Acta Scientific Gastrointestinal Disorders (ISSN: 2582-1091)

Volume 7 Issue 8 August 2024

Editorial

Reclamation and Passage-Carcinoma ex Pleomorphic Adenoma

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Received: June 14, 2024

Published: July 01, 2024

Carcinoma ex pleomorphic adenoma arises as an epithelial or myoepithelial malignancy emerging from primary or recurrent pleomorphic adenoma. For cogent categorization, tumefaction necessitates categorical discernment of benign and malignant components. Additionally, pertinent history of documented pleomorphic adenoma upon tumour site is required in lesions where benign component appears obliterated by carcinoma.

Additionally designated as carcinoma ex mixed tumour, the terminology of malignant mixed tumour is not recommended.

Commonly, malignant constituents appear as salivary duct carcinoma or adenocarcinoma not otherwise specified (NOS) along with myoepithelial carcinoma or epithelial- myoepithelial carcinoma.

As around ~5% of pleomorphic adenomas demonstrate malignant metamorphosis wherein recurrent pleomorphic adenoma or lesions of long standing duration possibly undergo transition into malignancy.

Typically, palpable mass of extended duration with recent, brisk augmentation of tumour magnitude appears confined to parotid region.

The uncommon carcinoma ex pleomorphic adenoma arises in ~5% of pleomorphic adenoma with malignant metamorphosis. Peak disease incidence occurs within seventh decade and neoplasm may emerge within 17 years to 97 years. A mild male predilection is observed [1,2].

Carcinoma ex pleomorphic adenoma commonly implicates parotid gland (77%) or submandibular gland (18%). Notwithstanding, various major salivary glands are uncommonly involved. Exceptionally, tumefaction is confined to oral cavity, pharynx, lacrimal gland, trachea or nasal cavity [1,2].

Of obscure aetiology and non comprehended pathophysiology, tumefaction expresses methodical acquisition of genetic aberrations associated with neoplastic progression.

Preliminary malignant metamorphosis of ductal epithelial cells is accompanied with dysfunctional p53 protein [1,2].

Subsequently, neoplastic evolution into intra-capsular carcinoma, minimally invasive carcinoma or widely invasive carcinoma may ensue. Neoplasm is associated with genomic amplification of HER2 and decimated expression of PLAG1. Notwithstanding, myoepithelial carcinoma may progress in concurrence with variable mechanisms [2,3].

Pleomorphic adenoma and carcinoma ex pleomorphic adenoma demonstrates genetic rearrangements or genomic amplifications within PLAG1, HMGA2, HMGIC or MDM2 genes. Nearly 40% lesions demonstrate amplification of HER2 gene. Besides, intra-capsular carcinoma ex pleomorphic adenoma may exemplify TP53 chromosomal mutations [2,3].

Carcinoma ex pleomorphic adenoma of lacrimal gland displays copy number gains within chromosomes 9p and 22q [2,3].

Commonly, carcinoma ex pleomorphic adenoma represents with a palpable tumefaction confined to the parotid region. Neoplasm may manifest with rapid enhancement of tumour magnitude within a pre-existent mass, pain and facial paresis or paralysis [2,3].

Tumour mass of extensive duration demonstrates brisk augmentation of tumour magnitude, thereby postulating therapeutic delay of pleomorphic adenoma as a factor contributing to malignant transformation.

Roughly ≤ 25% subjects display preceding history of pleomorphic adenoma subjected to therapy. Lesions of advanced grade may present with cutaneous ulceration or dysphagia [3,4].

Frozen section may be employed for ascertaining benefit of facial nerve excision, especially in lesions devoid of infiltration into perimeter of neural stump. Nevertheless, routine application of frozen section for discerning and categorizing salivary gland tumours appears inappropriate [3,4].

Cytological smears of pleomorphic adenoma component are comprised of sheets or cohesive groups of ductal epithelial cells admixed with singly dispersed or loosely cohesive clusters of myoepithelial cells. Intervening stromal matrix is typically dense, fibrillary and metachromatic wherein a magenta hue is obtained upon Romanowsky type stains [3,4]. Carcinomatous component is constituted of pleomorphic, hyperchromatic cells with elevated nucleocytoplasmic ratio and clumped nuclear chromatin. Tumour cells are commingled with focal necrosis. Morphological features indicative of carcinoma subtype emerge as mucous cells, squamoid cells or various constituent epithelial cells.

Fine needle aspiration may be accompanied by erroneous sampling of constituent cellular component and demonstrates minimal sensitivity of detecting carcinoma ex pleomorphic adenoma. Besides, distinction between non invasive and invasive neoplasms may be challenging. Notwithstanding, expansive, high grade carcinomatous component may be appropriately discerned upon fine needle aspiration cytology [3,4].

Grossly, tumour countenance is contingent to proportion of pleomorphic adenoma to carcinoma component. Lesions with predominant pleomorphic adenoma component appear as well circumscribed, glistening and grey/white or white. Lesions with indistinct pleomorphic adenoma component emerge as an irregular, incompletely circumscribed tumour mass with infiltration into adjacent anatomical structures. Foci of malignant neoplastic component may display necrosis or haemorrhage. The widely invasive neoplasms exceed ≥ 1.5 millimetre magnitude [4,5].

For appropriate categorization, tumefaction necessitates histological confirmation of benign and malignant neoplastic components or morphological ascertainment of carcinoma in concurrence with previously diagnosed pleomorphic adenoma upon tumour site.

Upon microscopy, tumefaction may depict carcinomatous component as salivary duct carcinoma, myoepithelial carcinoma or epithelial-myoepithelial carcinoma. Myoepithelial carcinoma component frequently emerges as a low grade lesion [4,5].

Constituent high grade adenocarcinoma commonly comprises of salivary duct carcinoma and adenocarcinoma not otherwise specified (NOS).

Additionally, neoplastic differentiation may occur as squamous cell carcinoma, mucoepidermoid carcinoma or polymorphous adenocarcinoma of salivary gland. An admixture of aforesaid subtypes may occur [4,5].

Staging of malignant salivary gland tumours is designated as [3,4]

- Stage 0: Tis, N0,M0
- Stage I: T1, N0, M0
- Stage II: T2, N0, M0
- Stage III: T3, N0, M0 OR T0, T1, T2, T3, N1, M0
- Stage IVA: T0, T1, T2, T3 or T4a, N2, M0 OR T4a, N0 or N1, M0
- Stage IVB: Any T, N3, M0 OR T4b, any N, M0
- Stage IVC: Any T, any N, M1

Ductal cells of pleomorphic adenoma component appear immune reactive to pancytokeratin, CK7, CK18, epithelial membrane antigen (EMA) or carcinoembryonic antigen (CEA). Myoepithelial cells appear immune reactive to smooth muscle actin (SMA), calponin, muscle specific actin (MSA), smooth muscle myosin heavy chain (SMMHC), p63, CK14, glial fibrillary acidic protein (GFAP) or S100 protein [5,6].

Carcinoma ex pleomorphic adenoma expresses immunohistochemistry pertaining to malignant component designated as

- Salivary duct carcinoma immune reactive to CK7, epithelial membrane antigen (EMA), HER2, androgen receptor (AR) or p53
- Myoepithelial carcinoma appears immune reactive to calponin, p40, p63 or smooth muscle myosin heavy chain (SMMHC)
- Mucoepidermoid carcinoma appears immune reactive to CK7, CK5/6, p63 or various mucin stains
- Adenocarcinoma not otherwise specified (NOS) appears devoid of cogent immunostaining [5,6].

Ki67 proliferative index may be beneficially employed to segregate benign and malignant neoplastic components wherein benign pleomorphic adenoma or recurrent tumour displays values < 5%

and malignant component is associated with elevated levels. Carcinoma ex pleomorphic adenoma displays specific immune reactive HMGA2 with minimal sensitivity [5,6].

Tumour cells appear immune non reactive to oestrogen receptors (ER), progesterone receptors (PR), melan A, human melanoma black 45 (HMB45) or desmin [5,6].

Carcinoma ex pleomorphic adenoma requires segregation from neoplasms as recurrent pleomorphic adenoma, pleomorphic adenoma with pseudopodia, de novo carcinoma or primary carcinoma with distant metastasis into salivary glands [7,8].

In contrast to computerized tomography (CT), magnetic resonance imaging (MRI) emerges as a sensitive modality for detecting malignant neoplasms. The technique depicts superior delineation of tissue planes and infiltrative tumour perimeter. MRI characteristically and aptly discerns encapsulated and invasive components of the tumefaction.

Encapsulated or pleomorphic adenoma component expounds variable signal intensities upon MRI, thereby indicating variation within tumour architecture and cytological or morphological features [7,8].

Invasive component expresses focal haemorrhage, necrosis, irregular tumour perimeter or infiltration into circumscribing soft tissues.

T2 weighted imaging demonstrates minimal to intermediate signal intensity.

Diffusion weighted imaging may be appropriately employed to segregate benign and malignant tumour constituents.

Signal avidity of positron emission tomography (PET) is inconsistently delineated within salivary gland tumours, thus the procedure is not recommended [7,8].

Cogent histological assessment appears appropriate for discerning benign pleomorphic adenoma and malignant neoplastic component. Rapid augmentation within magnitude of pleomorphic adenoma of extensive duration may clinically indicate emergence of carcinoma ex pleomorphic adenoma. Comprehensive histological assessment of entire lesion with multiple, deep seated sections is mandated [7,8].

Optimal therapy of carcinoma ex pleomorphic adenoma necessitates amalgamation of multidisciplinary strategies.

Surgical extermination of the neoplasm with tumour free surgical perimeter is suitably adopted. Optimal surgical extent is contingent to factors as magnitude and localization of tumour, status of adjacent basin of regional or cervical lymph nodes and concurrence of facial nerve, mandible, auditory canal or lateral temporal bone [7,8].

Adjuvant radiotherapy may be employed in instances demonstrating

- Tumour confined to surgical perimeter
- Advanced tumour stage
- Infiltration of bone, perineurium, lymphatic articulations or vascular structures
- Metastasis into regional cervical lymph nodes.

Adjuvant chemotherapy is employed in lesions delineating distant metastases [7,8].

Non invasive or minimally invasive carcinoma ex pleomorphic adenoma is associated with exceptionally superior prognostic outcomes.

Neoplastic stratification is contingent to proportion of capsular invasion.

Intra-capsular lesion is associated with superior prognostic outcomes. Minimally invasive lesions demonstrate magnitude < 1.5 millimetres.

Poorly defined neoplasms constituted of carcinomas with aggressive clinical course as salivary duct carcinoma may be associated with irrelevant factors as extent of tumour invasion [7,8].

Factors such as older age of implicated individuals, male gender, tumour diameter > 40 millimetres, proportionate capsular invasion, metastasis into regional lymph nodes or histological subtype of malignant component and metastasis into regional lymph nodes or distant metastases emerge as independent predictors of prognostic outcomes and disease specific survival [7,8].

Neoplastic features as histological tumour grade, neoplastic invasion, implication of regional lymph nodes or perineural invasion are associated with distant metastases.

Prognostic outcomes of carcinoma ex reoccurring pleomorphic adenoma is significantly inferior, in contrast to carcinoma ex primary pleomorphic adenoma.

Nearly 30% neoplasms delineate regional lymph node metastases. Distant metastases may ensue in ~4% neoplasms.

Neoplasms with myoepithelial carcinoma as malignant component is associated with adverse prognostic outcomes [7,8].

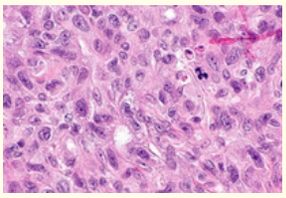

Figure 1: Carcinoma ex pleomorphic adenoma demonstrating malignant foci composed of pleomorphic, hyperchromatic cells with elevated nucleocytoplasmic ratio and clumped nuclear chromatin. Malignant epithelial cells appear adjacent to foci of classic pleomorphic adenoma [9].

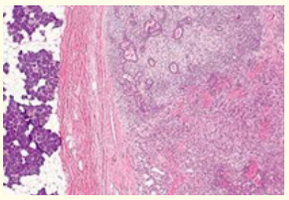

Figure 2: Carcinoma ex pleomorphic adenoma delineating malignant foci of pleomorphic, hyperchromatic cells with elevated nucleocytoplasmic ratio and clumped nuclear chromatin. Malignant epithelial cells appear adjacent to foci of classic pleomorphic adenoma [10].

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9. Image 1 Courtesy: Pathology apps.com.

10. Image 2 Courtesy: Libre pathology.