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Grist and Smidgen-neuroendocrine Carcinoma Breast

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Neuroendocrine carcinoma breast emerges as an infrequently discerned, primary, low grade to intermediate grade neoplasm implicating mammary gland parenchyma. Neoplasm represents with histological features pre-eminently (>90%) indicative of neuroendocrine cellular differentiation, tumour configuration and immunohistochemistry pertaining to neuroendocrine markers, as necessitated for appropriate tumour categorization. Nomenclature as carcinoid tumour or atypical carcinoid tumour of breast is not recommended. Initially categorized as tumours with neuroendocrine differentiation, the current World Health Organization (WHO) classification categorizes the lesion as neuroendocrine neoplasm, inclusive of designations as neuroendocrine tumour (NET) or small cell and large cell neuroendocrine carcinoma. Nevertheless, a formal grading system applicable to the neoplasm is absent.

However, segregation is required from distinctive breast neoplasms with neuroendocrine differentiation as solid papillary carcinoma, mucinous carcinoma of breast and invasive ductal carcinoma- no special type with neuroendocrine differentiation.

Neuroendocrine tumour breast contributes to < 1% of primary breast carcinomas. Generally, age of disease representation appears at > 65 years [1, 2].

Of obscure aetiology, tumefaction is posited to arise from neoplastic transformation of native neuroendocrine cells confined to the breast. Besides, neoplastic stem cells may expound diverging neuroendocrine differentiation [1,2]. Neuroendocrine carcinoma breast demonstrates genetic mutations within ARID1A, ATRX, FOXA1, GATA3 and PIK3CA genes. High grade neuroendocrine carcinomas frequently expound genomic mutations within TP53 gene (1,2). Typically, mammary gland neuroendocrine tumour represents as a mass lesion wherein ~10% lesions are bilateral. Tumour magnitude varies from one centimetre to 5 centimetres. Regional lymph node or distant, systemic metastasis may be commonly observed upon initial disease representation. Neuroendocrine tumours of breast appear devoid of carcinoid syndrome [2, 3].

Grossly, a well circumscribed, non-encapsulated tumefaction is encountered [2, 3]. Upon microscopy, a preponderant (> 90%) configuration of neuroendocrine tumour cells is necessitated in order to categorize the neoplasm as a specific neuroendocrine subtype. Neoplasm is densely cellular and configures organoid nests, trabeculae or an insular pattern. Besides, papillary and alveolar-like structures may be encountered. Tumour parenchyma is traversed by delicate intervening strands of fibro-vascular stroma [3, 4]. Tumour cells delineate classic neuroendocrine features and appear as spindle shaped cells, plasmacytoid cells or polygonal cells pervaded with granular, eosinophilic cytoplasm and eccentric nuclei with stippled, 'salt and pepper' nuclear chromatin. Intra-nuclear inclusions may be inconspicuous or discernible [3, 4]. Neuroendocrine tumour of mammary gland frequently lacks classic features of carcinoid-like morphology as ribbons, cords and rosettes configured of tumour cells. Predominantly, Nottingham grade 1 or grade 2 neoplasms are expounded. Ultrastructural examination depicts dense core vesicles and presynaptic vesicles [3, 4].

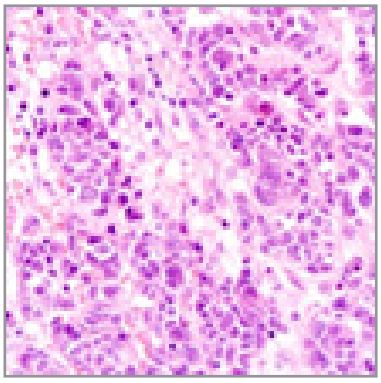

Figure 1: Neuroendocrine tumour depicting organoid nests and ribbons of tumour cells imbued with granular eosinophilic cytoplasm and eccentric nuclei with salt and pepper nuclear chromatin. Tumour parenchyma is traversed by delicate strands of fibro-vascular stroma(6)

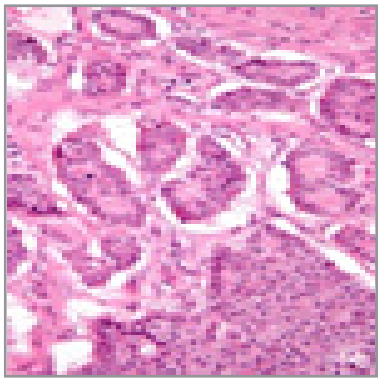

Figure 2: Neuroendocrine tumour delineating organoid nests and ribbons of tumour cells impregnated with granular, eosinophilic cytoplasm and eccentric nuclei salt and pepper nuclear chromatin. Tumour parenchyma is traversed by delicate strands of fibro-vascular stroma(7).

Nottingham Bloom-Richardson grading system is contingent to ~configuration of tubules by the tumour ~quantifiable mitotic figures per 10 high power fields as exemplified within actively proliferating, cellular areas ~occurrence of nuclear pleomorphism.

Configuration of tumour tubules contributes to pertinent scoring and is classified as ~ 1 point: tubules representing > 75% of tumefaction ~2 points: tubules articulating 10% to 75% of tumefaction ~3 points: tubules manifesting < 10% of tumefaction.

Mitotic figures are appropriately evaluated upon tumour periphery and are aptly quantified within mitotically active areas. Estimation of mitotic figures confined within 10 high power fields (hpf) constituting a singular, non-contiguous neoplastic area is optimal.

Nuclear pleomorphism is classified as ~1 point: neoplasms depicting minimal variation of nuclear magnitude and outline with configuration of miniature, regular, uniform neoplastic cells ~2 points: neoplasms delineating moderate variation in nuclear magnitude and outline ~3 points: neoplasms demonstrating significant variation in nuclear magnitude and outline. Carcinoma breast is graded and scored as ~3 - 5 points: accumulated by well differentiated, grade I carcinoma breast ~6 - 7 points: accumulated by moderately differentiated, grade II carcinoma breast ~8 - 9 points: accumulated by poorly differentiated, grade III carcinoma breast [3, 4].

Neuroendocrine tumour breast appears immune reactive to various neuroendocrine markers as synaptophysin, chromogranin, insulinoma associated-protein1 (INSM1), neuron specific enolase (NSE) and CD56. Tumour cells appear immune reactive to various hormonal markers as oestrogen receptors (ER), progesterone receptors (PR) and androgen receptors (AR). Besides, immune reactivity to CK7, GATA3 and gross cystic disease fluid protein 15(GCDFP 15) may be observed. Tumour cells are immune non-reactive to HER2, thyroid transcription factor 1(TTF1), glypican 3 and CDX2 [4,5]. Neuroendocrine tumour breast requires segregation from neoplasms as metastatic neuroendocrine tumours arising from various primaries, breast neoplasms with neuroendocrine differentiation, neuroendocrine carcinomas as small cell carcinoma, large cell carcinoma, invasive carcinoma with neuroendocrine differentiation, solid papillary carcinoma, mucinous carcinoma, apocrine carcinoma or lobular neoplasia [4, 5]. For appropriate categorization, histological evidence of neuroendocrine differentiation in addition to immune reactivity to various neuroendocrine markers is necessitated. Radiographic imaging or evaluation of serological parameters appear nonspecific and insensitive for cogent diagnosis of the neoplasm. Biochemical assay depicts elevated serum chromogranin levels. Upon mammography, a lobular, well defined, dense tumour mass is encountered. Generally, foci of micro-calcification appear absent. Ultrasonography delineates a hypo-echogenic and hyper-echogenic tumour mass with enhanced vascular perfusion [4, 5]. Neuroendocrine tumour breast may be appropriately alleviated with surgical extermination of the neoplasm. Resection of regional lymph nodes may or may not be adopted. Neoplasms associated with distant metastasis may be managed with an amalgamation of traditional chemotherapy and somatostatin analogues [4, 5]. In contrast to invasive ductal carcinoma of no special type, prognostic outcomes are inferior. Factors contributing to prognostic outcomes emerge as tumour stage, histological grade and levels of Ki67 proliferative index. Majority of neuroendocrine tumours of breast configure as Nottingham grade 1 or grade 2 neoplasms. Elevated Ki67 proliferative index values are indicative of aggressive neoplasms [4, 5].

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