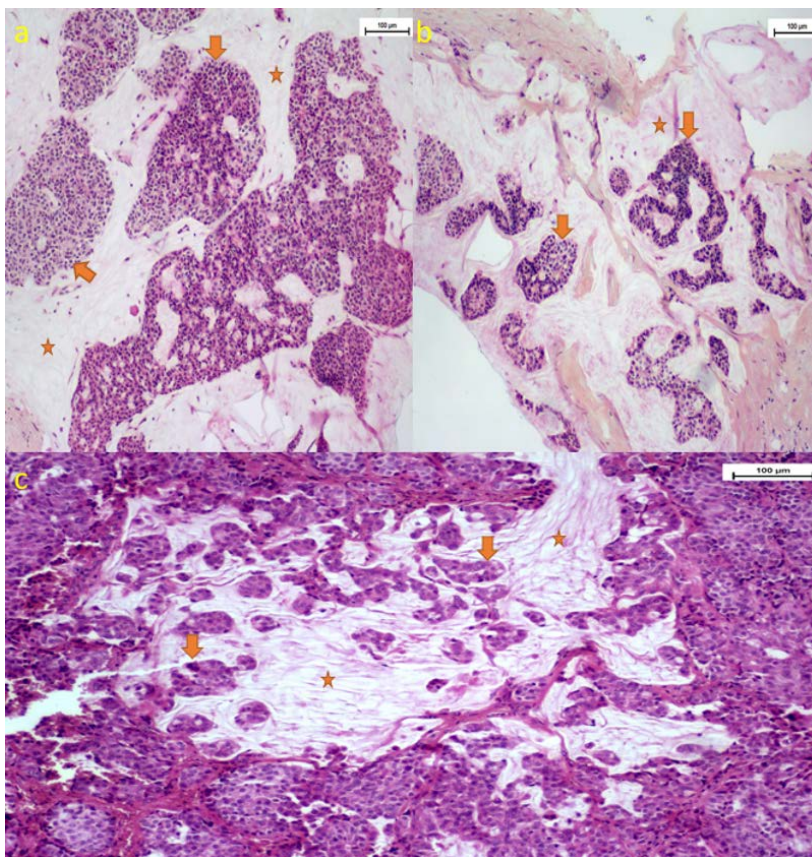


Figure 7: Histopathological correlation (HES stain, $\times 100$): (a, b) Core biopsy of the left breast demonstrates features of Type A (hypocellular) mucinous breast carcinoma (MBC), characterized by scant tumor cell clusters (arrow) within abundant extracellular mucin (asterisk). (c) Excisional biopsy of the right ovarian mass reveals similar histologic pattern, with tumor cell clusters (arrow) floating in mucin pools (asterisk).

KEYWORDS

Mucinous breast carcinoma; Ovarian metastasis; Magnetic resonance imaging; O-RADS MRI, CA 15-3 biomarker; Immunohistochemistry

ABBREVIATIONS

ADC = Apparent Diffusion Coefficient
 AFP = Alpha-fetoprotein
 BI-RADS = Breast Imaging-Reporting and Data System
 BRCA1 = Breast cancer gene 1
 BRCA2 = Breast cancer gene 2
 CA 19-9 = Carbohydrate Antigen 19-9
 CA-125 = Cancer Antigen 125
 CEA = Carcinoembryonic Antigen
 DWI = Diffusion-Weighted Imaging
 ER = Estrogen Receptor
 FDG = Fluorodeoxyglucose
 FISH = Fluorescence In Situ Hybridization
 GATA3 = GATA Binding Protein 3
 GCDP-15 = Gross Cystic Disease Fluid Protein-15
 HER2 = Human Epidermal Growth Factor Receptor 2
 HES = Hematoxylin-Eosin-Safran
 IHC = Immunohistochemistry
 Ki-67 = Marker of Proliferation Ki-67 (Proliferation Index)
 LDH = Lactate Dehydrogenase
 MBC = Mucinous Breast Carcinoma
 MMBC = Mixed type Mucinous Breast Carcinoma
 MRI = Magnetic Resonance Imaging
 OM = Ovarian Metastasis(es)
 O-RADS = Ovarian-Adnexal Reporting and Data System
 PAX8 = Paired Box 8
 PET = Positron Emission Tomography
 PMBC = Pure Mucinous Breast Carcinoma
 PMBC-A = Pure hypocellular Mucinous Breast Carcinoma
 PMBC-B = Pure hypercellular Mucinous Breast Carcinoma
 POC = Primary Ovarian Carcinoma
 PR = Progesterone Receptor
 WT1 = Wilms' Tumor Antigen-1

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