Case Series

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Hematolymphoid Neoplasms of Breast – A Case Series with Review of Lymphoid Cell Rich Lesions of Breast

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Abstract

Objective: Hematolymphoid neoplasms involving breast (HLNB) are rare with majority of lesions in breast being epithelial in nature. There are no characteristic clinical and radiologic features to distinguish breast carcinomas from HLNB. However, it is essential to recognise lesion as hematolymphoid in nature for appropriate patient management. This case series highlights clinical, radiologic, and pathologic features of HLNB of breast.

Methods: Clinical data (age, sex, laterality, site and size of breast tumor, interval of secondary breast involvement, stage, treatment and clinical follow up), radiologic and pathologic features of patients with HLNB over a period of 6 years (2014-20) were recorded. Pathologic differential diagnosis of lymphoid cell rich lesions of breast are also discussed.

Results: Six cases of HLNB were identified during this period. This constitutes 0.22 % of malignancies of breast, 0.4% of non-Hodgkin lymphoma (NHL), 1.2% of extra nodal NHL and one case each of myeloid sarcoma and plasmacytoma.

Conclusion: HLNB are extremely rare and histologically mimics numerous other entities, which may be misdiagnosed without immunohistochemical evaluation. Thus, it is critical for a pathologist to be aware of the diagnostic features and pitfalls to avoid misinterpretation.

Keywords: Breast, lymphoma, myeloid sarcoma, plasmacytoma, hematolymphoid neoplasm

Introduction

Breast masses are frequently encountered in clinical practice. Fibroadenoma and ductal carcinoma are the most common benign and malignant conditions affecting breast respectively. Hematolymphoid neoplasms of breast (HLNB) are extremely rare. Primary breast lymphoma (PBL) accounts for less than 0.5% of breast tumors, [1] 0.38-0.7% of non-Hodgkin lymphoma and 1.7-2.2% of extra nodal lymphomas.[2] Although hematolymphoid neoplasms are the commonest metastasis to breast, secondary breast lymphoma is still very rare with annual incidence of <0.007%.[3] Other tumors including myeloid sarcoma, plasmacytoma, histiocytic/dendritic or T cell lymphomas form a rare group with few case reports cited in literature.[3] Due to its rarity, limited data is available in literature regarding clinical, radiologic and pathologic features of HLNB. This study shows retrospective evaluation of various attributes of these neoplasms affecting breast over a period of six years.

Material and methods

Clinical data: This retrospective study was approved by institutional review board, thus waiving the requirement of informed consent. The database of Histopathology department was searched for all HLNB occurring over a period of 6 years (January, 2014 to December 2020). Clinical data comprising of age, sex, laterality, site and size of breast tumor, interval of secondary breast involvement, stage, treatment and clinical follow up (No evidence of disease, alive with disease, death, lost to follow up) were recorded.

Radiology: Imaging [mammography, ultrasonography, computed tomography, magnetic resonance imaging] characteristic of cases was recorded from available reports.

Pathology: The diagnostic material was obtained by trucut biopsy. The available histologic material [Haematoxylin and eosin (Hand E) and immunohistochemical (IHC) stained sections] were evaluated in conjunction with the original

surgical pathology reports. Hand E stained slides were prepared from formalin-fixed paraffin embedded tissue sections. IHC for all antibodies (except ER) was performed using heat induced epitope retrieval using an automated immunostainer [Ventana Medical Systems, Tucson, Arizona]. ER IHC was done on Dako Aziland autostainer (Denmark).

The antibody panel utilized included CD20, CD3, CD45, cytokeratin(CK), Ki67, Mum1, bcl-6, CD10, bcl-2, CD 79A, CD23, CD34, and CD117 , MPO, CD68, GATA3, ER, CD138, CD 56, monoclonal kappa and lambda.

Result

A total of six cases of HLNB were identified during a period of 6 years (January 2014-December, 2020). Three thousand eight hundred fifty two breast biopsies were performed during this period, out of which 2,259 were malignant. Thus, HLNB constitutes 0.22 % of malignancies of breast. There were 4 lymphoma cases along with one case each of myeloid sarcoma and plasmacytoma. All lymphoma cases were placed under the category of secondary breast lymphoma with breast involvement forming a part of disseminated lymphomas. There was no primary breast lymphoma case in this series. Breast lymphomas accounted for 0.4% of non-Hodgkin lymphoma and 1.2% of extra nodal non-Hodgkin lymphoma.

Lymphoma*:* Four cases of breast lymphoma were diagnosed during a study period of 5 years. All patients were females and age range was 29 to 80 years. All patients had disseminated disease at presentation with simultaneous involvement of breast and multiple lesions in other organs of body. Three patients (Cases 1, 2, 3) showed unilateral right breast involvement with tumor size ranging from 1 to 2.5 cm. All patients had stage IV disease. Pathologically, two cases were classified as diffuse large B cell lymphoma (Cases 2 and 4), one as High grade B-cell non-Hodgkin lymphoma (NOS) (Case 1) and one as follicular lymphoma (Case 3). Bone marrow infiltration was absent at the time of diagnosis. However, patient with follicular lymphoma showed bone marrow infiltration after an interval of two years and showed concordant morphology. Follow up period ranged from 2 to 5 years. Two patients(Cases 1 and 2) were in complete remission at the end of three years follow up, while one(Case3) was alive with disease (5 years follow up) and one (Case 4)had waxing and waning course (2 years follow up). Two patient's had history of Sjogren's syndrome (Case2) and right breast carcinoma (case 3) respectively (Table-1).

Ultrasonography revealed hypo echoic lesions. Ultrasonography of Case 4 showed multiple thick walled cystic lesions with internal septa and internal echo. Mammography revealed irregular dense masses with no spiculation, architectural distortion or pleomorphic micro calcification. Positron emission tomography-computerized tomography (PET CT) scan showed evidence of lesions in breast with lytic lesions in bone and other organs (Table-1).

Diffuse large B cell lymphoma (n=2) was the most common histologic type of lymphoma. Tumor cells showed diffuse infiltration in sheet like pattern with centroblastic morphology. Mitoses was brisk with Ki-67 index 80-95%. Immunophenotypically, cells expressed CD20, CD45 and lacked expression of CK and GATA 3. According to Hans's algorithm, these were classified as GCB type (Case 2) and non GCB type (Case 4) (Table-2).

Case 2 had a history of Sjogren's syndrome and presented with breast mass only. There were no B symptoms and there was a high clinical suspicion for carcinoma. Morphologically (Figure-1) cells were large with opened up chromatin, conspicuous nucleoli. On initial limited panel of IHC, tumor cells stained negative for CK and GATA3 but positive for LCA. Further IHC evaluation confirmed it to be diffuse large B cell lymphoma. PET CT scan done subsequently revealed lytic lesions in bones only.

Case 1 with High grade B cell NHL (NOS) showed medium sized cells with blastic chromatin and high Ki67 index. Case 4 with follicular lymphoma showed diffuse pattern of infiltration with centrocytic morphology (Figure-2). Immunophenotypically, cells showed CD 20, CD10, bcl 2 and bcl-6 positivity. No necrosis or lymphoepithelial lesions were seen in this case.

Two other extremely rare non lymphomatous hematologic malignancies were seen in this case series as a part of disseminated disease.

Myeloid sarcoma*:* Single case of myeloid sarcoma (case 5) was a young lactating female who presented with 15 days history of fever and weakness. She was diagnosed as acute myeloid leukemia (approximately 97% blasts) at an outside hospital. The molecular analysis showed normal karyotype with FLT3 mutation. She was referred to our hospital for further management. Her breast showed local changes in

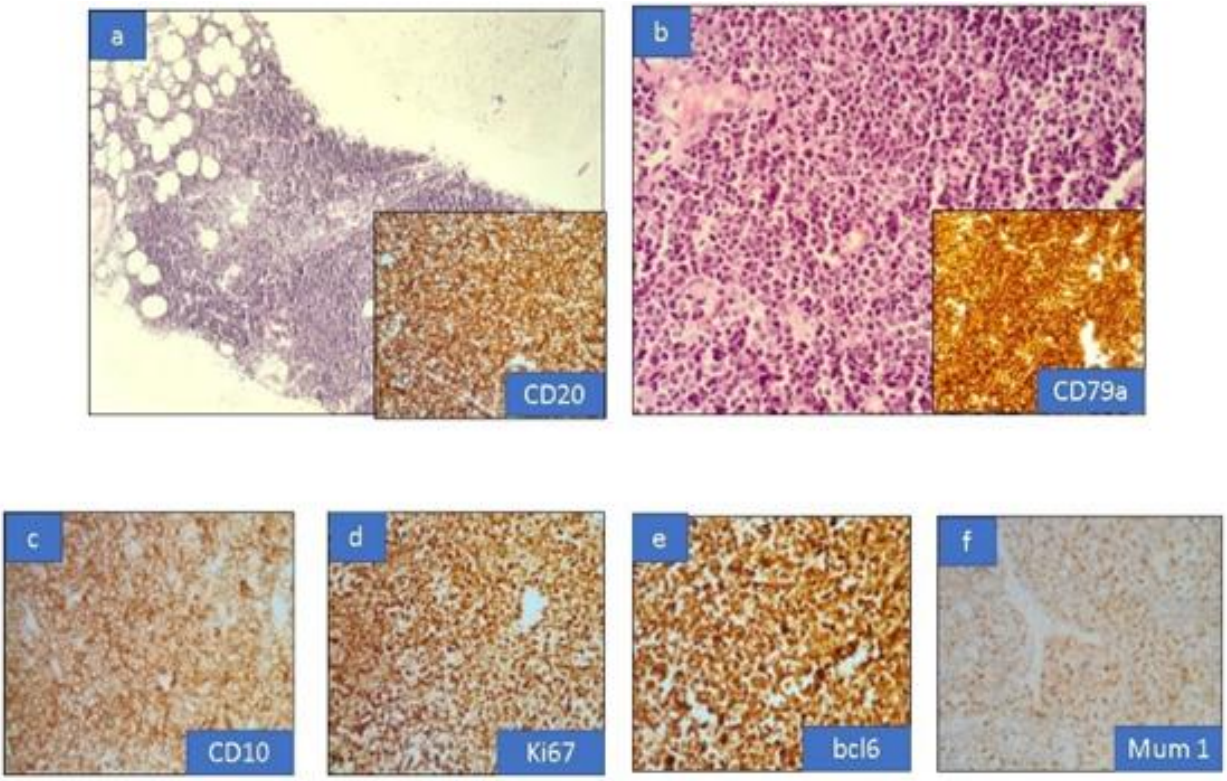

Figure 2: Diffuse large B cell lymphoma (a) Core breast biopsy with diffuse involvement by tumour. H and E, 40x. Inset: CD 20 positive immunostaining (b) Tumour cells arranged in diffuse sheet like pattern. Hand E, 100x. Inset: CD 79a positive immunostaining (c-f) Positive immunostaining with CD10, Ki67, bcl6, Mum1.IHC, 400x.

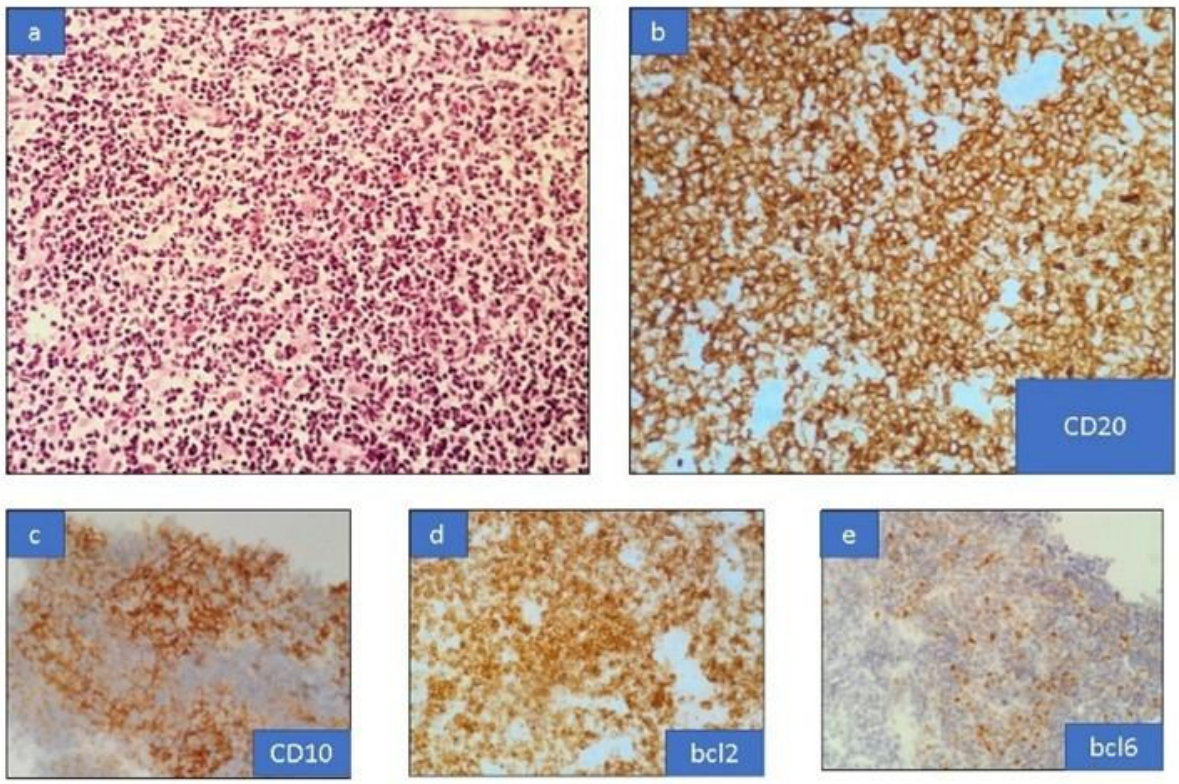

Figure 1: Follicular lymphoma (a) Small to medium sized tumour cells arranged in diffuse sheet like pattern. Hand E, 100x. (b-e) Positive immunostaining with CD20, CD10, bcl2, bcl6.IHC, 400x.

Table 1: Clinical and imaging features of patients with Hematolymphoid neoplasms of breast

Case no.	Age/sex/ Clinical history	Primary site/Diagnosis	Breast site/ size/axillary lymph node	Breast diagnosis/ interval of appearance	Bone marrow at diagnosis/ subsequent	Breast local examination	Imaging	Treat-ment	Follow up
1.	47/F	Right cervical LN/ High grade B cell NHL	Right breast/9'-10'0 clock/1.9X1.4 X1.4cm/No LN	High grade B cell NHL/Simulta neous	Not done	No local skin changes	Mammo- Irregular, obscured margin, No S,M,AD USG: Irregular, hypo echoic with angular margins PET CT: Multiple Thyroid, bones	CT	Alive with NED(3 years FU)
2.	80/F/ K/C/O Sjogren's syndrome	Right breast/DLBCL	Right breast/3.5cm X2.5 cmX2cm/No LN	DLBCL	No BM infiltration	No local skin changes	Mammo: irregular dense mass, USG: hypo echoic mass PETCT: Multiple skeletal lesions, No LN	CT	Alive with NED (2 years FU)
3.	67/F K/C/O Carcinoma, left breast	Left hard palate /Follicular lymphoma	Right breast/ Upper outer quadrant/5X5 mm/ Bilateral	Follicular lymphoma/ Simultaneous	No infiltration/ 2 years later: B/M infiltration	No local skin changes	Mammo: No lesion USG:1.5X1.0cm , well circumscribed, hypo echoic with increased vascularity	CT	Alive with disease
4.	29/F	Left cervical lymph node/ DLBCL	Bilateral multiple breast lesions	DLBCL/ simultaneous	No infiltration	No local skin changes	USG: Multiple bilateral breast lesions, thick walled cysts1.8x1.8cm to 2.5 x1.6cm. PET CT: multiple cervical, thyroid, pancreas, kidney	CT	Partial remission, lost to FU (2 years after beginning of treatment)
5.	27/F Lactational	Right breast/ Myeloid sarcoma	Right breast/ 12-6'o clock/6.8X3c m/ Right axilla	Myeloid sarcoma/ Simultaneous	AML/ Normal karyotype, FLT3 mutation	Enlarged, engorged, edematous, skin thickening	USG: Hypo echoic mass PET CT: Multiple cervical, supraclavicular and axillary LN	Sepsis with MODS (No CT)	Dead
6.	43/F	Bone marrow/ multiple myeloma (Kappa restriction)	Left breast/ Lower inner quadrant/ !0x7x8cm/ Left axillary LN	Anaplastic plasmacytom a (Kappa restriction)/ Simultaneous	Infiltration present/ deletion 13p and 17p	No local skin changes	USG: Hypo echoic mass PET CT: Multiple bone lesions	CT	Waxing and waning course (2 years FU)

LN: Lymph node, NHL: Non-Hodgkin lymphoma, Mammo: Mammography, S: Spiculation, M: Micro calcification, AD: architectural distortion, USG: Ultrasonography, PET CT: Positron emission tomography and computed tomography, CT: Chemotherapy, NED: No evidence of disease, FU: follow up, K/C/O: Known case of, DLBCL: Diffuse large B cell lymphoma, AML: acute myeloid leukaemi**a**, MODS: Multiple organ dysfunction syndrome

the form of edema. The breast biopsy revealed blastoid cells with absence of eosinophilic precursors (Figure-3). IHC showed negative immunostaining for CK, GATA3 and ER and immunopositivity for CD117, CD33 and MPO and a diagnosis of myeloid sarcoma with axillary lymph node involvement was rendered. Unfortunately, patient succumbed to her illness with sepsis and multiple organ dysfunction before initiation of chemotherapy.

Plasmacytoma: One case of plasmacytoma breast was seen in this case series. This patient had a history of multiple myeloma with mass lesion involving left breast. Breast biopsy showed atypical, markedly pleomorphic plasmacytoid cells showing immunopositivity for CD138 and Kappa restriction (Figure-4). This was diagnosed as anaplastic plasmacytoma. Molecular analysis revealed deletion 13 p and 17p. Patient showed partial response to chemotherapy and opted for treatment at native place after 1 year of follow up.

Discussion

Hematolymphoid neoplasms show infrequent occurrence in breast. Predominant mass forming lesions in the breast are epithelial in nature. However, it is clinically important to recognize lesion as hematolymphoid in nature for appropriate patient management. This case series highlights clinical, radiologic, and pathologic features of disseminated lymphomas along with myeloid sarcoma and plasmacytoma occurring in breast. Most of the studies report the clinical or radiologic aspects of lymphomas in breast. We aimed to discuss the clinicoradiological features with emphasis on pathologic differential diagnosis of hematolymphoid lesions

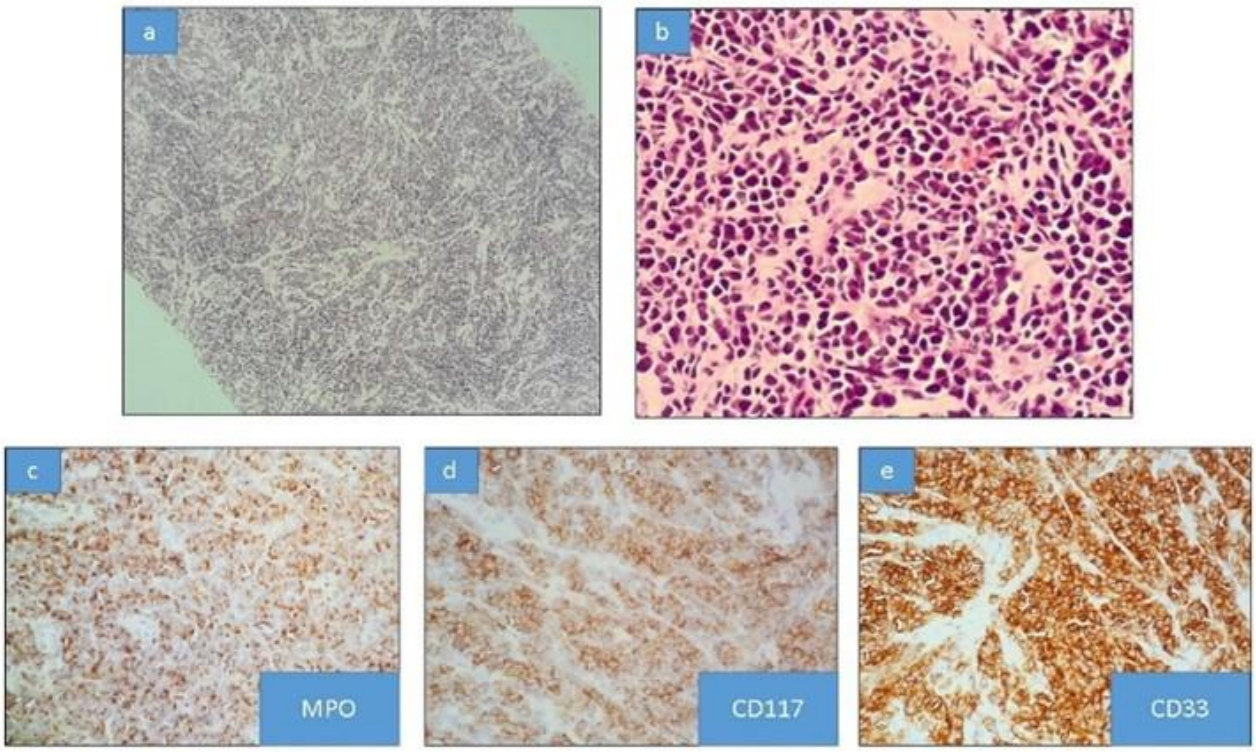

Figure 3: Myeloid sarcoma (a) Core breast biopsy with diffuse pattern of infiltration. . H and E, 400x. (b) Medium to large discohesive tumour cells. Hand E, 200x. (c-e) Positive immunostaining with MPO, CD117, CD33. IHC, 400x.

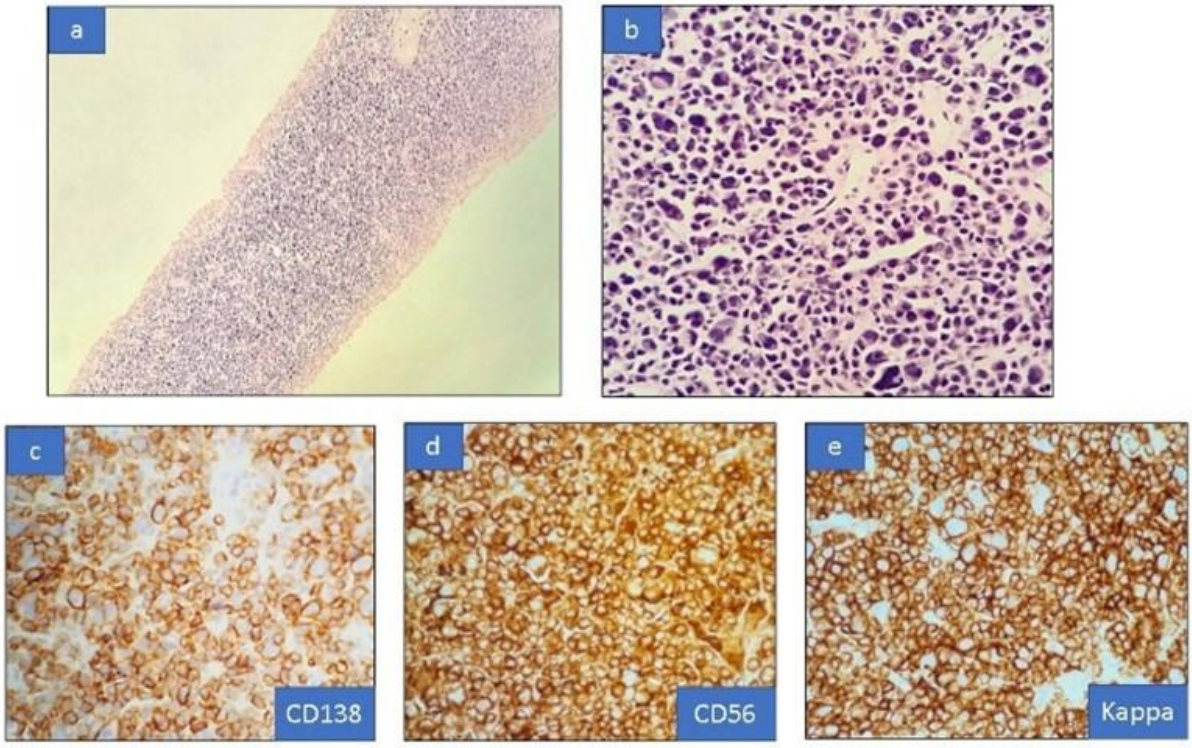

Figure 4: Plasmacytoma (a) Core breast biopsy with diffusely infiltrating tumour cells. Hand E, 40x. (b) Markedly pleomorphic tumour cells with focal plasmacytoid appearance. Hand E, 400x. (c-e) Positive immunostaining with CD138, CD56 and Kappa. IHC,

Table 2: Histopathologic and immunohistochemical features of patients with Hematolymphoid lesions of breast

Case no.	Effacement of architecture	Preserved ducts/ lobules	Pattern of infiltration	Fat infiltration	Lympho epithelial lesion	Cell morphology	Mitosis	Necrosis	IHC markers
1. High grade B cell NHL	+	+	Diffuse sheet like pattern	+	+	Large atypical lymphoid cells	4-5/HPF	Not seen	CD 45 + CD20+ CD3-, Ki67: 90-95%CK-, GATA3-, E cadherin -, ER, PR, Hercept-
2. DLBCL	+	+	Diffuse sheet like pattern	+	-	Large atypical lymphoid cells	3-4/HPF	Not seen	CD20+, MUM 1 +, bcl6and CD10- , Ki67: 85-90%, CK-, GATA3-, E-cadherin-, ER, PR, Hercept-
3. FL	+	Not seen	Diffuse sheet like pattern	+	_	Small atypical lymphoid cells	0-1/HPF	Not seen	CD20+, CD10, bcl6, bcl2+, Ki67-20-30%
4. DLBCL	+	Not seen	Diffuse sheet like pattern	+	-	Large atypical lymphoid cells	4-5/HPF	Not seen	CD20+, CD10+, bcl6 +, Mum 1-, CD79a+ , CD3-, GATA3-, E-cadh-, ER, PR, Hercept-
5. MS	+	Not seen	Diffuse sheet like pattern	+	-	Blastic morphology	3-4/HPF	Not seen	CD 33+, MPO+, CD117+, CD68-, Cd34-, CK-, GATA3-, E-cadh-, ER, PR, Hercept-
6. PC	+	Not seen	Diffuse sheet like pattern	-	-	Markedly pleomorphic plasmacytoid cells, Binucleate and multinucleate forms	5-6/HPF	Not seen	CD20-, Cd138+, Kappa restricted, CD56+, CD3-, Ki67-20-25%

NHL: Non Hodgkin lymphoma, DLBCL: Diffuse large B cell lymphoma, FL: Follicular lymphoma, MS: Myeloid sarcoma, PC: Plasmacytoma

involving breast.

Breast lymphoma have been classified as primary or secondary breast lymphoma based on criteria laid down by Wiseman and Liao.[4] It may also be subdivided into disseminated and localised depending on the extent of disease at the initial presentation. The preponderance of one subtype on another has been variably reported in literature and its true prevalence is difficult to determine.[2] All breast lymphomas in this case series is seen as a part of disseminated disease with breast involvement being diagnosed at the time of initial presentation. There was no primary breast lymphoma. This further highlights the rarity of the disease. The lymphocytes in the breast form a part of mucosal immunologic system and the scarcity of lymphocyte component in breast may be responsible for the rarity of lymphomas involving breast tissue.[2]

Lymphoid neoplasms of breast closely mimic carcinoma breast clinically as well as radiologically. Due to its rarity, the likelihood of misdiagnosis increases manifold. Clinically, it may present as localised breast mass, diffuse swelling or detected radiologically. Localised skin changes as well as systemic symptoms are also reported to occur very rarely (8-9%).[5] Autoimmune diseases are known to be associated with increased risk of lymphomas in various organs. Single case (Case 2) in this series had a history of Sjogren's syndrome and was diagnosed with breast DLBCL and bony lytic lesions. We have also found a preponderance of right breast involvement in lymphoma as has been reported earlier2 although this finding holds no clinical importance.

Radiologically, few authors [5,6] have attempted to provide an insight into the relevant imaging features of breast lymphomas. Majority of case reports and series have suggested oval, hypo echoic, well circumscribed masses on mammography. This is in concordance with this study where all lesions were solid, hypo echoic with no architectural distortion or micro calcifications. Although rare, architectural distortion and micro calcifications have also been reported in lymphoma in occasional cases reports.[5,7] An interesting finding in this case was multiple cystic lesions in breast on USG in case 4. This observation has been described previously [5] and Surov et

al [5] have suggested MRI evaluation of such cystic lesions in patients with lymphoma or suspected lymphoma for correct diagnosis.

Thus, there is no reliable and definitive method to distinguish breast lymphoma from carcinoma on clinical or radiologic grounds. Pathological examination forms the mainstay of diagnosis. However, considering the rarity of these lesions in breast, a high index of suspicion is warranted to achieve correct diagnosis and avoid possible misinterpretation.

Lymphoid cell infiltrate may be seen in breast tissue in a wide variety of conditions ranging from benign non-neoplastic to high grade malignant tumours. Based on the nature of lymphoid cells, differential diagnosis of low and high-grade lymphomas varies.

Low grade lymphomas in breast need to be differentiated from chronic inflammatory infiltrates seen in infections, granulomatous inflammation, diabetic mastopathy and in association with ductal carcinoma (in situ and invasive) as well as low grade lobular carcinoma. This may be diagnostically challenging in small biopsies where limited tissue is available. However, there are some characteristics which may provide some clues.

Low grade lymphomas involving breast include marginal zone lymphoma, follicular lymphoma, mantle cell lymphoma and chronic lymphocytic lymphoma. A diffuse pattern of infiltration with involvement of majority of core tissue is seen. A monotonous population of lymphoid cells should raise a suspicion for lymphoma. Reactive infiltrates will usually show associated lesions such as cyst or fat necrosis, which will be occupying a good proportion of breast core.

There are certain benign breast diseases like diabetic mastopathy and T cell lymphocytic lobulitis with a predominant periductular and perilobular pattern of lymphocytic infiltration. This pattern can also be noted in chronic lymphocytic lymphoma. According to Guilbert et al,[8] diabetic mastopathy shows periductular and perivascular infiltrate with sparing of intervening stroma which is dense collagenous. In contrast, intervening stroma is involved with lymphocytic infiltrate in chronic lymphocytic lymphoma. T cell lymphocytic lobulitis does not involve interlobular stroma and blood vessels.

These reactive lesions in general may show specific features associated with each condition along with well-defined, non-infiltrating margins, polymorphic infiltrate and absence of lobular and ductal destruction. IHC and gene arrangement studies may be needed in difficult cases.

The other end of spectrum encompasses poorly differentiated malignant tumours which include invasive ductal carcinoma, lobular carcinoma, neuroendocrine carcinoma, lymphoma, sarcoma, melanoma, blastoid and undifferentiated myeloid sarcoma and plasmablastic plasmacytoma. The list is exhaustive and unwary may diagnose it as triple negative breast carcinoma with limited IHC panel, which is not uncommon in the absence of a leading history.

Lymphomas may include diffuse large B cell lymphoma, high grade B-cell NHL (NOS), Burkitt's lymphoma and blastoid mantle cell lymphoma. The closest differential diagnosis in breast includes invasive ductal carcinoma (grade III) and high grade lobular carcinoma.

Although IHC plays a pivotal role in diagnosis of these conditions, there are certain morphologic features which may favor a possibility of one over the other specifically in breast. Grade III invasive ductal carcinoma is the initial thought in breast with discohesive large atypical cells present in sheet like pattern. However complete absence of cohesion, lack of carcinoma in situ component along with absent receptor expression should alert pathologist for some other entity.[8] Likewise lobular carcinoma with its typical Indian file pattern of infiltration is a close mimic for lymphoma. However, lobular carcinoma in general express strong ER positivity in 95% of cases [9] and its absence in a suspected case of lobular carcinoma should be taken as a lead for further evaluation. Invasive carcinoma with medullary like features shows pushing margins on radiology and pathologically reveals highly pleomorphic tumor cells associated with lymphoid cells. Cohesiveness of tumor cells with presence of abundant cytoplasm may be a feature favoring carcinoma. Small cell carcinoma also needs to be differentiated due to its morphologic similarity (singly dispersed, discohesive cells with crushing artefact) to lymphoma. However, a careful review of nuclear features (salt and pepper chromatin and inconspicuous nucleoli) will assist in ordering appropriate IHC markers.

Myeloid sarcoma is morphologically subdivided into well, blastoid and undifferentiated subtypes, although this classification holds no clinical relevance. The presence of eosinophilic precursors admixed with atypical cells is a useful diagnostic clue for myeloid sarcoma. However, blastoid and undifferentiated subtypes require an extended panel of IHC markers as there are rare case reports where

aberrant expression of Bell antigens have also been reported.[10]

Presence of plasmacytoid cells in breast biopsy may be seen in lobular carcinoma, plasmacytoma, melanoma or neuroendocrine tumor.

Morphologic features and IHC in these lymphomas are similar to those seen elsewhere in the body. Other tumours in this category can be differentiated on the basis of immunohistochemical evaluation.

The underlying pathology and genetics of HLNBis not well understood but there are certain features which need a mention. Patients with primary diffuse large B cell lymphoma, breast are more likely to relapse in extra nodal sites indicating that it may have unique characteristics, which are yet unknown.[1] Primary breast localization of follicular lymphoma is also reported to have inferior progression free survival and overall survival as compared to limited stage nodal follicular lymphoma, thus suggesting poor prognosis. "Inv16 or amplification of CBFB, trisomy 8 and KM2A-MLLT3" fusion have been suggested to have increased incidence in myeloid sarcoma involving breast.[11]

This study is limited by small sample size making it difficult to draw definitive conclusions. However, the review of lymphoid cell rich lesions involving breast aims at raising an awareness among pathologists regarding HNLB, especially in limited resource settings to avoid unnecessary surgeries.

Conclusion

To conclude, HLNB are rare with evolving genetics and pathology. This study showed occurrence of HLNB as 0.22% of breast malignancies in a high volume tertiary care centre. Clinical and radiologic features of HLNB are essentially uncharacteristic. Histologically, HLNB mimics numerous other entities including breast carcinoma, which may be misdiagnosed without immunohistochemical evaluation. Thus, it is critical for a pathologist to be aware of the diagnostic features and pitfalls to avoid misinterpretation.

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