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Case report / Caso clínico

Primary breast follicular lymphoma: Case report

Linfoma folicular primario de mama: reporte de caso

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ABSTRACT
Introduction: Primary follicular lymphoma of the breast is a rare entity with unique clinical and pathological features. This report highlights the diagnostic challenges and management of this condition. **Case presentation:** A 63-year-old patient presented with an irregular nodule in the left breast, which was classified as BIRADS IV/C on core needle biopsy. Suspecting an intramammary tumor, she was referred for surgical excision. Histopathological and immunohistochemical studies confirmed a grade 1/2 follicular lymphoma. **Conclusion:** This case highlights the importance of integrating imaging, histology and immunohistochemistry for accurate diagnosis of primary mammary follicular lymphoma. Early multidisciplinary management is crucial for a favorable outcome.

Keywords: Breast neoplasms; Follicular Lymphoma; Immunohistochemistry; Mastectomy.

RESUMEN
Introducción: El linfoma folicular primario de mama es una entidad poco frecuente con características clínicas y patológicas únicas. Este informe destaca los retos diagnósticos y el tratamiento de esta enfermedad. **Caso clínico:** Una paciente de 63 años presentó un nódulo irregular en la mama izquierda, clasificado como BIRADS IV/C en la biopsia con aguja gruesa. Ante la sospecha de un tumor intramamario, fue remitida para extirpación quirúrgica. Los estudios histopatológicos e inmunohistoquímicos confirmaron un linfoma folicular de grado 1/2. **Conclusión:** Este caso enfatiza la importancia de integrar imágenes, histología e inmunohistoquímica para el diagnóstico preciso del linfoma folicular mamario primario. El tratamiento multidisciplinar precoz es fundamental para obtener resultados favorables.

Palabras Clave: Neoplasias de la mama; Linfoma folicular; Inmunohistoquímica; Mastectomía.

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1. Introduction

Primary breast lymphoma (PML) is a rare neoplasm of the lymphoid tissue of the breast [1-2] that occurs almost exclusively in women, with a median age of 60-65 years [3-4]. It is defined as a malignant neoplasm occurring primarily in the breast in the absence of previously identified sites of lymphoma.[5] This pathology is identified by the presence of neoplastic B or T cells, which classifies it as non-Hodgkin's lymphoma (NHL) [6] according to the World Health Organization (WHO) diagnostic criteria. There are several types of NHL: the follicular lymphoma (FL) subtype accounts for 22% of cases [7]. Primary follicular breast lymphoma (PFBL) is a rare disease without extramammary involvement; its pathogenesis is not yet understood. In general, primary breast lymphoma presents clinically as a painless palpable mass and is nonspecific on imaging. It may have a differential diagnosis with breast carcinoma, and a definitive diagnosis should be made by tumor biopsy [1,6,8]. The aim of this article is to report a rare case of primary follicular breast lymphoma in a 63-year-old woman, focusing on the diagnostic challenges and the clinical, pathologic, and imaging features of this unusual presentation. Our goal is to highlight the importance of integrating radiologic, histopathologic, and immunohistochemical findings in the accurate diagnosis and management of breast lymphoma. In addition, we emphasize the role of a multidisciplinary approach in obtaining favorable outcomes. The report was written in accordance with CARE guidelines to ensure a comprehensive presentation of cases.

2. Case report

A 63-year-old patient with no pathologic or family history of cancer presented to a mastologist fourteen months ago for the presence of a nodule in her breast. An ultrasound was requested and revealed an irregular solid nodule (BIRADS IV/B) in the left breast, and she was referred for core needle biopsy. This biopsy revealed follicular lymphoid hyperplasia, consistent with a probable intramammary tumor. The lesion was not consistent with radiologic imaging and, therefore, was reclassified as BIRADS IV/C.

Three months after diagnosis, the patient underwent surgical resection with intraoperative frozen pathology. A left breast quadrantectomy and excision of the sentinel node with intraoperative margin extension was performed with a frozen section diagnosis of undifferentiated malignant small cell neoplasm, and the material was sent for anatomic pathology and immunohistochemistry. Macroscopic examination revealed a firm, elastic, whitish nodular tumor measuring 5.2x3x3 cm along the superior and anterior margins (Figure 1). In addition, a 1.2 cm left axillary sentinel lymph node, and the surgical margins of the breast tissue were examined.

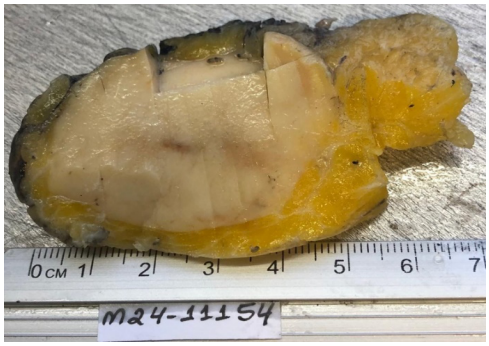

Figure 1. Macroscopic examination revealed a firm elastic whitish nodular tumor measuring 5.2x3x3cm along the upper and anterior margins.

Microscopic examination of the nodule revealed an undifferentiated small round cell neoplasm compatible with a follicular lymphoproliferative process (Figure 2), as well as adjacent mammary parenchyma with discrete ductal ectasia. Immunohistochemistry was requested for definitive diagnosis. Microscopy of the lymph node showed no evidence of neoplastic involvement. Surgical margins were free of neoplastic involvement.

Immunohistochemistry (Figure 3) was positive for CD3, CD20, CD5, CD10, BCL2, BCL6, and PAX5 in the perifollicular region. The CICLINAD1 marker was negative. The final diagnosis was primary follicular breast lymphoma grade 1/2. The patient was referred to by a hematologist who ordered a positron emission tomography scan (PET-Scan) for tumor control. The scan results were negative for evidence of abnormal metabolic activity in the examined body areas. As a result, ambulatory monitoring was without indicated the need for chemotherapy or radiotherapy.

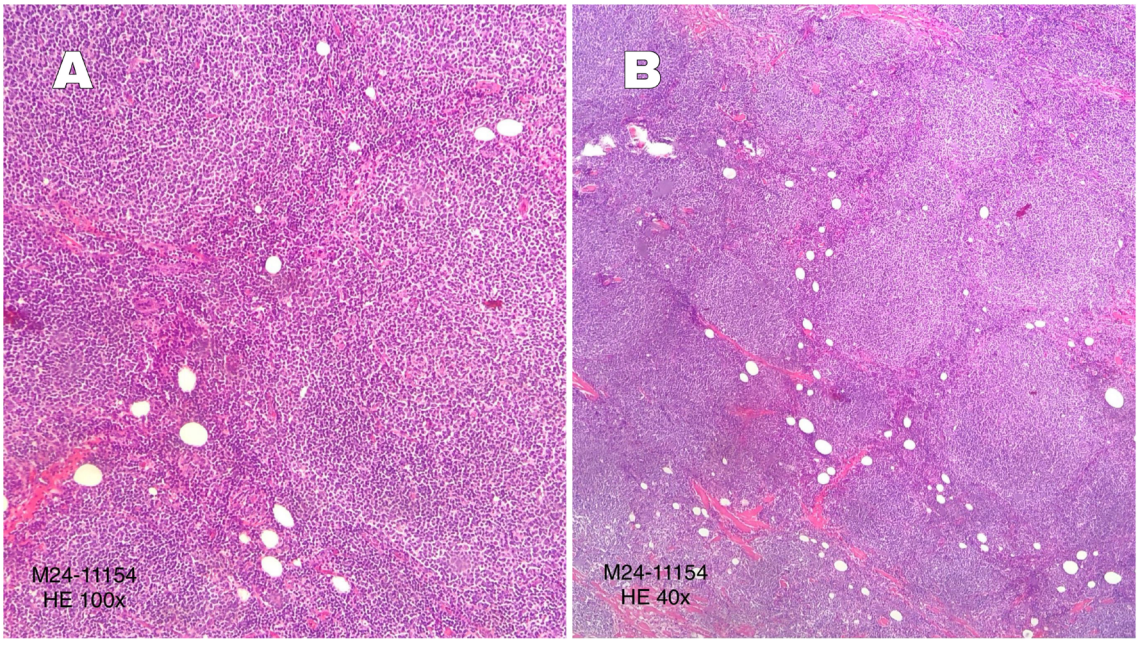

Figure 2A. Histopathology showing a follicular lymphoproliferative process consistent with follicular lymphoma (HE:100x). **Figure 2B.** Microscopic examination showing an undifferentiated small round cell neoplasm with a follicular lymphoproliferative process and adjacent breast parenchyma with discrete ductal ectasia (HE:40x).

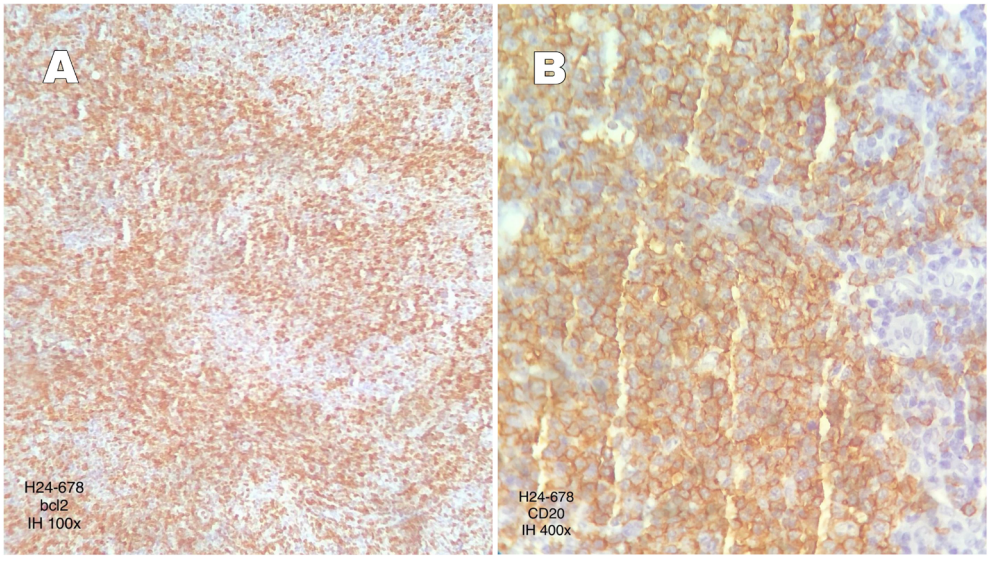

Figure 3A. Immunohistochemical image showing positive perifollicular Bcl-2 staining in the tumor (HE:100x). **Figure 3B.** Immunohistochemical image showing positive perifollicular CD20 staining in the tumor (HE:100x).

3. Discussion

Primary lymphoma accounts for less than 1-2% of all non-Hodgkin lymphomas and less than 0.5% of all malignant breast neoplasms [4-9]. Diffuse large B-cell lymphoma is the most common subtype of primary breast lymphoma, accounting for 40% to 70% of cases. Other less common subtypes include marginal zone lymphoma, follicular lymphoma, and mucosa-associated lymphoid tissue (MALT) [10]. PBL is characterized as a potentially curable neoplasm with clinical features and prognostic factors that are not yet well established. Its pathophysiology is still unknown, but it is thought to be derived from MALT, lymphoid tissue adjacent to mammary ducts and lobules or even from intramammary lymph nodes. Its clinical and imaging presentation is not different from that of breast carcinoma, the most common manifestations being a palpable, painless nodule, and about 12% of cases are incidental findings on mammography, as the patient is asymptomatic [3]. The low incidence of primary follicular lymphoma in the breast makes it difficult to generalize therapeutic approaches and prognoses [1,5]. Although a suspicious lesion was observed on ultrasound, core needle biopsy yielded inconclusive results, which raised doubts and made a definitive diagnosis difficult.

Criteria defined for the diagnosis of PBL [11] are breast as the site of presentation, breast tissue in association with lymphomatous infiltration, absence of disseminated disease beyond the ipsilateral axillary lymph nodes, and no previous diagnosis of lymphoma [3,9]. It is worth noting that these criteria exclude secondary breast lymphomas, i.e., those arising at a primary site but disseminating and manifesting in the breast [6]. Diagnostic criteria include the presence of breast tissue and lymphomatous infiltrate in an adequate specimen and the absence of previous disseminated or extramammary lymphoma, except in ipsilateral axillary lymph nodes [3]. PFBL is thought to originate from follicular B cells in mammary lymphoid tissue and is histologically distinct from other variants of PBL due to the presence of small follicles with small atypical centrocytes with cleaved nuclei. The clinical behavior of primary follicular lymphoma in the breast is heterogeneous, with unpredictable recurrence rates [2,4].

On mammography, most lesions are hyperdense oval masses, whereas on ultrasound they are single oval, circumscribed, microlobulated lesions. They are usually hypoechoic and calcifications or spiculated margins are uncommon [3,12]. The diagnosis of PFBL is usually made by excisional biopsy or wide excision of the tumor, confirmed by anatomopathological examination [7]. Characteristically, tumor cells express CD19, CD20, CD10 and BCL64 proteins, as well as the anti-apoptotic protein BCL25. In the case presented by Urooj et al., 2022, the immunophenotypic analysis was positive for CD20, CD10, BCL2 and BCL6 markers, resulting in a histological diagnosis of follicular Non-Hodgkin's Lymphoma and corroborating the results found in the examinations of this article [13-14].

PFBL has an excellent prognosis after treatment, with an overall response rate of 97% according to one study [6]. There is still no consensus on the best therapeutic approach, which may include surgery, radiotherapy, chemotherapy, or immunotherapy [3]. Mastectomy has been a common component of therapy for primary breast lymphoma, but some studies show that there is no benefit to this type of approach, with radical surgery being an unnecessary option. In this case, surgery would be limited to a biopsy to establish the correct histologic diagnosis, leaving treatment with curative intent to radiotherapy and chemotherapy [2,5]. In the reported case, breast quadrantectomy at the site of the nodule was curative for the neoplasm, and no other affected areas were found by PET-Scan, thus excluding the indication for adjuvant radiotherapy or chemotherapy. One study revealed a reduced risk of recurrence in treatment with radiotherapy alone or in combination with surgery, and this has since been supported by others [6]. Therapeutic decisions, such as the choice between radiotherapy and chemotherapy, still lack consensus due to the rarity of the condition [6,9].

As for chemotherapy, the regimen of Cyclophosphamide, Doxorubicin, Vincristine and Prednisone (CHOP) is the most widely accepted. However, there is still controversy about the selection criteria for combination therapy. Five-year survival varies from 89% in stage I cases to 50% in stage II and, in some reports, age is considered an independent factor for long-term survival [3]. One study showed successful treatment of high-grade PFBL with radiotherapy in combination with Rituximab-Cyclophosphamide, Hydroxyunorubicin, Oncovin, and Prednisone (R-CHOP) [7].

Primary breast lymphoma behaves differently from nodal lymphomas and its early diagnosis is of great relevance. Prognosis depends mainly on the type, grade, and stage of the lymphoma. Its clinical presentation and nonspecific imaging features require a review of the clinical history, a multimodality imaging approach and histopathology for diagnosis and treatment [6,12,13,15]. As noted by Picasso et al., the lack of specific data on this subtype contributes to uncertainties regarding survival [15]. Therefore, primary and secondary lymphomas, although rare, should be considered in the differential diagnosis of breast neoplasms [1,6,7].

4. Conclusion

Although primary follicular breast lymphoma is a rare entity, it should be considered in the differential diagnosis of breast neoplasms, especially in older women. Diagnosis by imaging tests is challenging, which makes anatomopathological and immunohistochemical analysis essential for a definitive diagnosis.

5. Abbreviations

PBL: Primary breast lymphoma

WHO: World Health Organization

NHL: Non-Hodgkin's lymphomas

FL: Follicular lymphoma

PFBL: Primary follicular breast lymphoma

PET-Scan: Positron Emission Tomography scan

MALT: mucosa-associated lymphoid tissue

CHOP: Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone

R-CHOP: Rituximab-Cyclophosphamide, Hydroxide-Unorubicin, Uncovin, and Prednisone

6. Administrative information

6.1 Additional files

No

6.2 Acknowledgements

None

6.3 Author Contributions

Bruno Pelinson Fogaça Duarte: conceptualization, methodology, formal analysis, research, project administration, writing of the original draft.

Julia Saccaro Duzzi: visualization and writing.

José Gabriel Kiel Francisco Petillo: visualization and writing.

Geovanna Vieira Araújo: visualization and writing.

Angelo Sementilli: supervision, review, and editing.

All authors read and approved the final version of the manuscript

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6.5 Availability of data and materials

Data are available upon request to the corresponding author. No other materials are reported.

7. Disclosures

7.1 Consent to publication

The patient gave written informed consent for the present study.

7.2 Conflict of Interest

The authors declare no conflict of interest.

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