Breast Lymphoma: Multimodality Case-Based Imaging Review

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Disclosures

- E.A. Gillis & L.R. Lamb: Neither have a financial relationship with a commercial organization that may have a direct or indirect interest in the content.
- C. Lehman: GE research grant, consultant on a GE Medical Advisory Board

Educational Goals

1. Summarize epidemiological studies
2. Describe common clinical presentations of primary breast lymphoma (PBL), secondary breast lymphoma (SBL), and breast implant-associated anaplastic large cell lymphoma (BIAALCL)
3. Present cases with classic imaging features to provide familiarity with these rare entities
4. Review pathology requirements at the time of biopsy when lymphoma is in the differential diagnosis

Target Audience and Objectives

- After reviewing this educational exhibit, radiologists-in-training, general radiologists, and sub-specialized breast radiologists will:
  1. Gain an understanding of the epidemiology of breast lymphoma
  2. Learn about common clinical presentations of patients with breast lymphoma
  3. Expand their experience of this uncommon entity through multimodality case examples
  4. Understand requirements for diagnosis in cases of suspected breast lymphoma

Epidemiology

Epidemiology – PBL and SBL

- Both PBL and SBL are relatively uncommon:
  - Prevalence of 0.04-0.7%[1,2]
- PBL accounts for less than 1% of all breast malignancies and less than 2% of extranodal Non-Hodgkin Lymphoma (NHL) [3-5]
  - More aggressive with poor prognosis compared to other extranodal NHL
- SBL is most common metastasis to the breast, and accounts for 17% of breast metastases[1]
- Clinical presentations and imaging features can be indistinguishable from primary breast carcinoma

Epidemiology – BIAALCL

- First use of breast implants: 1950s
- First hypothesis of association between breast implants and cutaneous T-cell lymphoma by Duvic et al in Journal of American Academy of Dermatology: 1995[6]
- FDA identifies “possible association between breast implants and the development of anaplastic large cell lymphoma” (ALCL): 2011[7]
  - Very few cases
  - Further research required

Epidemiology – BIAALCL

- FDA agrees with World Health Organization "designation of breast implant-associated anaplastic large cell lymphoma as a rare T-cell lymphoma that can develop following breast implants": 2016/2017[8,9]
  - Data suggests this entity occurs more frequently after placement of implants with textured surfaces compared to those with smooth surfaces[9]
  - Limitations: lack of information (reporting, incomplete data about implants, and implant sales numbers)[9]

Epidemiology – BIAALCL

- Medical device reports (MDRs): 2/1/2017
  - Total of 359 MDRs of BIAALCL, including 9 deaths
- MDR update as of 7/6/2019: 573 cases tracked with 33 deaths[9]
- FDA recall of specific implant model in July 2019, with recommendations for physicians to inform patients of BIAALCL risk and for patients to be aware of potential symptoms and to be evaluated if these arise
  - No need to remove the recalled implants from asymptomatic patients given low risk of BIAALCL
  - Do report all cases of BIAALCL to MedWatch (FDA) and Patient Registry and Outcomes For breast Implants and anaplastic large cell Lymphoma etiology and Epidemiology (PROFILE) registry[7]

Clinical Presentation and Imaging Features

Clinical Features of Breast Lymphoma

Primary Breast Lymphoma

- Almost always NHL
  - Most often diffuse large B cell lymphoma (DLBCL)[10]
- Often solitary palpable mass[11,12]
- Median age at presentation: 60-65y[1]
- Bilateral breast involvement is rare but is more often seen in pregnant/post-partum patients

Secondary Breast Lymphoma

- Most common metastasis to breast
- Occult clinical presentation
- Usually solitary, but multiple masses/bilateral involvement is more common in SBL compared to PBL[12]
- Median age at presentation: 60-70y[1]
- B symptoms (fever, weight loss, night sweats)
- Relatively poor prognosis

Clinical Features of BIAALCL

- Rare type of NHL
- Patients may present with: effusion/seroma, mass, both, neither[13]
- Usually > 1 yr from implant placement, average 8-10 years[13,14]
- Treatment: excision of lymphoma, removal of implant, capsulotomy, lymphadenectomy[14]

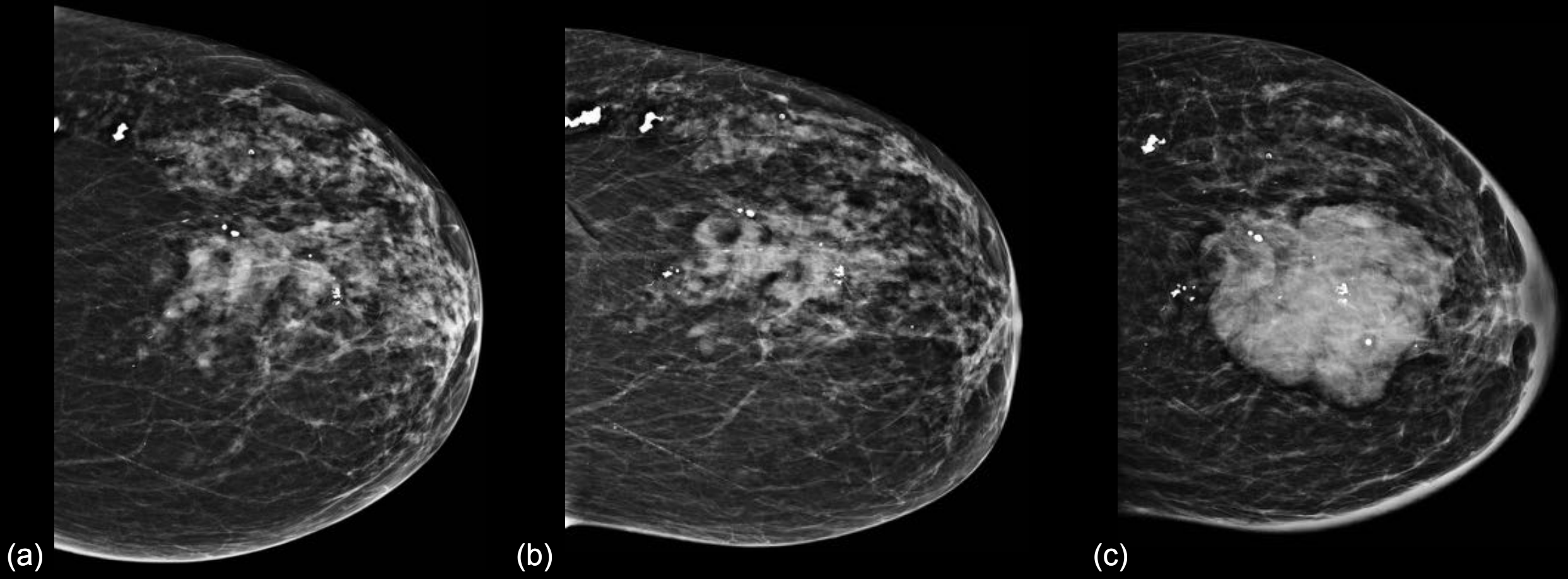
Imaging Features of Breast Lymphoma

- Imaging phenotypes overlap with primary breast carcinoma:
  - Iso- to hyperdense oval mass or masses at mammography
  - Hypoechoic or mixed-echogenicity hypervascular mass at ultrasound (US)
  - Enhancing mass with type II kinetics at MRI
  - High fluorine 18–fluorodeoxyglucose avidity at positron emission tomography (PET)/computed tomography (CT)[1,15]
- Crucial to investigate clinical history and to evaluate for multiplicity, bilaterality, and distant disease at time of imaging

Multimodality Cases

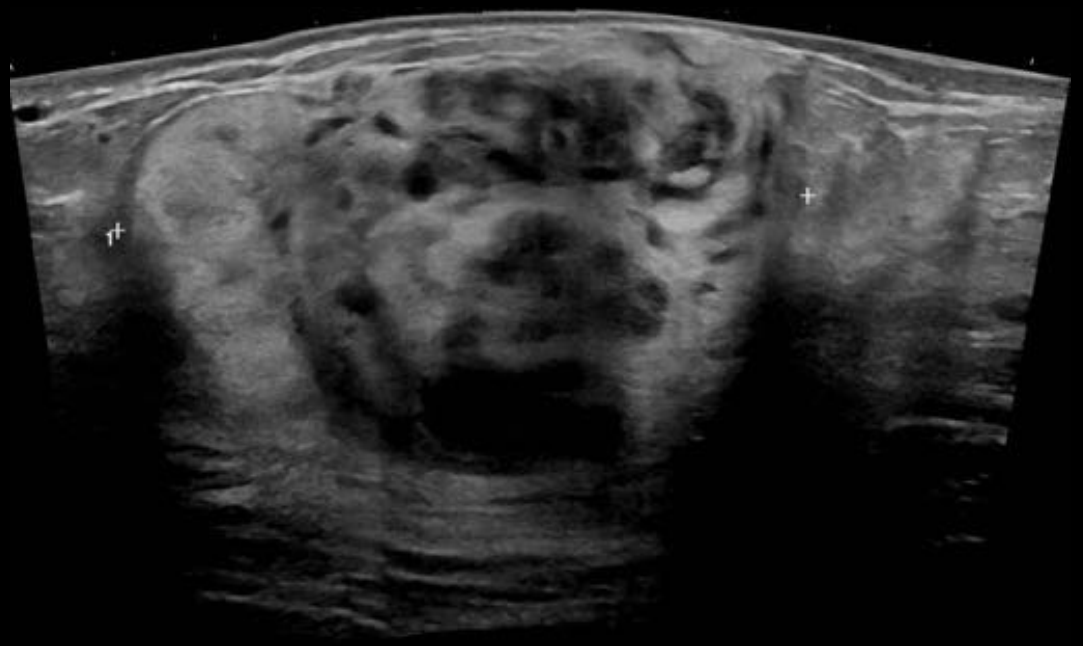
Primary Breast Lymphoma – Case 1

86 year old female presented for diagnostic evaluation of a palpable abnormality in the left breast.



Left craniocaudal (CC) mammographic views from negative screening mammograms in (a) January 2018 and (b) January 2019. (c) Diagnostic mammogram from June 2019 demonstrates a large irregular mass with associated skin thickening at 12:00 in the palpable area of concern.

Primary Breast Lymphoma – Case 1



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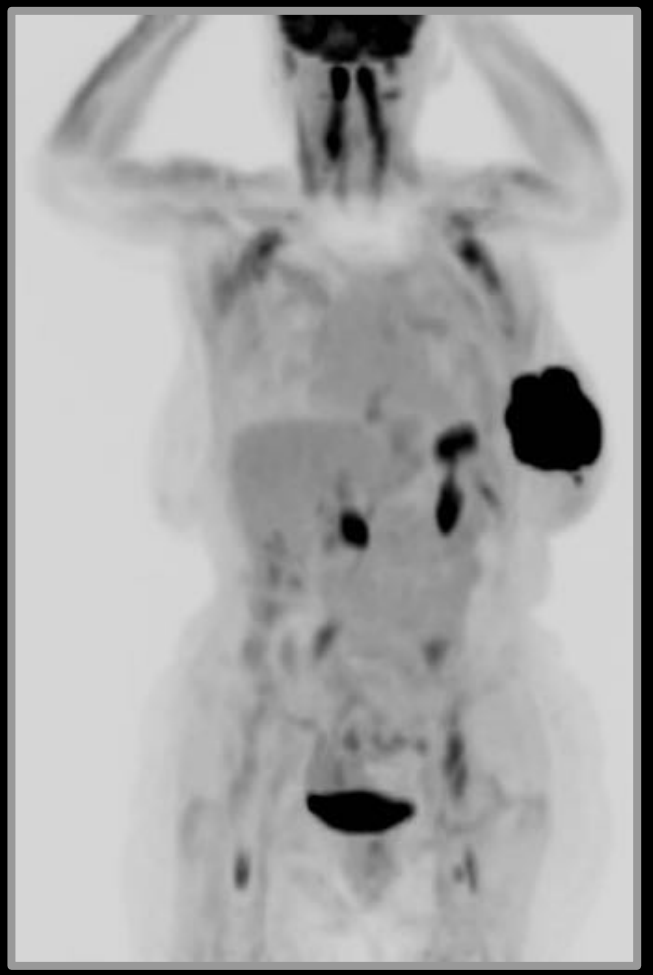
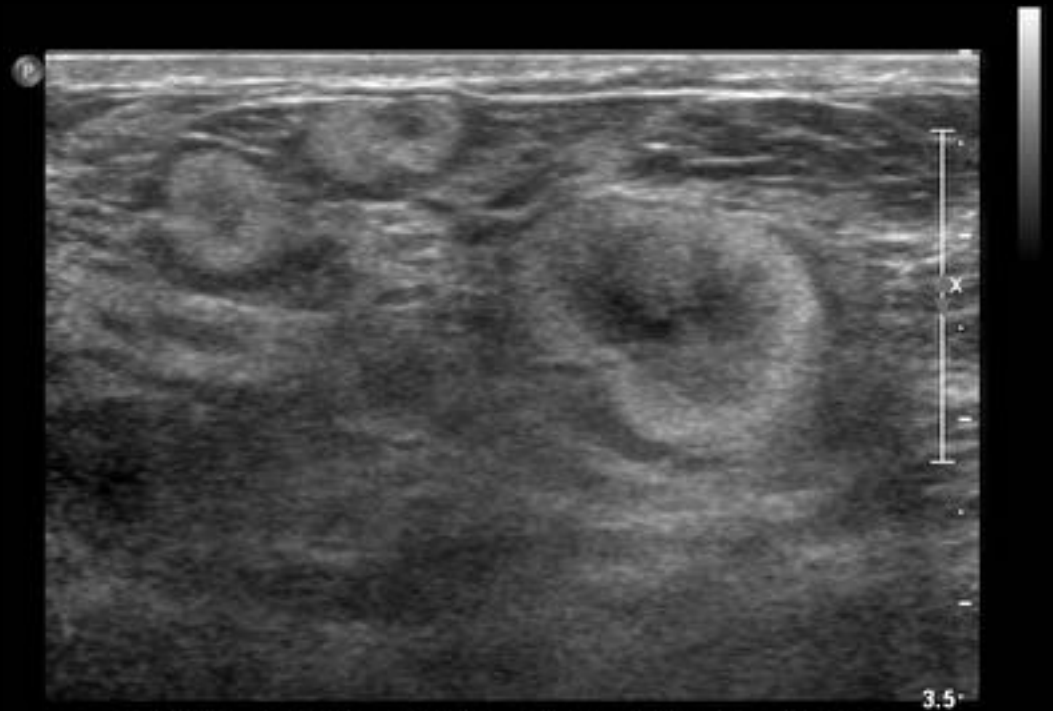


(e)

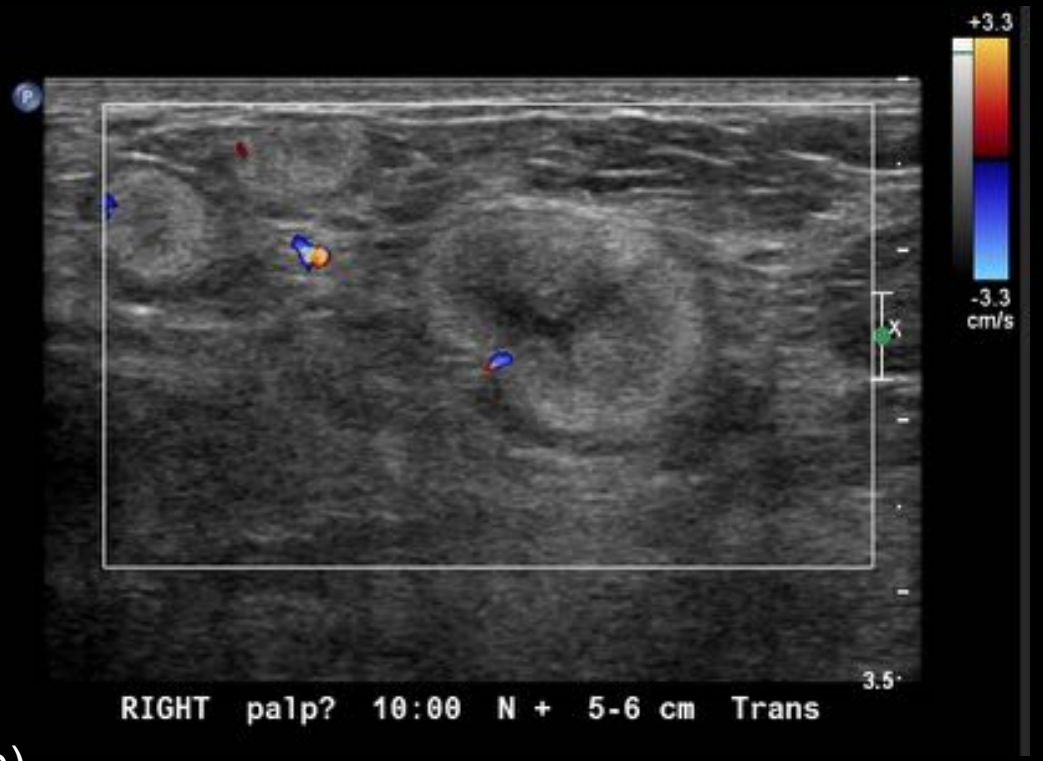
(d) Corresponding US image demonstrates an irregular heterogeneous mass. The patient subsequently underwent US-guided core biopsy. **Diagnosis: diffuse large B cell lymphoma.** (e) MIP PET image from staging PET/CT demonstrates a hypermetabolic left breast mass with no other sites of disease.

Primary Breast Lymphoma – Case 2

35 year old female, 36 weeks pregnant, presented for diagnostic evaluation of a palpable abnormality in the right breast.



(a)

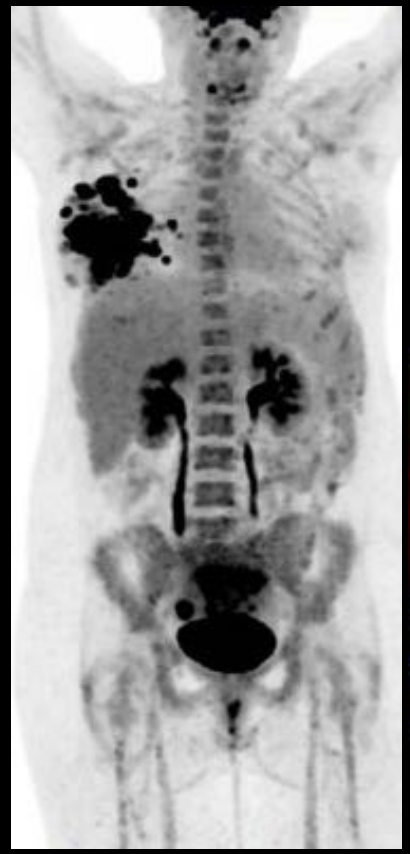


(b)

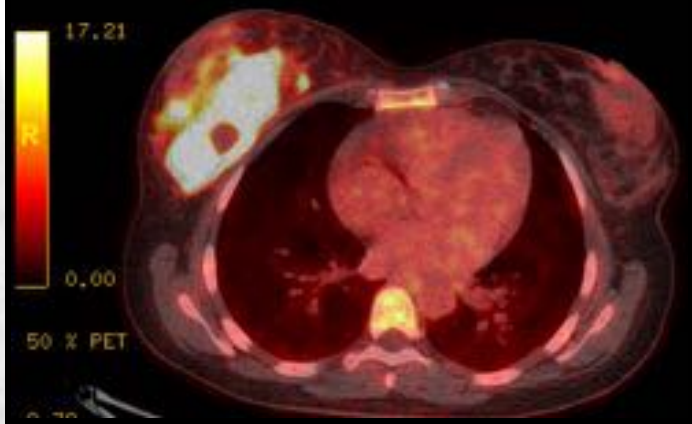
(a) Grayscale and (b) color static sonographic images from diagnostic US of the right breast demonstrate several round/oval predominantly hyperechoic masses in the area of palpable concern. Mammography was not obtained in this pregnant patient. The patient subsequently underwent US-guided core biopsy. **Diagnosis: diffuse large B cell lymphoma.**

Case courtesy of Partners Health Care/Brigham and Women's Hospital

Primary Breast Lymphoma – Case 2



(c)



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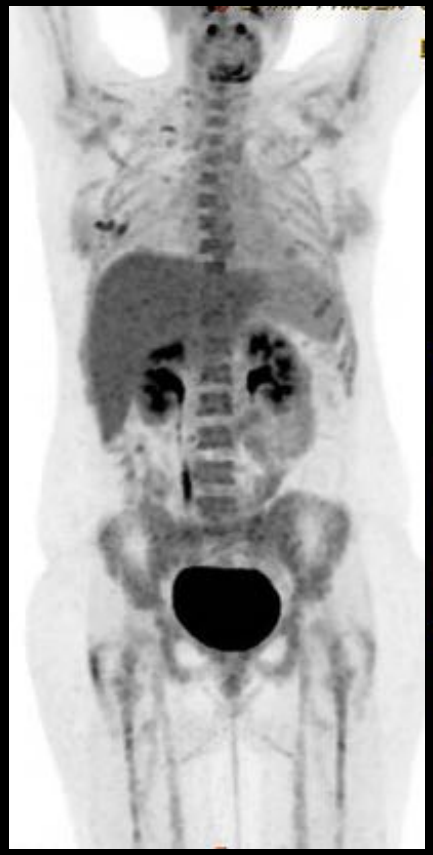

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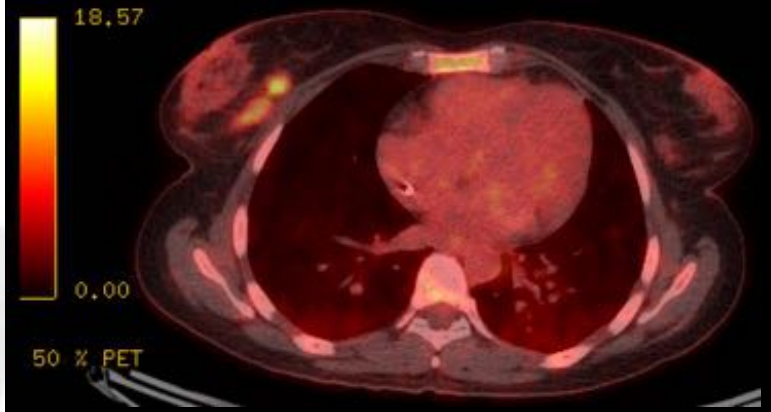
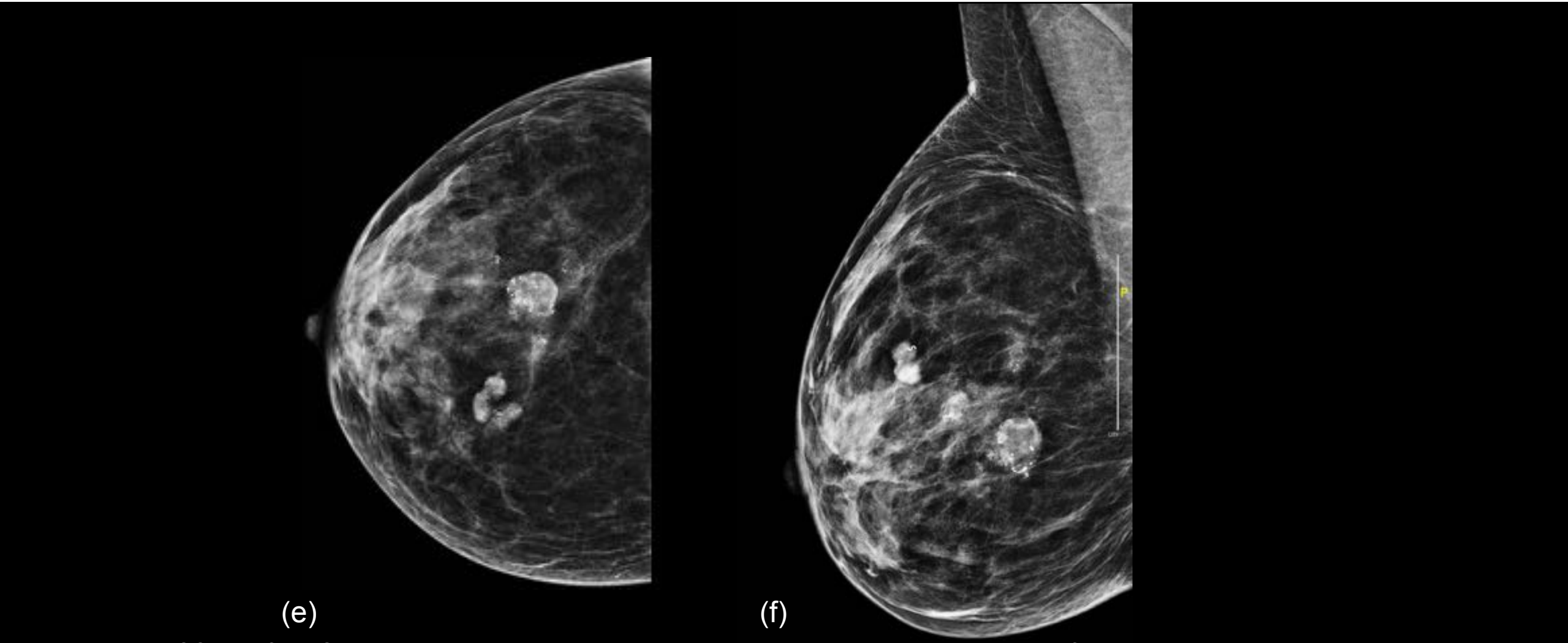


(f)

(c) MIP PET image and (d) fused axial image from staging PET/CT demonstrate hypermetabolic right breast masses with no other sites of disease (uptake in the pelvis was thought to correspond to activity in the distal ureter). (e) MIP PET image and (f) fused axial image after 3 cycles of chemotherapy shows metabolic response with some areas of residual uptake greater than hepatic uptake in the right breast.

Case courtesy of Partners Health Care/Brigham and Women's Hospital

Primary Breast Lymphoma – Case 2



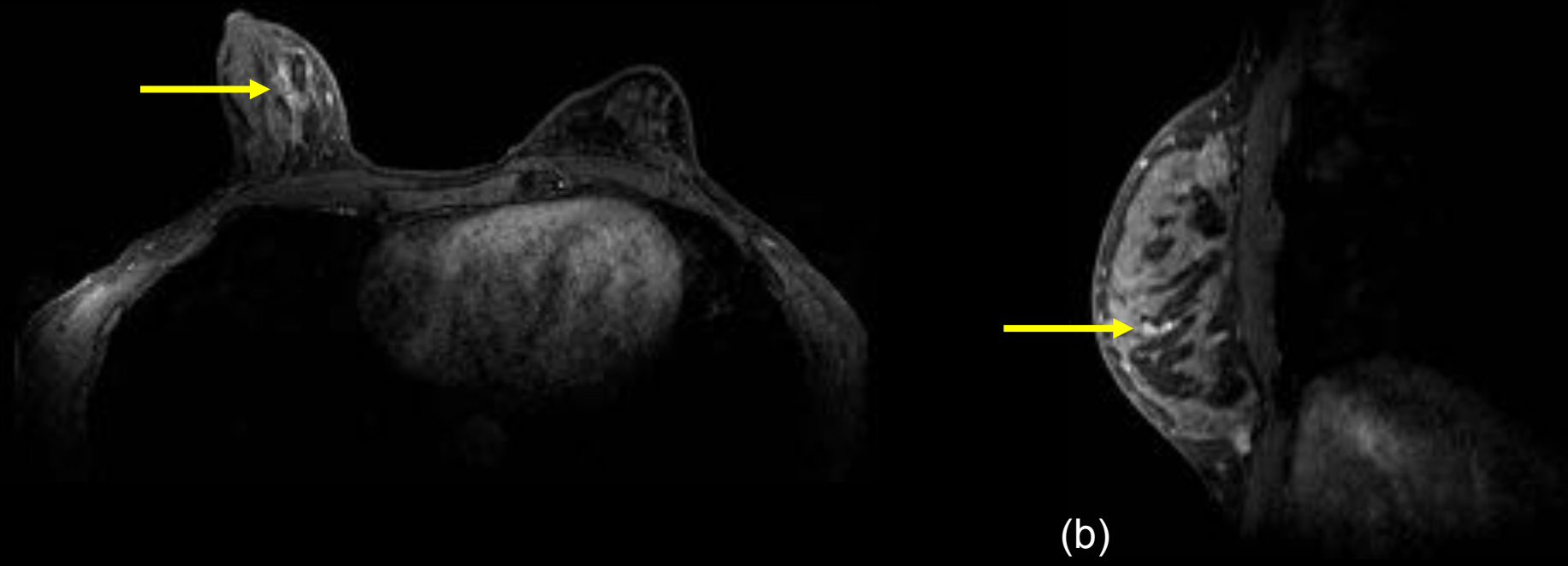
(e) (f)

Right breast (e) CC and (f) MLO (mediolateral oblique) mammographic views show multiple partially calcified masses corresponding to masses seen on initial diagnostic US. Calcifications thought to be related to post-treatment changes (chemotherapy and radiation to the right breast).

Case courtesy of Partners Health Care/Brigham and Women's Hospital

Primary Breast Lymphoma – Case 3

47 year old female with remote history of left breast invasive tubular carcinoma treated with breast conserving therapy 6 years ago. Recently diagnosed with invasive lobular carcinoma (ILC) of the right lower outer quadrant. Status post US-guided biopsy of palpable but mammographically occult mass. Presented for MRI extent of disease evaluation.



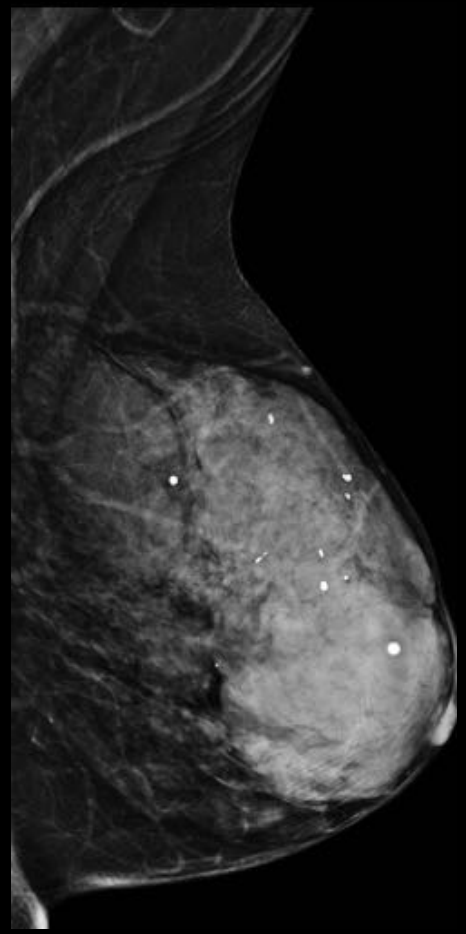
(a) (b)

(a) Axial and (b) sagittal post-contrast T1W fat suppressed images from breast MRI demonstrate non-mass enhancement (NME) in a linear distribution spanning 18 mm in the central region of the right breast at middle depth (yellow arrows). This area is remote from the previously biopsied mass representing known ILC. The patient subsequently underwent MRI-guided core biopsy of NME. **Diagnosis: extranodal marginal zone lymphoma (MALT lymphoma) with extensive plasmacytic differentiation.** Staging PET/CT did not show evidence of lymphoma elsewhere in the body. The patient ultimately elected to undergo bilateral mastectomy and reconstruction.

Secondary Breast Lymphoma – Case 4

58 year old female with history of treated diffuse large B-cell lymphoma with negative PET/CT 6 months prior presented for diagnostic evaluation of a left breast palpable abnormality.

(a)



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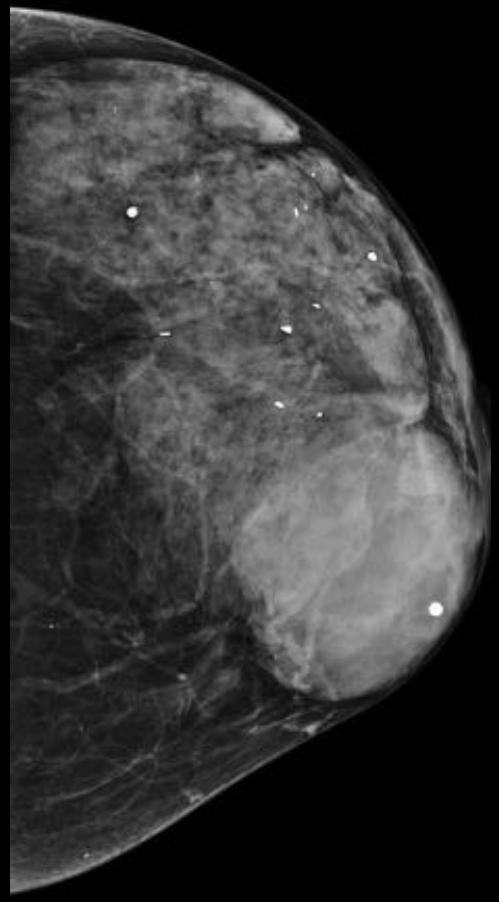
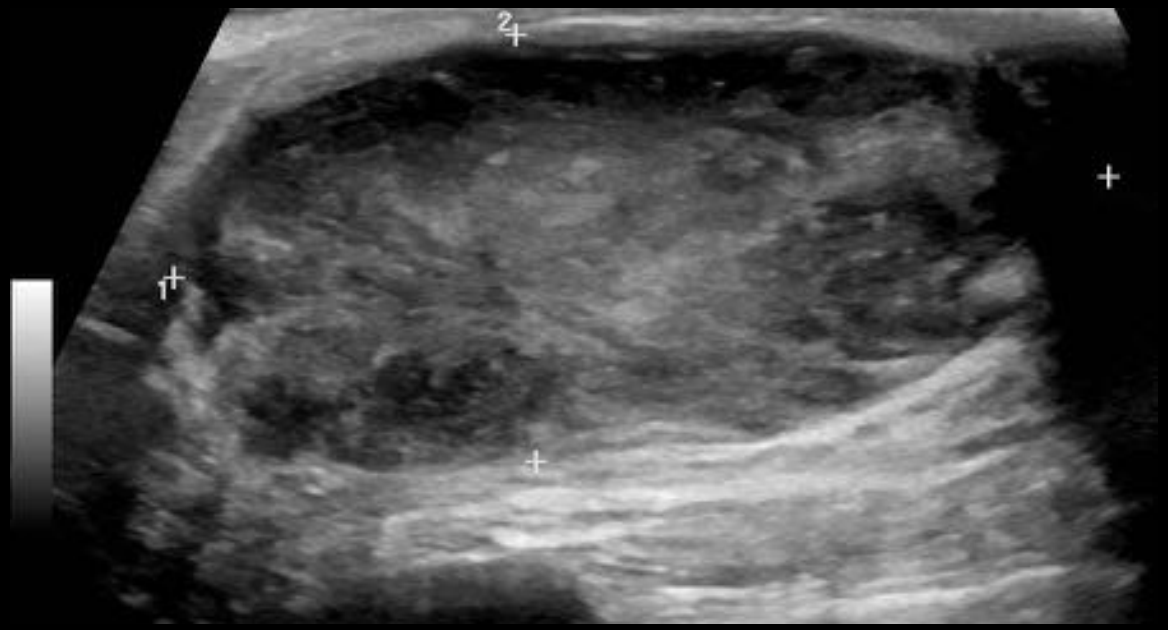


Left breast (a) MLO and (b) CC mammographic views from diagnostic mammogram demonstrate a large irregular mass in the area of palpable concern in the upper inner quadrant of the left breast at anterior depth.

Secondary Breast Lymphoma – Case 4



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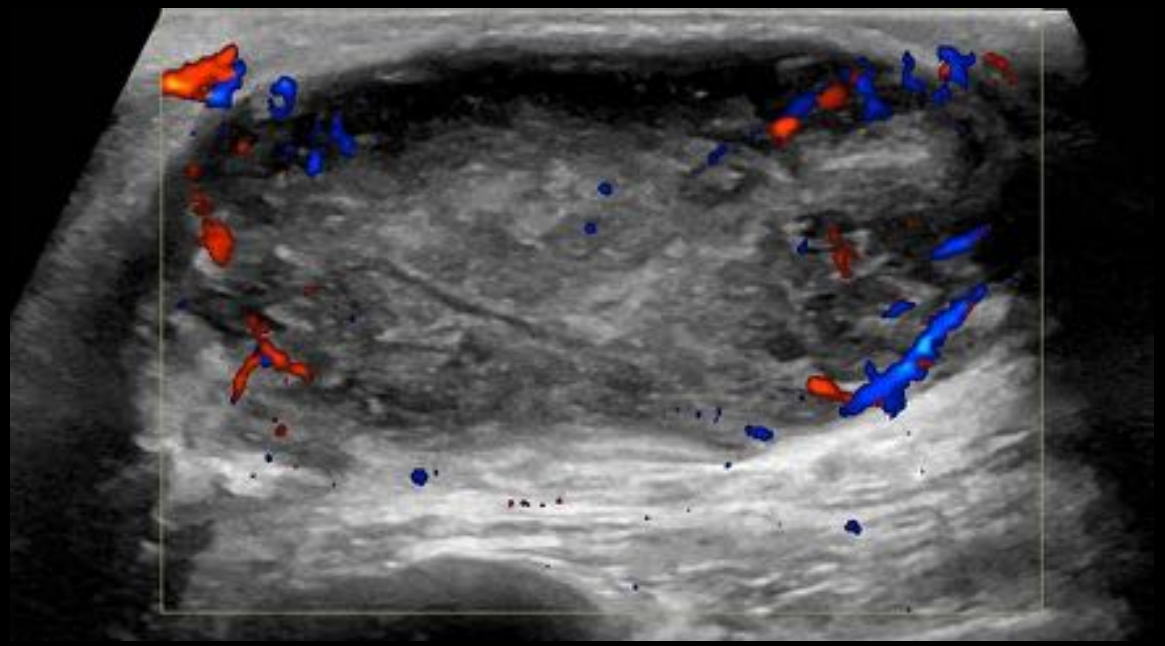
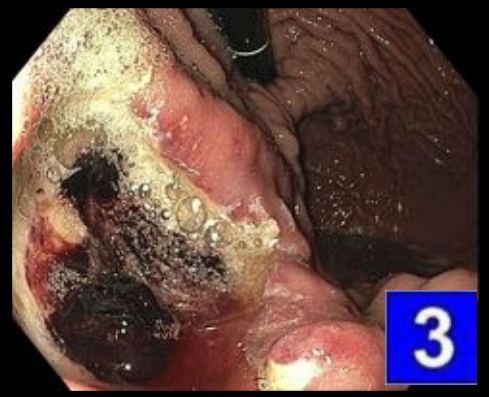


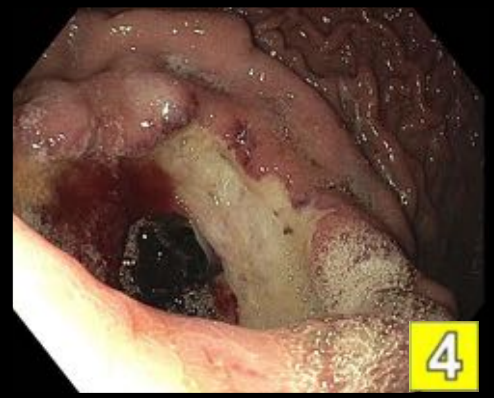
(e)

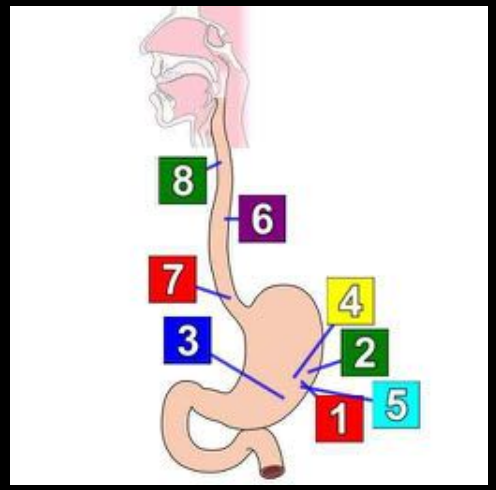
(d) Grayscale and (e) color static sonographic images from diagnostic US of the left breast demonstrate an oval, parallel hypoechoic hypervascular mass in the area of palpable concern corresponding to the large irregular mass on diagnostic mammogram. The patient subsequently underwent US-guided core biopsy. **Diagnosis: diffuse large B cell lymphoma.**

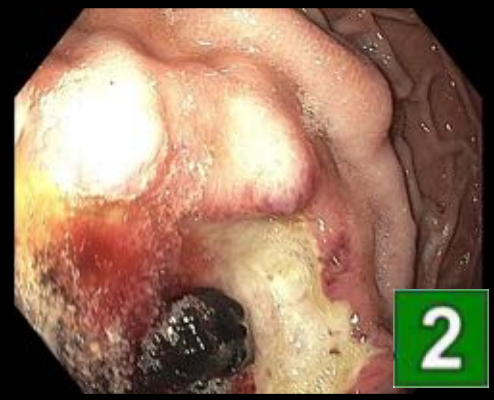
Secondary Breast Lymphoma – Case 5

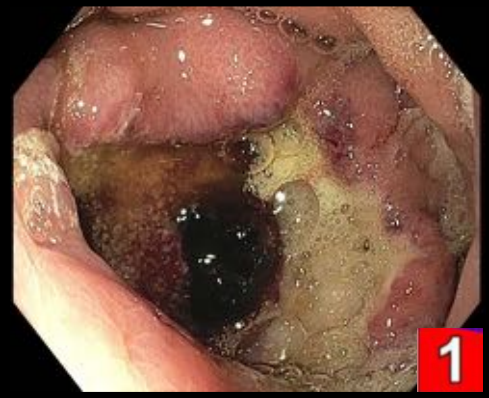
61 year old female presented with melena, hematemesis, fatigue, hypogastric pain. Found to have large gastric ulcer at upper endoscopy with pathology showing diffuse large B cell lymphoma.







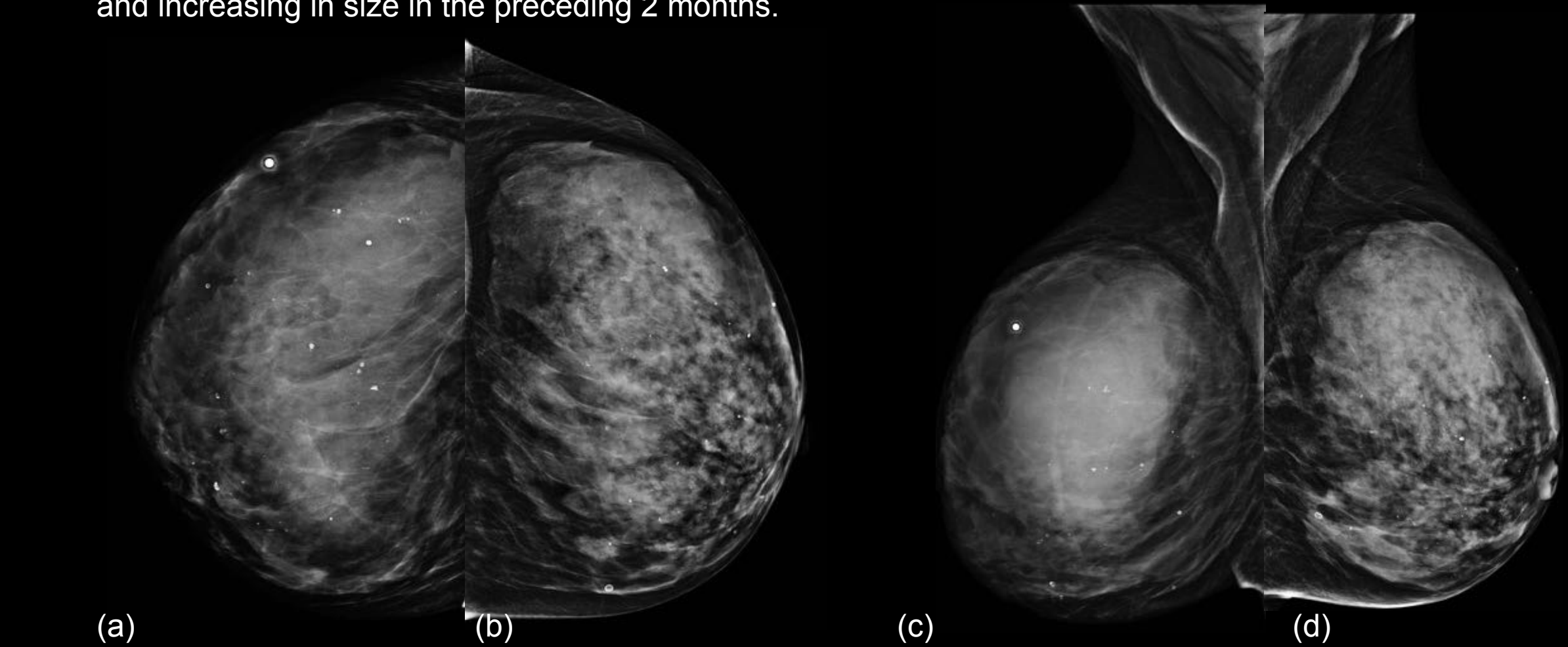




Representative images from upper endoscopy showing non-obstructing non-bleeding cratered gastric ulcer, which measured 4.5 cm in greatest dimension, of significant severity with adherent clot on the greater curvature of the stomach. **Diagnosis: diffuse large B cell lymphoma.**

Secondary Breast Lymphoma – Case 5

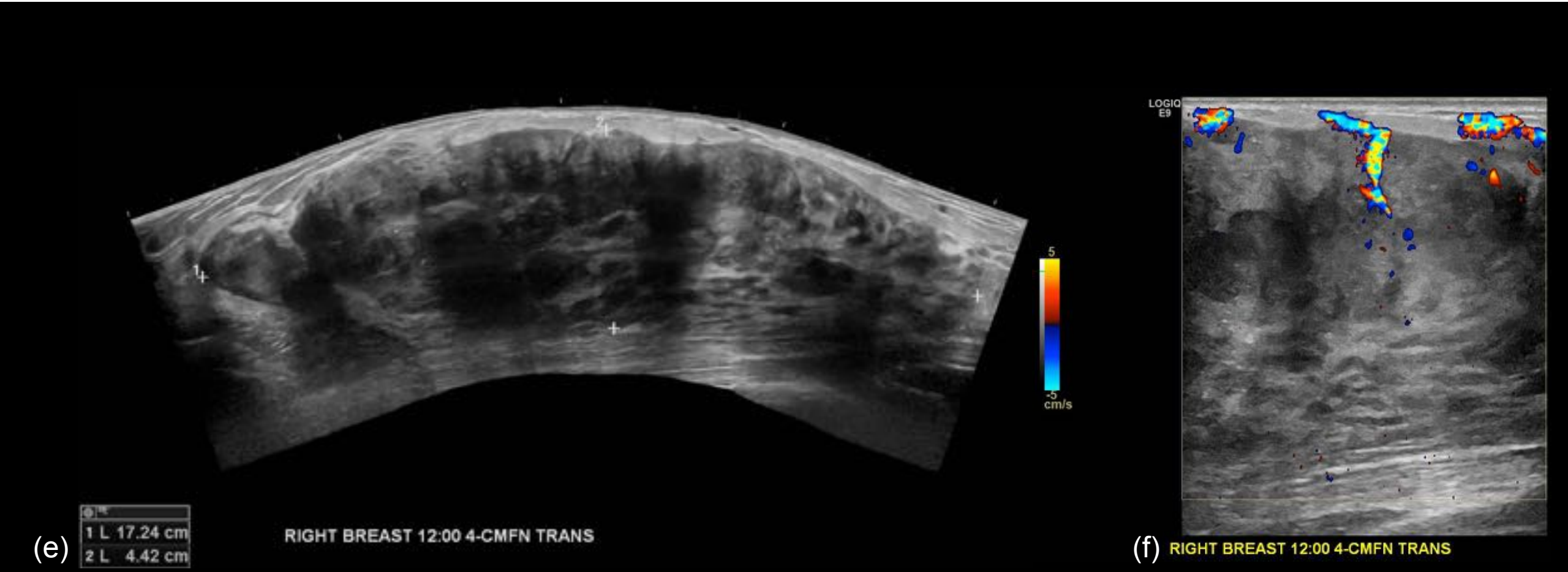
Patient was admitted to hospital and complained of a right breast mass, which had been present, painful, and increasing in size in the preceding 2 months.



(a) (b) (c) (d)

Bilateral CC (a, b) and MLO (c, d) mammographic views demonstrate a large mass occupying nearly the entire right breast, corresponding to the palpable area of concern indicated by the patient.

Secondary Breast Lymphoma – Case 5

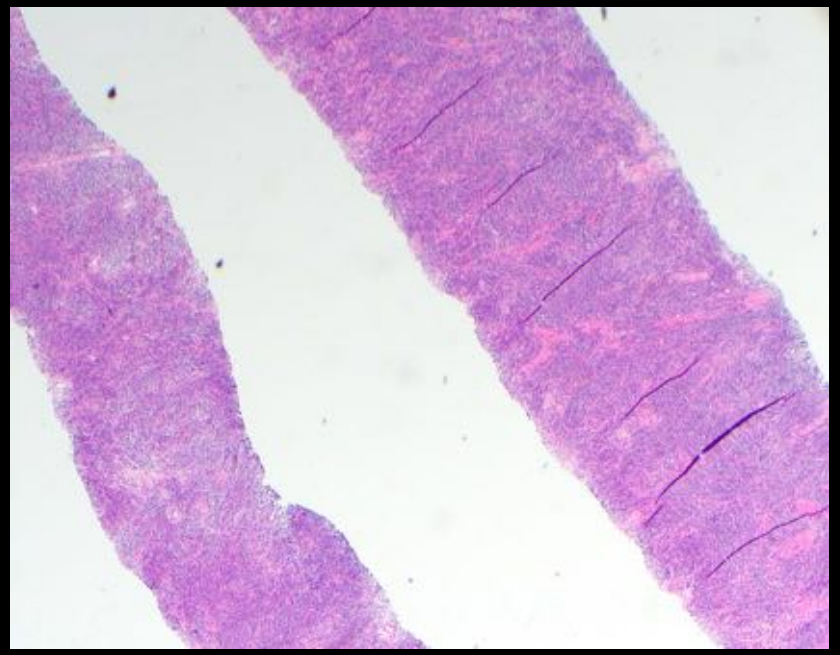


(e)

(f)

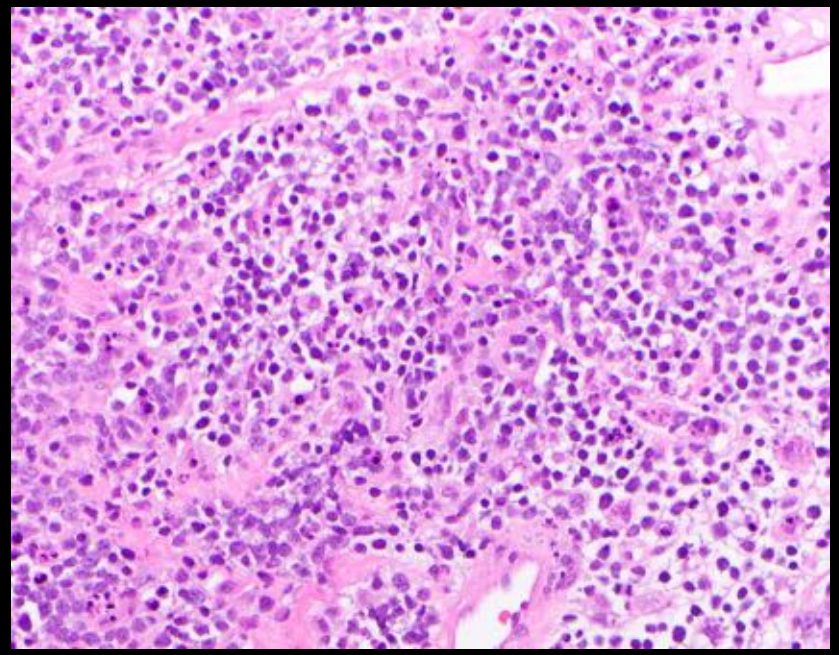
(e) Grayscale and (f) color static images from diagnostic US of the right breast demonstrate a heterogeneous hypervascular mass corresponding to the mass on mammography. The patient subsequently underwent US-guided core biopsy. **Diagnosis: diffuse large B cell lymphoma.**

Secondary Breast Lymphoma – Case 5



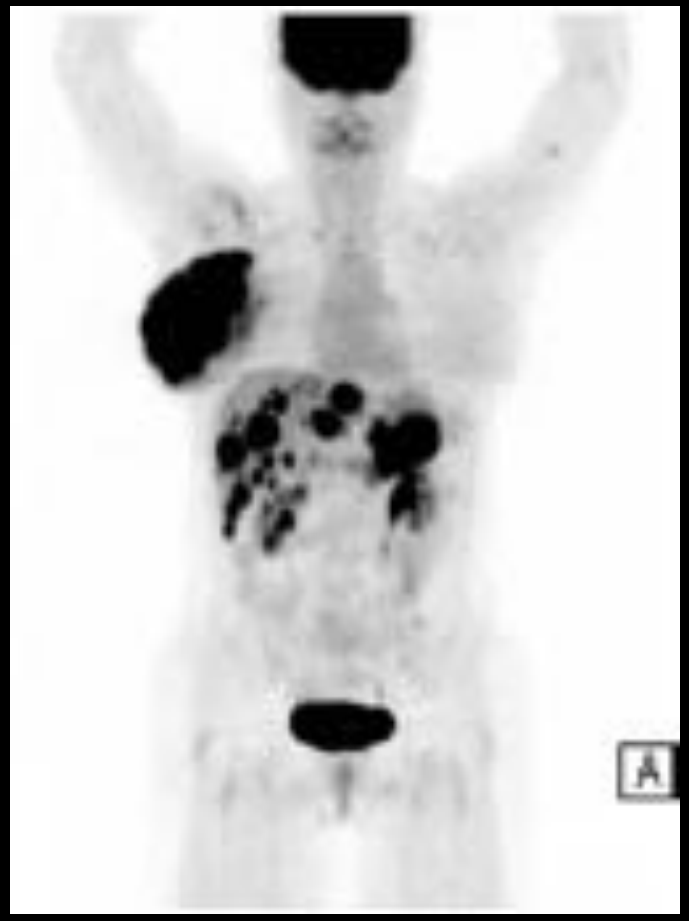
4x H&E

(g)



40x H&E

(h)



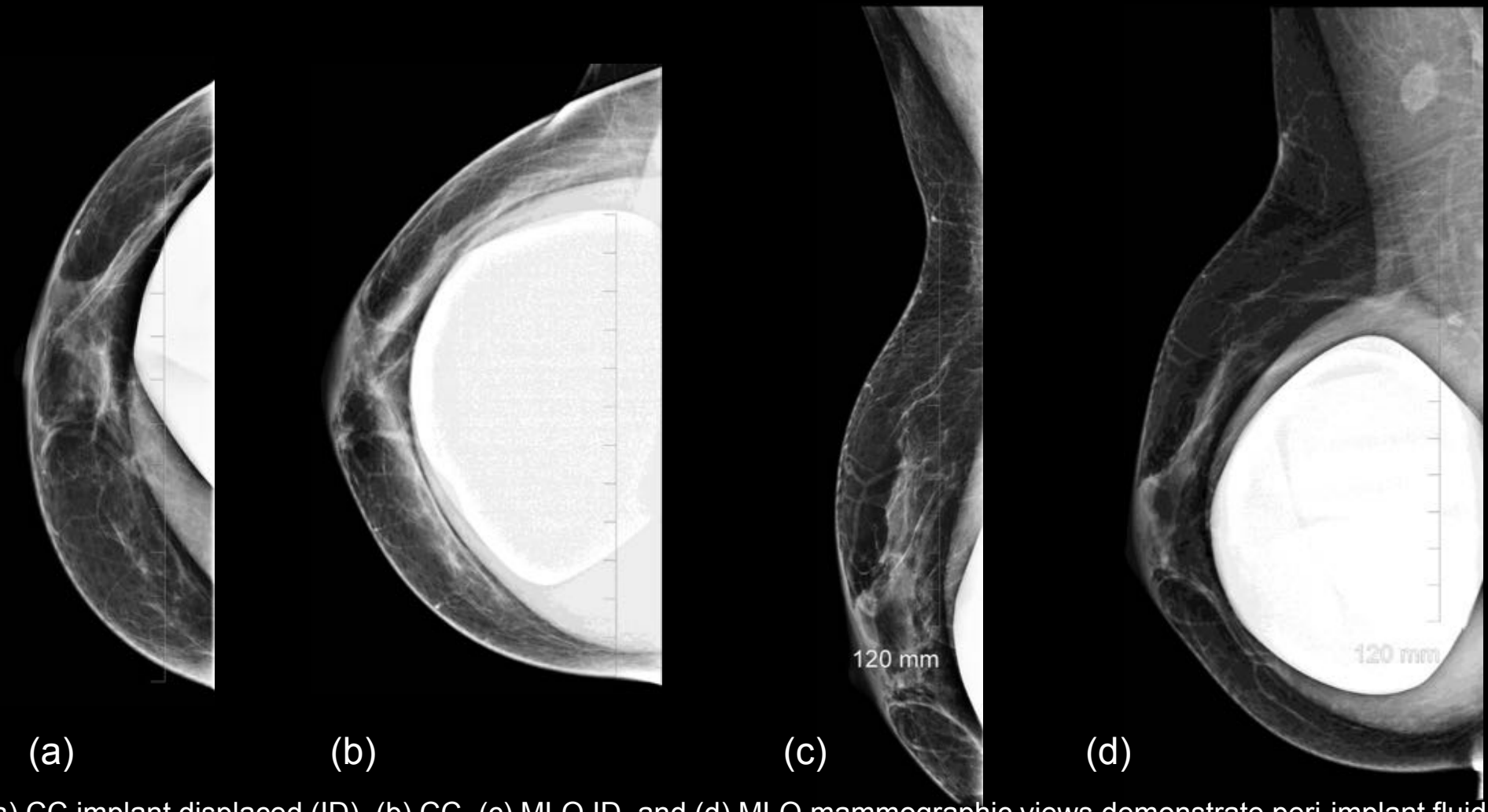
(i)

(g) Tissue from ultrasound-guided breast core biopsy almost completely replaced by DLBCL. (h) High power view of medium to large neoplastic B-cells with scant cytoplasm and irregular nuclei in core biopsy samples. (i) MIP PET image from staging PET/CT demonstrates a hypermetabolic right breast mass and intense circumferential FDG uptake localized to the thickened gastric fundus, consistent with biopsy-proven lymphoma. Multiple foci of FDG uptake in the liver and small foci of FDG uptake in the left mid humerus and left iliac bone likely reflect additional sites of involvement.

Pathology slides courtesy of Dr. Michael Astudillo

Breast Implant Associated Anaplastic Large Cell Lymphoma – Case 6

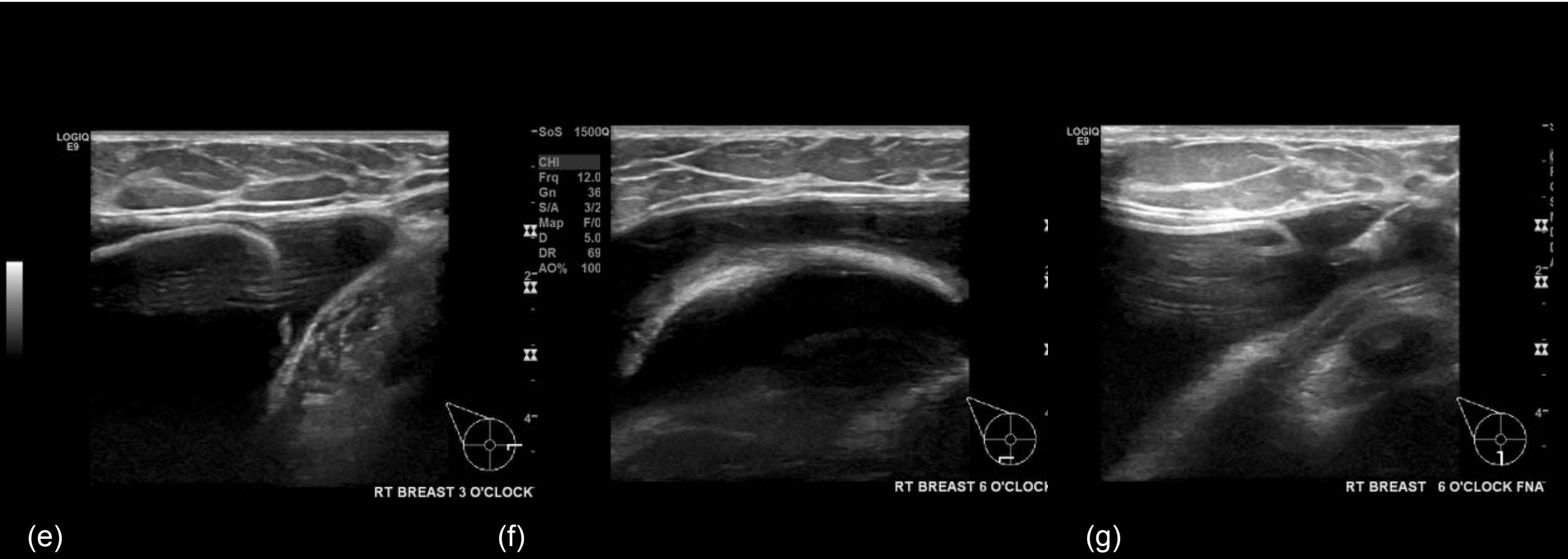
44 year old female presented with increasing right breast pain. Previous bilateral silicone implant augmentation 10 years ago.



Right breast (a) CC implant displaced (ID), (b) CC, (c) MLO ID, and (d) MLO mammographic views demonstrate peri-implant fluid.

Case courtesy of Dr. Jean Seely, The Ottawa Hospital

Breast Implant Associated Anaplastic Large Cell Lymphoma – Case 6



(e) (f) (g)

Right breast US images (e) at 3 o'clock and (f) 6 o'clock showing a moderate right peri-implant fluid collection. No evidence of a mass nor implant rupture. No axillary lymphadenopathy. (g) Image from US-guided aspiration of peri-implant fluid, yielding 45 cc of clear serous fluid, sent for flow cytometry and cytology analysis. **Diagnosis: anaplastic large cell lymphoma.**

Case courtesy of Dr. Jean Seely, The Ottawa Hospital

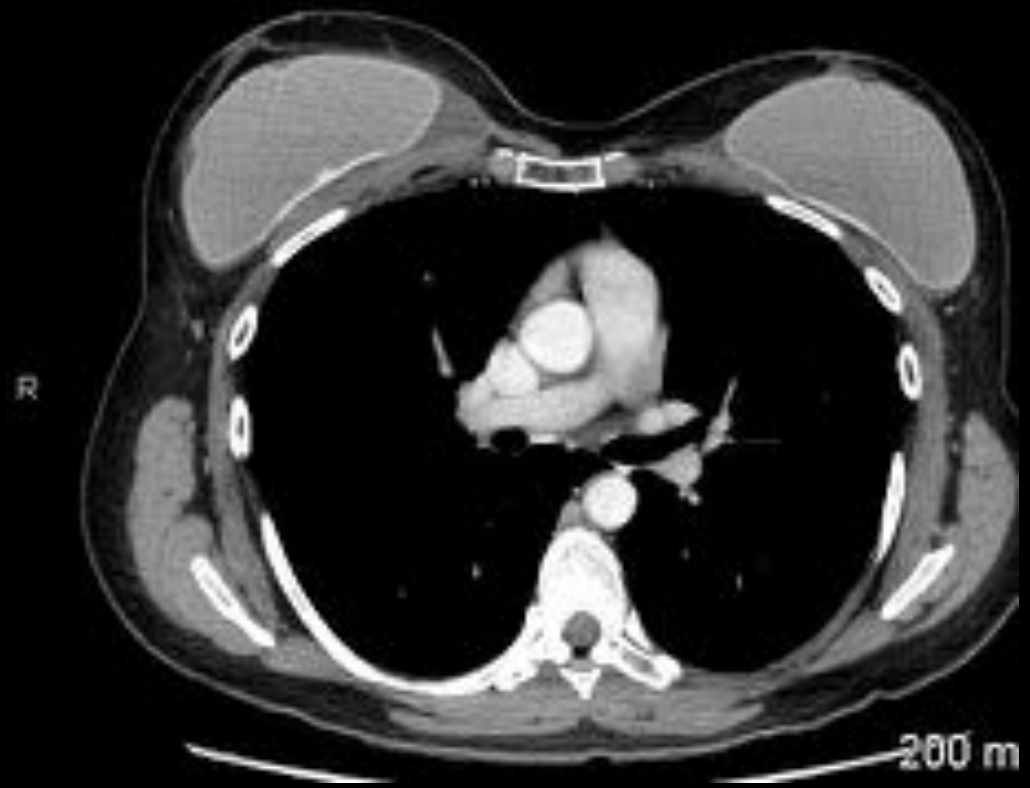
Breast Implant Associated Anaplastic Large Cell Lymphoma – Case 6

(h) (i) (j) (k)

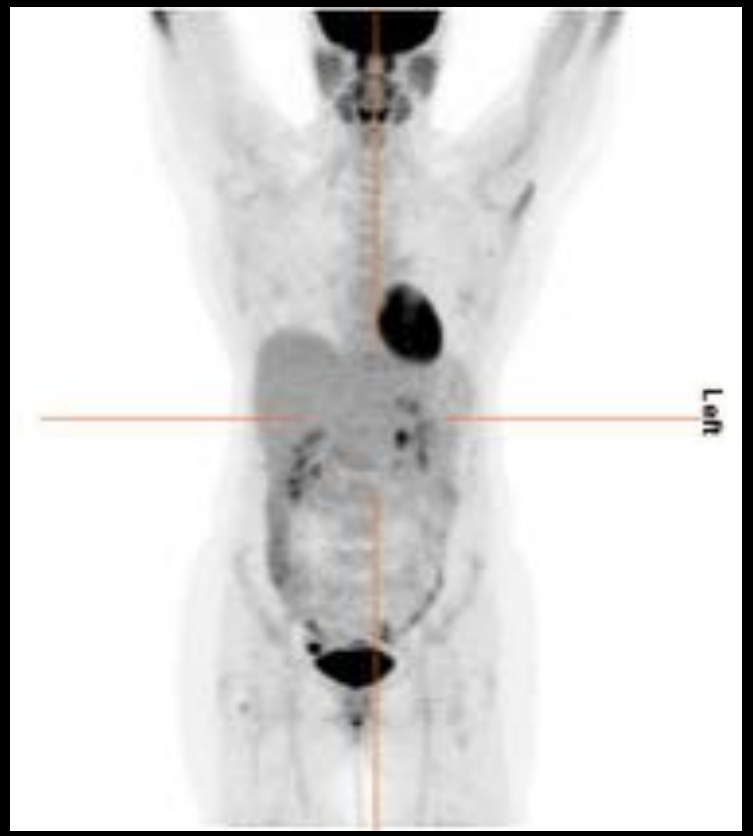
(h-k) Multi-planar, multi-sequence MRI demonstrates fluid surrounding the right implant, without enhancement nor mass. No implant rupture. No lymphadenopathy.

Case courtesy of Dr. Jean Seely, The Ottawa Hospital

Breast Implant Associated Anaplastic Large Cell Lymphoma – Case 6



(l)



(m)

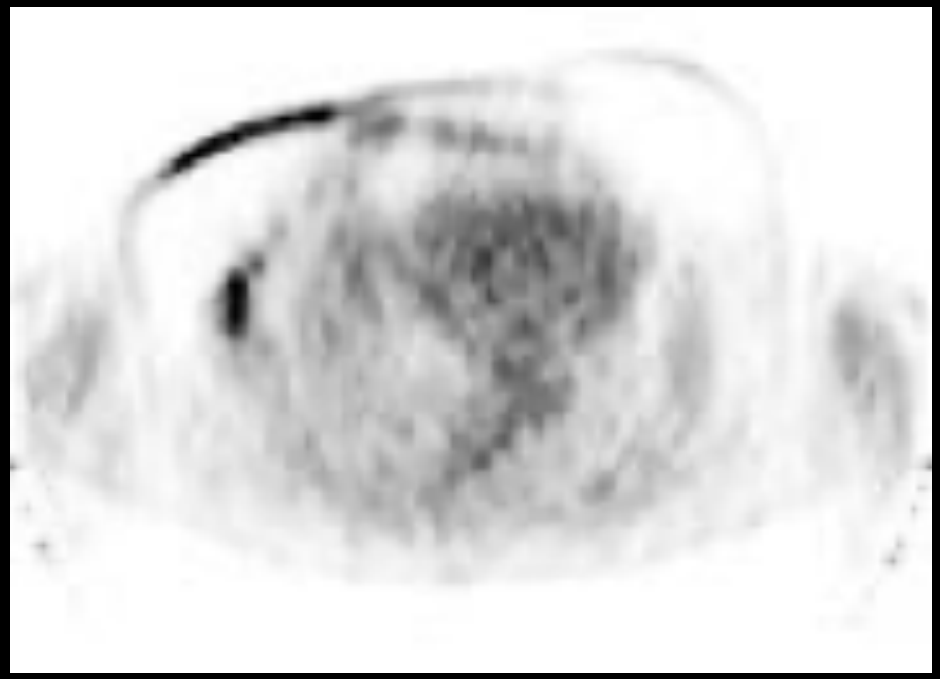
(l) Axial CT image demonstrates peri-implant fluid about the right breast implant. No axillary nor mediastinal lymphadenopathy. (m) MIP PET image does not demonstrate abnormal FDG suspicious for hypermetabolic disease in the breasts or elsewhere.

Case courtesy of Dr. Jean Seely, The Ottawa Hospital

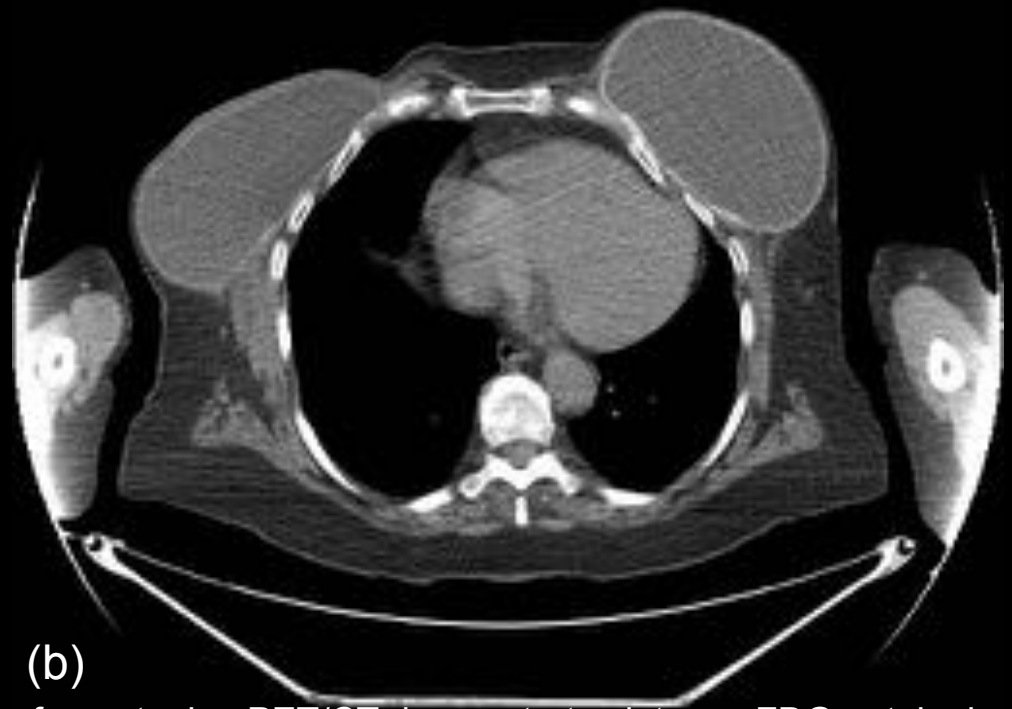
Breast Implant Associated Anaplastic Large Cell Lymphoma – Case 7

71 year old female with history of bilateral mastectomy and implant reconstruction 10 years ago for risk reduction. Three year history of right breast implant complaints, including chronic peri-implant fluid with repeat aspirations. Pathology reported negative at outside institution. Underwent right implant exchange and found to have anaplastic large cell lymphoma at pathologic analysis of explant.

(a)



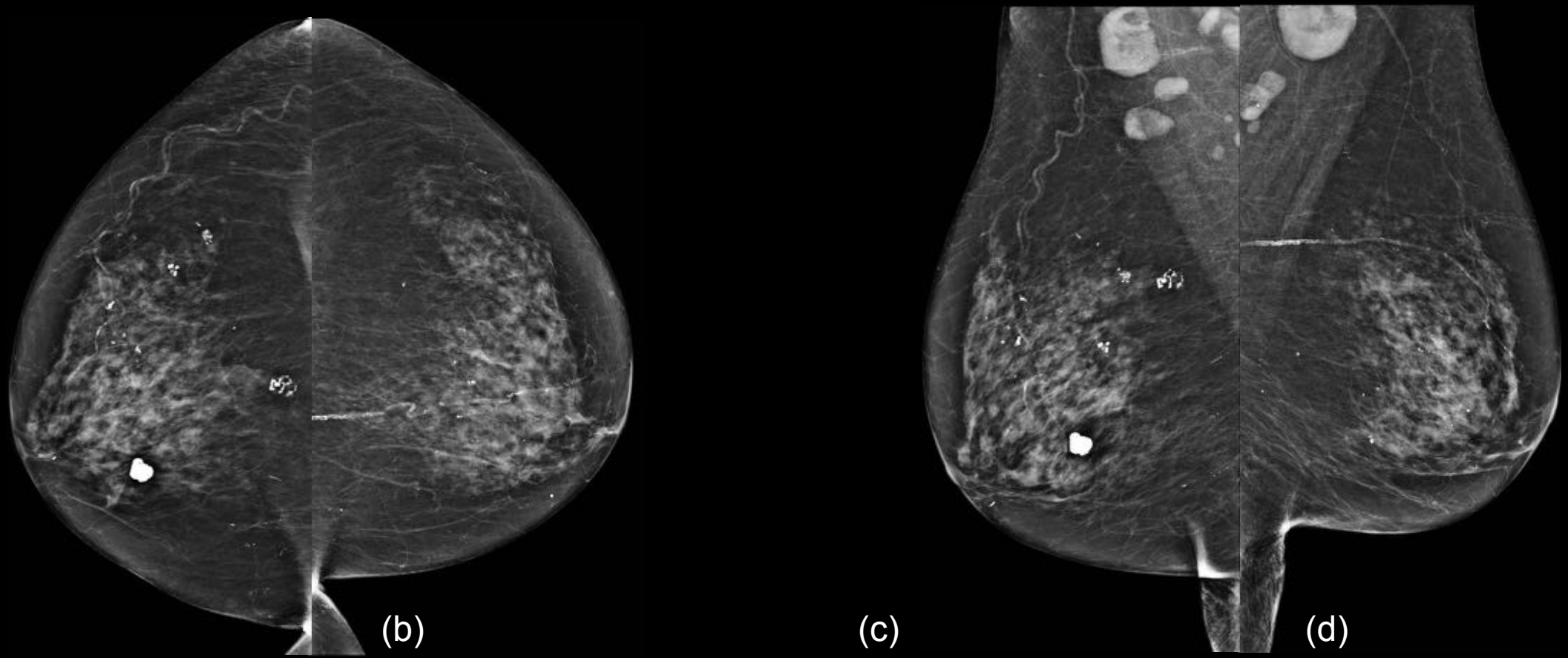
(b)



(a) Attenuation corrected PET image with (b) corresponding axial CT image from staging PET/CT demonstrates intense FDG uptake in a curvilinear distribution at the anterior aspect of the right implant and in a focal distribution associated with soft tissue attenuation at the posterolateral aspect of the right implant. Uptake at the left implant is not above background. Mild FDG uptake in an 8 mm right axillary node was indeterminate, possibly metastatic or reactive. There were no other sites of disease elsewhere. The patient underwent implant bilateral removal and capsulectomy and was subsequently treated with systemic chemotherapy.

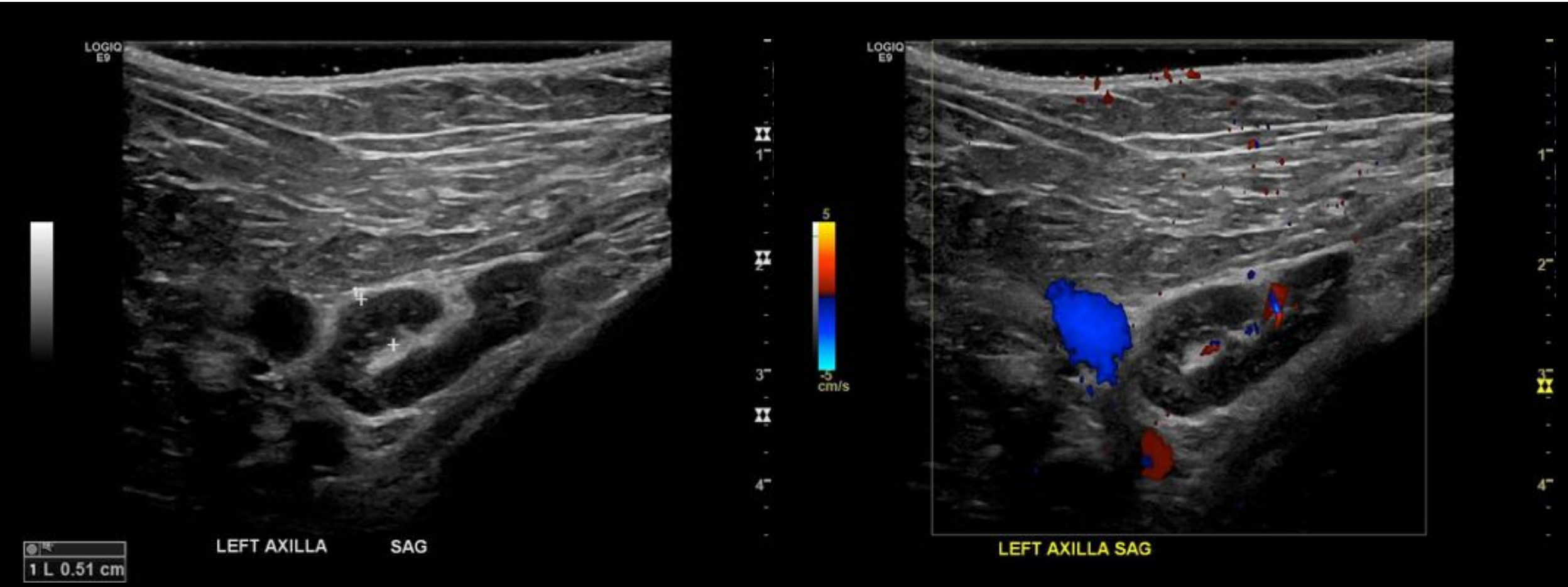
Axillary Adenopathy – A Common Manifestation of Systemic Lymphoma at Screening Mammography

75 year old female presented for screening mammography.



Bilateral CC (a, b) and MLO (c, d) mammographic views show bilateral benign calcifications and enlarged bilateral axillary lymph nodes. Attributed BI-RADS 0.

Axillary Adenopathy – A Common Manifestation of Systemic Lymphoma at Screening Mammography



(e) (f)

(e) Grayscale and (f) color static diagnostic US images of the left axilla demonstrate an axillary lymph node with cortical thickening, corresponding to mammographic findings. The patient subsequently underwent US-guided core biopsy. **Diagnosis: small B-cell lymphoma with plasmacytic differentiation.** No evidence of breast involvement.

Diagnosis of Breast Lymphoma

Pathology Diagnosis

- Core biopsy is typically the standard in breast and axillary sampling (fixative is usually 10% neutral buffered formalin)[1]
  - If breast lymphoma is suspected, saline or Roswell Park Memorial Institute (RPMI) medium should be used also for flow cytometry
- Fine-needle aspiration has high sensitivity but can be problematic for subclassification of breast lymphoma[1]
- Excisional biopsy after needle localization can be helpful for evaluation of discordant radiology-pathology findings

Pathology Diagnosis

- If a patient presents with effusion/seroma in the setting of breast implants, BIAALCL may be considered but other more common diagnoses such as infection should also be excluded[16]
  - If a mass is identified in addition to effusion/seroma, it must be biopsied; fluid sampling alone is not sufficient
- Development of institutional protocols is especially helpful for diagnosis of breast lymphoma in general and BIAALCL in particular[1]
  - Fluorescent in situ hybridization (FISH) for chromosomal translocation (8,14) in DLBCL is important[14]
  - For suspected BIAALCL, consider immunohistochemical (IHC) staining for CD30, ALK, CD3, CE4, CD8[1]

Summary

Take Away Points

- PBL, SBL, and BIAALCL are rare
- Clinical presentation of breast-related complaints and imaging features can overlap with the far more common primary breast carcinomas
- Consideration of associated symptoms and the clinical milieu is important for formulation of a complete differential diagnosis
- If lymphoma is a diagnostic consideration, appropriate steps should be taken to increase diagnostic certainty, including creation of institutional protocols in conjunction with pathology, surgery, and other relevant disciplines

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Thank you for your time!

We welcome your questions, comments, and feedback

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