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Locally advanced primary breast lymphoma: a rare case report

Rafaela Pereira[1*], Luísa Amado Costa[1], José Eduardo Rosa[1] and Isabel Duarte[1]

Abstract

Background Primary Breast Lymphoma is a rare manifestation of extranodal non-Hodgkin lymphoma and accounts for less than 1% of all breast malignancies. It is defined by localized involvement of the mammary tissue by lymphomatous infiltrate in the absence of prior extramammary lymphoma and concomitant widespread disease.

Case presentation A 46-year-old melanodermic woman was referred to our hospital due to an extensive ulcerated right breast lesion with signs of infection. Imaging studies revealed a large breast tumor invading the chest wall, with cortical disruption of adjacent ribs and associated pleural thickening. Later, it was complicated with a bronchopleural cutaneous fistula. Biopsy of the mass was performed and the histopathologic diagnosis was consistent with breast infiltration by diffuse large B-cell lymphoma. Concurrent widespread lymphomatous disease and preceding extramammary lymphoma were excluded. Firstly, antibiotic therapy was instituted and surgical debridement was performed in order to control the infection. Afterwards, she underwent chemotherapy and local radiotherapy, with radiologic complete response.

Conclusions The diagnosis of primary breast lymphoma is challenging because this disease has non-specific symptoms and imaging features. Radio–pathological correlation and exclusion of systemic lymphoma are essential to establish the diagnosis and to minimize potential complications.

Keywords Primary breast lymphoma, Extranodal non-Hodgkin lymphoma, Breast cancer

Background

Primary Breast Lymphoma (PBL) is a rare entity, defined by close association of breast tissue and lymphomatous infiltrate, in the absence of concurrent widespread disease and preceding extramammary lymphoma, with or without ipsilateral axillary lymph node involvement [1, 2]. In the literature, PBL is mainly described in case reports and case series. It corresponds to less than 1% of all breast malignancies and less than 2% of extranodal non-Hodgkin lymphomas (NHLs) [2]. Diffuse large B-cell lymphoma (DLBCL) is the most common type [2].

PBL has a wide spectrum of imaging presentations that can mimic benign and malignant conditions [3]. It usually presents as a painless breast mass [4] and has no pathognomonic radiologic features [3]. Therefore, the histopathological study is essential to establish the diagnosis and to identify the lymphoma subtype.

PBL treatment is usually based on a combination of chemotherapy and radiation therapy. Mastectomy is not recommended [2, 5].

We report a case of primary non-Hodgkin lymphoma of the breast, with B-cell phenotype, extensively ulcerated and locally advanced at diagnosis, complicated by local infection and bronchopleural cutaneous fistula.

Case presentation

A 46-year-old melanodermic woman presented with a rapidly enlarging and ulcerating right breast lump, fatigue, weight loss, night sweats, and fever. The result

*Correspondence:
Rafaela Pereira
rafaelapereira.18@hotmail.com; 25920@chln.min-saude.pt
[1] Serviço de Imagiologia Geral, CHULN – Hospital de Santa Maria, Centro Hospitalar Universitário Lisboa Norte, Avenida Prof. Egas Moniz, 1649-035 Lisbon, Portugal

of the breast biopsy initially performed in her country of origin was inconclusive and the diagnosis of breast tuberculosis was assumed. She underwent therapy with tuberculostatic agents. The patient also had human immunodeficiency virus (HIV) infection with undetectable viral load under antiretroviral drugs. She had no other relevant medical history and no family history of breast cancer.

Since there was no clinical improvement of the breast lesion after several weeks of treatment, the biopsy was repeated, and the histopathologic analysis revealed a breast malignant neoplasm with features of high-grade lymphoma. She was then referred to our hospital, in order to perform additional investigation and staging of the breast lymphoma, as well as to receive appropriate treatment.

At our institution, physical examination revealed a large ulcerated lesion of the right breast, centered in the upper-outer quadrant, and extending to the right axillary region. The lesion was associated with inflammatory signs, including erythema and edema, as well as profuse purulent exudate from the ulcerated wound. The patient had fever and blood analysis revealed leukocytosis 19.65×10^9/L (normal range $4.0–11.0 \times 10^9$/L) with neutrophilia (94.4%) and elevated C-reactive protein—18.4 mg/dL (normal range < 0.5 mg/dL). The bacteriological study of the wound exudate identified *Escherichia coli*, *Acinetobacter baumanni* e *Enterococcus faecalis*.

Due to the extensive skin ulceration, large dimension and deep infiltration of the breast lesion, a mammogram was not obtained and an accurate evaluation on ultrasound (US) was difficult. The right breast US showed skin thickening and extensive subcutaneous edema, as well as a heterogenous infiltrative collection with hyperechoic foci compatible with gas bubbles (Fig. 1).

Thoraco-abdominopelvic computed tomography (CT) images (Fig. 2) demonstrated an extensive and ulcerated lesion in the right breast with heterogenous contrast enhancement, extending to the right axillary region. It had multiloculated fluid collections and gas bubbles, in keeping with the clinical signs of local infection. There was deep invasion of the chest wall with cortical bone disruption of three adjacent ribs, as well as adjacent pleural thickening. Right axillary lymphadenopathies were also noted.

Core biopsy of the lesion was performed and the pathology findings showed an extensively necrotic neoplasm, consisting of cells with large, irregular and pleomorphic nuclei. The immunohistochemical study revealed positivity for PAX5, CD20, CD10, bcl-6 and MUM-1. The proliferative index was high and Epstein-Barr virus test was negative. These findings were consistent with the diagnosis of diffuse large B-cell lymphoma infiltrating the breast tissue (subtype: germinal center B-cell—like).

The patient had no previous history of lymphoma and the CT scan excluded distant lesions and other lymphadenopathies, thus meeting the diagnostic criteria for PBL.

Due to the advanced local infection, the patient was hospitalized and first treated with appropriate antibiotic therapy and underwent local surgical debridement of the lesion. She also required transfusion support and

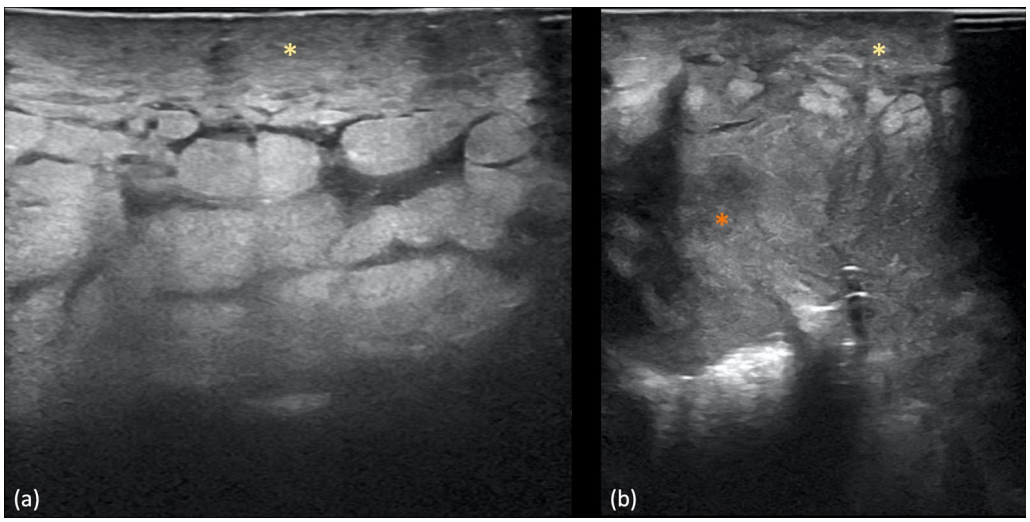

Fig. 1 US findings of PBL in a 46-year-old HIV-infected woman. Transverse gray-scale US images (**a**, **b**) of the right breast show skin thickening (yellow asterisk), diffuse increased echogenicity of the adipose tissue and extensive subcutaneous edema; on image **b**, a heterogenous infiltrative collection (orange asterisk) with hyperechoic foci corresponding to gas bubbles is also seen

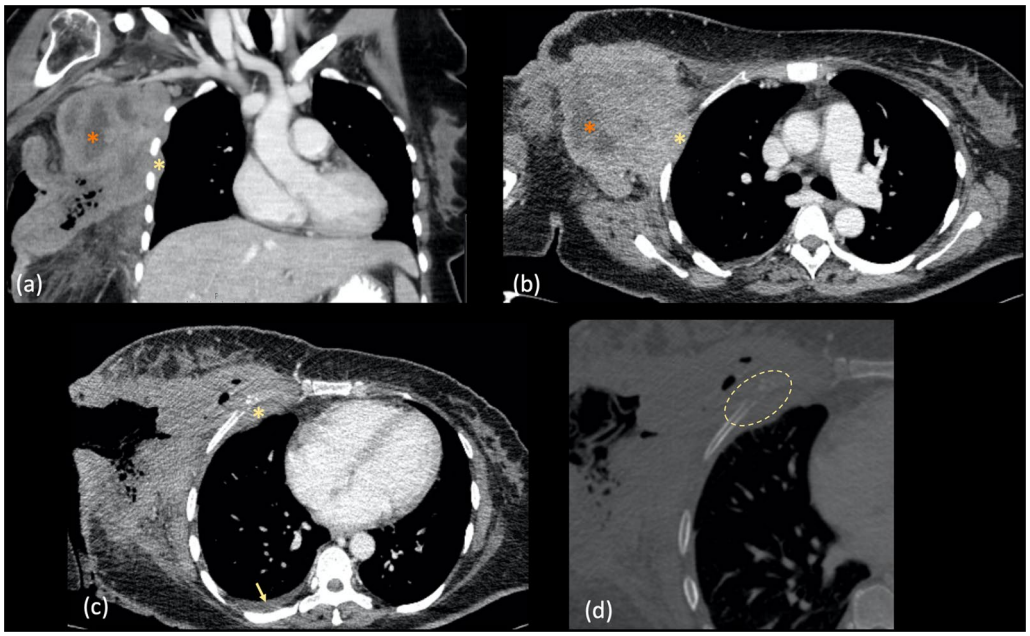

Fig. 2 CT findings of PBL in the same patient. Images of the CT scan obtained with intravenous contrast media [coronal image on a mediastinum window (**a**); axial images on a mediastinum window (**b**, **c**), and axial image on a bone window (**d**)] demonstrate an extensive ulcerated lesion in the right breast with heterogenous contrast enhancement, extending to the ipsilateral axillary region. It presents multiloculated fluid collections (orange asterisk) and multiple gas bubbles. There is deep invasion of the chest wall, with infiltration of the muscular planes (pectoralis major, pectoralis minor and intercostal muscles) and cortical bone disruption of adjacent ribs (yellow circle), as well as associated pleural invasion (yellow asterisk). Small right pleural effusion can also be noted (yellow arrow)

hemostatic radiotherapy on the right breast to control bleeding from the wound.

After case discussion in a multidisciplinary tumor board meeting, systemic treatment with R-CHOP (Rituximab, Cyclophosphamide, Doxorubicin hydrochloride, Vincristine and Prednisone) was initiated.

Additionally, on the tenth day of hospitalization, it was noticed an air leakage from the wound and a bronchopleural cutaneous fistula was detected on CT and on Magnetic Resonance Imaging (MRI) (Fig. 3). Progressive resolution of the fistula was observed after initiation of chemotherapy. The patient remained hospitalized for about six months, which included the period of the systemic treatment, due to numerous infectious complications and multifactorial anemia.

After chemotherapy (6 cycles of R-CHOP), the 18F-fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG-PET/CT) findings of the patient were consistent with partial response on radiological assessment (Fig. 4), due to significant decrease in size and hypermetabolism of the right breast lesion. The patient then underwent consolidative local radiotherapy (30 Gy in 15 fractions), after which there was a complete response on PET/CT. The patient is under regular monitoring, and two years after the diagnosis there were no clinical or radiological signs of recurrence of the disease.

Discussion

Primary breast lymphoma (PBL) was first defined by Wiseman and Liao in 1972 [1]. The diagnosis of PBL implies exclusion of prior extramammary lymphoma and concomitant widespread lymphomatous disease, except for synchronous ipsilateral axillary lymphadenopathies [1, 2]. Updated criteria also include homolateral supraclavicular lymphadenopathies being classified as regional disease [2].

The low prevalence of PBL could be partly explained by the paucity of lymphoid tissue in the breast. The most accepted hypothesis regarding its pathogenesis proposes that PBL develops in intramammary lymph nodes [2].

Additionally, our patient had HIV infection, which has been associated with an increased risk of developing extranodal lymphomas [6]. Despite the plausibility of the association between HIV infection and PBL, it has seldom been reported, given the rarity of these cases [6].

Primary breast lymphomas are often B-type non-Hodgkin lymphomas [3], and DLBCL has been reported to be the most common type (45–79%) [2]. Follicular lymphoma, mucosa associated lymphoid tissue lymphoma, and Burkitt lymphoma have a lower prevalence [2]. Involvement of the breast by T-cell lymphoma or Hodgkin's disease is extremely rare [2, 5]. Anaplastic

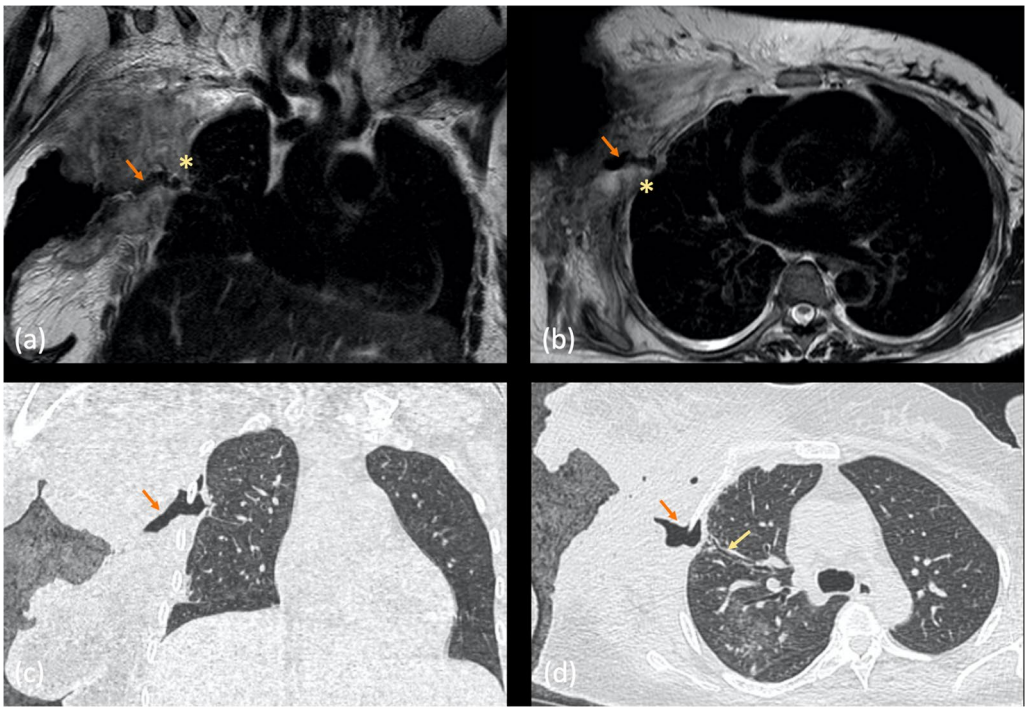

Fig. 3 Chest MRI and CT findings of PBL in the same patient, complicated with bronchopleural cutaneous fistula. Chest MRI [(**a**) coronal and (**b**) axial T2-weighted images] and chest CT scan [(**c**) coronal and (**d**) axial images on a lung window]. MRI images show the extensive ulcerated lesion in the right breast with heterogenous signal intensity, extending to the ipsilateral axilla and deeply invading the chest wall, associated with pleural thickening (yellow asterisk). A fistulous tract filled with gas can also be seen (orange arrow), communicating with a peripheral bronchus of the right lung (yellow arrow) and extending into the pleural space and into the chest wall, traversing the breast lesion—it corresponds to a bronchopleural cutaneous fistula

lymphoma is a rare T-cell type lymphoma that has been reported in women with breast implants [2, 7].

Primary breast lymphoma is mainly reported among female patients (95–100%) and is very rare in males [8]. It has a bimodal age distribution, with the median age of PBL patients ranging from 60 to 65 years [2]. PBL is most often unilateral (89–95%) and a right-sided predominance has been extensively reported [1, 2, 5, 8], as seen in our case.

Clinical signs and symptoms of PBL are diverse and nonspecific, overlapping with those of other breast malignancies [2, 7]. The most common manifestation is a palpable mass that develops rapidly [3, 8], which is usually painless and frequently located in the supero-external quadrant [4, 7]. Other clinical manifestations include pain, erythema or other local inflammatory signs, nipple or skin retraction, nipple discharge, "orange peel" skin and ulceration [4, 5, 7]. Palpable axillary lymphadenopathies are present in up to 25% of cases [4, 7]. Occasionally, asymptomatic PBL can be diagnosed as an incidental finding on mammography screening [4]. The B symptoms usually seen in lymphomas, such as fever, weight loss and night sweats, are very rare in PBL [5, 7].

The imaging findings of PBL are also nonspecific and can mimic those of other breast malignancies [3, 5]. Furthermore, PBL may present benign imaging features [5]. The most common mammographic presentation is a solitary hyperdense and noncalcified mass [2]. It can have a round or oval shape and may be well-circumscribed or present indistinct margins [2, 3, 5]. Multiple masses and diffuse increased density on mammogram have also been reported [3, 5]. Skin thickening or edema and diffuse parenchymal involvement have been reported in cases with high-grade lymphomas [3]. It is important to mention that some of the mammographic features commonly present in breast carcinoma, such as desmoplastic reactions with architectural distortion, spiculations and microcalcifications, are unusual in PBL [3, 5].

Although mammography is part of the initial workup of a suspicious breast mass, it was not performed in this patient, due to the voluminous size and extensive local complications, including ulceration and infection. Because of those reasons, the lesion was also difficult to accurately assess on US.

On US, PBL most often presents as a hypoechoic mass, that may display mixed internal echogenicity or even a pseudocystic pattern [3]. It can present circumscribed,

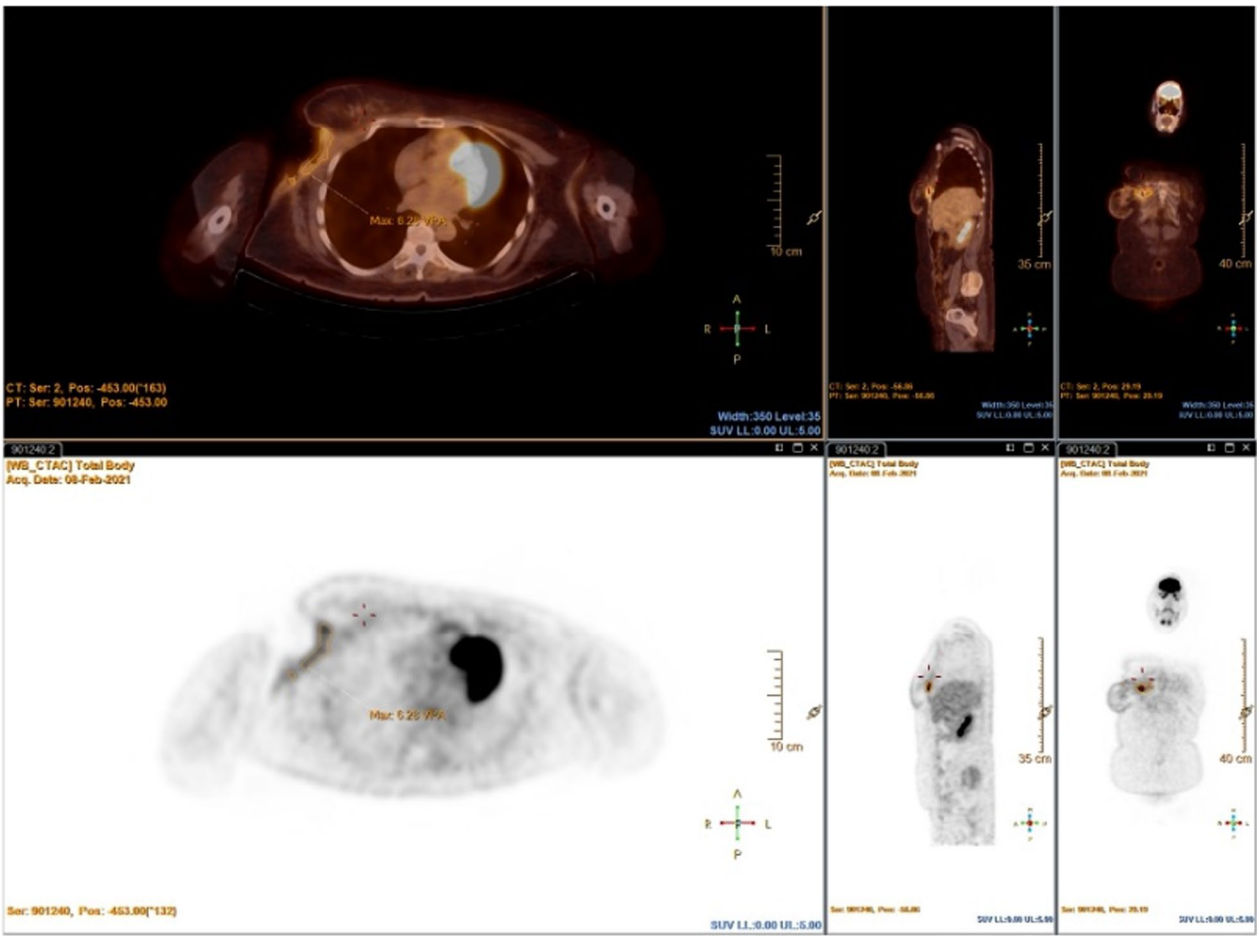

Fig. 4 18F-FDG-PET/CT findings of PBL in the same patient, after 6 cycles of R-CHOP. The images show a decrease in size of the right breast lesion with intense FDG uptake ($SUV_{max} = 6.3$), consistent with partial response

indistinct or microlobulated margins [2, 3]. Posterior acoustic enhancement and an echogenic rim may also be identified [2]. Besides, PBL frequently demonstrates high vascularity on Doppler US [2, 3].

Magnetic resonance imaging is useful to evaluate the presence and extent of multicentric and multifocal breast lesions, as well as to assess treatment response, and recurrent disease [2]. It is also useful to identify signs of chest wall invasion. On MRI, PBL masses typically have areas of hypointensity or isointensity at T1-weighted imaging, and areas of hyperintensity at T2-weighted imaging [2], which were not evident in our patient possibly due to the associated infection. Contrast enhancement of the mass may be homogeneous or heterogeneous, most often with a type II kinetic curve [2].

Computed tomography has a major role in staging lymphomas, allowing the detection and accurate characterization of local disease, namely involvement of the chest wall or lung, as well as lymphadenopathies and distant disease [9]. It can also be used to detect potential complications, such as abscesses or bronchopleural fistulas, as occurred in our case. Besides, it provides important information for treatment planning (including radiotherapy treatment planning) and response to treatment.

18F-FDG-PET/CT is highly sensitive and specific in lymphoma staging, having an important role in the exclusion of additional sites of nodal or extranodal lymphoma and in the evaluation of treatment efficacy [2, 3]. PBL has avid homogeneous or ring-type FDG uptake at PET/CT [2, 3].

The definitive diagnosis of PBL is made by histopathological examination. The pathological specimen should ideally be obtained with core needle or surgical biopsy, and sent for flow cytometry, histopathologic, and cytogenetic evaluations [2].

The staging and lymphoma subtype are determining factors in patient morbidity and mortality [2, 10]. The Ann Arbor staging system for lymphomas is used to stage PBL, comprising only stage IE (confined to the

breast with no axillary lymph node involvement) and IIE (with involvement of axillary lymph nodes) [2, 10]. Our patient presented a stage IIE PBL, given the ipsilateral axillary lymphadenopathies.

Primary breast lymphoma is more aggressive and has a worse prognosis in comparison to other extranodal NHL. Stage II PBL has been reported to present a higher recurrence rate and a higher mortality in comparison with Stage I PBL [2]. Diffuse large cell subtype has also been associated with a poorer prognosis and a higher rate of recurrence [2].

Currently, there are no established guidelines for the treatment of PBL [2, 5, 8]. It can comprise a combination of chemotherapy (Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone ± Rituximab) and radiotherapy [7, 10]. Mastectomy is not recommended since it offers no improvement in overall survival or recurrence risk [2, 4, 11]. Surgery is usually reserved for diagnostic purposes and/or for patients who require better local control [2, 7]. In our case, antibiotic treatment and surgical debridement were initially performed to control local infection. Our patient also underwent chemotherapy (6 cycles of R-CHOP) and local radiotherapy, with a radiologic complete response insofar as it can be ascertained at the date of completion of this case report.

Conclusions

PBL is very rare and challenging to diagnose, given the fact that it has non-specific clinical signs and symptoms and it does not present pathognomonic imaging features. It should be considered in the differential diagnosis of a rapidly growing breast mass. Prompt biopsy with adequate pathologic specimens and exclusion of systemic lymphoma are essential to establish the diagnosis and to minimize potential complications.

Abbreviations

PBL	Primary breast lymphoma
NHLs	Non-Hodgkin lymphomas
DLBCL	Diffuse large B-cell lymphoma
HIV	Human immunodeficiency virus
US	Ultrasound
CT	Computed tomography
R-CHOP	Rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine and prednisone
MRI	Magnetic resonance imaging
PET/CT	Positron emission tomography–computed tomography

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Author contributions

RP wrote and edited the manuscript. LAC, JER and ID made the critical revision of the manuscript. All authors have read and approved the manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Ethical approval is not required for the publication of isolated case reports. The patient was informed about the procedure, and a written informed consent was obtained.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Competing interests

The authors declare no competing interests.

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