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EDITORIAL

Percolated and Spiked-Medullary Carcinoma Breast

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Medullary pattern is a histological pattern discerned within invasive carcinoma breast no special type (NST) comprised of a 'pushing' tumour perimeter, syncytial pattern of tumour evolution, high grade nuclei and prominent stromal lymphocytic infiltrate.

In contrast to a distinct morphological subcategory, medullary carcinoma breast is contemplated to represent a morphological continuum of tumour infiltrating lymphocyte (TIL) rich invasive carcinoma breast no special type (NST).

As per World Health Organization (WHO), preferred terminology is invasive breast carcinoma no special type (NST) with medullary pattern. Nevertheless, neoplasm can be designated as medullary carcinoma, atypical medullary carcinoma, or invasive carcinoma breast with medullary features.

Medullary carcinoma breast is an exceptional neoplasm afflicting young individuals with a median age of disease emergence at 53 years although tumefaction may be discerned within 45 years to 62 years.

Genetic, hormonal, or environmental factors contribute to emergence of medullary carcinoma breast.

Hormonal factors engendering medullary carcinoma are early menarche, delayed menopause, nulliparous state, primigravida > 30 years, obesity with postmenopausal state, occurrence of oestrogen- producing ovarian neoplasms or administration of oestrogens or combined hormone- replacement therapy with progestogens.

Hormonal induction of carcinoma breast is concurrent with intense, prolonged oestrogenic stimulation which may induce secretion of growth promoters.

Li-Fraumeni syndrome exhibiting germline mutations of p53 gene is associated with occurrence of carcinoma breast.

Chromosomal mutations of BRCA1 and BRCA2 genes may appear in familial carcinoma breast exemplified in young individuals. Few (~15%) neoplasms emerging within carriers of BRCA1 genetic mutation configure an invasive carcinoma breast with medullary pattern.

Heterozygous carriers of ataxia-telangiectasia may depict carcinoma breast by 50 years. Medullary carcinoma breast frequently depicts genomic instability and majority of neoplasms exhibit a basal-like molecular profile. Medullary carcinoma breast commonly emerges within young subjects and represents as a soft, palpable, well circumscribed tumefaction. Accompanying lymphadenopathy is possibly due to lymph node hyperplasia whereas regional lymph node metastasis is uncommon. Medullary pattern of invasive breast carcinoma special type (NST) enunciates characteristic histological features mandated for appropriate disease discernment as a

- 'pushing' tumour perimeter
- syncytial pattern of tumour evolution
- pleomorphic or high-grade tumour cell nuclei
- preponderant lymphocytic stromal inflammatory infiltrate.

Upon gross examination, a grey/white, well circumscribed, soft to moderately firm, fleshy tumefaction of ~ 3-centimetre magnitude is observed which may simulate a fibroadenoma. The miniature neoplasms depict a median tumour diameter of up to 3 centimetres. Cut surface is homogenous and lobular or nodular. Foci of hemorrhage, necrosis or cystic degeneration may be discerned.

Cytological evaluation exhibits a hyper-cellular specimen configured of innumerable isolated tumour cells and loosely cohesive clusters. Neoplastic cells are significantly enlarged and imbued with vesicular nuclei with prominent, irregular macro-nucleoli. An inflammatory exudate of innumerable lymphocytes and plasma cells appear intermingled with tumour cells.

Upon microscopy, the well circumscribed medullary carcinoma enunciates distinctive morphological criteria as designated by World Health Organization (WHO) which are enumerated as

- a predominant syncytial pattern of tumor evolution as >75% of neoplasm
- complete absence of glandular or tubular articulations
- moderate to prominent diffuse lymphocytic and plasma cell infiltrate confined to neoplastic stroma
- moderate to preponderant nuclear pleomorphism
- comprehensive circumscription of tumefaction upon histological assessment
- Mitotic figures are numerous. Atypical giant cells may occur

Terminology of 'atypical medullary carcinoma' and 'carcinoma with medullary features' can be adopted for neoplasms which lack aforesaid diagnostic criteria.

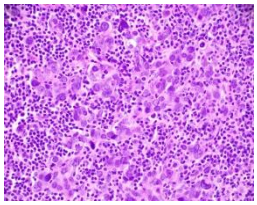

Figure 1 Medullary carcinoma breast depicting aggregates of pleomorphic neoplastic cells with significant anaplasia and a dense stromal inflammatory infiltrate of lymphocytes.[5]

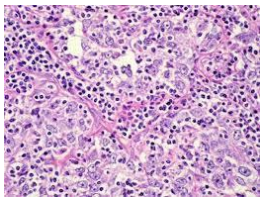

Figure 2 Medullary carcinoma breast depicting lobules and nests of anaplastic tumour cells with prominent nucleoli with significant stromal inflammatory infiltrate of lymphocytes and plasma cells.[6]

World Health Organization (WHO) recommends inclusion of classic medullary carcinoma, atypical medullary carcinoma, and invasive carcinoma breast no special type with medullary features within a singular category of 'carcinomas with medullary features.

Upon clinical assessment, medullary carcinoma breast is a low-grade neoplasm, especially in instances which are devoid of metastasis into regional lymph nodes.

Upon histological assessment, medullary

carcinoma breast is a high-grade neoplasm.

Bloom-Scarff-Richardson grading appears non applicable to medullary carcinoma.

As per frequently employed TNM staging of invasive carcinoma breast (NST), critical staging criteria for regional lymph nodes is denominated as

- isolated tumour cell clusters which can be identified with cogent haematoxylin and eosin stain or pertinent immunohistochemistry. Magnitude of tumour cell cluster is ≤ 0.2 millimetres and multiple clusters may pervade a singular or multiple regional lymph nodes
- micro-metastasis is designated as tumour cell cluster > 0.2 millimetres and ≤ 2.0 millimetres •metastasis is exemplified by minimally a singular focus of neoplastic cells ≥ 2.0 millimetre magnitude

Additionally, remaining lymph nodes with miniature foci of neoplastic cells ≤ 2.0 millimetre necessitate quantification and assessment. Contingent to disease stage, incriminated regional lymph nodes are quantified as one to three, four to nine and >10. Extra-nodal tumour extension requires evaluation.

Surgical excision adopted for infiltrative carcinoma breast necessitates evaluation of tumour grade with comprehensive tumour score and individual components, tumour magnitude with greatest dimension, assessment of neoplastic infiltration at critical zone of 0.5 centimetres, 2.0 centimetres and surgical perimeter. Precise distance of invasive and in situ carcinoma requires documentation.

Occurrence and location of angio-lymphatic invasion necessitates evaluation configured within tumour mass, adjacent to tumour mass or confined to dermis. Extensive component of ductal carcinoma in situ (DCIS) is not contemplated to be significant predictor of biological behaviour of the neoplasm.

Immunohistochemistry with oestrogen receptors (ER), progesterone receptors (PR), HER2/neu and Ki67 proliferative index can be adopted for appropriate tumour discernment, assaying prognostic outcomes, to be adopted upon a previously obtained tissue sample or deferred for subsequently obtained neoplastic surgical excision.

Fine needle or core tissue samples may be employed to obtain a provisional tumour grade although assessment of definitive grade may be deferred.

Medullary carcinoma breast is variably immune reactive to various basal markers as CK5/6, CK14, epidermal growth factor receptor (EGFR/HER1) or p53. Enhanced PDL1 expression is observed. Medullary carcinoma breast is immune non-reactive to oestrogen receptors (ER), progesterone receptors (PR) and HER2/neu (triple negative).

Medullary carcinoma requires segregation from neoplasms such as metastatic high grade carcinoma breast from a distant primary, normal lymph node, lymphoma, invasive carcinoma breast (NST), chronic breast inflammation, lymphoepithelioma-like carcinoma, or malignant melanoma.

Akin to invasive carcinoma breast, medullary carcinoma can be appropriately discerned with manoeuvres as screening or diagnostic mammography, ultrasonography, or core needle tissue sampling. Upon mammography, a spherical, lobulated, or elliptical tumefaction is observed.

Ultrasonography exhibits a hypoechoic tumefaction circumscribed by a dense, echogenic halo.

As applicable to invasive carcinoma breast (NST), medullary carcinoma can be treated with targeted therapy contingent to immune reactivity to oestrogen receptors (ER), progesterone receptors (PR) and HER2/neu.

In the current scenario, tumour infiltrating lymphocytes may not appear to alter course of therapy.

Factors contributing to prognostic outcomes are denominated as age of incriminated subject, histological grade and stage of neoplasm, occurrence of lymphatic and vascular invasion, pertinent molecular subtype of tumefaction and immune reactivity to oestrogen receptors (ER), progesterone receptors (PR) and HER2/neu. Additionally, triple negative medullary carcinoma breast enunciates an unfavourable prognosis.

Prognostic outcomes may simulate stage matched grade III ductal carcinoma with prominent inflammation or appear superior to grade III ductal carcinoma devoid of prominent inflammation.

Tumour infiltrating lymphocytes may enhance prognostic outcomes.

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Conflict of Interest

Author declares that there is no conflict of interest.

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5. Image 1 Courtesy: Pathology outlines
6. Image 2 Courtesy: Pathpedia