Clinico-pathological analysis of primary breast lymphoma: A cross sectional study in a tertiary care hospital

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Abstract

Introduction: Breast being well-developed mammary organ in females is a common site for many non-neoplastic and malignant lesions due to varied underlying etio-pathogenesis. Lymphoma being a malignant clonal proliferation of lymphoid cells, primary breast lymphoma is an unusual entity with non-epithelial origin characterized by florid proliferation of neoplastic lymphoid cells. With uncertain etiology, the clinical presentation is vague with varied radiological and histopathological patterns. In the present study, we analyzed the incidence of primary breast lymphoma with a study on clinico-histopathological pathological spectrum.

Methodology: The study was conducted retrospectively and included patients with breast lesions and the histopathological evaluation from their subsequent tissue biopsies. All the clinical data was documented and cytological correlation were done in available cases. Hematological and radiological interpretations are analyzed subsequently as pre-op work up of the patients. Clinico-pathological analysis of the results were done based on knowledge from research works.

Results and Observation: The seven years retrospective study included nine cases which fell into the criteria of PBL with average age incidence between 4th & 5th decade occurring retroareolar region with right breast preponderance. Radiological studies picked up malignancy only in few cases but categorization of lymphoma were not reported by imaging. Hematological parameters showed anaemia, leucopenia and pancytopenia depending on extent and involvement of the bone marrow. Histomorphology and subsequent IHC expression stayed gold standard role in diagnosis compared to radiological interpretations.

Conclusion: Primary breast lymphoma is rare type of breast cancer with varied presentation. Any patient presenting with solitary, lobulated breast lump in 5th decade, PBL should be kept as one of the differentials especially with anaemia and axillary node enlargement. Clinico-hematological correlation with subsequent histomorphology helps the Pathologist is diagnosing the condition thereby aiding the in Prompt management.

Keywords: Breast Lymphoma, Hematological parameters, Histopathology, IHC, Radio-imaging.

Introduction

Human breast is a bilateral mammary organ in the thoracic region which is well developed in females compared to males.[1] It is influenced by various hormones and imbalances, biological processes and many other Physio-pathological changes constantly. Being a mammary organ, it serves as a vulnerable platform for many lesions including non-neoplastic and neoplastic entities.[2] While the incidence of both the entities are common in equal proportion, the latter holds an upper hand in terms of its associated morbidities.[3]

Histology of breast comprises of two major components namely glands and Ducts both embedded in stroma. The ducts in turn branches repeatedly giving rise to an entity termed as terminal duct lobular unit (TDLU)[2,3] The ducts and glands are lined by dual population of cells (epithelial and myoepithelial layers) which in turn is supported by a basement membrane.[4] Lymphocytes being a chronic inflammatory is bsparsely distributed in breast lesions indicating immune response.[5]

Non neoplastic lesions of breast includes fat necrosis, mammary duct ectasia, granulomatous mastitis, Breast abscess, mastopathy, galactocele, etc. Neoplastic lesions includes benign and malignant conditions.[6] Most of the malignant lesions of breast arise from the epithelial origin which are broadly termed as "Carcinoma" and it has many sub-types as specified by World Health Organization (WHO) classification of breast tumours, the commonest type being Invasive ductalcarcinoma, (NOS), Invasivelobularcarcinoma, Medullarycarcinoma etc.[7] Most of the epithelial carcinomas are picked up on Routine Histomorphology, Molecular techniques, Immunohistochemistry and radiological tools which high specificity.

Lymphomas being a neoplasm pertaining to Lympho-reticular system, it is classified into low, intermediate and high grade based on the aggressiveness and Immunohistochemistry (IHC) marker expression. However lymphoma occurring other than lymp nodes are termed as' extra-nodal lymphoma'. Organ system exhibiting such lymphoma includes breast, Central Nervous system, Gastro-intestinal system which are categorized as 'primary lymphoma of that organ.'

Breast malignancies arising non-epithelial origin includes mesenchymal (mostly stromal and neural) and lymphoid etiology.[8] While the earlier entity is termed as "sarcomatous tumour", the later one is commonly labeled as "Primary Breast Lymphoma" (PBL). Non-epithelial malignancy of breast itself is rare terminology compared to epithelial origin, its diagnosis usually happens as incidental finding frequently varying from

the pre-operative diagnosis.[8] PBL is entirely different from other breast tumours which can present as a primary mammary neoplasm or may show breast involvement as a portion of systemic process.[9]

WHO has proposed a definition for the entity primary breast lymphoma" (PBL) as "a malignant lymphoma primarily occurring in the breast in the absence of previously detected lymphoma localizations." which accounts for <1% of the total incidence of breast malignancies.[10] It is often manifested by axillary node involvement with median age being 50-60 years. The pathogenesis is unclear but exorbent hormonal stimulation with imbalance leading to clonal lymphoid proliferation is the proposed underlying etiological factor. PBL includes many types namely: Diffuse Large B cell Lymphoma (DLBCL), Follicular Lymphoma (FL), MALT lymphoma and burkitt's lymphoma.[11]

Most of the cases present with painless swelling with or without generalized lymphadenopathy with hematological manifestations. Radiological investigations namely ultrasound scan and Mammogram are useful in picking up malignancy but their role in categorizing the tumour from non-epithelial origin is debatable.[11,12] Histomorphology followed by IHC expression and subsequent clinico-pathological correlation stays as a Gold standard method for diagnosis PBL. Research studies pertaining to PBLvery sparse in Tropical countries as priority is given for epithelial tumors.[12] In the present study, an extensive analysis on PBL is studied with Clinico-Pathological correlation throwing limelight on this entity aiding is prompt diagnosis of the condition.

Methodology

The Retrospective study was conducted for a period of 7 years at our Tertiary Care Hospital. All the details including age, socio-demographic status and other details are entered in a proforma. Radiological investigations like Mammogram grading and ultrasound scan interpretations are documented including evidence of calcification, necrosis, extension, axillary lymph node enlargement, etc. Family history for any incidence of carcinoma breast is noted (if any) for inheritance along with history lactation, nulliparous status. Hematological investigation including peripheral smear and bone marrow (in available cases) findings were noted. IHC study performed in all the available cases were found and the markers included ER, PR, Her2neu, (for epithelial origin) and CD-19 &CD-20 panel (for PBL) with their expressions and staining pattern

Results and Observations

The study conducted over a period of 7 years retrospectively showed maximum age incidence at fifth decade with site predilection towards at Retro-areolar region followed by outer quadrant. Among the types of PBL, DLBCL rated the highest incidence noted in 6 cases followed by Follicular lymphoma as describe in Table 1.

In the aspect of hematological profile, anaemia of microcytic type was common presentation followed Lymphocytosis in peripheral smear. Total leucocyte was reduced in majority of cases as elaborated in Table-2.Bone marrow in 3 cases showed increased precursors of lymphoid series with altered M:E ratio.

As Mammogram imaging is based on BIRADS grading, in none of the cases PBL was categorized though it had high sensitivity on epithelial tumours as described in Table 3.

Immunohistochemistry study was helpful in assessing the receptor status with varied expressions and helpful in segregating from the other epithelial origin of the tumour as shown in Table 4.

Table 1: Age distribution of cases with PBL types

Age of the Patient (In Years)	No. of PBL cases	Types of PBL		
		DLBCL	FL	MZL
30-40	2		2	
41-50	2	1		1
51-60	3	2		1
>60	2	1		1

*DLBCL- Diffuse Large B cell Lymphoma; FL-Follicuar Lymphoma; MZL-Mantle Zone Lymphoma

Table 2: Spectrum of clinico-hematological profile

PBL	RBC Parameter	WBC Counts	Differential WBC Counts	Platelets	Peripheral smear
DLBCL	Anaemia	Leucocytosis	Lymphocytosis	Thrombocytopenia	Microcytic type
MZL	Anaemia	Leucopenia	Lymphocytosis	Reduced	Dimorphic
FL	Anaemia	Leucocytosis	Lymphocytosis with cleaving	Mildly reduced	Normocytic type

Table 3: Correlation of Histo-Radiological interpretations

Histology Report of Mastectomy specimen	Mammogram	Trucut biopsy/Cytology
Histopathology proved cases of PBL	Phyllodes Tumour-BIRADS-III	Lymphoid lesion with mastitis
Histopathology proved cases of PBL	Suspicious malignancy-BIRADS-IV	Lobular carcinoma
Histopathology proved cases of PBL	? Necrotic mass	Malignancy- Ductal carcinoma

Table 4: Profile of Immunohistochemistry markers expression

Cells of origin	IHC Profile	PBL types	Axillary node involvement
	ER status	Faintly ++ (n=3)	NIL
Epithelial origin	PR status	Weakly +(n=2)	NIL
	Her 2Neu	Negative	NIL
Non epithelial	CD 19	Strongly +++	4
(Lymphoid origin)	CD 20	Strongly +++	3

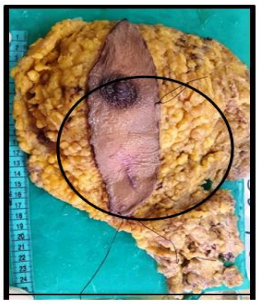

Fig. 1: Mastectomy specimen of PBL showing nipple areola with lobulation of tumour in retro-areolar region

Fig. 2: Mastectomy specimen from patient with breast lymphoma shows circumscribed solitary lump.

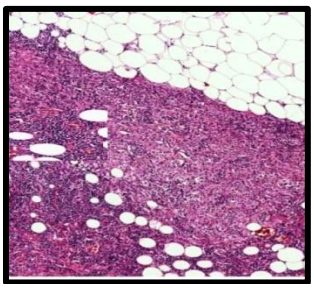

Fig. 3: Primary Breast Lymphoma (DLBCL type) showing lymphoid aggregates with fatty infiltration of adjacent tissue. H&E, 40X

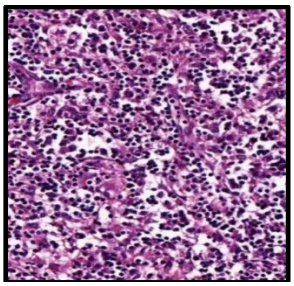

Fig. 4: Primary Breast Lymphoma showing nodular aggregates of neoplastic lymphoid cells admixed with epithelial cells with nodular sclerosis, H&E, 40X

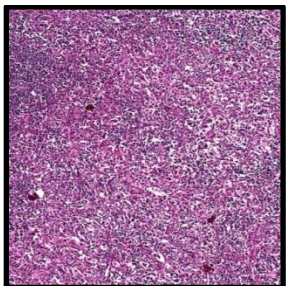

Fig. 5: Breast Lymphoma showing small follicles of lymphoid proliferation with areas of sclerosis and stromal hyperplasia, H&E-40X

Discussion

Breast lesions being an highly volatile organ system for neoplastic lesions, tumors arising from clonal proliferation of lymphoid cells is an infrequent entity termed under a broad category as "Primary Breast Lymphoma.[1,2] It usually occurs in later middle age period as observed in the present study which showed maximum incidence at 4th & 5th decade involving retroareolar region with average age incidence was 55 years with right breast preponderance.[3,4] PBL is an extra nodal manifestation often exhibiting hematological manifestations.[5,6] In the present study, all the cases showed Anaemia with

lymphocytosis which indicates an impact on bone marrow dearrangements. The underlying reason proposed by previous workers Aviles et al., showed that stem-line alteration of hematopoietic precursor cells leads to anaemia and thrombocytopenia with lymphocytosis.[3] Majority of the cases with these manifestations showed axillary lymph node involvement, thus justifying the proposed etiopathogenesis.[5,6]

Breast lesions are easily picked up by Radiological investigations especially Mammogram. However breast cancers with non-epithelial origin is a challenging entity for radiological interpretation as observed in the present study concording with prior Researches.[7,8]Most common differentials in Mammogram includes Malignancy, Mastitis followed by Phyllodes tumour as observed in the present study and correlating with Previous Researchers Domchek etal. [7] Ultrasound investigations are useful in picking up associated lymphadenopathy, inflammation, necrosis etc. it seldom identifies PBL. Thus the diagnosis and categorizations remains incomplete to the Clinicians by radiological investigations

PBL is known to occur as single lobulated mass, solitary lesion, circumscribed, oval often involving adjacent fibrofatty infiltration showing nodular growth with calcification as observed in the present study. (Fig. 1 & 2) Fine needle aspiration cytology and Tru-cut biopsy is useful in evaluation of breast nodules provided tissue and material is adequate, thus often warranting for lumpectomy in confirming the diagnosis. Breast Lymphoma probably originates in lymphatic tissue within breast adjacent to ducts and lobules or from the extra nodal tissue/inflammatory lymph nodes.[8]

Diffuse Large B cell Lymphoma (DLBCL) is the most commonly encountered sub-type of PBL showing non-germinal proliferation mainly of B-cell phenotype.[9] (Fig. 3) The high intensity of proliferative index can be assessed by Immunohistochemical markers especially CD 19 &CD 20 as observed in the study concording with previous Researchers. The most common misdiagnosis based on IHC study in negative expression of ER/PR &Her2neu often making the Pathologist to limit to Triple Negative /Basal Breast Cancer excluding the possibility of PBL. Histomorphology includes proliferation of lymphoid follicular cells in sheets, scattered associated with apocrine changes. (Fig. 4) Stromal changes includes sclerosis and stromal hyperplasia.[11,12] (Fig-5) Fatty infiltration is an hallmark microscopical feature in PBL followed by axillary node involvement as noted in majority of the cases in the present study

Conclusion

Primary Breast Lymphoma is a non-epithelial breast neoplastic condition of breast, it is rare type with varied presentation. Any patient presenting with solitary, lobulated breast lump in 5th decade, PBL should be kept as one of the differentials especially with anaemia, pancytopenia and axillary node enlargement. Clinico-Hematological correlation with subsequent histomorphology helps the Pathologist is diagnosing the condition thereby aiding the in Prompt management by the Surgeons.

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