

Primary Breast Lymphoma: A Rare Entity

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ABSTRACT

In the past two decades there has been an increase in the incidence of Non-Hodgkin Lymphoma and Hodgkin disease. This has been accompanied by an increase in the numbers of extranodal lymphoma. Despite this primary breast lymphoma is a rare disease. We present a case of a 74 year old female with primary breast lymphoma. Methods of imaging including PET/CT are discussed. Criteria for diagnosing primary breast lymphoma are presented. In addition diagnostic methods and therapeutic options are considered.

CASE REPORT

CASE REPORT

A 74 year old female presented to her general physician with a two day history of a lump in her right breast. She had no past history of breast pathology and had regularly attended for screening mammograms every two years. The patient was nulliparous. She had a history of osteoarthritis and hyperlipidaemia. Previous surgical history included a laparoscopic cholecystectomy and hysterectomy. She had taken hormone replacement therapy (Ogen 1.25 mg daily) which was stopped 7 years prior to presentation with this breast mass. Her family history included oesophageal cancer in her sister, maternal bowel cancer and breast cancer in an aunt.

At presentation she had a smooth 20-30 mm lump, 10mm lateral to the right nipple. There was no palpable axillary lymphadenopathy. The left breast was normal on clinical examination.

Mammogram and ultrasound were performed. On mammography the breast density was 25-50%. An asymmetric density was noted in the upper outer quadrant of the right breast. No spiculate mass or clustered microcalcifications were noted. (Fig. 1, 2, 3 and 4). On ultrasound, correlating to the palpable lump was a 36 x 13 x 26mm hypoechoic mass. It was

in the 10.30 position, 40mm from the nipple. The mass was irregularly outlined and heterogeneous in echogenicity. It had increased vascularity. No posterior acoustic shadowing was present. No associated significant lymphadenopathy was noted. (Fig. 5). The mass was classified as BIRADS 4 being a suspicious abnormality. Subsequent ultrasound guided core biopsy was unable to provide a histological diagnosis.

The patient was referred to a surgeon and underwent lumpectomy. The histology from the surgical specimen revealed a well defined mass composed of sheets of markedly pleomorphic cells. The individual cells were discrete with large pleomorphic vesicular nuclei; some with nucleoli. The mitotic count was more than 20 per 10 high power fields. No typical Reed Sternberg cells were identified. In between there were lymphocytes and other inflammatory cells. The infiltrating tumour had a pushing border. There was no tubule formation or duct carcinoma in-situ component. No lymphovascular invasion was seen. The surgical margins were clear. (Fig. 6)

The initial conclusion was that of a poorly differentiated tumour. The differential was a poorly differentiated breast carcinoma or a Non Hodgkin lymphoma. Immunohistochemistry markers were performed to assess for

lymphoma. The tumour cells were strongly positive with CD45 and negative with epithelial markers, AE1/AE3 and EMA. The tumour was ER, PR, Her-2 negative.

Further immunohistochemistry for lymphoma was done. They revealed a patchy diffuse staining for CD3 and CD5 along with very occasional cells positive for CD10 and negative staining for CD15. CD79a was strongly positive in a diffuse manner in keeping with a B-Cell lymphoproliferative disorder. Immunohistochemistry staining with CD 20 was also positive. Features identified were consistent with a diffuse large B-Cell lymphoma. (Fig 7)

With the diagnosis confirmed as large B-cell non Hodgkin lymphoma the patient was placed under the care of a haematology oncologist. A staging PET/CT scan was negative. There was mild uptake in the right breast in keeping with recent surgery but no other abnormal uptake was detected. (Fig 8, 9, 10) Bone marrow biopsy was negative. The lymphoma therefore was a primary breast lymphoma (PBL), with no evidence of metastatic disease. The patient completed a course of chemotherapy using a combination of MabThera (rituximab) and CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone). The patient is currently in remission 2 years post diagnosis.

DISCUSSION

Lymphoma is a histologically heterogeneous group of cancers derived from the immune system. It represents approximately 5 % of all cancers in the United States. The disease is characterised by the enlargement and proliferation of lymph nodes or secondary lymphoid tissue. It may arise from or involve almost any organ of the body. Extranodal lymphoma is the uncommon neoplastic proliferation beyond the lymph nodes or lymphoid tissue. There has been an increase incidence of NHL and Hodgkin disease over the past 2 decades, with a notable increase in the occurrence of extranodal lymphoma [7].

The aetiology remains incompletely understood [13]. Risk factors include chronic infection (e.g. Epstein-Barr virus), immune suppression (e.g. Acquired Immune Deficiency syndrome (AIDS), transplant recipients and collagen vascular disorders), environmental exposures (e.g. ionizing radiation, pesticides and dark hair dyes prior to 1980) and hereditary traits [7, 13].

The breast is an uncommon site for the development of malignant lymphomas. Secondary forms of the disease are considered more common than primary disease with primary lymphoma of the breast accounting for 0.05-0.53% of all breast malignancies [1]. Less than 0.5% of all malignant lymphomas involve the breast primarily [2]. The small amount of lymphoid tissue in the breast would account for the rarity of primary breast lymphoma (PBL) when compared with other organs [3, 5]. B-cell lymphoma occurs more frequently than T-cell lymphoma in the breast [4].

The diagnosis of primary versus secondary extranodal lymphoma remains challenging [7]. The original criteria for PBL suggested by Wiseman and Liao (1972) are as follows:

1. The availability of adequate pathology material.
2. Both mammary tissue and lymphomatous infiltrate are present.
3. No widespread disease or preceding extramammary lymphoma.
4. Ipsilateral axillary node involvement is considered acceptable [8].

These criteria are now accepted as a standard method of differentiating PBL from a secondary form [5]. Secondary breast lymphoma occurs more frequently. This presents with either multiple breast lesions in a patient with known lymphoma or simultaneous disease in the breast and extra mammary organs [2].

According to the WHO classification system for breast tumours, malignant lymphomas of the breast are subdivided into diffuse large B-cell lymphoma, Burkitt lymphoma, extranodal marginal-zone-B-cell lymphoma of MALT type, and follicular type [11]. PBL are usually non-Hodgkin with a B-cell lineage [11].

The age incidence of PBL is variable. It occurs between 9 and 85 years [9].

The median age of onset of non- Hodgkin breast lymphoma is 58 years [6,10]. A few cases have been reported in males [9]. Sixty percent develop in the upper outer quadrant [2,9]. The disease is bilateral in 10 % [2,9]. A right sided predominance is noted with a 60:40 distribution ratio [2, 9]. Bilateral synchronous breast lymphoma occurs in 10% of patients and contralateral metachronous disease occurs in up to 15% [2].

Patients present most frequently with a mass that may mimic carcinoma [1]. Twenty five percent of masses are painful [1]. There may be skin fixation and cutaneous inflammatory change [2, 4]. The presence of erythema and peau d'orange may simulate inflammatory breast cancer [4]. Skin involvement is seen with diffuse parenchymal involvement, which is more common in a high grade lymphoma [1]. Nipple retraction or discharge and skin retraction are not commonly present [1].

Mammographic findings of PBL are not pathognomonic and the diagnosis cannot be made on mammographic features alone [1]. Two groups are noted on imaging. They are well circumscribed masses (solitary or multiple) or a diffuse infiltrative type [10, 11]. A solitary mass is the commonest finding [1, 2]. The masses tend to be of high density on mammogram [5]. The margins of the masses are most commonly irregular or partially defined. Only 12.5 % of cases have well defined contours [1].

In 16- 33% of patients diffuse increased parenchymal density with or without skin thickening is seen on mammogram [1, 2, 11]. This is more common in high grade lymphoma [1]. In cases of dense breast parenchyma a mass may not be visualised at all [4]. The mammographic finding of bilateral

axillary lymphadenopathy should arouse suspicion of the presence of a secondary lymphoma [11]. Other causes of bilateral axillary adenopathy include leukaemia, collagen vascular disease, nodal hyperplasia, granulomatous disease, HIV, silicone related adenopathy and metastases [11].

Differentiating features between PBL and primary breast carcinoma are summarised in Table 1 [1]. Mammographically PBL should be considered in the differential diagnosis of a breast mass lacking the typical features of microcalcification and spiculation [10].

The role of ultrasound in the diagnosis of breast lymphoma is to confirm the presence of a solid mass, since the sonographic features are nonspecific [1]. Reported appearances range from well-defined to poorly defined, focal to diffuse, and hypo to hyperechoic. Most commonly the mass is a solitary and hypervascular, irregular in shape with indistinct margins [2, 5]. Echogenic margins may be present [2, 5]. Posterior acoustic shadowing is not a feature [2] although its presence is strictly variable [10]. In extensive involvement of the breast diffuse parenchymal infiltration is noted. [2].

MRI demonstrates a hypointense or isointense, usually well defined mass on T1WI [10]. On T2WI PBL is hyperintense [17]. Post contrast there is intense global heterogeneous enhancement with rapid initial increase and washout kinetics on dynamic contrast enhanced images [2, 10]. These features are characteristic of malignancy [2].

PET/CT has become the imaging modality of choice for staging and follow up of patients with extranodal involvement in Hodgkin disease and in most cases of NHL [7]. Imaging of tumour metabolism with 2-[fluorine-18] fluoro-2-deoxy-d-glucose (FDG) positron emission tomography (PET) identifies sites that may not be evident with CT. Hybrid PET/CT has become the standard imaging modality for staging, follow up and treatment response in patients with lymphoma [7]. Breast lymphomatous involvement is characterised by increased FDG uptake. There may be bilateral diffuse FDG uptake, unilateral, ring shaped FDG uptake or intense, focal uptake in a breast mass [7].

PET/CT is useful for assessing therapy response. It differentiates metabolically active tumour and areas of necrosis and fibrosis [7]. FDG PET/CT also detects FDG avid normal sized lymph nodes (usually <1cm) and extranodal sites that would be undetected at CT [7].

The indications for PET/CT in lymphoma are:

1. Staging of patients with FDG-avid potentially curable lymphomas.
2. Incurable, non-FDG-avid or lymphomas with variable FDG activity do not routinely undergo staging PET scanning.
3. Mid treatment PET should only be performed as part of clinical trials [7].

Diagnosis can be made ultrasound guided biopsy. Fine needle aspiration with flow cytometry can provide the diagnosis. Core biopsy is superior for subtyping of lymphomas. If lymphoma or leukaemia is suspected, biopsy specimen should be stored in saline or RPMI medium instead of formalin [11].

The differential diagnosis of PBL presenting as a breast mass is:

- Primary breast cancer
- Benign breast tumours-fibroadenoma, phyllodes tumour
- Metastatic disease
- Infectious disease-chronic abscess, TB [10].

The differential diagnosis of PBL presenting as an infiltrative process:

- Inflammatory breast cancer
- Mastitis
- Venous congestion e.g. due to heart failure or venous compromise [10].

The disease is staged according to the Ann Arbor system and classified according to the Revised European American Classification of Lymphoid Neoplasms (REAL) based on WHO criteria. Prognosis is difficult to determine from the literature because PBL is rare and staging and treatment have varied [1]. The prognosis depends on staging and histologic subtype [1, 10]. Poor prognostic factors include a younger age, tumour size > 5cm, synchronous bilateral disease and axillary nodal involvement. Low grade and MALT lymphomas have a better prognosis than diffuse large B-cell type. The International Prognostic Index predicts 5 year survival based on age, LDH level, staging, extranodal disease, performance status [10, 13].

Treatment options include surgery, chemotherapy and radiation therapy. There is no general agreement on the appropriate treatment of PBL. Recent articles recommend chemotherapy for bulky or stage II disease [1]. Chemotherapy regimes vary with histologic subtype [10]. Radiation therapy can be used to provide effective local control or may be adjuvant to chemotherapy. Surgical treatment ranging from biopsy to radical mastectomy is often not indicated [4, 10].

PBL is a rare entity in the spectrum of malignant breast disease. There are at present no clear clinical or radiological features that distinguish PBL from any other type of infiltrating breast carcinoma. It should be considered in the differential of breast masses lacking features of spiculation and microcalcification. Adequate tissue biopsy for histological evaluation and immunophenotyping is essential. PBL is not a surgical disease and can be treated successfully with combined chemotherapy and radiation therapy [12].

TEACHING POINT

Although rare, primary breast lymphoma must be considered in the differential diagnosis of a breast mass lacking spiculation and microcalcification. Diagnosis requires adequate tissue for histology and immunophenotyping. Primary breast lymphoma is no longer considered a surgical disease.

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FIGURES

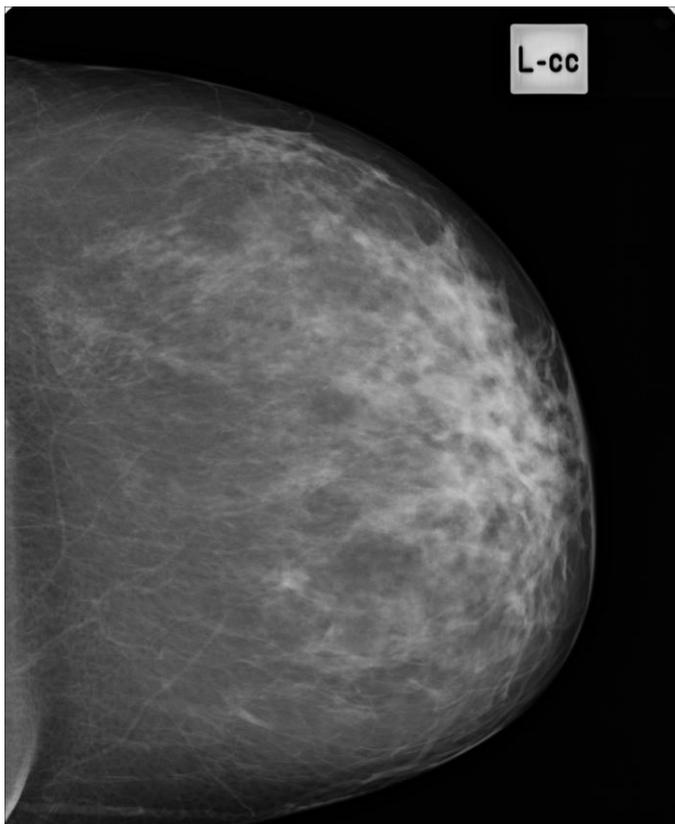


Figure 1: 74 year old female, diagnosed with a right primary breast lymphoma. The left cranio caudal view (LCC) mammogram demonstrates breast density of 25-50%. No focal lesion identified on the left breast.

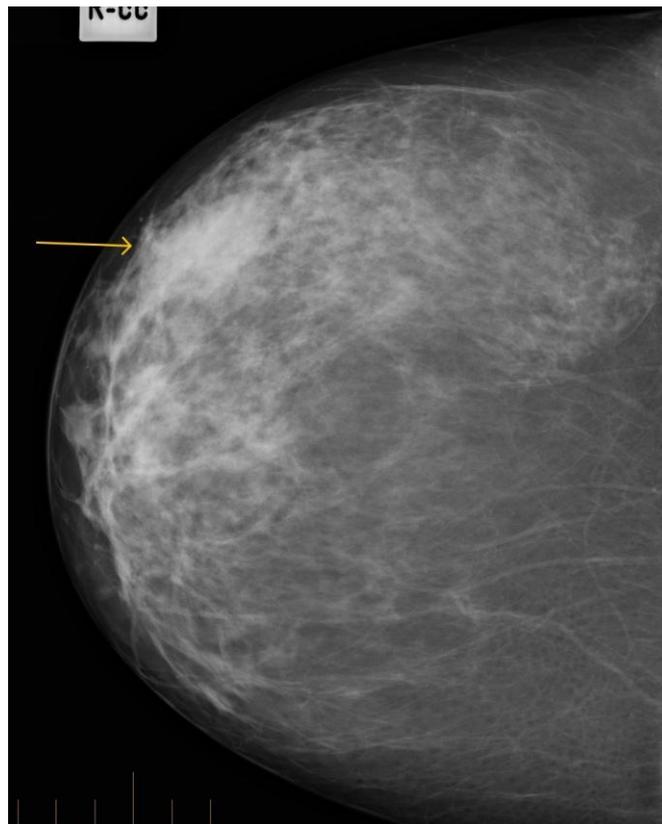


Figure 2: 74 year old female with a primary breast lymphoma on the right. The right cranio caudal view (RCC) mammogram demonstrates an asymmetric density in the outer half of the breast. No spiculation or architectural distortion is present. No suspicious microcalcification is noted.



Figure 3: 74 year old female, diagnosed with a right primary breast lymphoma. The left mediolateral oblique view (LMLO) mammogram is normal.

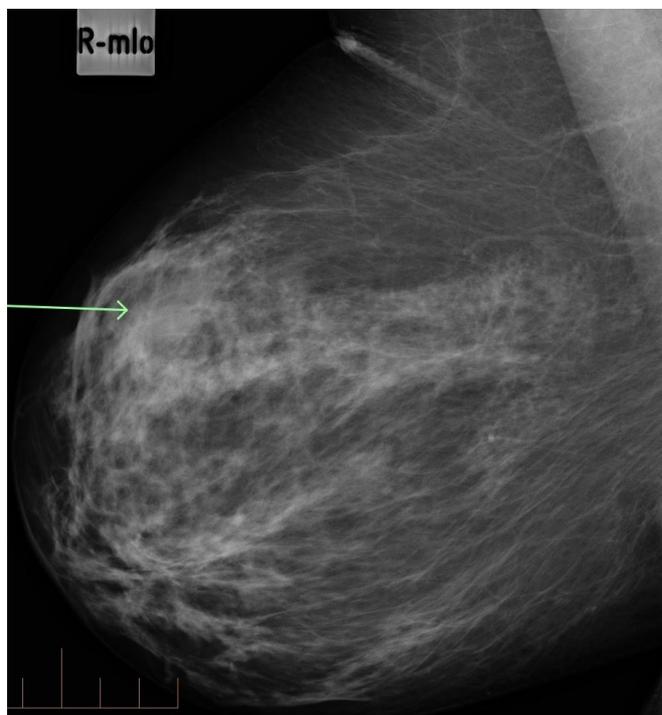


Figure 4: 74 year old female with a primary lymphoma of the right breast. The right mediolateral oblique view (RMLO) mammogram demonstrates an asymmetric density in the upper half of the right breast (arrowed). No spiculation or architectural distortion is present. No suspicious microcalcification is noted.

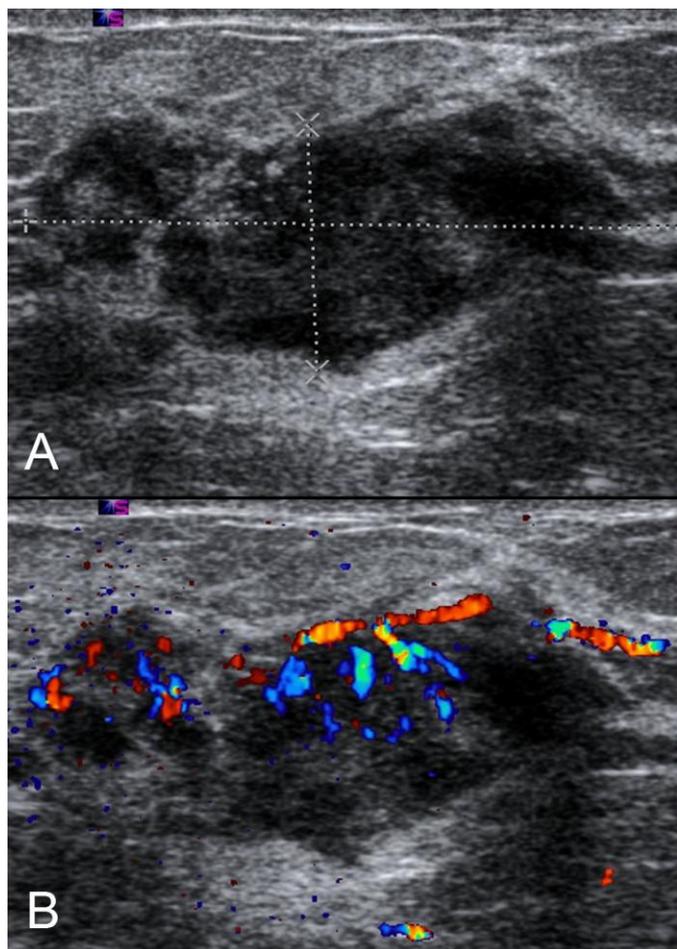


Figure 5: 74 year old female diagnosed with a right sided primary breast lymphoma. Ultrasound using a high frequency linear probe demonstrates a solid mass in the right breast in the 10.30 position 40mm from the nipple. It measured 36mm x 13mm x 26mm in size (A). The mass was hypoechoic and heterogenous in echotexture. The borders of the mass were irregular and there was increased vascularity on colour Doppler (B).

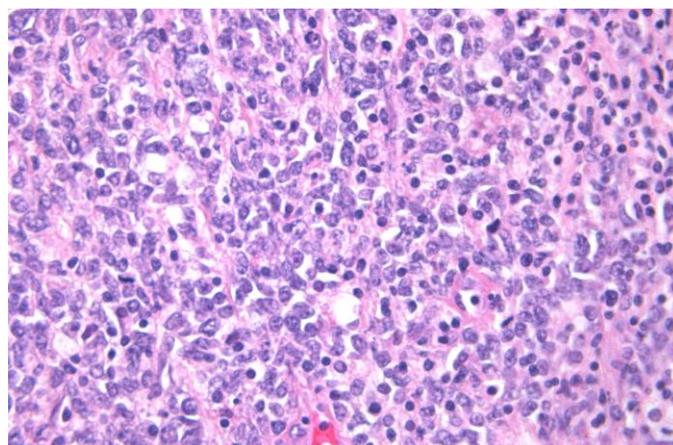


Figure 6: Haematoxylin and eosin stained section of the breast tumour x 400. 74 year old female with a diagnosis of a right sided primary breast lymphoma. The histology is from a surgical biopsy of the mass. The tumour shows sheets of rounded pleomorphic cells with vesicular nuclei resembling lymphoid cells. Some nuclei show nucleoli. Mitoses are seen.

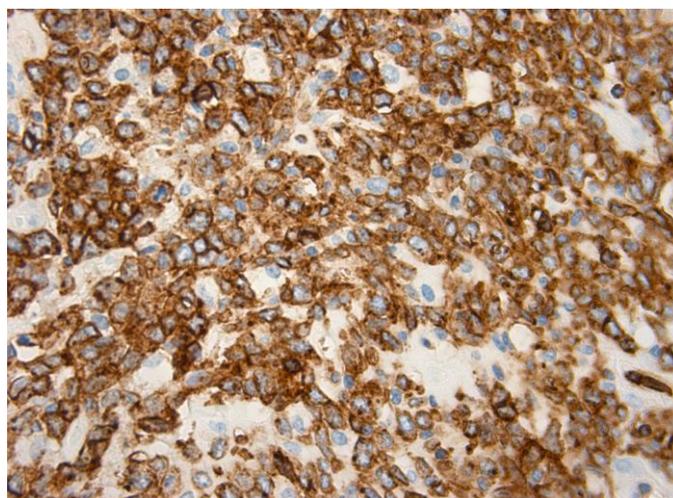


Figure 7: Immunohistochemistry with CD 20 x 400. 74 year old female with a diagnosis of a primary breast lymphoma. Special stains were used to diagnose the lymphoma. This slide shows positive CD 20 marker staining. Positive staining is seen along the membranes of the lymphoid cells. CD 20 marker expression is seen with B-cell lymphomas.

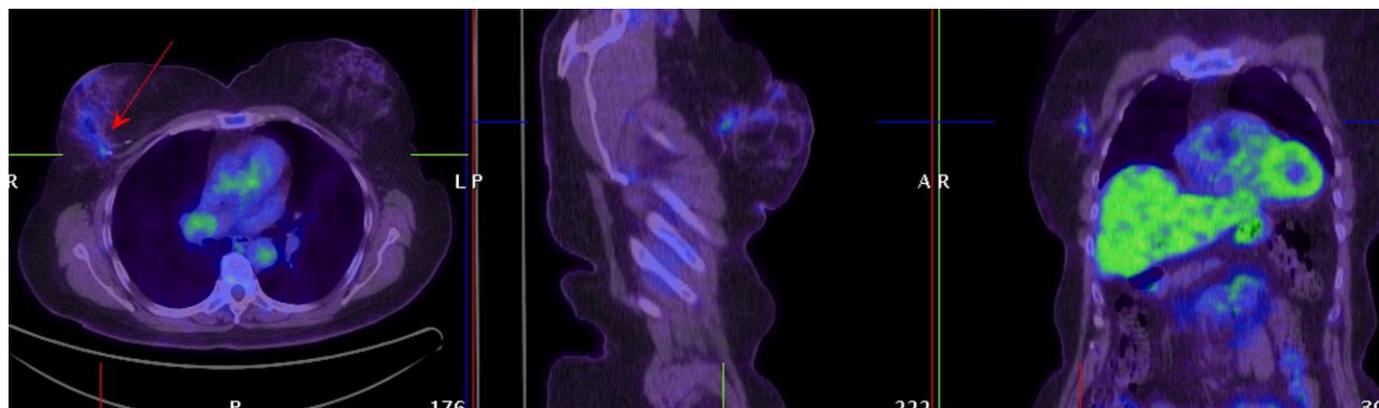


Figure 8: 74 year old female with primary breast lymphoma. FDG PET CT scanning performed from the base of skull to proximal thighs on combined PET CT scanner. Intravenous FDG dose of 10mCi given. PET CT images taken 60 minutes after injection. Increased uptake noted in the right breast in keeping with recent surgery. No other abnormal tracer uptake noted. FDG PET images in axial, sagittal and coronal planes.

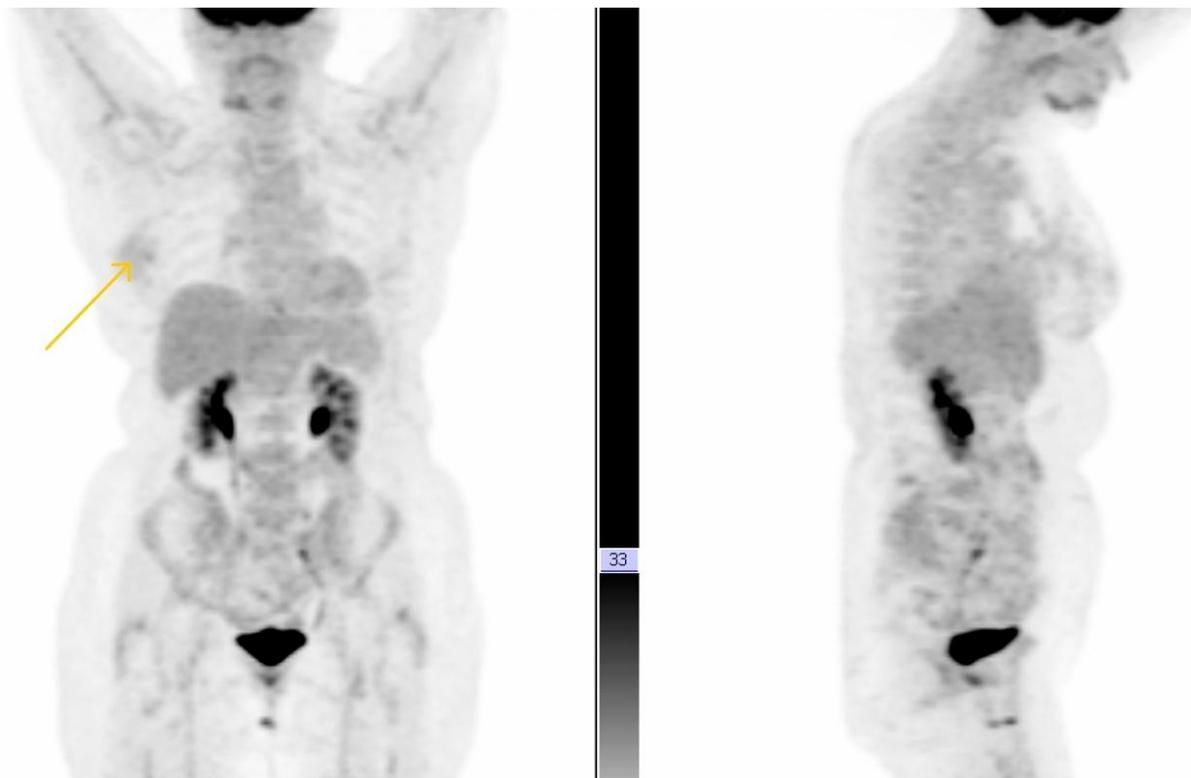


Figure 9: 74 year old female with primary breast lymphoma. FDG PET scanning performed from the base of skull to proximal thighs on combined PET CT scanner. Intravenous FDG dose of 10mCi given. PET images taken 60 minutes after injection. Coronal and sagittal images demonstrate increased uptake in the right breast in keeping with recent surgery. No other abnormal tracer uptake noted.



Figure 10: 74 year old female with primary breast lymphoma. FDG PET scanning performed from the base of skull to proximal thighs on combined PET CT scanner. Intravenous FDG dose of 10mCi given. PET images taken 60 minutes after injection. Increased uptake noted in the right breast in keeping with recent surgery. No other abnormal tracer uptake noted. Images show axial, sagittal and coronal planes.

	PBL	PRIMARY BREAST CARCINOMA
SIDE	Right side predominance	Left side predominance
SIZE AT DIAGNOSIS	>5cm	2-3cm
ARCHITECTURAL DISTORTION	No	Often seen
MICROCALCIFICATION	No	May be present
SPICULATION	No	May be present

Table 1. Differentiating features of a primary breast lymphoma (PBL) and primary breast carcinoma [1, 10]

	Mammogram	Ultrasound	MRI T1	MRI T2	MRI CONTRAST ENHANCEMENT PATTERN	CT/PET
PBL	Mass-may be well defined or ill circumscribed. Right side predominance No spiculation No calcification	Partially circumscribed to irregular oval mass.	Hypo or isointense.	High signal on T2 WI	Rapid initial enhancement with delayed washout. Kinetics characteristic of malignancy.	Increased FDG uptake in the breast.
Primary breast cancer	Dense mass with spiculated margins. May have associated microcalcifications	Irregular hypoechoic shadowing mass. Architectural distortion. Taller than wide.	Variable signal intensity depending on subtype.	Variable.	Intense and rapid enhancement. Washout after 5-10 minutes. May have rim enhancement and internal septation enhancement.	Whole body FDG PET insensitive to tumours < 2cm. Dedicated devices with compression 89% sensitive, median diameter 21mm.
Fibroadenoma	Oval or lobulated circumscribed mass with dense coarse calcifications.	Hypoechoic circumscribed oval mass with homogenous internal echoes.	Low signal intensity	High signal with hypointense septations. High signal in surrounding tissues in 1.2%	Varies. Usually continuous and gradual increase in signal over time.	Usually low FDG uptake.
Phyllodes	Dense round/oval mass. Circumscribed or lobulated margins. Calcification not common.	Oval, round or lobulated. Hypoechoic mass. Variable posterior enhancement. Intramural cystic spaces may be present.	Heterogenous low signal.	Lobulated mass. Variable intensity. Hyperintense fluid in slit like spaces. High signal in surrounding tissues in 21%.	Rapidly enhancing. 33% have suspicious enhancement pattern.	Increased uptake of FDG may occur.
Metastatic disease	Circumscribed breast masses. Round, circumscribed or slightly irregular mass. No spiculation, microcalcification or architectural distortion.	Round/ ovoid. Hypoechoic to anechoic solid mass/es. Margins may be indistinct/ microlobulated. Posterior enhancement more common than shadowing.			Rapidly enhancing round or ill-defined mass/es. Rim enhancement possible.	Increased FDG uptake. PET/CT moderately high sensitivity for masses >8mm.
Abscess	Ill defined mass or focal asymmetry. Local trabecular thickening. Can be spiculated.	Hypoechoic, complex mass. Thick walled. Colour Doppler flow at the periphery. Surrounding increased echogenicity due to oedema.	Low signal on T1WI	High signal on T2WI.	Intense rim enhancement of abscess cavity.	Increased FDG uptake.

Table 2. Differential diagnosis table for primary breast lymphoma (References 4, 5, 10, 11, 14, 15, 16)

AETIOLOGY	<ul style="list-style-type: none"> • Neoplastic
INCIDENCE	<ul style="list-style-type: none"> • PBL is a rare neoplasm • 0.05-0.53% of all breast malignancies. • Less than 0.5% of malignant lymphomas involve the breast primarily.
GENDER RATIO	<ul style="list-style-type: none"> • Predominantly female disease. • Male breast lymphoma only a few reported cases.
AGE PREDILECTION	<ul style="list-style-type: none"> • Bimodal peaks at 38 and 58 years • Range 9-85 years • Median age at diagnosis of 58 years
RISK FACTORS	<p>Incompletely understood. Risk for lymphoma in general includes:</p> <ul style="list-style-type: none"> • Chronic infection e.g. EBV • Autoimmune diseases e.g. Sjogren's syndrome, rheumatoid arthritis • Immunosuppression e.g. HIV and transplant patients • Hereditary traits –risk are increased for first degree relatives. • Environmental stressors-ionization radiation, pesticides, dark hair dyes (prior to 1980).
TREATMENT	<ul style="list-style-type: none"> • Chemotherapy-regimes vary with histological subtype • Radiotherapy-may be adjuvant to chemotherapy or for local control • Surgery often not indicated.
PROGNOSIS	<p>International Prognostic Index factors of:</p> <ul style="list-style-type: none"> • Age • Performance Status • LDH • Extranodal disease • Stage (Ann Arbor) <p>Categorizes patient into risk group and predicts 5 year survival.</p>
FINDINGS ON IMAGING	<ul style="list-style-type: none"> • Solitary or multiple masses. Well circumscribed. No spiculation. No microcalcification. • Diffuse infiltration with increased breast density, trabecular thickening and skin thickening.

Table 3. Summary table for primary breast lymphoma

ABBREVIATIONS

WHO: World Health Organisation

RMPI: RPMI is a culture medium for normal and neoplastic cells. It was developed at the Roswell Park Memorial Institute (hence the acronym).

KEYWORDS

Breast Imaging; Lymphoma; Breast Lymphoma; Breast Cancer

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