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BREAST IMAGING (H OJEDA-FOURNIER AND A ELMI, SECTION EDITORS)

Case-Based Review of Breast Lymphomas

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Abstract

Purpose of Review This article will review several cases of histologically-proven primary and secondary breast lymphomas to demonstrate the multimodal radiologic features, as well as to discuss the approach to diagnostic work up of lymphomas encountered during imaging of the breast and axilla.

Recent Findings Imaging findings of breast lymphoma can overlap with those of primary breast cancer. When there is any clinical suspicion for lymphoma in indeterminate or suspicious breast or axillary findings, definitive tissue diagnosis should be pursued with flow cytometry in addition to routine histologic analysis.

Summary Breast lymphomas can have varied clinical presentations and nonspecific mammographic and sonographic findings. It can be challenging to radiologically differentiate lymphomas seen in the breast and axilla from primary breast cancers or benign lesions. Without pathognomonic imaging features, tissue sampling via imaging guided biopsy is frequently required. Knowledge of the spectrum of imaging findings and clinical presentations are fundamental to ensure appropriate clinical management.

Keywords Breast lymphoma · Axillary lymph nodes · Subcutaneous panniculitis-like T-cell lymphoma (SPTCL) · Mucosa-associated lymphoid tissue (MALT) lymphoma · Breast implant-associated anaplastic large cell lymphoma (BIA-ALCL) · Follicular lymphoma

Introduction

Primary breast lymphoma is rare, representing 0.5% of all breast cancers, and when present, is most commonly diffuse large B cell lymphoma [1]. Breast metastases of non-mammary origin represent only 0.5% to 6.6% of all breast malignancies, and usually portend a poor prognosis [2]. Interestingly, for lymphoma of the breast, secondary breast lymphoma is more common than primary breast lymphoma, and represents approximately 17% of all breast metastases [3]. Primary breast lymphoma is seen in slightly younger patients compared to secondary breast cancer—60–65 years old versus 60–70 years old [4]. Additionally, while lymphoma of the breast is generally more commonly seen in older women in Western countries, with a median age 62–64 years, the median age of diagnosis in East Asian countries is around 45–53 years old [1]. The rarity of breast lymphoma is likely due to the relatively low amount of lymphoid tissue within the breast, however, intraparenchymal lymphatics or intramammary lymph nodes can be potential sites of origin. Other sites of origin may include mucosal immune sites, as seen in marginal zone lymphoma. In this case series, we present different manifestations of primary and secondary breast lymphomas, as well as their unique imaging features and diagnostic challenges.

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Case 1: Subcutaneous Panniculitis-Like T-Cell Lymphoma (SPTCL) of the Breast

A 30-year-old female with medically managed SPTCL presented with a new palpable right breast mass and right spontaneous bloody nipple discharge. Diagnostic mammogram demonstrated an indistinct equal density focal asymmetry in the right breast at 12:00 position, with suggestion of small areas of intralesional fat density (Fig. 1a). Ultrasound demonstrated an ill-defined, hyperechoic area in the right breast at 12:00, with overlying skin thickening (Fig. 1b), corresponding to the area of patient reported palpable

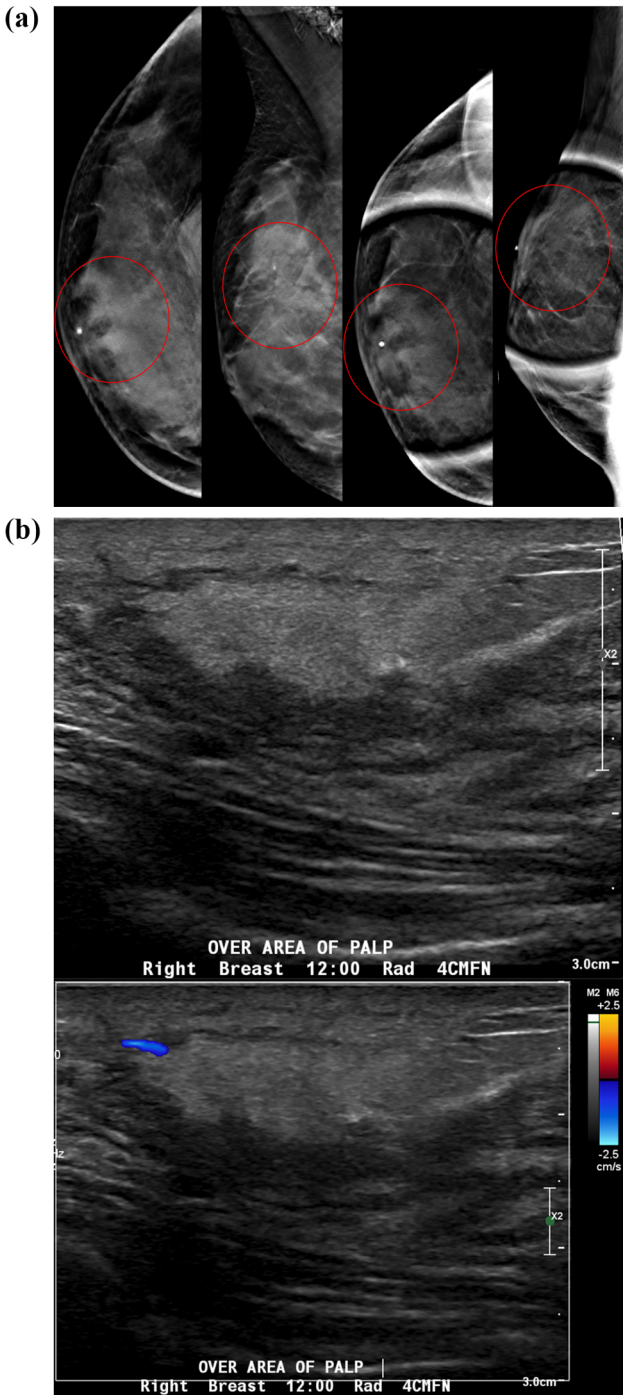


Fig. 1 **a** Diagnostic mammogram of the right breast in craniocaudal (CC) and mediolateral oblique (MLO) views showed an indistinct equal density focal asymmetry (circles) at the 12:00 position, anterior depth. There was probable intralesional fat, best seen on spot compression views. The overlying skin BB marker denoted the area of patient reported palpable concern. **b** Diagnostic ultrasound of the right breast at 12:00, located 4 cm from the nipple showed an indistinct hyperechoic area with overlying skin thickening measuring up to 5 mm. The lesion demonstrated local replacement of the subcutaneous and anterior preglandular fat, with probable extension into the underlying glandular tissue. There was no significant internal vascularity

abnormality. No associated significant right axillary lymphadenopathy was seen. An ultrasound-guided breast biopsy was performed, with the pathology result of SPTCL. To treat recurrent SPTCL, the patient's methotrexate dose was increased and intralesional steroid injections were given, resulting in decreased size of the biopsy proven recurrence.

SPTCL is usually seen in young adults with a median age of 39 years old [5], and is slightly more common in females [6]. It is categorized as a type of skin lymphoma involving the subcutaneous fat, without nodal involvement. Histologically, SPTCL can appear similar to lupus erythematosus panniculitis [7]. There are two types of SPTCL which are distinguished by receptor phenotype on immunohistochemistry. The more common type, T-cell receptor αβ, is indolent, presenting as a self-healing, painless subcutaneous nodules on the trunk and extremities; this type of SPTCL can be difficult to initially diagnose as clinical presentation mimics benign inflammatory skin conditions, such as mastitis. The second type of SPTCL, T-cell receptor γδ, is more aggressive, often resulting in rapid clinical deterioration. It is associated with serosal effusions, hemophagocytosis syndrome, and pancytopenia. Chemotherapy is the treatment of choice for the second type of SPTCL, with a remission rate of 50% [5].

Case 2: Mucosa-Associated Lymphoid Tissue (MALT) Lymphoma of the Breast

A 70-year-old female presented for screening mammogram, which showed a mass in the left breast at 6:00, new from her screening mammogram from one year prior (Fig. 2a). Subsequent diagnostic mammogram of the left breast demonstrated an oval, circumscribed hyperdense mass in the left breast at 6:00, at anterior depth (Fig. 2b). Targeted ultrasound showed a correlating oval, circumscribed hypoechoic mass measuring 1.3 cm (Fig. 2c). An ultrasound-guided core needle biopsy of the mass was performed. Flow cytometry yielded low grade B cell non-Hodgkin lymphoma with plasmacytic differentiation, IgM lambda, consistent with extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue.

MALT lymphoma is a type of marginal zone lymphoma (MZL), which belongs to the non-Hodgkin lymphoma group. It makes up 9–28% of primary breast lymphomas [1]. MALT lymphoma is more commonly seen in older women, with the median age of diagnosis around 68 years old [1]. The pathophysiology of MALT lymphoma in the breast is unique from other extranodal MALT lymphomas in that there is no association with chronic infection (for example, *Helicobacter pylori* in the stomach). The clinical course is indolent, with an excellent prognosis and an overall

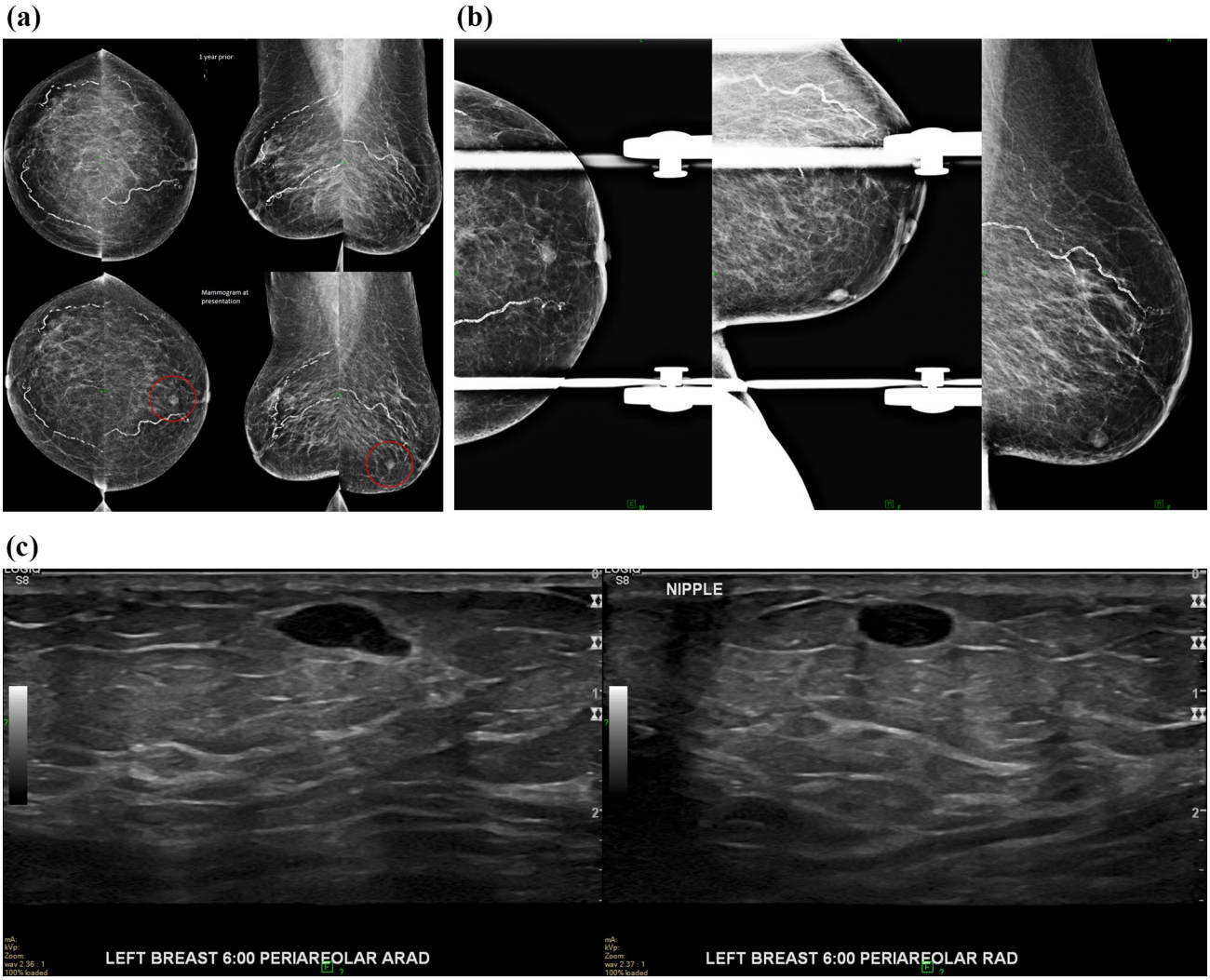


Fig. 2 **a** Screening mammogram demonstrated a left 6:00 breast mass (circles), new compared to screening mammogram from 1 year prior. **b** Diagnostic mammogram of the left breast with CC and MLO spot compression and ML views showed an oval, circumscribed hyperdense mass at the 6:00 position, at anterior depth. **c** Diagnostic ultrasound of the left periareolar breast at 6:00, showed an oval, circumscribed hypoechoic mass measuring 1.3 cm

survival rate of 92% [1]. The most effective treatment regimen involves radiation therapy for local disease and chemotherapy for distant disease [1].

Case 3: Breast Implant-Associated Anaplastic Large Cell Lymphoma (BIA-ALCL)

A 55-year-old female presented for a routine screening mammogram which showed bilateral retropectoral saline implants with a large, hyperdense left peri-implant fluid collection (Fig. 3a). Subsequent diagnostic ultrasound demonstrated a complex fluid collection with thick internal septations around the left breast implant (Fig. 3b). Ultrasound guided aspiration was performed, which yielded approximately 255 cm^3 of frankly bloody fluid (Fig. 3c). Additionally, ultrasound guided core needle biopsy of the thick internal septations was performed. These tissue samples were sent for both histological and flow cytometric analysis. Histology demonstrated degenerating blood with a mixed population of histiocytes and lymphoid cells. Flow cytometry demonstrated abnormal T-cell population with CD2, CD4, and CD5

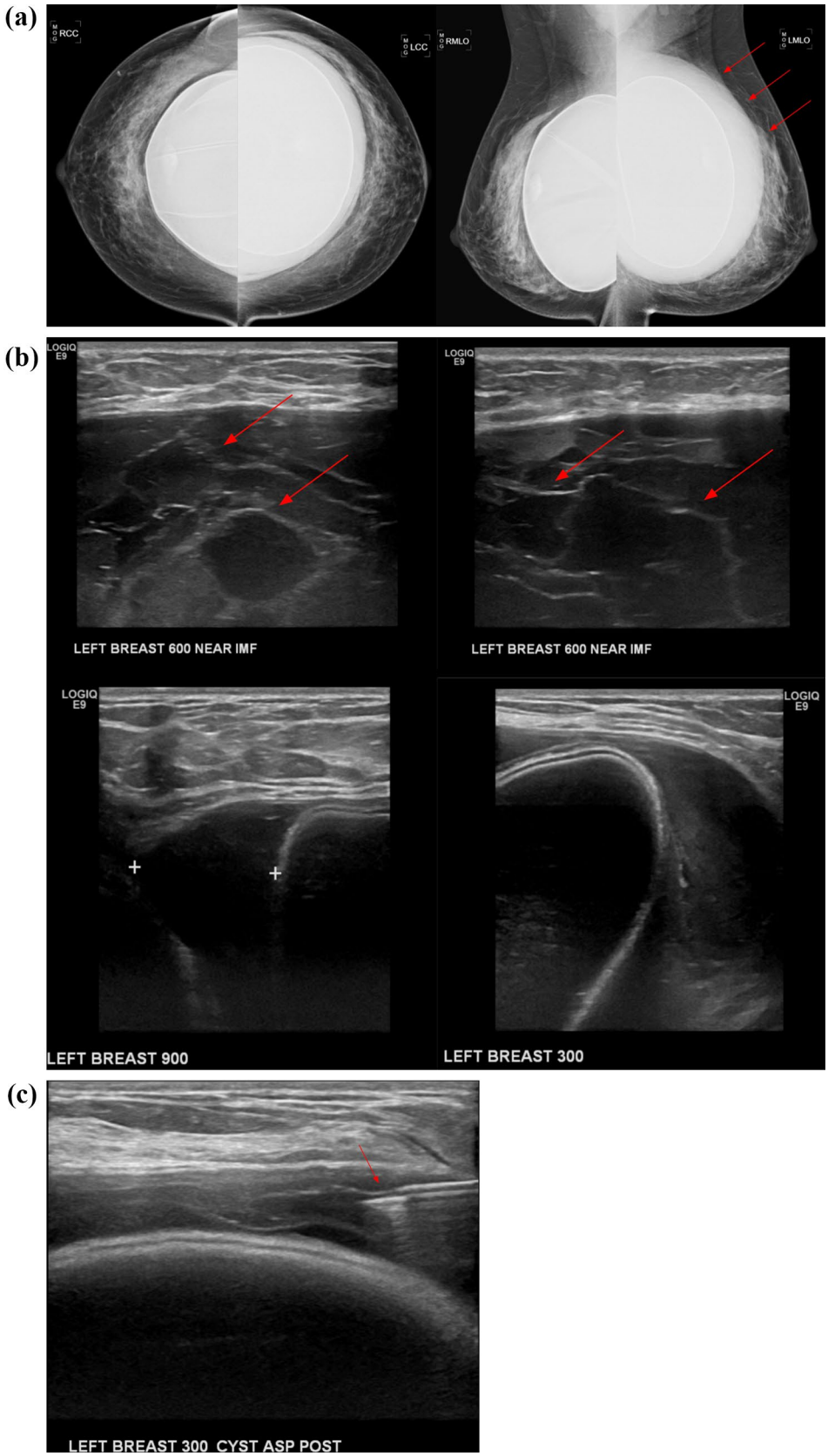


Fig. 3 **a** Screening mammogram demonstrated bilateral subpectoral saline implants in place. A hyperdense left-sided peri-implant fluid collection (arrows) was seen. No significant mammographic findings were seen in the breast parenchyma on CC and MLO implant-displaced views. **b** Left breast diagnostic ultrasound demonstrated a large complex, loculated peri-implant fluid collection containing thick internal septations (arrows). **c** Ultrasound guided core needle biopsy as well as needle aspiration of the fluid (arrow) were performed, yielding approximately 255 cm^3 of frankly bloody fluid. Pathology and flow cytometry results yielded findings concerning for T-cell neoplasm suggestive of BIA-ALCL

expression, suspicious for T-cell neoplasm and suggestive of breast implant-associated anaplastic large cell lymphoma.

Cases of BIA-ALCL are rare, with median age of diagnosis around 52 years old and median time from implant placement to diagnosis of 10 years [8•]. It is associated with textured breast implants. It has been hypothesized that mechanical friction of textured implants may result in greater implant shell or component shedding, leading to chronic inflammation and resulting in BIA-ALCL [1, 9]. An additional mechanism involves the surface of textured implants promoting bacterial biofilms, which proceed to trigger a pathophysiologic cascade leading to BIA-ALCL [9].

There are two types of BIA-ALCL, the more common type being indolent, presenting as a late onset (> 1 year after implant placement) peri-implant effusion between the implant and fibrous capsule [1]. The differential diagnosis for the indolent type BIA-ALCL includes seroma, hematoma, infection, or implant rupture. The second, more aggressive type presents as a mass, usually with concurrent peri-implant effusion. Ultrasound-guided aspiration of the fluid should be performed, as well as biopsy of solid elements if present, with samples sent for pathologic and flow cytometric analysis. Contrary to other types of lymphoma, the first line of therapy for the peri-implant effusion type is surgical treatment with complete resection and capsulectomy. Aggressive cases with mass formation, unresectable local invasion, associated lymph node involvement, or distant metastases may benefit from chemotherapy. While overall survival has been shown to be over 90% [10], patients who present with effusion without associated masses are shown to have improved event-free survival compared to those with associated masses, with 93% achieving complete remission [8•].

Case 4: Diffuse Large B-Cell Lymphoma (DLBCL) of the Breast

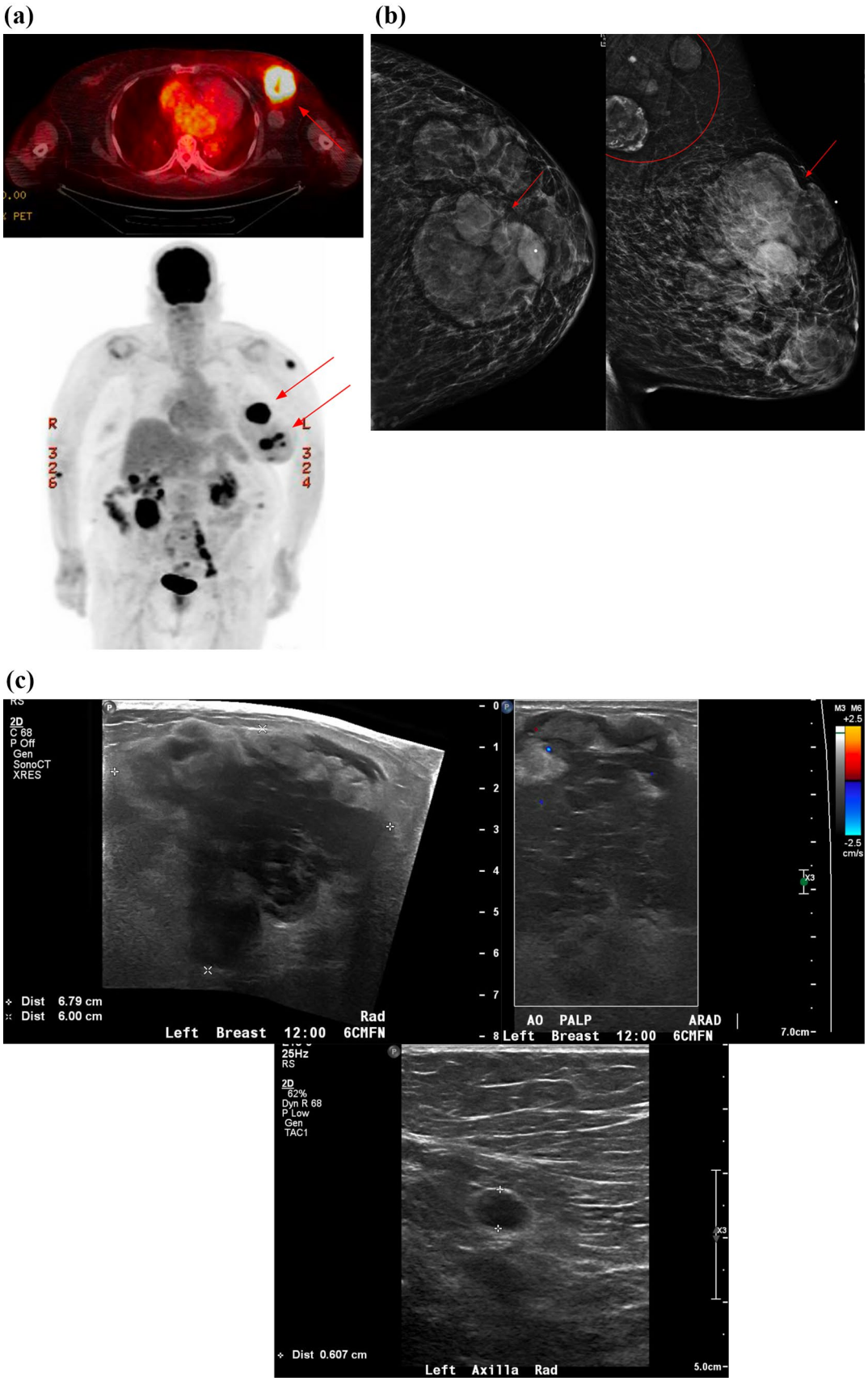
An 83-year-old female with a personal history of DLBCL presented with a new left breast palpable abnormality. PET–CT revealed new FDG avid left breast lesions (Fig. 4a). Subsequent diagnostic mammogram showed multiple left breast masses and enlarged left axillary lymph nodes (Fig. 4b). Diagnostic ultrasound demonstrated multiple irregular hypoechoic left breast masses with indistinct margins and heterogeneous echotexture, measuring up to 7.0 cm, as well as multiple abnormally enlarged left axillary lymph nodes (Fig. 4c). Ultrasound guided core needle biopsy of the largest mass demonstrated high grade B-cell lymphoma. Biopsy of the left axilla showed reactive lymphoid hyperplasia with no evidence of malignancy. The patient unfortunately had poor treatment response with disease progression, and eventually passed away from an unrelated respiratory illness.

DLBCL of the breast is a rare subtype of non-Hodgkin's lymphoma and is a rare extranodal site of involvement. Women commonly present in their 50s and 60s with painless breast lumps, swelling, and/or enlarged axillary lymph nodes. Systemic symptoms, such as fever and weight loss, are less commonly seen in DLBCL. There are several subtypes of DLBCL, which differ in treatment planning, with the more common subtypes being germinal center B cell (GCB) and activated B cell (ABC/non-GCB) [11]. Treatment often includes a combination of chemotherapy, radiation therapy and, in some cases, surgery. Prognosis varies based on factors such as disease stage, subtype, and treatment response is usually poor [12].

Case 5: Follicular Lymphoma of the Breast and Axilla

A 38-year-old female with known history of relapsed follicular lymphoma, presented for evaluation of a new left breast palpable abnormality. She was diagnosed with follicular lymphoma 10 years prior, which responded poorly to chemotherapy and was subsequently lost to follow up. She resumed care after repeated hospitalizations for pneumonia, culminating in a PET–CT which demonstrated disease involving the lungs, soft tissues, and widespread lymphadenopathy (Fig. 5a). Also noted was a new hypermetabolic left breast mass (Fig. 5a). Diagnostic mammogram and ultrasound revealed bilateral breast masses—one measuring 5 cm on the left (Fig. 5b, c), two measuring 0.7 cm on the right (Fig. 5e, f), in addition to left axillary lymphadenopathy (Fig. 5d). Ultrasound-guided biopsy of the left breast mass and a left axillary lymph node demonstrated follicular lymphoma of the breast and left axillary lymph node. She was started on immunotherapy, and follow up PET–CT 1 month later demonstrated decrease in size and metabolic activity of the left breast mass, as well as decreased metabolic activity of the left axillary lymph nodes (Fig. 5g).

Follicular lymphoma makes up 10–19% of primary breast lymphoma histology, with a median presentation age of 62 years old [1]. In general, it is more aggressive than MZL but less aggressive than DLBCL. Treatment of choice


(a)
(b)
(c)
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Dist 6.00 cm
Left Breast 12:00 6CMFN
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AO PALP ARAD
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7.0cm
Dist 0.607 cm
Left Axilla Rad
5.0cm

◂**Fig. 4** **a** PET–CT demonstrated multiple hypermetabolic left breast masses (arrows). **b** Diagnostic mammogram of the left breast in CC and MLO views showed multiple left breast masses, the largest breast mass at 12:00, 5 cm from the nipple (arrow), and corresponding to the patient's palpable abnormality denoted by a skin BB marker. Also noted were enlarged left axillary lymph nodes (circle). **c** Diagnostic ultrasound of the left breast demonstrated multiple irregular hypoechoic masses with indistinct margins and heterogeneous echotexture in the left breast, spanning from 12:00 to 6:00. The largest of these masses measured approximately 7.0 cm at 12:00, 6 cm from the nipple, without significant internal vascularity. Additionally, there were left axillary lymph nodes with cortical thickening measuring up to 6 mm, with partially effaced fatty hilum

is radiation therapy, usually with no relapse typically seen within the irradiated fields. However, relapse may be seen at distant sites. Risk of relapse may be reduced with chemotherapy, however further studies are needed due to the rarity of this entity [1].

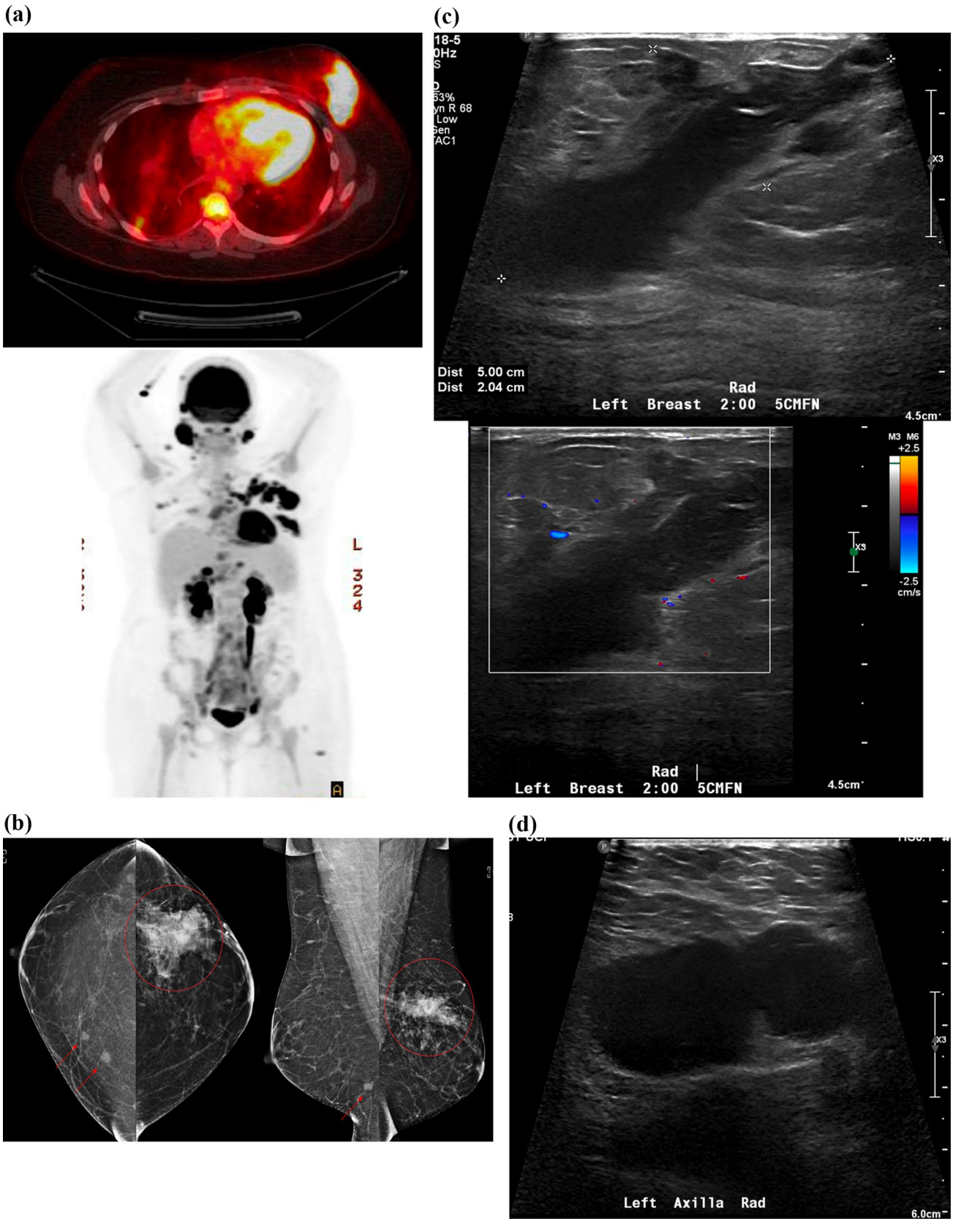
Conclusions

Lymphoma of the breast has varying presentations on imaging, but more commonly presents as a mass or masses, with or without lymph node involvement apparent on imaging. Barring the relatively unique presentations of SPTCL and BIA-ALCL, findings of breast lymphoma can be similar to that of invasive breast cancer. Clinical presentation is typically a painless palpable breast mass. Constitutional symptoms are rare, and if present, are indicative of widespread disease [1].

As with all clinically concerning palpable abnormalities in the breast, imaging workup should begin with diagnostic mammogram and breast ultrasound. Mammographically, primary and secondary breast lymphoma commonly present as a solitary oval or round mass with circumscribed or indistinct margins and no associated calcifications, while secondary breast lymphoma can more commonly also present as multiple smaller masses with associated inflammatory change [4]. On ultrasound, correlating mass can be seen with parallel orientation and hypervascularity with variable shape and margins, possibly with echogenic rim [4]. MRI findings of breast lymphoma are also nonspecific, but may appear as an enhancing mass with plateau or washout kinetics [4]. On PET–CT, sites of disease will be hypermetabolic, although lower grade lymphomas may not demonstrate significant metabolic activity [13].

Axillary nodal involvement may also be a patient's initial presentation for lymphoma. If lymph nodes demonstrate abnormal morphology, such as rounded appearance with loss of fatty hilum or cortical thickness greater than 3 mm, ultrasound-guided axillary lymph node biopsy should be performed. If lymph nodes demonstrate cortical thickening with otherwise normal morphology and potential explanations for prominent lymph nodes (such as recent vaccination, illness, or autoimmune disease) short-term follow up could be considered. With the advent of the COVID vaccine, the Society of Breast Imaging (SBI) updated their guidelines in that BIRADS-2 (benign findings) may be given to the following: average-risk women with unilateral axillary lymphadenopathy without concerning breast findings and recent history of vaccine administration to the ipsilateral arm or improving lymphadenopathy on short-term follow up [14••]. If lymph nodes demonstrate unchanged cortical thickening in the event of short- term follow up (≥ 12 weeks), subsequent 6 month follow up should be considered [14••]. However, if there is increased cortical thickening on imaging follow up, definitive tissue diagnosis via ultrasound-guided biopsy should be considered [14••].

If lymphoma is suspected, it is important to send the tissue samples for flow cytometry in addition to routine histologic analysis. Practices differ between institutions, but tissue samples for flow cytometry may need to be sent fresh or in saline. Formalin interferes with the processing of flow


(a)
(c)
Dist 5.00 cm
Dist 2.04 cm
Rad
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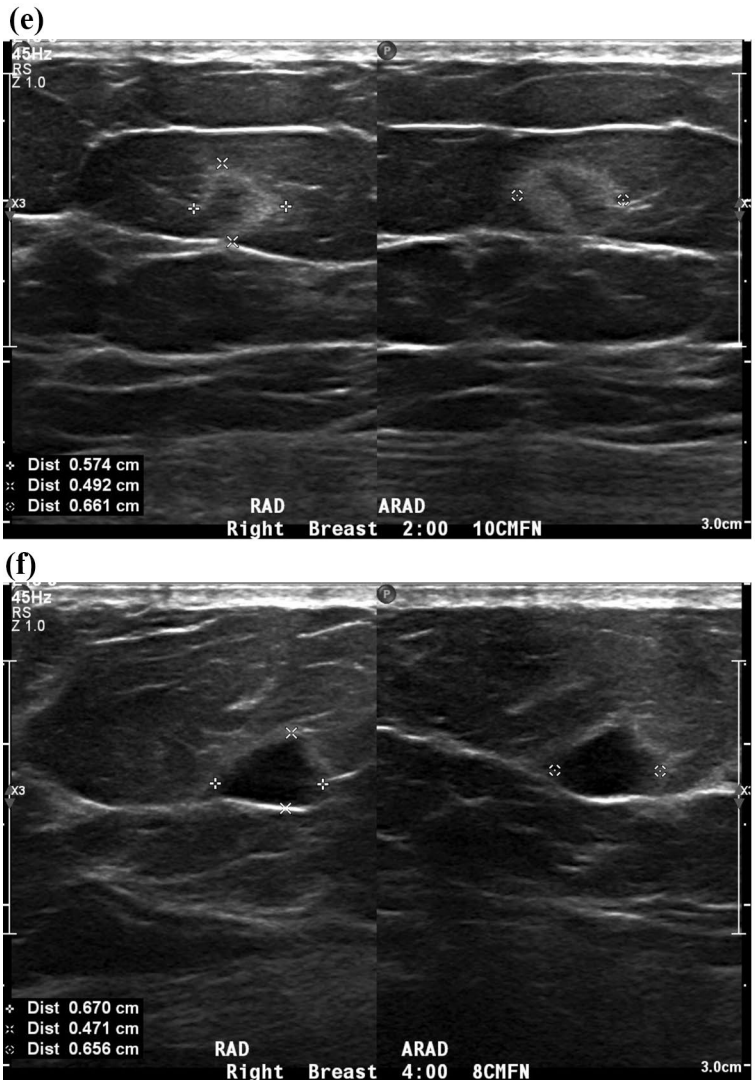
4.5cm
M3 M6
+2.5
-2.5
cm/s
Rad
Left Breast 2:00 5CMFN
4.5cm
(b)
(d)
Left Axilla Rad
6.0cm

◂ **Fig. 5** **a** PET–CT demonstrated an ill-defined hypermetabolic left breast mass measuring up to 5.8 cm. MIP imaging demonstrated widespread nodal disease. An index hypermetabolic left axillary lymph node measured 3.8 cm. **b** Diagnostic mammogram of the bilateral breasts demonstrated a large irregular mass (circles) measuring 5 cm in the left breast upper outer quadrant and two smaller masses (arrows) in the right lower inner breast, both measuring 0.7 cm. **c**, **d** Diagnostic ultrasound of the left breast demonstrated an irregular hypoechoic mass with indistinct margins at 2:00, 5 cm from the nipple, measuring 5 cm. There was no significant internal vascularity. Evaluation of the bilateral axillae also demonstrated lymphadenopathy, largest on the left, measuring 2.1 cm in greatest short axis dimension. **e**, **f** Diagnostic ultrasound of the right breast demonstrated an irregular hyperechoic mass with indistinct margins and echogenic rind at 2:00, 10 cm from the nipple, measuring 0.7 cm, and an oval hypoechoic mass with indistinct and angular margins at 4:00, 8 cm from the nipple, measuring 0.7 cm. **g** PET–CT showed decreased size and metabolic activity of the left breast mass, now 4.5 cm, previously 5.8 cm. The left axillary lymph nodes also demonstrated interval treatment response, now measuring 2.5 cm, previously 3.8 cm

cytometry, and can lead to false positive results. If there is the possibility that the samples cannot be processed within 60 min, then placing the tissue samples in RPMI media may be appropriate, as this preserves the cells without fixing them. RPMI can also facilitate rapid immunostaining [15].

In general, treatment strategies for lymphoma involve radiation therapy for local disease and chemotherapy for systemic disease. In contrast to treatment for primary breast cancer, surgery is generally not considered for lymphoma due to suboptimal local and distant disease control with resection [1]. An exception to this is seroma-type BIA-ACL, for which capsulectomy is considered the standard of care for definitive treatment. Treatment for breast lymphoma differs significantly from other breast malignancies, therefore accurate diagnosis is vital for appropriate treatment planning.



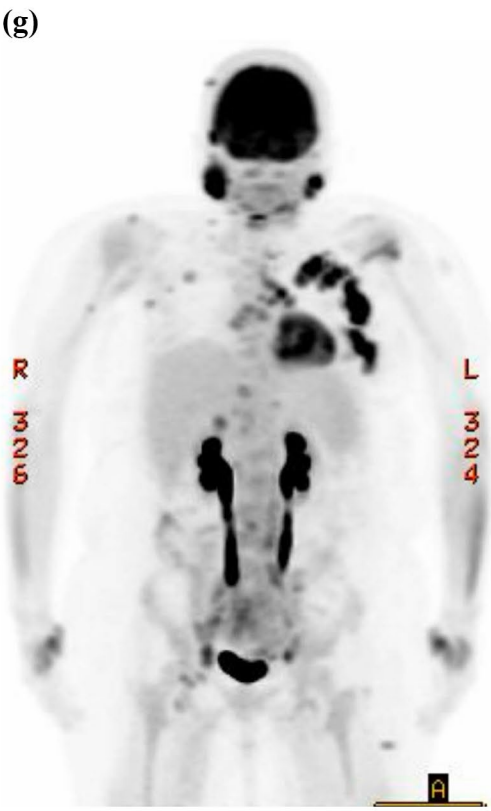


Fig. 5 (continued)

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Declarations

Conflict of interest The authors have no relevant financial or non-financial interests to disclose.

Ethical Approval This article does not contain any research involving human or animal subjects.

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Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

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