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Review article

Hematolymphoid lesions of the breast

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ABSTRACT

Hematolymphoid malignancies of the breast are most commonly neoplasms of mature B-lymphocytes, and may arise as a primary disease or by secondary involvement of a systemic disease. Primary breast lymphomas (PBL) account for 0.04–0.5% of breast malignancies, less than 1% of all non-Hodgkin's lymphomas (NHL), and less than 5% of extranodal lymphomas (Lakhani et al., 2012; Swerdlow et al., 2008; Joks et al., 2011; Barişta et al., 2000; Giardini et al., 1992; Brogi and Harris, 1999; Topalovski et al., 1999).[1–7] Secondary breast lymphomas (SBL) are also rare, with an estimated annual incidence of 0.07% (Domchek et al., 2002; Talwalkar et al., 2008).[8,9] Recognition of breast lesions as hematolymphoid is critical to distinguish them from other entities that can occur in the breast.

Introduction

Making a diagnosis of a hematolymphoid malignancy of the breast first requires exclusion of other more common conditions of the breast involving inflammatory cells. Lymphoid cells can be seen in chronic inflammatory infiltrates related to infection, foreign body reactions, chronic granulomatous mastitis, lymphocytic lobulitis/diabetic mastopathy, and in association with in situ and invasive breast carcinomas. While primary breast lymphomas most often present nonspecifically as a unilateral breast mass in an older woman with or without ipsilateral axillary lymphadenopathy, certain clinicoradiological features should prompt one to consider the possibily of a hematolymphoid neoplasm and reserve tissue for flow cytometry immunophenotyping.[3–10] For instance, an effusion surrounding a breast implant may serve as a clue for an underlying lymphoma, since this is the most common presentation of primary breast anaplastic large cell lymphoma, for which patients with saline or silicone breast implants are at an increased risk of developing.[10–16] Additionally, a history or clinical presentation suggestive of a systemic lymphoma (e.g. lymphadenopathy, hepatosplenomegaly, and/or B-symptoms), should prompt one to consider secondary involvement of the breast.

Breast lymphomas are biologically heterogeneous, and can show variable morphology, immunophenotype, and genetic alterations, however, there are certain general pathologic features which can suggest a malignant rather than reactive hematolymphoid process. The most common type of breast lymphoma is diffuse large B-cell lymphoma (DLBCL), which by definition shows predominantly large cells, and may be less challenging to differentiate from reactive lymphoid processes than from other malignancies such as poorly differentiated carcinoma.[1–9] In cases where small lymphocytes predominant, clues that one may be dealing with a low-grade lymphoma include a dense infiltrate composed of a monotonous population of cells, although a polymorphous population of cells does not exclude a lymphoma. Flow cytometry immunophenotyping can be a very useful ancillary test, especially in cases where small lymphocytes predominant. Evidence of B-cell monotypia or aberrant antigen expression can be used to support the diagnosis of lymphoma. Detection of clonal T-cell receptor (TCR) and immunoglobulin heavy chain rearrangements (IgH) can also be helpful, but demonstration of T or B-cell clone is neither sufficient or necessary to establish the diagnosis of lymphoma (Table 1). At times, despite best efforts, it can often still be difficult to distinguish between reactive and neoplastic lymphoid

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processes and a definitive diagnosis cannot be made. This is especially true with small biopsies and in the absence of ancillary testing. In this event, diagnosis as an atypical lymphoid infiltrate with a recommendation for clinical follow up and consideration for repeat sampling is appropriate.

Once a diagnosis of lymphoma of the breast has been made, it is important to realize that it can represent primary or secondary disease. The distinction between primary breast lymphoma (PBL) and secondary breast lymphoma (SBL) is based on several criteria first defined by Wiseman et al. in 1972 (Table 2).[17]

PBLs are predominantly B-cell lymphomas, most commonly DLBCL, followed by follicular lymphoma (FL) and extranodal marginal zone lymphoma (MZL), then Burkitt lymphoma.[1,17,18] PBLs of T-cell lineage are very rare, but of these, anaplastic large cell lymphoma is the most common type and is associated with unique clinical features.[1,17,18] PBL tend to affect older women in their 6th or 7th decade of life, but may rarely occur in younger women, often in association with pregnancy and lactation.[1]

The majority of secondary breast lymphomas are also of B-cell lineage, and reflect the most common lymphomas seen in nodal and extranodal sites, mostly commonly DLBCL, but also MZL, FL, chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), and others. Secondary involvement of the breast by myeloid, histiocytic, plasma cell, and T-cell neoplasms is exceptionally rare.[19]

Diffuse large B-cell lymphoma (DLBCL)

DLBCL is the most common malignant hematolymphoid neoplasm seen in the breast, and can represent either primary or secondary disease.[1,20] Currently, DLBCL can be divided into two molecular subgroups by gene expression profiling and immunohistochemical staining algorithms, including a germinal center B-like (GCB) and activated B-like (ABC) subtype. The 5-year progression free survival (PFS) and overall survival (OS) rates of the GCB group is superior to the ABC group.[21–23] Recent studies have shown that primary breast DLBCLs are of predominantly of the ABC subtype using immunohistochemical staining algorithms,[9,24–28] although the prognostic significance in this setting is unclear. Two studies have shown that patients with ABC type DLBCL have a similar prognosis to patients with GCB type DLBCL,[26,27], while one study showed that patients with the ABC subtype DLBCLs of the breast have an inferior PFS rate, but similar OS rate.[28]

Morphologically, DLBCLs of the breast frequently appear as a poorly circumscribed mass composed of a proliferation of large lymphoid cells, with frequent infiltration of normal breast epithelium and occasional lymphoepithelial lesions.[24] The diagnosis here can be morphologically complex as DLBCL of the breast may infiltrate in a single cell, linear, or dispersed pattern, mimicking invasive lobular carcinoma of the breast (Fig. 1, Table 3). The lymphoma cells can vary in appearance, ranging from pleomorphic to relatively uniform, and can take on a centroblastic appearance with open chromatin and multiple nuclei, or an immunoblastic appearance with a single centrally located prominent nucleoli.[1,24] Cases may be associated with a low-grade component, most often extranodal marginal zone lymphoma.[20]

Table 2
Wiseman criteria for primary lymphoma of the breast.

1) Close association between the lymphomatous infiltrate and breast tissue on biopsy
2) No evidence of widespread disease or prior extra-mammary lymphoma
   - Ipsilateral axillary lymph nodes can be involved if both the breast lesion and lymphadenopathy develop concomitantly
3) No preceding diagnosis of extra-mammary lymphoma
4) Adequate quality of the biopsy

The immunophenotype of primary breast DLBCLs has previously been described in the literature. The lymphomatous cells express CD20, show variable expression of CD5, bcl-2, and bcl-6, and typically lack expression of CD10, CD21, and CD23.[24–28] Rare cases are CD30 positive.[16] In addition, primary DLBCLs of the breast show a high proliferation index, often greater than 40% by Ki67 immunohistochemistry.[24,25]

High grade B-cell lymphomas

The 2016 revision to the World Health Organization (WHO) classification of hematolymphoid neoplasms has recognized two distinct groups of high grade B-cell lymphomas: high grade B-cell lymphomas with *MYC* and *BCL2* and/or *BCL6* translocations and high grade B-cell lymphomas, not otherwise specified (NOS).[29] In nodal sites, both high grade B-cell lymphoma groups are particularly aggressive lymphomas which have poor prognostic outcomes. The morphologic appearance in high grade cases is a diffuse proliferation of large cells with blastic chromatin. While the presence of *MYC* and *BCL2* and/or *BCL6* translocations in a B-cell lymphoma with large cells allows for a clear diagnosis as a high grade B-cell lymphomas with *MYC* and *BCL2* and/or *BCL6* translocations, the diagnosis of a high grade lymphoma, NOS is much more complex and frequently relies, in part on a low-power morphologic appearance of a starry sky pattern with a high-power morphology of large cells with blastic chromatin; the mitotic index is typically very high in such cases as well (Table 3). The frequency, relevance and prognosis of high grade B-cell lymphomas with

Table 1
Features of benign versus malignant lymphoid infiltrates in the breast.

Consider malignant	More likely benign
Excess of large lymphocytes (in sheets, clusters, linear arrays, single cells)	Heterogeneous population of predominantly small lymphocytes, fewer larger lymphocytes, plasma cells, histiocytes
Dense infiltrate of monotonous population of lymphocytes[a]	Lacking monocytoid differentation
Atypical cytologic features (e.g. irregular nuclear contours, coarse blocky chromatin, blastic chromatin, prominent nucleoli)	No atypical cytologic features
Abnormal immunophenotype (B-cell monotypia, aberrant Ag expression, by flow or immunohistochemistry)	No aberrant immunophenotype
Clonal *IGH* or TCR gene rearrangements	No clonal *IGH* or TCR gene rearrangements
Presence of mass	No mass identified/alternative explanation for mass (e.g. inflammatory carcinoma)
High clinical or radiologic suspicion for lymphoma (e.g. lymphadenopathy, hepatosplenomegaly, B-symptoms; effusion in setting of breast implant)	Low clinical suspicion for lymphoma
History of lymphoma	No history of lymphoma

FL shows follicle formation and shows mixture of centrocytes & centroblasts .

[a] Extranodal MZL can appear more heterogeneous with larger monocytoid B-cells occurring alongside small lymphocytes and centrocyte-like cells.