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CASE REPORT

Clinico-radiologic features and management of hematological tumors in the breast: a case series

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Abstract
Hematological tumors arising in the breast are uncommon and require different treatment modalities dependent upon tumor type. Current treatment options include surgical excision, chemotherapy, and radiotherapy. Management of these breast malignancies are poorly outlined in the literature. The purpose of this case series is to report five cases consisting of extranodal marginal zone lymphoma, lymphoplasmacytic lymphoma, and extramedullary plasmacytoma occurring in the breast. The cases illustrate heterogeneous radiologic findings and varying management approaches to these tumors. The case series underscores the importance of having a wide differential at diagnosis and recognizes management of disease should be taken on an individual basis with consideration of prognosis and first-line treatment options.

Keywords Breast lymphoma · Extramedullary plasmacytoma · Breast cancer · Imaging

Introduction

Breast cancer is the most common malignancy in women [1]. Most are invasive, with the majority infiltrating ductal carcinoma and invasive lobular carcinoma [1]. Among breast malignancies, primary breast lymphomas are extremely rare, while breast lymphomas due to secondary involvement are more frequent. Beyond primary breast lymphomas, breast extramedullary plasmacytomas are also uncommon. They are a rare localized plasma cell disorder found outside of the bone marrow, arising from lymphoid tissues in the upper respiratory tract submucosa [2]. The sinonasal area is the most common site of origin, but they can be found in other locations [2]. Evaluation of a breast mass with suspicion of cancer should include common and rare etiologies. Clinical symptoms and radiologic findings are largely nonspecific for breast hematological tumors requiring biopsy for a definitive diagnosis. Diagnosis is crucial as treatments of breast cancers are different from hematological malignancies. Herein, we present five cases of breast hematological malignancies.

Case reports

Case 1

A 29-year-old female with a history of sclerosing lymphocytic lobulitis of the left breast presented with a palpable lump in her left breast. A heterogeneously dense mass in the location of her lobulitis was seen on mammography that appeared to be stable over the last year (Fig. 1a). Ultrasound results demonstrated a hypoechoic, ill-defined mass that had increased from 2.5 to 2.9 cm with posterior shadowing (Fig. 2a). Lumpectomy was performed and clear margins were obtained. Pathology of the resected lesion showed extensive perivascular and periductal lymphoid infiltrate with a few lymphoepithelial lesions. Immunohistochemical staining showed strong expression of CD20, with weaker positivity for CD3 and CD5. With high expression of CD20 and the morphology, low grade extranodal marginal zone lymphoma (EMZL) was diagnosed.

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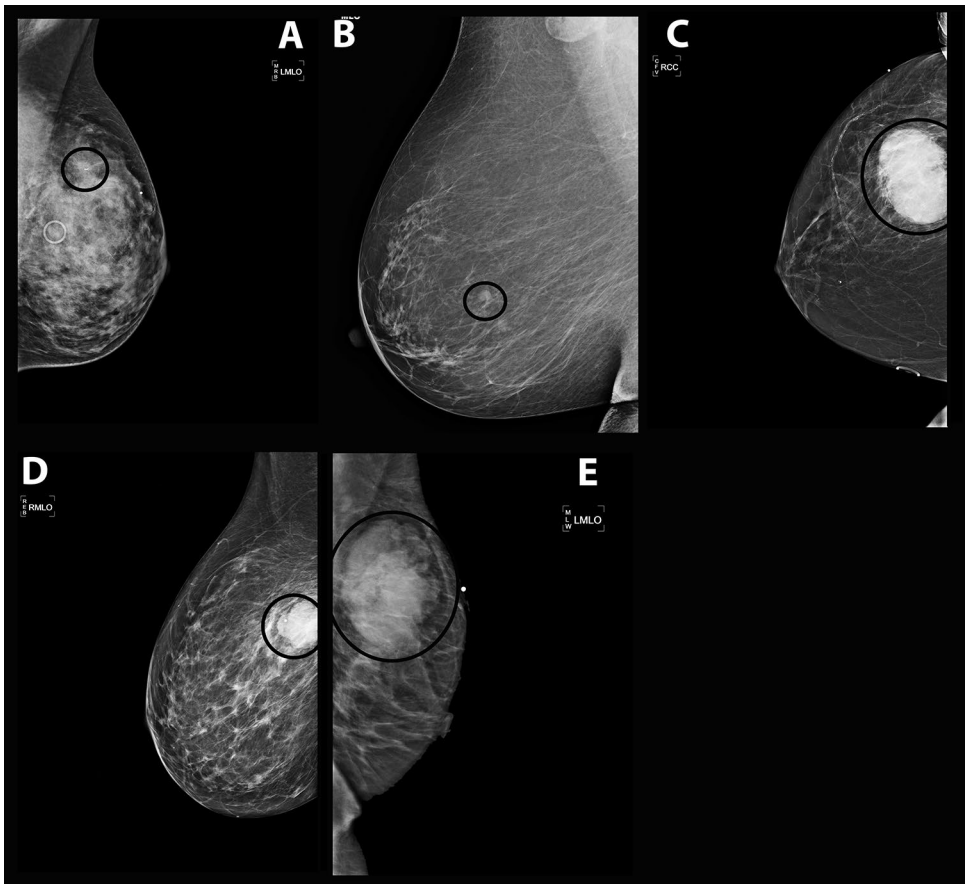

Fig. 1 Diagnostic Mammograms of all five patients showing their breast lesions. Diagnostic mammograms corresponding to patients 1–5 (**a**–**e**). The round black circles show the location of the breast tumor

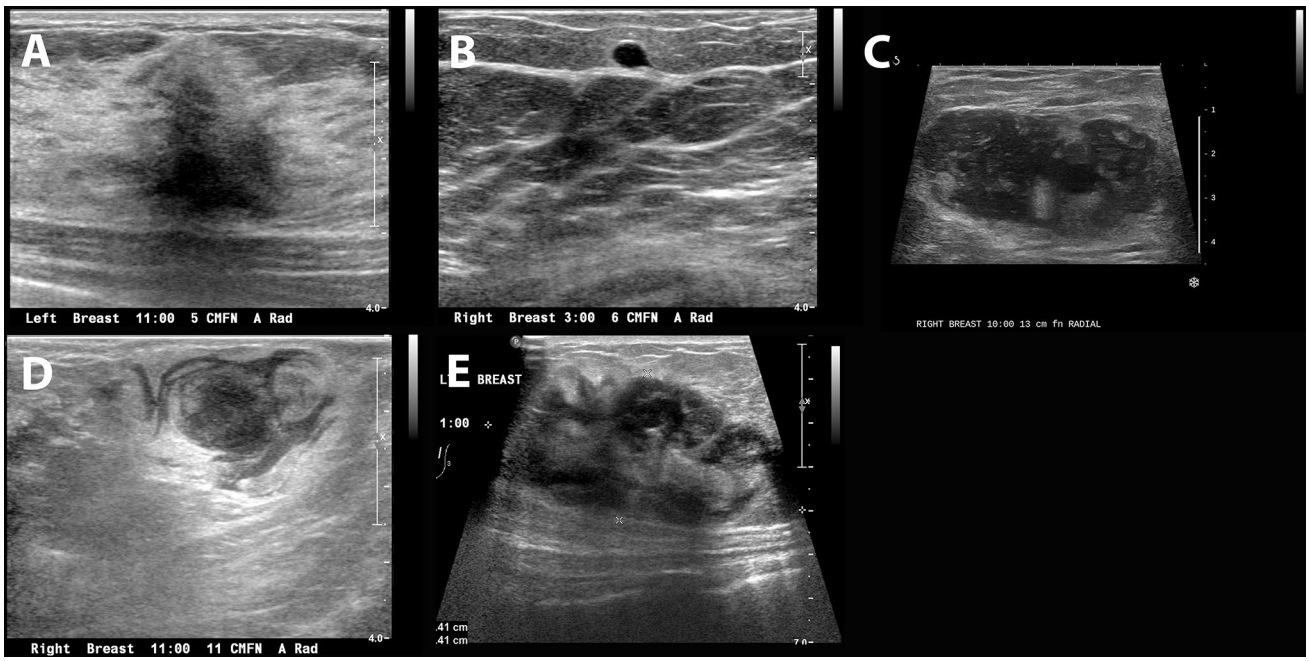

Fig. 2 Diagnostic Sonograms of all five patients showing their breast lesions. Diagnostic sonograms corresponding to patients 1–5 (**a**–**e**)

Case 2

An abnormality was found on a screening mammogram performed on a 69-year-old female. Using diagnostic mammography, an irregular mass in the right breast, ~ 7 cm from the nipple was seen (Fig. 1b). Ultrasound showed a cyst-like 6.0 mm oval nearly anechoic lesion (Fig. 2b). Several attempts at aspiration were unsuccessful. Histological examination of a core needle biopsy demonstrated atypical lymphoplasmacytic infiltrate with small B lymphocytes and kappa restricted plasma cells. Immunohistochemical analyses showed tumor cells positive for CD138, while CD56 was negative. CD20 and CD3 were positive in normal appearing B and T cells, respectively. The*MYD88* L265P mutation was not detected. Lymphoplasmacytic lymphoma (LL) was diagnosed using histopathological features with positive CD138 and CD20 staining.

Case 3

An 84-year-old female with a history of multiple myeloma (MM) since 2002 presented after falling on her chest. Physical examination revealed a palpable lump in the upper outer quadrant of her right breast. Review of her mammogram 9 months prior showed no abnormalities, however, current diagnostic mammography revealed a large dense mass (Fig. 1c). Ultrasound demonstrated a heterogeneous mass with mixed internal echogenicity and peripheral vascularity (Fig. 2c). Immunohistochemical staining of biopsy tissue was positive for CD3, CD45, and CD138, along with diffuse lambda ISH positive staining. Serum protein electrophoresis showed lambda light chains and M-spike levels trending upwards to 1324 mg/dL and 2.40 g/dL, respectively. These findings are consistent with the diagnosis of extramedullary plasmacytoma (EP) of the breast with lambda light chain restriction.

Case 4

A 78-year-old female with a 2-year history of MM began developing pain in her lateral right breast which correlated with a palpable lesion upon physical exam. It appeared that her MM had progressed since her partial remission in 2015. Mammography demonstrated a large dense mass measuring ~ 3.0 cm (Fig. 1d). Ultrasound showed a 3.7 cm well-circumscribed, hetero-echoic lesion with peripheral vascularity (Fig. 2d). Significant overlying ecchymoses were identified and that combined with mass heterogeneity and overlying skin changes were suggestive of a hematoma. Prior to a 3-month follow-up sonogram, a breast oncologic surgeon performed a core needle biopsy. Tissue sections showed sheets of plasma cells with a number of binucleated cells. Immunohistochemical analysis showed kappa restricted plasma cells with positive staining for CD138 and CD56, but negative for CD20, making for a final diagnosis of a plasmacytoma.

Case 5

A 55-year-old woman with a history of MM presented to an outside institution with a large palpable left breast lump. Parts of her case have been reported previously [3]. Mammography revealed an indeterminate round, solid mass (Fig. 1e). Ultrasonography demonstrated it to be a hypoechoic 7.4 cm lobulated lesion with posterior shadowing (Fig. 2e). Initial immunohistochemical analysis showed positive staining for CD31 and vimentin, thus, early diagnosis was an angiosarcoma [3]. Upon referral, we diagnosed a plasmablastic plasmacytoma. Due to its increased size (11 × 8 cm), she was referred for surgical resection. Immunohistochemical analysis showed plasma cells that were positive for CD138, CD31, and CD56. Lambda staining was in 100% of the plasma cells. Plasma cells had enlarged, eccentric nuclei and moderately frequent mitotic figures. This examination corresponded to the diagnosis of plasmacytic plasmacytoma of the breast.

Discussion

Extranodal marginal zone lymphoma

Extranodal marginal zone lymphoma is a proliferation of indolent B cells that arises from the marginal zone of secondary lymphoid follicles outside of lymph nodes. EMZL mainly occurs in the gastrointestinal tract, but can also be seen in tissue number of other tissues [4]. Less than 0.5% of all lymphomas occur in the breast, and only 2% of extranodal non-Hodgkin lymphomas are localized in the breast [5].

The differential diagnoses includes benign inflammatory processes such as lymphocytic mastitis [6], IgG4-related sclerosing mastitis [7], and cutaneous lymphoid hyperplasia [8]. These inflammatory processes can present as a breast mass composed of T and/or B cells without intact tissue architecture. Morphological, flow cytometric, and molecular studies are needed to help differentiate between an inflammatory process and malignant neoplasm because imaging findings are nonspecific for lymphoma. Mammography can show increased stromal density, skin thickening, nodular masses, and axillary lymphadenopathy with well-circumscribed or incompletely circumscribed lesions [9]. Ultrasonography has characteristics ranging from well-defined to poorly defined, hypo- to hyperechoic masses with focal or diffuse involvement with variable attenuation [9]. Diagnosis of EMZL requires histopathological and cytological examination. Since it is from a B-cell lineage, presence of

the B-cell marker CD20 is part of an immunophenotypic pattern for marginal zone lymphoma, while CD5 and CD10 are not commonly expressed [10]. In this case, positive staining for CD3 and CD5 was found and may indicate T cells were present. This may be due to inflammation as the result of sclerosing lymphocytic lobulitis or the presence of reactive plasma cells in the lymphoma. It is unknown what role sclerosing lymphocytic lobulitis may have played in this case.

Treatment for EMZL varies dependent upon disease location, but it normally entails radiation therapy. Radiotherapy alone is effective in early stage, localized cases and can be the main treatment option as EMZL is very sensitive to low dose radiation. Surgical resection can be used for curative purposes or when tumor location is unfavorable for radiation. For the current patient, excisional biopsy not only helped to diagnose EZML, but it provided clinical remission since the entire tumor was removed. In more advanced cases, lesions involving lymph nodes or discontiguous spread can be treated with a combination of radiation and chemotherapy, with or without immunotherapy [4]. Overall survival for marginal zone lymphoma was 100% at 3 years, 92% at 5 years, and 64% at 10 years [11].

Lymphoplasmacytic lymphoma (LL)

B-cell LL is characterized by proliferation of malignant IgM producing lymphocytes, plasmacytoid lymphocytes, and plasma cells in bone marrow or other tissues [12] and it makes up 1–2% of all Non-Hodgkin's lymphomas. The *MYD88* L265P mutation has been identified in > 90% of bone marrow-based LL, but correlation with nodal LL is undetermined [13].

Mammography and ultrasonography are nonspecific in diagnosing breast lymphoma, but they have been described as anechoic, and in this case of LL, the sonogram demonstrated atypical cyst-like structures [14]. However, unremarkable sonogram findings have been reported in other cases [15]. Therefore, the differential for this case includes breast cyst, marginal zone lymphoma with plasmacytic differentiation, or an atypical presentation of a plasma cell neoplasm. Since LL commonly expresses CD19, CD20, and CD22 [16], immunohistochemical and flow cytometric studies confirm the diagnosis. The median serum monoclonal protein level for symptomatic patients is 4 g/dL with a 3:1 kappa and lambda cell ratio, a normal ratio is about 2:1 [16]. This mass had CD56 negative cells, scattered positive CD138 and CD20 cells, and a κ:λ ratio of > 5:1. The immunophenotype expression and kappa restriction reduce the likelihood of a plasma cell neoplasm and marginal zone lymphoma with plasmacytic differentiation [17].

Immunotherapy or chemotherapy is commonly used for symptomatic disease. Rituximab, alkylating agents, and nucleoside analogs are usually first-line therapy options with possible use of plasmapheresis and corticosteroids [18]. Relapsed patients may be eligible for stem cell transplant or use of different classes of drugs such as bortezomib and alemtuzumab may be effective in refractory cases [18]. LL is indolent in nature and the overall relative 5-year survival is about 78% with a median survival 5–10 years [19].

Extramedullary plasmacytoma

Extramedullary plasmacytoma is made up of an abnormal proliferation of plasma cells in an extraosseous site. It can be isolated or in conjunction with multiple myeloma. Only 4% of plasmacytomas are found entirely in the extramedullary region [20]. Symptoms are related to tumor site or location. The most common site for EPs are in the head and neck region in 80% of cases, but in one study of EP, 53 (1.5%) patients had a breast plasmacytoma [21], accounting for 0.2% of all of their breast cancer cases. Of these patients with breast EP, 85% had secondary involvement due to pre-existing multiple myeloma [21].

The differential diagnoses for the last 3 cases includes hematoma, plasmablastic lymphoma, B-cell lymphoma with extensive plasmacytic differentiation, or plasmacytoma [17]. Upon mammography, EP appears as a dense, round mass and can have well or poorly defined margins [21]. On ultrasonography breast EP can appear as a hypoechoic well-defined mass with hypervascularity, but mixed echogenicity lesions with indistinct margins have been documented [21]. Clinical findings are important when differentiating between plasmablastic lymphoma and EP as they both express CD138 with negative pan-B-cell markers [22]. Plasmablastic lymphoma commonly occurs in immunocompromised patients arising in the oral cavity and mucosal regions in the head with EBV RNA in the tumor. In another study, imaging findings of a breast mass thought to be hematoma given a history of trauma, but subsequent biopsy revealed a plasmacytoma. Histological analysis is needed for accurately diagnosis and can help to distinguish EP from adenocarcinoma through atypical plasma cells containing irregular nuclei and prominent nucleoli in mature plasma cells. Evaluating monoclonal gammopathy with serum protein electrophoresis can aid in diagnosing and differentiating EP from a benign lesion or carcinoma. The presence of CD138 can help identify plasma cells in a mass suspicious for EP [23]. Positivity for CD56 can be used for EPs associated with multiple myeloma as its expression can have prognostic consequences [23].

Chemotherapy is first-line treatment of EP associated with multiple myeloma [24]. Lenalidomide and dexamethasone are most commonly used, however, survival improved with addition of a proteasome inhibitor. Patients 3 and 4 were prescribed first-line therapy with lenalidomide, dexamethasone and ixazomib for EP and symptoms of multiple myeloma. Complete surgical resection of EP can be performed, but

the use of adjuvant radiotherapy for improved survival is unclear. Patient 5 underwent complete surgical resection of her lesion, but she recurred 6 months later because she declined adjuvant therapy. Radiotherapy was performed on the T9 vertebra in patient 4, in conjunction with her breast lesions for palliation of severe pain from multiple myeloma complications. Patients with plasmacytoma have a median survival of 8.12 years, dependent on age of occurrence [25]. With patients > 60 years, 5-year survival rates were greater for those who patients initially diagnosed with multiple myeloma than for patients diagnosed with plasmacytoma which progressed to multiple myeloma [25].

Baylor University Medical Center has a 914 bed capacity along with a dedicated cancer center involved in bone marrow transplant, cancer clinical trials, and research. The breast malignancies presented occurred over a 6-month period. The short time frame for presentation of these patients gives support for a wide differential when evaluating breast lesions. And in patients 2 and 4, the masses were thought to be benign, but eventually resulted in hematological diseases.

Treatments for EMZL, LPL, and EP have been examined, but not many have determined treatment outcomes on primary breast lesions, due to the small number of people affected. The cases described here offer possible treatment options for patients with similar disease presentation.

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Compliance with ethical standards

Conflict of interest None of the authors have any potential conflicts to disclose.

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