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Case Report

Pathology Section

Primary Extranodal Marginal Zone Lymphoma of the Breast: A Case Report Highlighting the Clinicopathological Paradigm of an Indolent B-Cell Neoplasm

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ABSTRACT

Primary or secondary lymphoma of the breast is an uncommon entity, accounting for less than 0.5% of all breast malignancies and approximately 1-2% of extranodal lymphomas. Diffuse Large B-Cell Lymphoma (DLBCL) is the most frequently reported histological subtype. Marginal zone B-cell lymphoma involving the breast is exceedingly rare, particularly in patients with a prior history of DLBCL. The present case describes an unusual occurrence of synchronous second primary lymphoid neoplasm of breast in a patient previously treated for DLBCL, highlighting its diagnostic rarity. The authors report a rare case of a 57-year-old female with a past history of DLBCL, diagnosed two years ago on histopathological examination of excised lymph node over left neck region. Patient received chemoradiotherapy post-diagnosis and had recovered completely. She now presented with bilateral breast lumps and an additional lump in the left axillary region. An initial histopathological diagnosis of Non-Hodgkin's Lymphoma of breast was made which needed further immunophenotypic characterisation. Immunohistochemistry (IHC) was done which showed strong positivity for CD45, CD19, CD20, PAX5, Bcl2, Ki-67 which confirmed the diagnosis of Marginal Zone B-cell Lymphoma, emphasising diagnostic challenges. Post histopathological diagnosis and immunohistochemistry, patient received targeted therapy along with chemotherapy to which she responded well. The present case is noteworthy because of the uncommon involvement of both breasts and the axillary region in a patient with a prior diagnosis of DLBCL, suggesting potential disease recurrence or extranodal extension.

Keywords: Breast neoplasms, Extranodal lymphoma, Immunohistochemistry, Lymphoma-marginal zone, Lymphoma-mucosa-associated lymphoid tissue

CASE REPORT

A 57-year-old female presented with lump over left axilla since one month and lump over bilateral breast since ten days. The patient was a known case of DLBCL of cervical lymph node diagnosed in 2022 and has undergone three cycles of Rituximab, Cyclophosphamide, Hydroxydaunorubicin, Oncovin, Prednisone (RCHOP) regimen and 18 fractions of radiotherapy.

Ultrasonography (USG) of the left arm done shows evidence of a large, well-defined, heterogeneously hypoechoic mass measuring approximately 15×10 cm, arising from left axilla in distal aspect of left arm taking central vascularity on Doppler likely suggestive of lymphoma, also surrounded by superficial hyperechoic fat lobules separated by fluid filled areas suggestive of Cellulitis.

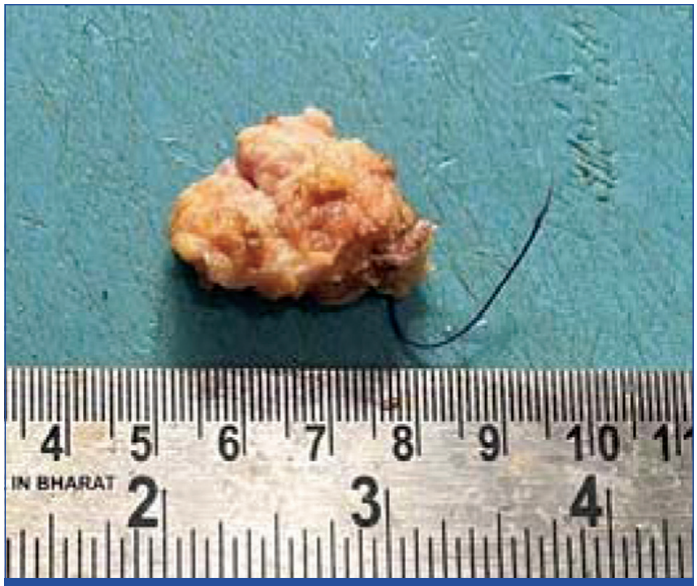
Contrast-Enhanced Computed Tomography (CECT) abdomen and thorax revealed large, lobulated, enhancing, soft-tissue density lesion in left axilla measuring approximately 10×9×6 cm, extending into infraclavicular region without bony erosions along with new lymphadenopathy in neck, abdomen and bilateral inguinal regions suggestive of anatomical disease progression/recurrence.

On examination: a) left axillary lump- swelling of size measuring approximately 10×8 cm present over left arm, no punctum seen, edge of swelling is diffuse, superficial veins are not engorged and tense and shiny skin seen; b) left breast lump- a single, globular, mobile, tender lump with irregular margins present in the upper inner quadrant measuring approximately 4×3 cm. No nipple discharge, peau d'orange, nipple retraction seen; c) right breast lump- a single, globular, mobile, tender lump with irregular margins present in the upper inner quadrant measuring approximately 2×2 cm. No nipple discharge, peau d'orange, nipple retraction seen.

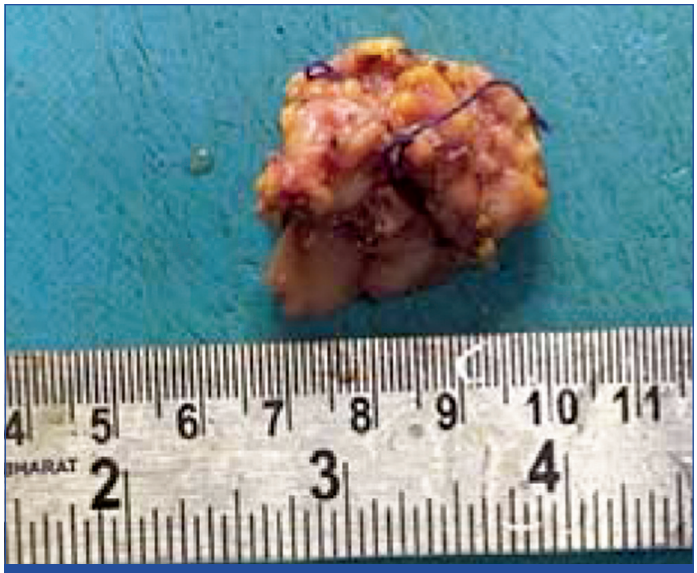
After examination by the surgical team and consultation from the surgical oncologist, since the patient was already a known case of DLBCL, new lumps in the breast and axilla raised suspicion of recurrence of the disease and hence the patient then underwent excisional biopsy of both right and left breast lumps and axillary lymphadenopathy. All the specimens were sent for histopathological examination. On histopathological examination, grossly bilateral breast lumps and left axillary lump were greyish-yellow tissues [Table/Fig-1-3], firm in consistency and cut-sections showed whitish, homogeneous areas [Table/Fig-4]. On microscopy, sections showed predominantly lymphocytic infiltrate with diffuse growth pattern along with invasion of adipose tissue and breast parenchyma [Table/Fig-5-7]. The infiltrate mostly consists of predominantly medium-sized monocytoid-like lymphocytes admixed with large immunoblasts with slightly irregular nuclei, dispersed chromatin, inconspicuous nucleoli and variable amounts of pale cytoplasm [Table/Fig-8,9] favouring the diagnosis of non-Hodgkins lymphoma of breast which then required immunohistochemical examination for further subtyping.

Histopathology confirmed the primary diagnosis of non-Hodgkins Lymphoma in a known case of DLBCL, the following differentials were kept in mind when diagnosing the same i.e., Extranodal Marginal Zone Lymphoma (EMZL), follicular lymphoma, mantle cell lymphoma, lymphoblastic lymphoma, Burkitt lymphoma. A lymphoma panel IHC was framed to rule out each of the differentials which included the following IHC markers: CD45, CD19, CD20, CD3, CD5, CD10, PAX5, BCL2, BCL6, CD23, CyclinD1 and Ki-67.

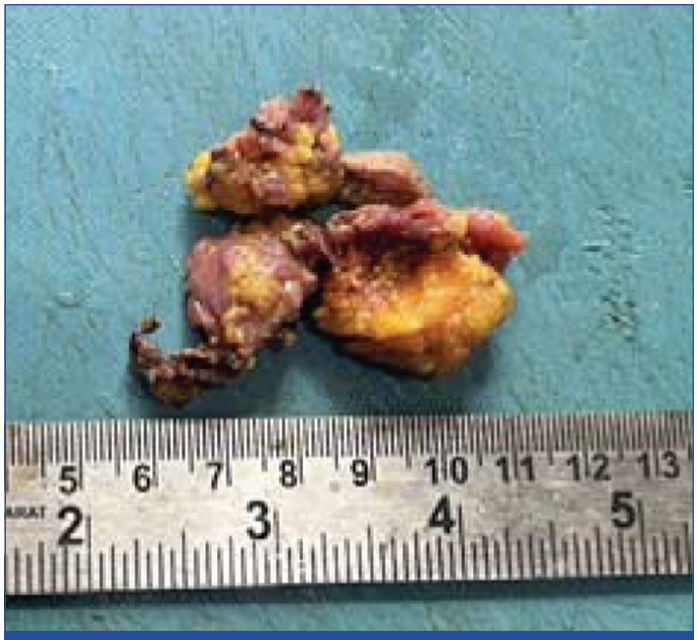
Immunohistochemistry studies done showed positivity for the following markers: CD19, CD20, CD45, PAX-5, BCL2, Ki-67->95% [Table/Fig-10a-f] and was negative for - CD3, CD5, CD10, CyclinD1, BCL6, CD23, thus confirming the subtype as Marginal



[Table/Fig-1]: Gross image of right breast lump.

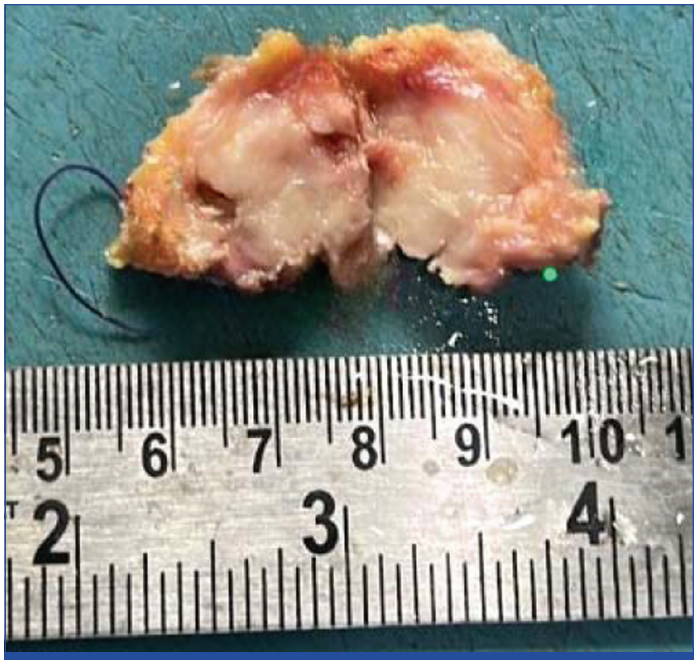


[Table/Fig-2]: Gross image of left breast lump.

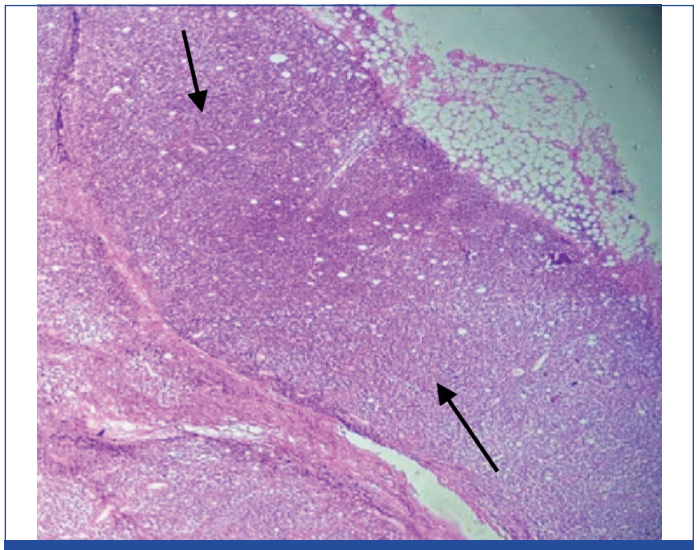


[Table/Fig-3]: Gross image of left axillary lump.

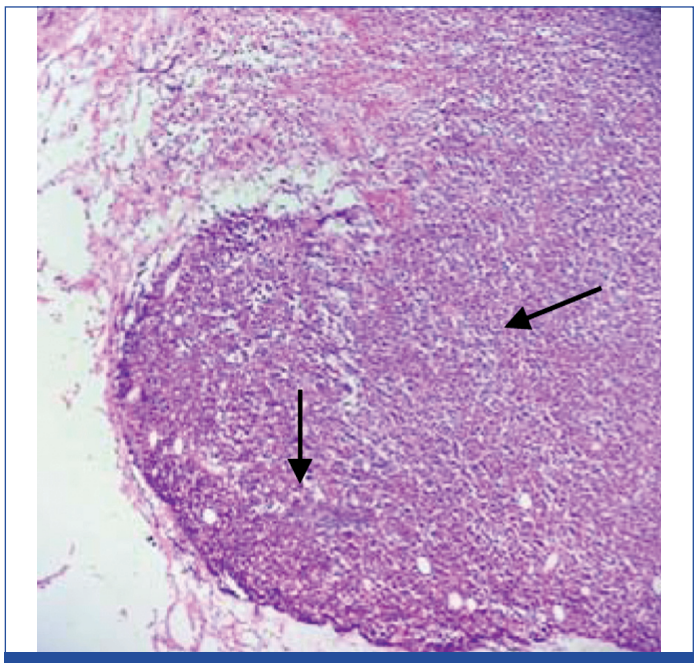
Zone Lymphoma- extranodal Type. The patient was stable post-operatively and after consultation with the Oncology team, she was started on R-ICE regimen protocol (Rituximab, Ifosfamide, Carboplatin and Etoposide) along with supportive care. She was



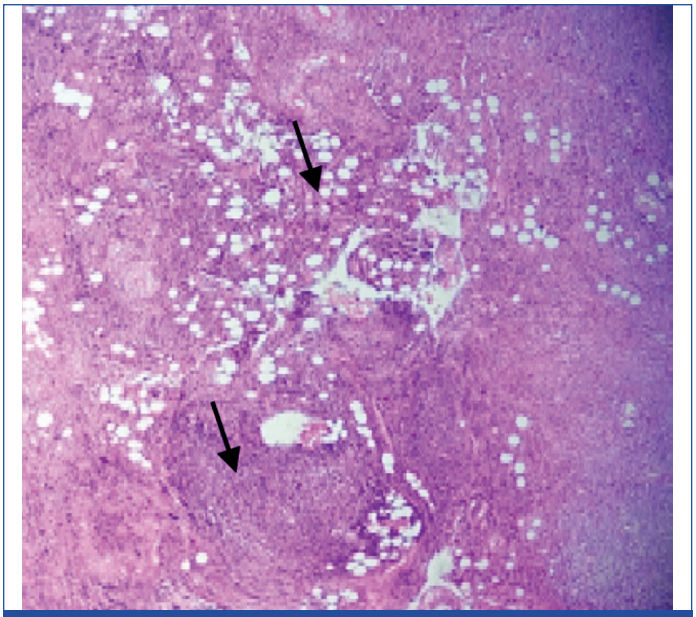
[Table/Fig-4]: Cut-section of right breast lump showing whitish homogenous areas grossly.



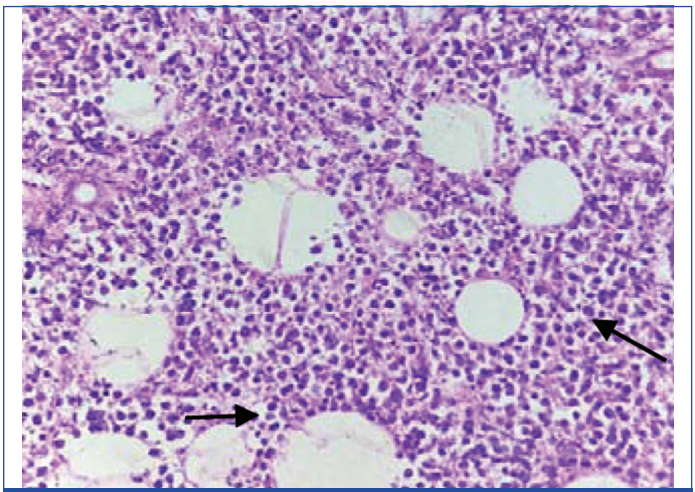
[Table/Fig-5]: Section of lump in breast showing breast parenchyma infiltrated with lymphocytes (black arrow) (H&E, 10x).



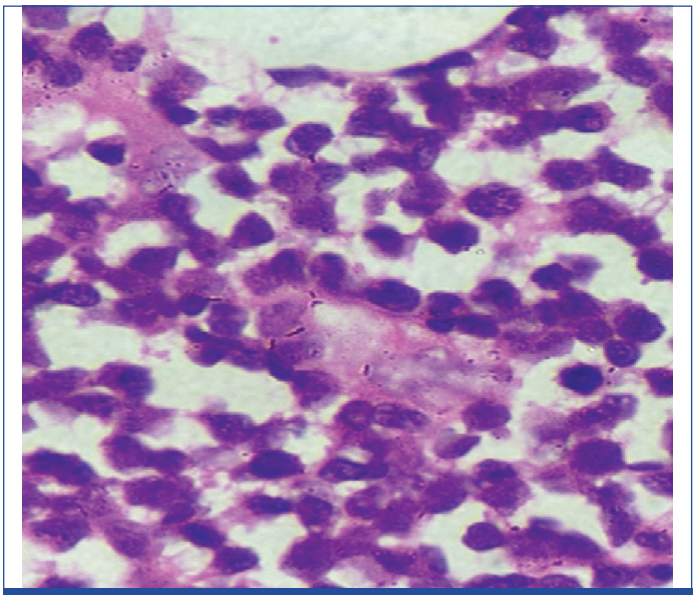
[Table/Fig-6]: Section of lump in axilla showing lymphocytic infiltration (black arrow) (H&E, 20x).



[Table/Fig-7]: Infiltration of lymphocytes into adipose tissue of breast parenchyma (black arrow) (H&E, 20x).

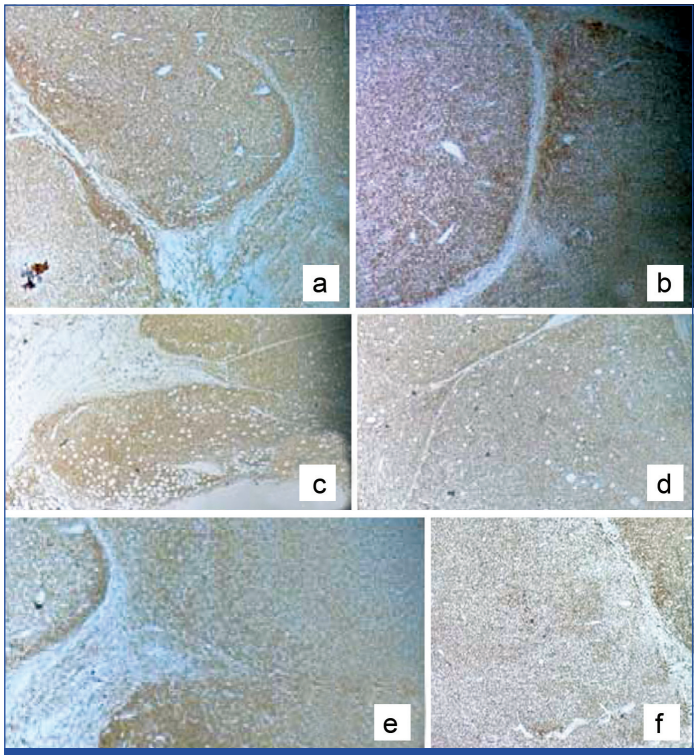


[Table/Fig-8]: Section showing predominantly medium-sized monocytoid-like lymphocytes admixed with large immunoblasts (black arrow) (H&E, 40x).



[Table/Fig-9]: Section showing atypical lymphocytes with slightly irregular nuclei, dispersed chromatin, inconspicuous nucleoli and variable amounts of pale cytoplasm (H&E, 100x).

initiated with the first cycle prior to her discharge, to which she responded well and had no adverse effects. Patient was advised three cycles of R-ICE regimen every 21 days. By the time this report was written patient had completed two cycles of the regimen, was haemodynamically stable and responding well to the treatment.



[Table/Fig-10]: Immunohistochemistry demonstrating positivity for markers. a) CD45; b) PAX5; c) CD19; d) CD20; e) BCL2; f) Ki-67->95% (IHC, 4x).

DISCUSSION

Primary Breast Lymphoma (PBL) is an uncommon neoplastic condition, comprising about 1% of all non-Hodgkin lymphomas and less than 1% of breast cancers. DLBCL is the most common histological subtype, accounting for almost 56-84% of cases. The rest of the cases are due to indolent lymphomas, such as marginal zone lymphoma (9-28%) and follicular lymphoma (10-19%) [1]. The World Health Organisation classifies marginal zone lymphoma into three types: nodal, splenic, and EMZL. The last type (EMZL) is also known as Mucosa-Associated Lymphoid Tissue (MALT) lymphoma.

The EMZL, or MALT lymphoma, is a unique subtype of indolent B-cell non-Hodgkin lymphoma that originates from post-germinal center marginal zone B lymphocytes. It is distinguished by its origin in extranodal sites and its robust correlation with chronic antigenic stimulation, encompassing infections and autoimmune disorders. Chronic immune stimulation is closely linked to the growth of EMZL. Infectious agents, including *Helicobacter pylori* (gastric EMZL), *Chlamydia psittaci* (ocular adnexa), and *Borrelia burgdorferi* (cutaneous EMZL), have been associated with site-specific lymphomagenesis. Sjögren's syndrome and Hashimoto's thyroiditis are two autoimmune diseases that are also well-known risk factors [2,3]. At the molecular level, EMZL is linked to recurring genetic anomalies characterised by the activation of the NF-κB signalling pathway, including translocations like t(11;18) (q21;q21) involving the MALT1 gene, along with modifications in BCL10 and other regulatory genes [4].

The EMZL commonly involves the gastrointestinal tract accounting for about 50%, followed by the ocular adnexa (5-10%) and salivary glands, while breast involvement is exceedingly rare, comprising nearly 3% of EMZL cases [5]. Thus, primary EMZL of the breast is a very rare type of clinicopathological entity. EMZL originating from various anatomical locations has been demonstrated to correlate with autoimmune disorders, including Hashimoto's thyroiditis in thyroid EMZL and Sjögren's syndrome in salivary gland involvement. Clinically, breast lymphoma typically manifests as a palpable breast lump, although certain cases may be incidentally identified

S. No.	Author (year)	Study type	Sample size	Key clinical features	Diagnostic findings	Treatment
1.	Sakhri S et al., (2023) [7]	Case series	Small series	Painless lump in breast, mimicking carcinoma	Histopathology + IHC essential	Surgery chemotherapy
2.	Yan M et al., (2023) [8]	Retrospective study	Limited cohort	Variable presentation, primary vs secondary	Consistent EMZL immunophenotype	Mixed treatment modalities
3.	Sawano T et al., (2024) [11]	Case report	Single case	Mimicked aggressive breast carcinoma	IHC confirmed EMZL	Surgery + RT
4.	Wang H et al., (2024) [3]	Case report	Single case	Breast mass without systemic symptoms	Classic CD20+, CD5-, CD10- profile	Rituximab-based therapy
5.	Hui J et al. (2025) [10]	Case report + review	Single case	Indolent breast lump	Histology decisive	Conservative + Immunotherapy
6.	Lee KJ et al., (2025) [12]	Case report	Single case	Coexistent carcinoma + lymphoma	Dual pathology on biopsy	Combined management

[Table/Fig-11]: Comparative literature review of various cases reported on EMZL [3,7,8,10-12].
RT: Radiotherapy

during screening mammography [6]. The median age at diagnosis is between 61 and 65 years, and the ages of females who have breast EMZL range from 23 to 88 years. About 85% of breast EMZL cases occur in women who have attained menopause. There have been few reports of bilateral breast involvement. Diagnostic evaluation usually starts with mammography or ultrasonography, and then a core needle or excisional biopsy is done to confirm the histopathological diagnosis. Primary breast EMZL shows a slower clinical course than other breast lymphomas and is usually linked to good outcomes.

Various studies have been done in the past in correlation to diagnostic findings and clinical features to narrow down the significance of this entity. In a study done on case series by Sakhri S et al., they analysed multiple cases of PBL and highlighted the extreme rarity and heterogeneity of presentation which included histopathological as well as immunohistochemical parameters [7]. A retrospective study conducted by Yan M et al., evaluated both primary and secondary breast MALT lymphomas over a long duration, emphasising Institutional experience rather than population-level data [8]. More recent studies done by Shibahara Y et al., and Hui J et al., aimed at single case reports and small case-based reviews reflecting the lack of large scale prospective data [9,10]. A single case report study done by Sawano T et al., highlighted the stress of aggressive breast carcinoma like triple-negative carcinomas mimicking EMZL, which was then confirmed on IHC, providing an outlook on diagnostic pitfalls [11]. Another interesting insight, as observed in a single case report by Lee KJ et al., was evidence of coexistence of primary breast carcinoma and lymphoma in the same breast which indicated the presence of synchronous malignancy [12]. A few other studies have documented studies on treatment protocols and management of EMZL, which still includes the standard R-CHOP, Rituximab, Ifosfamide, Carboplatin and Etoposide (R-ICE) regimens (as mentioned earlier) along with supportive care. Luo S et al., in their study concluded that currently, research has primarily focused on the pathogenesis and treatment of gastric MALT lymphoma, while there is a lack of standardised treatment and follow-up protocols for breast MALT lymphoma. Additionally, it is unclear whether oestrogen plays a role in its development and if there are specific treatments targeting this aspect. In recent years, the incidence of breast lymphomas has been on the rise. Therefore, it is important to remain vigilant when diagnosing and treating BL, continuously investigate its pathogenesis, and develop appropriate diagnostic methods and treatment strategies that are tailored to each patient's needs in order to maximise their chances of recovery [13]. The comparative studies of various authors in recent years have been summarised in a tabulated form [Table/Fig-11] [3,7,8,10-12].

It is imperative to differentiate between EMZL and reactive lymphoid hyperplasia and other small B-cell lymphomas like follicular lymphoma, mantle cell lymphoma, chronic lymphocytic leukaemia/small lymphocytic lymphoma, lymphoplasmacytic lymphoma, and DLBCL. Reactive lesions typically exhibit a polymorphous infiltrate comprising polyclonal lymphoid cells, whereas EMZL displays a homogeneous population of atypical small lymphocytes characterised by marginal zone differentiation. Follicular lymphoma usually has CD10 and BCL6, mantle cell lymphoma has CD5 and Cyclin D1, and CLL/SLL has CD5 and CD23. Histopathological examination, augmented by immunohistochemistry, is imperative for a conclusive diagnosis. Tumour cells in EMZL typically express CD20, CD79a, and BCL2, indicating B-cell lineage, while they lack expression of CD5, CD10, CD23, and Cyclin D1. The Ki-67 proliferation index is usually low in most cases favouring its indolent behaviour but in the present case the high proliferative index indicates poor prognosis and possible clonal evolution due to prior history of DLBCL.

As much as pathological and immunohistochemical diagnosis portrays importance, a few foci on disease progression and survival also calls for discussion. Breast EMZL usually stays in the primary site for a long time and may follow a chronic relapsing–remitting course. Even though it can spread to other extranodal sites and the bone marrow, it usually happens late and is not very serious or fatal. Prognostically, EMZL exhibits superior outcomes, with 5-year survival rates surpassing 90% [14]. In contrast, DLBCL, although potentially curable with immunochemotherapy, presents a comparatively unfavourable prognosis, especially in high-risk populations and instances of relapse. For patients with a previous diagnosis of DLBCL who present with new breast lesions, it is essential to differentiate between relapse and a second primary EMZL, as the treatment strategies and clinical outcomes vary significantly. This highlights the significance of excisional biopsy and thorough immunohistochemical assessment to achieve an accurate diagnosis and inform suitable management.

CONCLUSION(S)

Breast MALT lymphoma is an uncommon malignant neoplasm of the breast. Clinically, it most frequently presents as a painless breast mass, closely resembling carcinoma and thus presenting diagnostic difficulties. A definitive diagnosis depends on the immunohistochemical analysis of tumour tissue. Although standardised treatment and follow-up protocols for breast MALT lymphoma are still absent. Furthermore, the prospective impact of oestrogen on disease progression and the accessibility of hormone-targeted therapeutic strategies remain inadequately defined. There has been a rise in breast lymphoma cases in recent years, which underscores the importance of clinician awareness of this condition. To get the best results for patients, it is important to keep looking into its underlying mechanisms and come up with the right diagnostic and personalised treatment plans.

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