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Motley and Immured-Lobular Carcinoma *In situ* Pleomorphic

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Abstract

Pleomorphic lobular carcinoma in situ represents as an exceptionally discerned, morphological subtype of lobular carcinoma in situ (LCIS). Neoplasm is contemplated to express a genetic and biological advancement of classic lobular carcinoma in situ and emerges as a direct precursor to invasive carcinoma breast. Initially scripted by Frost et al in 1996, pleomorphic lobular carcinoma in situ is contemplated as a morphologic variant of classic lobular carcinoma in situ.

Keywords: Classic Lobular Carcinoma; Neoplasm; Invasive Carcinoma; Contiguous Lesion

Abbreviations: DCIS: Ductal Carcinoma In Situ; FNAC: Fine Needle Aspiration Cytology; TDLUs: Terminal Duct Lobular Units; MRI: Magnetic Resonance Imaging; WHO: World Health Organization; DL: Ductal Lavage; LCIS: Lobular Carcinoma *In-Situ*.

Introduction

A category of lobular neoplasia, nomenclature of non-classic lobular carcinoma in situ or variant lobular carcinoma in situ is not recommended. However, lobular lesions delineating minimally 10% of tumour cells pervaded with high grade nuclei may be designated as pleomorphic neoplasms. In contrast to classic lobular carcinoma in situ, the non-invasive tumefaction is composed of proliferation of enlarged, dis-cohesive cells demonstrating significant nuclear pleomorphism. The neoplastic component may or may not delineate morphological features of apocrine cells. Tumour expounds lobulocentric proliferation of pleomorphic, enlarged ductal epithelial cells which frequently expand lobular acini. Akin to the classic variant, tumour cells may depict lack of cellular cohesion, cell polarity, loss or dysfunction of E-cadherin and pagetoid dissemination of cells. Neoplastic cells may depict intracytoplasmic lumens with occurrence of signet ring cells. Lobular acini permeated with pleomorphic lobular cells appear significantly expanded, mildly distended or appear devoid of distension.

Pleomorphic lobular carcinoma in situ emerges as an exceptional disease representing an incidence of < 5% of lobular carcinoma in situ. Commonly implicating elderly, postmenopausal Caucasian female subjects, mean age of disease emergence is~55 years although lesions may be discerned within 36 years to 86 years [1,2]. Apocrine pleomorphic lobular carcinoma in situ occurs preponderantly within postmenopausal women and exhibits mean age of disease occurrence at 60 years whereas mean age for non-apocrine pleomorphic lesions appears at 51 years [1,2]. Pleomorphic lobular carcinoma in situ is preponderantly confined to the breast wherein predilection for specific quadrants is absent. Pleomorphic variant emerges as unifocal, contiguous lesion, in contrast to classic variant demonstrating multi-centric, bilateral neoplasms [1,2].

Lobular lesions and pleomorphic lobular carcinoma in situ depict a preliminary, pathognomonic inactivation of CDH1 gene with consequent loss or impaired function of E-cadherin, a molecule which contributes significantly to intercellular adhesion and cellular polarity. Additionally, gain in chromosome 1q and loss in chromosome 16q may concur. In contrast to classic variant, tumour cells accumulate additional genetic alterations and expound significant genomic instability. However, progression of pleomorphic lobular carcinoma in situ from classic variant as a distinct disease process or representation of a genetically advanced lesion remains debatable [1,2]. Pleomorphic lobular carcinoma in situ and pleomorphic invasive lobular carcinoma are frequently associated with foci of classic invasive lobular carcinoma and zones of morphological continuum between pleomorphic and classic variants [1,2]. Synchronous classic and apocrine pleomorphic lobular carcinoma in situ expound identical chromosomal alterations with additional modifications occurring within apocrine pleomorphic lobular carcinoma in situ, thereby indicating disease evolution from singular precursor lesion or engagement of common genetic pathway [1,2].

Of obscure aetiology, individuals with non-classic lobular carcinoma in situ, florid lobular carcinoma in situ and pleomorphic lobular carcinoma in situ appear devoid of individual history of invasive carcinoma breast or BRCA1 or BRCA 2 gene carrier state. However, subjects may represent with first degree relative or family history of carcinoma breast [2,3].

Characteristics

Tumour cells appear devoid of expression or function of membranous E-cadherin which is a transmembrane glycoprotein encoded by CDH1 gene situated upon long arm of chromosome 16 (16q). Akin to classic variant, pleomorphic lobular carcinoma in situ depicts characteristic genomic alterations as gain of chromosome 1q or loss of chromosome 16q [2,3]. Tumefaction is posited to emerge and progress through a molecular genetic pathway recapitulating genomic pathway applicable to classic variant along with additional genetic events [2,3]. The neoplasm expounds significant genomic instability with enhanced copy number alterations, genetic amplifications and additional chromosomal mutations Genomic mutations and amplification of ERBB2 (HER2) gene are frequently encountered. Besides, mutually exclusive chromosomal mutations and genetic amplification of HER2 may appear. Additionally, HER2 genetic alterations are commonly observed within lesions devoid of oestrogen receptors(ER-) [2,3].

Few neoplasm configure as non-obligate precursors of pleomorphic invasive lobular carcinoma, analogous to high grade ductal carcinoma in situ and invasive ductal carcinoma. Aforesaid lesions delineate additional molecular genetic modifications as gains of c-myc situated upon chromosome 8q24 and HER2 situated upon chromosome 17q12 along with gains within chromosomes 8p, 8q and 13q and losses within chromosomes 1p, 8p, 12p, 14q, 18q, 19p and 19q. Overall genomic alterations between non apocrine pleomorphic lobular carcinoma in situ and classic variant appear identical. Additional genomic modifications are singularly confined to apocrine pleomorphic lobular carcinoma in situ [2,3].

Pleomorphic lobular carcinoma in situ commonly appears as an asymptomatic lesion wherein majority (~87%) of individuals represent with anomalous features as calcification on screening mammograms. Few lesions appear devoid of specific radiological features and may be discerned as an incidental microscopic feature upon examination of surgical tissue samples. Uncommonly, a palpable tumefaction or nipple discharge may be observed [2,3]. Subjects delineating a palpable tumefaction enunciate pleomorphic lobular carcinoma in situ concurrent with various lesions as a fibro-adenoma or associated invasive carcinoma breast. Up to 50% neoplasms configure pure pleomorphic lobular carcinoma in situ with tissue samples obtained with core needle biopsy or surgical excision. Tumefaction preponderantly (~77%) is associated with invasive carcinoma breast, commonly pleomorphic invasive lobular carcinoma although classic invasive lobular carcinoma or diverse histologic subtypes may be encountered [2,3]. Cytological examination depicts significantly cellular smears. Tumour cells appear preponderantly dis-cohesive and singularly disseminated although miniature, loosely cohesive aggregates and cell clusters may be discerned. Tumour cells may simulate cellular component of ductal carcinoma in situ (DCIS). Tumour cells are permeated with abundant, dense cytoplasm and may configure signet ring cells with intracytoplasmic mucin, which may segregate the neoplasm from ductal carcinoma in situ. Tumour cell nuclei appear enlarged and pleomorphic with frequent nucleoli. Tumour cells may appear bi-nucleated, multinucleated or exhibit lobulated, indented or eccentric nucleoli [3,4].

Foci of micro-calcification or necrosis may be exemplified. Smears from ductal lavage (DL) delineate decimated proportion of cytological atypia, in contrast to cells obtained with fine needle aspiration cytology (FNAC). However, specific cytological criteria demarcating pleomorphic lobular carcinoma in situ from invasive lobular carcinoma appear inconsistent [3,4].

Grossly

Tumefaction is devoid of a specific macroscopic anomaly. Cut surface is faintly granular, especially on tangential

section as implicated lobules appear enlarged, visible and display micro-calcification [3,4]. Upon microscopy, pleomorphic lobular carcinoma in situ depicts architectural features simulating the classic variant. Characteristically, tumour mass exemplifies proliferation of dis-cohesive neoplastic cells within terminal duct lobular units (TDLUs) and configuration of solid cellular nests. Pagetoid spread of neoplastic cells into adjacent ducts may occur. In contrast to classic variant, pleomorphic lobular carcinoma in situ expounds lobular acinar expansion. Lobular acini impacted with pleomorphic lobular cells appear significantly expanded, mildly distended or appear devoid of lobular distension. Individual tumour cells appear intermediate to enlarged with elevated nucleocytoplasmic ratio [3,4].

Tumour cells are permeated with moderate to abundant, dense, eosinophilic or granular cytoplasm. Frequently observed intracytoplasmic vacuoles may or may not contain mucin. The vacuoles may be enlarged and configure signet ring cells. Tumour cells nuclei are variable, significantly enlarged and expound nuclear atypia. Enlarged tumour cell nuclei delineate ≥ 4x the magnitude of small lymphocyte, recapitulating nuclei of high grade ductal carcinoma in situ. Nuclei display moderate to marked nuclear pleomorphism with > 2 to 3x variation within nuclear diameter, variable nuclear outline and miniature to prominent nucleoli [3,4]. Frequently, tumour cell nuclei are eccentric, bi-nucleated or multinucleated. Nuclear chromatin is coarse. Tumefaction may be associated with necrosis or exemplify focal comedo-necrosis. Mitotic figures may be discerned.

A subset of neoplasms delineates apocrine differentiation wherein the neoplasm is designated as apocrine pleomorphic lobular carcinoma in situ. Tumour cells are characteristically pervaded by abundant, eosinophilic cytoplasm, cytoplasmic granules and prominent nucleoli. Centric, comedo subtype of necrosis is frequently discerned although remains superfluous for neoplastic discernment. Micro-calcification is commonly observed [3,4]. An estimated >40% pleomorphic lobular carcinoma in situ may coexist with classic lobular carcinoma in situ. Tumefaction is concurrent with invasive carcinoma, commonly pleomorphic invasive lobular carcinoma although concordance of diverse histological subtypes may occur. Thus, meticulous assessment of circumscribing and implicated breast tissue is mandated [3,4].

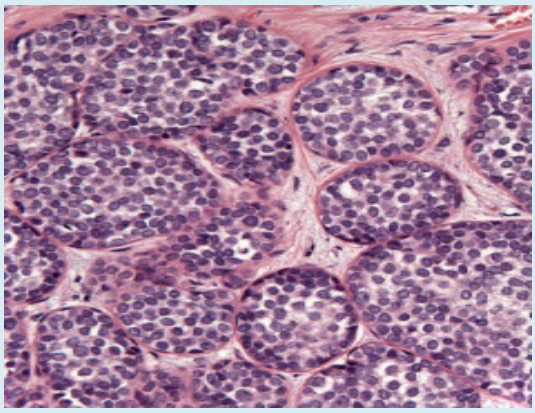

Figure 1: Pleomorphic lobular carcinoma in situ demonstrating lobular expansion with tumour cells imbued with abundant, eosinophilic cytoplasm, intracytoplasmic mucin and pleomorphic nuclei with variable outline and prominent nucleoli [5].

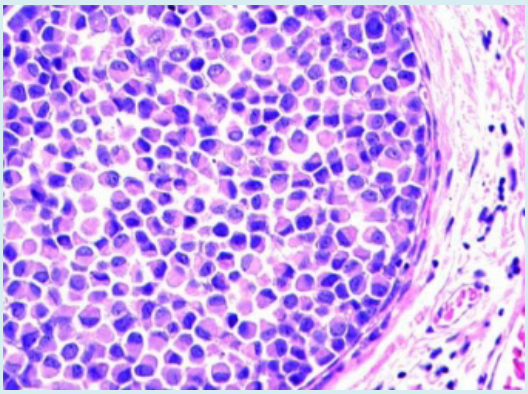

Figure 2: Pleomorphic lobular carcinoma in situ delineating lobular expansion with tumour cells pervade with abundant, eosinophilic cytoplasm, intracytoplasmic mucin and pleomorphic nuclei with variable outlined and prominent nucleoli [6].

Subtype	Nuclear magnitude	Pleomorphic nuclei	Nucleoli	Cytoplasm	Dis-cohesive cells	Central necrosis/ calcification
Pleomorphic LCIS	≥4x	Moderate/ marked	Miniature	Moderate/ abundant	Present	Present
Classic LCIS type A	1.5x	Absent	Indistinct	Scant	Absent	Absent
Classic LCIS type B	2x	Mild/ moderate	Indistinct	Moderate	Present	Absent
Florid LCIS	1.5 to 2x	Absent/ moderate	Indistinct	Scant/ moderate	Occasional	Present

Table 1: Morphological features of lobular carcinoma *in situ* variants.

Pleomorphic lobular carcinoma in situ appears immune reactive to oestrogen receptors, progesterone receptors, HER2 and moderately immune reactive to androgen receptors. Pleomorphic lobular carcinoma in situ appears immune non-reactive to oestrogen receptors, progesterone receptors and immune reactive to HER2, in contrast to classic variant or florid lobular carcinoma in situ. Notwithstanding, ~18% lesions appear as triple negative [7,8]. Tumour cells appear immune non-reactive to E-cadherin, p120 or β catenin. Ki67 labelling index is elevated wherein accumulation of p53 protein may be discerned by immunohistochemistry, features which are indicative of aggressive biological behaviour [7,8]. Pleomorphic lobular carcinoma in situ requires segregation from neoplasms as florid lobular carcinoma in situ, classic lobular carcinoma in situ, high grade ductal carcinoma in situ or apocrine intra-ductal carcinoma [7,8].

Upon Mammography or Ultrasonography

The lesion preponderantly expounds anomalous features. Majority of lesions represent with calcification upon mammography, reminiscent of calcification associated with ductal carcinoma in situ (DCIS). Exceptionally, a circumscribed tumefaction may be identified upon diagnostic mammogram or ultrasonography. Cogent mammographic features appear as fine, pleomorphic aggregates of calcification or image distortion [7,8]. Screening magnetic resonance imaging (MRI) exhibits amorphous calcification, regional accumulation of clumped calcification or non-mass forming image enhancement. Advanced breast imaging with MRI may demonstrate non mass forming image enhancement, absence of anomalous features, tumour mass or space occupying lesion or focal area of image enhancement < 5 millimetre magnitude. Subsequently, core needle tissue sampling may be adopted. A subset of lesions may be discerned within tissue samples obtained from surgical excision or procedures adopted for diverse breast lesions [7,8].

Therapeutic strategies applicable to pleomorphic lobular carcinoma in situ are currently inadequately defined. Modalities as surgical resection with tumour free perimeter or adjuvant radiation therapy remain debatable. Contemporary guidelines of World Health Organization (WHO) recommends surgical extermination of pleomorphic lobular carcinoma in situ in concurrence with tumour discernment upon core needle biopsy [7,8]. Surgical resection specimens may necessitate evaluation of status of surgical perimeter for optimal therapeutic management. Achieving tumour free surgical margin is recommended. Additionally, pleomorphic lobular carcinoma in situ may be subjected to therapeutic strategies akin to ductal carcinoma in situ as surgical eradication with tumour free perimeter in combination with or absence of adjuvant therapies [7,8]. As employed in high grade ductal carcinoma in situ, sentinel lymph node biopsy may be adopted during surgical excision of pleomorphic lobular variant. Proportionate tumour reoccurrence with conservative management along with or absence of anti-oestrogen therapy appear in up to 57% instances. Surgical margins invaded with tumour cells may or may not influence proportionate tumour relapse. Appropriate chemotherapy may be adopted within neoplasms immune reactive to oestrogen receptors(ER) [7,8]. Although the infrequent, pure pleomorphic lobular carcinoma in situ un-associated with invasive carcinoma breast expounds a predominantly obscure history of disease occurrence, tumefaction genetically configures as a direct precursor of invasive lobular carcinoma or pleomorphic invasive lobular carcinoma [7,8].

Conclusion

Pleomorphic lobular carcinoma in situ expounds enhanced incidence of associated invasive carcinoma breast which may be detected upon core needle biopsy or surgical excision specimens. However, discernible concurrent invasive disease within surgical excision specimens may be enhanced [7,8]. Lesion is associated with significant genomic instability wherein possible occurrence of subsequent carcinoma breast cancer is elevated, in contrast to the classic variant. In contrast to the classic variant, prognostic outcomes are inferior on account of unfavourable immunoreactivity and enhanced possible emergence of associated invasive disease [7,8].

References

1. Limaiem F, Khan M, Lotfollahzadeh S (2024) Lobular Breast Carcinoma. Stat Pearls International.

2. Göker M, Deblaere S, Denys H, Vergauwen G, Naert E, et al. (2023) Tumour-Infiltrating Lymphocytes and PD-L1 Expression in Pleomorphic Lobular Breast Carcinoma. Cancers (Basel) 15(11): 2894.

3. Cosar R, Sut N, Topaloglu S, Tastekin E, Nurlu D, et al. (2023) Classifying Invasive Lobular Carcinoma as Special Type Breast Cancer May be Reducing its Treatment Success: A Comparison of Survival among Invasive Lobular Carcinoma, Invasive Ductal Carcinoma, and No-Lobular Special Type Breast Cancer. PLoS One 18(7): e0283445.

4. Timbres J, Kohut K, Caneppele M, Troy M, Schmidt MK, et al. (2023) DCIS and LCIS are the Risk Factors for Developing In Situ Breast Cancer Different?. Cancers (Basel) 15(17): 4397.

5. Image 1 Courtesy: Science direct

6. Image 2 Courtesy: Research gate

7. Kuba MG, Brogi E (2023) Update on Lobular Lesions of the Breast. Histopathology 82(1): 36-52.

8. Wen HY, Brogi E (2018) Lobular Carcinoma in Situ. Surg Pathol Clin 11(1): 123-145.