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The Miniscule Eaves-Micro-papillary Carcinoma Breast

Anubha Bajaj*

Department of Pathology, Panjab University, India

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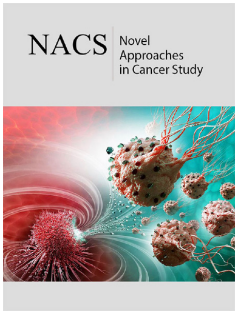

***Corresponding author:** Anubha Bajaj, Department of Pathology, Panjab University, India

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Abstract

Micro-papillary carcinoma breast emerges as an invasive, exfoliative neoplasm delineating characteristic pseudo-papillary, tubular or morula-like epithelial structures with an inverted or 'inside out' tumour pattern. Tumefaction exhibits upregulation of various nutrient transporters as glucose transporter 1 (GLUT1) through activation of transcription factor as hypoxia-inducible factor or upregulation of BC-1514 (C21 or f118), especially within micro-papillary areas. Tumour cells exhibit gains of chromosome 1q, 8q, 17q, 20q and loss of chromosome 1p, 8p, 13q, 16q and 20q. Cellular cytological smears delineate angulated clusters, abortive papillae and isolated malignant cells. Densely cellular tufts of cells configure pseudo-papillae, hollow tubules or morula with circumscribing clear spaces and minimal encompassing fibro-collagenous stroma. Characteristic reverse polarity or an 'inside out' pattern of tumour cells pervaded with abundant, eosinophilic cytoplasm, intracytoplasmic mucin and nuclei with a peripheral bulge, knobby or serrated appearance is observed. Neoplastic cells appear immune reactive to Epithelial Membrane Antigen (EMA), CD15s, E-cadherin, p120 catenin, oestrogen receptor(ER), Progesterone Receptor (PR), HER2 or GATA3.

Keywords: Pseudo-papillae; Reverse polarity; Anti-oestrogen therapy

Introduction

Micro-papillary carcinoma breast emerges as an invasive neoplasm exemplifying an exfoliative countenance. Characteristically, neoplasm delineates pseudo-papillary, tubular or morula-like epithelial structures enunciating an inverted or 'inside out' pattern of tumour evolution. Neoplastic micro-papillae are constituted of clusters of cells demonstrating reversed polarity. Cellular aggregates appear to float within vacant spaces and are frequently segregated by delicate strands of fibrous tissue stroma. Initially scripted by Fisher et al, nomenclature of micro-papillary carcinoma was preliminarily employed by Tavassoli. An estimated >90% of invasive neoplastic component is constituted of micro-papillary carcinoma. Commonly, invasive breast carcinoma with a predominant micro-papillary component may be concurrent with various histological subtypes of carcinoma breast. Commonly implicating male or female breast parenchyma, invasive micro-papillary carcinoma expounds <2% to 8% instances of carcinoma breast. Pure micro-papillary carcinoma is exceptionally encountered and configures up to 2% of carcinoma breast. However, tumefaction may frequently be admixed with diverse histological subtypes of invasive carcinoma breast [1,2]. Median age of disease emergence is 50 years to 62 years with mean age of disease occurrence at 59 years and an age range of 25 years to 92 years [1,2]. Of obscure aetiology, tumefaction depicts upregulation of various nutrient transporters as Glucose Transporter 1 (GLUT1) through activation of transcription factor as hypoxia-inducible factor. Neoplasm is frequently associated with cytoplasmic overexpression of MUC4. Besides, plakoglobin is a characteristic component of cellular adhesion which augments distant metastasis in concurrence with downregulation of apoptosis within cellular clusters through activation of PI3K/Akt/BCL2 signalling pathway. Constituent tumour infiltrating lymphocytes appear devoid of specific cytotoxic phenotype.

Lymphocytes depict decimated expression of Fas and FasL [1,2]. Neoplasm expounds elevated expression of CD146 and augmented micro-vessel density. Generally, overexpression

of β1 integrin with consequent upregulation of Rac1 contributes to reversal polarity within tumour cells and occurrence of distant metastasis. Molecules such as sialyl Lewis X or CD15s which is a ligand of E-selectin may contribute to reversed cell polarity. Quantifiably augmented CD44+/CD24-/low tumour cells are observed [2,3]. Invasive micro-papillary carcinoma breast commonly depicts upregulation of BC-1514 (C21orf118), especially within the micro-papillary area. Besides, genes as CAMK2N1, CD1d, PJA2, RPL5, SAMD13, TCF4 and TXNIP are frequently downregulated within micro-papillary zone [2,3]. Tumefaction exhibits gains of chromosome 1q, 8q, 17q, 20q and loss of chromosome 1p, 8p, 13q, 16q and 20q. Mixed tumours delineate genetic profiles identical to pure tumours, in contrast to ductal carcinoma. Neoplastic cells demonstrate enhanced expression of cyclin D1, enhanced proportionate cellular proliferation and amplification of MYC gene situated upon chromosome 8q24 [2,3]. The majority (~90%) of lesions represent as a palpable tumefaction. Upon radiographic imaging, neoplasm may represent with localization and macroscopic features identical to conventional invasive breast carcinoma [2,3]. In contrast to invasive ductal carcinoma, enlarged tumours of stage T2 manifest with aggressive clinical representation, frequently discerned regional lymph nodes metastasis upon initial disease representation and advanced tumour stage. Mean tumour magnitude emerges at 1.5 centimeters to 3.9 centimeters [2,3]. Upon initial disease representation, tumefaction is preponderantly (~85%) associated with quantifiably enhanced axillary lymph node metastasis [2,3]. Cytological smears appear cellular with configuration of angulated clusters, abortive papillae and isolated malignant cells. An estimated one third (~35%) of lesions depict staghorn epithelial structures with the configuration of a 'serrated' border.

Neoplasm may expound multinucleated giant cells with a malignant countenance or focal mucin aggregates. A definitive fibro-vascular core appears absent [2,3]. Grossly, specific features are absent. Neoplasm may expound a lobulated outline and tumour diameter varying from 0.1 centimeters to 10 centimeters with mean tumour magnitude of 2 centimeters. Generally, tumefaction demonstrating >50% of micro-papillary component appears enlarged with a mean magnitude of 6 centimeters, in contrast to neoplasms with <50% of micro-papillary pattern and mean magnitude of 3.5 centimeters [3,4]. Upon microscopy, a densely cellular tumefaction exemplifies tufts of tumour cells which configure pseudo-papillae, hollow tubules or morula circumscribed by vacant, clear spaces. Encompassing fibro-collagenous stroma is minimal [3,4]. Characteristically, tumour cells exhibit reverse polarity or an 'inside out' pattern where in apical surface of cells about the epithelial-stromal interface. Tumour cells are pervaded with abundant, eosinophilic cytoplasm, intracytoplasmic mucin and nuclei depicting a peripheral bulge with knobby or serrated appearance [3,4]. The neoplasm preponderantly (~78%) delineates foci of extensive and true angio-lymphatic invasion. Focal necrosis may be observed. Uncommonly, morphological features as psammoma bodies, micro-cystic dilation of glandular lumens accompanying cell clusters, focal apocrine differentiation or osteoclast-like multinucleated giant cells may be variably discerned. Generally, neoplasm expounds variable histological grade and emerges as a grade 2 or grade 3 neoplasm. Mucinous carcinoma may be imbued with micro-papillary component wherein the neoplasm is designated as mucinous micro-papillary carcinoma [3,4]. Ultrastructural examination depicts microvilli disseminated upon cell membrane layering extrinsic surface of cellular clusters. Stroma facing surface of neoplastic cells demonstrates secretory activity [3,4] (Figure 1 & 2).

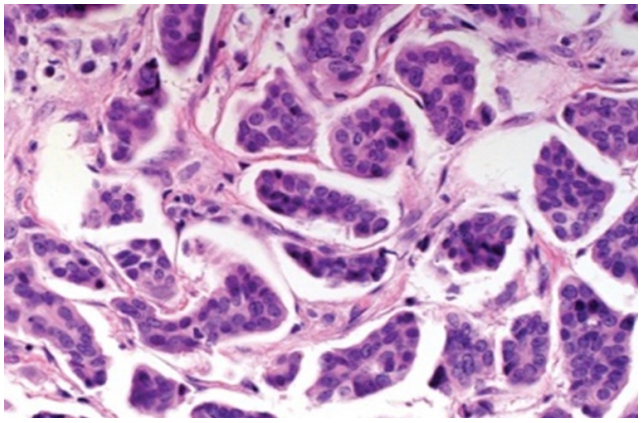

Figure 1: Micro-papillary carcinoma breast depicting tufts of tumour cells with reverse polarity, abundant, eosinophilic cytoplasm, intracytoplasmic mucin and knobby nuclei. Surrounding stroma is fibro-collagenous (Source: Nature.com).

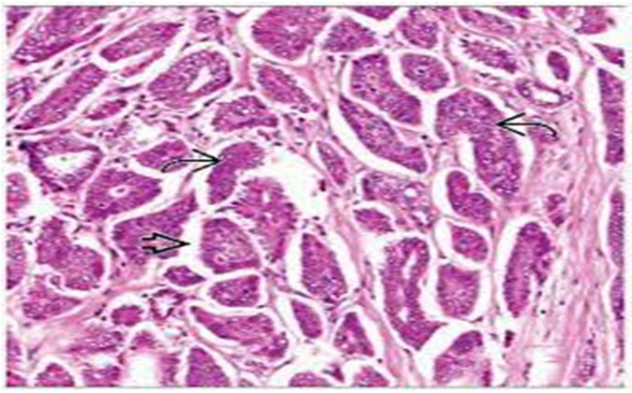

Figure 2: Micro-papillary carcinoma breast delineating mounds of tumour cells with reverse polarity, abundant, eosinophilic cytoplasm, intracytoplasmic mucin and knobby nuclei. Circumscribing stroma is fibro-collagenous (Source: Basic medical key).

Invasive micro-papillary carcinoma breast appears immune reactive to Epithelial Membrane Antigen (EMA), CD15s, E-cadherin, p120 catenin, oestrogen receptor (ER), Progesterone Receptor (PR), HER2 or GATA3. Tumour cells appear immune non-reactive to MUC2, CK5, CK20,CD117/KIT, epidermal growth factor receptor(EGFR) WT1 or PAX8 [5,6]. Invasive micro-papillary carcinoma breast requires segregation from neoplasms as metastatic ovarian papillary serous carcinoma, metastatic micro-papillary carcinoma of non-mammary/non ovarian origin, mucinous carcinoma with micro-papillary pattern or extensive lympho-vascular invasion by a primary or metastatic breast carcinoma [5,6]. Upon radiography,

neoplasm expounds multiple lesions and enlargement of axillary lymph nodes along with non-mass image enhancement. Mammography exemplifies an irregular, spiculated tumefaction (Table 1). Ultrasonography delineates an irregular, hypoechoic tumour mass with spiculated periphery and posterior acoustic shadowing. Magnetic resonance imaging (MRI) exhibits an irregular neoplasm with washout kinetics and diffuse, heterogeneous, mass-like image enhancement. Invasive micro-papillary carcinoma may be appropriately discerned upon histological assessment of surgical tissue or resection specimens. Enlargement of axillary lymph nodes as discerned within core needle biopsy specimens may be suitably subjected to axillary sonography [5,6]. Characteristically, neoplasm is immune reactive to oestrogen receptors and eligible to anti-oestrogen therapy. Applicable treatment strategy is variable and contingent to clinical stage as defined by tumour magnitude and regional lymph node metastasis [5,6]. Generally, occurrence of micro-papillary carcinoma component contributes to inferior prognostic outcomes. Nevertheless, prognostic outcomes are controversial and debatable. Concurrence of micro-papillary carcinomatous morphology appears as an unfavourable prognostic factor, especially for variables such as recurrence free survival and recurrence free survival associated with loco-regional metastasis [5,6]. However, micro-papillary carcinoma component may not significantly impact disease associated factors as overall survival, disease specific survival and distant metastasis free survival. In contrast to invasive ductal carcinoma, superior disease specific survival and equivalent overall survival may be encountered. Alternatively, inferior relapse free survival and overall survival may be encountered with micro-papillary carcinoma, in contrast to invasive ductal carcinoma. As observed with diverse subtypes of invasive carcinoma breast, prognostic outcomes are identical vis-a vis contributory factors as status of regional lymph nodes, tumour magnitude and occurrence of concurrent classic prognostic markers. Micro-papillary carcinoma may configure as a focal component in an estimated 6% of breast carcinomas wherein aforesaid invasive neoplasms delineate inferior prognostic outcomes irrespective of quantifiable micro-papillary component [5,6]. The occurrence of micro-papillary pattern within mucinous carcinoma breast or colloid carcinoma breast appears to lack clinical significance. Discernible micro-papillary features and retraction artefact within core needle biopsy specimens may be indicative of regional lymph node metastases [5-7].

Table 1: Immune markers associated with lymphatic metastasis within IMPC(3).

IMPC: Invasive Micro-Papillary Carcinoma

Immune Marker	Clinical Significance
MUC1	Associated with tumour progression and lymphatic metastasis
ANX A2	Involved in impaired anti-apoptotic effects
sLex	Masking tumour antigen & interacting with E-selectin, evading immune surveillance
Galectin-3	Influencing tumour progression and cell surface polarity
Integrin β1	Involved in Rac1 expression and reversal of cell polarity
LEF1	Wnt pathway activation
IL-1b	Linked to increased micro-vessel density
SDF-1	Interacting with CXCR4 on lymphatic endothelial vessels

Conclusion

Invasive micro-papillary carcinoma breast requires segregation from neoplasms as metastatic ovarian papillary serous carcinoma, metastatic micro-papillary carcinoma of non-mammary/ non ovarian origin, mucinous carcinoma with micro-papillary pattern or extensive lympho-vascular invasion by a primary or metastatic breast carcinoma. Mammography exemplifies an irregular, spiculated tumefaction. Invasive micro-papillary carcinoma may be appropriately discerned upon histological assessment of surgical tissue or resection specimens. Characteristically, neoplasm is immune reactive to oestrogen receptors and eligible to anti-oestrogen therapy. Applicable treatment strategy is variable and contingent to clinical stage as defined by tumour magnitude and regional lymph node metastasis. Generally, occurrence of micro-papillary carcinoma component contributes to inferior prognostic outcomes.

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