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Editorial

The Metamorphosed Muzzle-Nasopharyngeal Carcinoma

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Nasopharyngeal carcinoma emerges within nasopharynx which is layered by nasopharyngeal mucosa demonstrating histologic and phenotypic differentiation into squamous epithelium. Majority of neoplasms occurring within endemic areas are immune reactive to Epstein-Barr virus (EBV) or Epstein-Barr encoded RNA (EBER). A subset of neoplasms may concur with high-risk variants of human papillomavirus (HPV).

Nasopharyngeal carcinoma commonly incriminates nasopharyngeal recess or fossa of Rosenmüller and subsequently spreads to superior posterior wall. Tumour extension into adjacent organs as nasal cavity, paranasal sinuses, oropharynx, bone, orbit or infratemporal fossa is frequent. Tumefaction commonly emerges between fourth decade to sixth decade [1,2].

Nasopharyngeal carcinoma is categorized into keratinizing squamous cell carcinoma, basaloid squamous cell carcinoma and non-keratinizing squamous cell carcinoma further subdivided into differentiated subtype or undifferentiated subtype [1,2].

Keratinizing nasopharyngeal carcinoma is scripted as squamous cell carcinoma, non-keratinizing differentiated squamous cell carcinoma is denominated as transitional carcinoma and is followed in frequency by basaloid squamous cell carcinoma [1,2].

The frequent non-keratinizing squamous cell carcinoma, undifferentiated subtype is additionally designated as lympho-epithelioma, lympho-epithelial carcinoma or undifferentiated carcinoma and preponderant in paediatric subjects. Differentiated or undifferentiated subtype of non-keratinizing nasopharyngeal carcinoma are classified contingent to predominant histology. Non-keratinizing, differentiated or undifferentiated nasopharyngeal carcinoma depicts an estimated ~65% five year survival [1,2].

Factors contributing to occurrence of nasopharyngeal carcinoma are genetic susceptibility with specific, class I genotypes of human leukocyte antigen (HLA), elevated levels of nitrosamines in preserved food as salted fish, cigarette smoking and occupational exposure to chemical fumes, smoke, formaldehyde or wood dust [1,2].

Keratinizing subtype may arise as a secondary malignancy following exposure to radiation therapy adopted for treating non-keratinizing nasopharyngeal carcinoma. Keratinizing subtype exhibits an inferior prognosis and enhanced mortality with frequent nodal metastasis.

Tumefaction commonly represents with painless lymphadenopathy of upper cervical lymph nodes secondary to lymph node metastasis or obstructive symptoms engendered by nasopharyngeal tumour as postnasal drip, nasal discharge, epistaxis, serous otitis media or tinnitus. Advanced neoplasms with incrimination of skull base are associated with headache and diverse symptoms of cranial nerve involvement [1,2].

Grossly, resection specimens exhibit a variable appearance and may demonstrate a smooth mucosal bulge, elevated tumour nodule along with or devoid of surface ulceration, an infiltrative mass lesion or occult tumefaction discernible on microscopic assessment. Specimens obtained with endoscopic tissue sampling are devoid of specific features on gross examination [1,2].

Cytological assessment of non-keratinizing, undifferentiated nasopharyngeal carcinoma demonstrates clustered tumour cells with an indistinct cellular perimeter and vesicular nuclei imbued with prominent, centric nucleoli. An admixture of mature lymphocytes and plasma cells is common [1,2]:

- Non-keratinizing, undifferentiated subtype is composed of cohesive tumour cells manifesting a distinct syncytial configuration:
    - Regaud pattern exhibits tumour cells with an indistinct cellular perimeter [1,2].
    - Schmincke pattern delineates a diffuse infiltrate of non-cohesive tumour cells [1,2].

  Tumour cells exemplify eosinophilic or amphophilic cytoplasm with spherical nuclei, prominent, centric, eosinophilic nucleoli and vesicular nuclear chromatin. Focal keratinization is absent. Apoptotic cells are observed. Mitosis is significant although necrotic foci are infrequent. Non-neoplastic, lympho-plasmacytic inflammatory infiltrate surrounding tumour cell nests is prominent [1,2].

- Non-keratinizing, differentiated subtype is comprised of interconnecting cords or trabeculae of tumour cells, simulating a urothelial carcinoma. Focal keratinization is minimal or absent. Tumour cells exhibit a well defined cellular perimeter with variable intercellular bridges. Intervening stroma is infiltrated with varying lymphocytic and plasma cell infiltrate. Desmoplastic reaction is absent [1,2].

- Keratinizing subtype simulates keratinizing squamous cell carcinoma and exhibits distinctive squamous differentiation as intercellular bridges or focal keratinization. Tumefaction can be graded as well differentiated, moderately differentiated or poorly differentiated. Focal desmoplasia may occur [1,2].

- Basaloid subtype resembles basaloid squamous cell carcinoma wherein tumour cells enunciate scanty cytoplasm and enlarged nuclei with enhanced nuclear/cytoplasmic ratio. Basaloid tumour cell nests or sheets frequently depict peripheral palisading and centric, comedo-type necrosis [1,2].

Nasopharyngeal carcinoma is immune reactive to EBV-LMP, pan-cytokeratin, high molecular weight cytokeratin, p63, p40 and rarely to CK7 [3,4].

Tumefaction is immune non reactive CK7, CK20, CD45, S100 protein, HMB45, Melan A, desmin, myoglobin or myogenin. Tumour cells are exceptionally immune non reactive to high molecular weight cytokeratin and p40 [3,4].

Majority (~100%) of instances depict Epstein-Barr virus (EBV) delineated with PCR or EBER which is discernible with ISH [3,4].

Nasopharyngeal carcinoma requires segregation from neoplasms such as diffuse large B cell lymphoma, mucosal malignant melanoma, oropharyngeal non keratinizing squamous cell carcinoma, sinonasal undifferentiated carcinoma and rhabdomyosarcoma as embryonal rhabdomyosarcoma with botryoid variant, alveolar rhabdomyosarcoma, spindle cell rhabdomyosarcoma or pleomorphic rhabdomyosarcoma.

Nasopharyngeal carcinoma can be appropriately discerned and categorized with histological assessment and cogent immunohistochemistry. Epstein-Barr virus (EBV) serology is reactive along with elevated, circulating EBV-DNA or RNA as plasma or serum EBV encoded small RNA (EBERs) [3,4].

Magnetic resonance imaging is an optimal modality adopted to assess extent of disease and intracranial tumour extension [3,4].

Factors associated with unfavourable prognostic outcomes are incrimination of elderly, male subjects, significant tumour volume and occurrence of cranial nerve palsies. Clinical stage is a pertinent prognostic indicator wherein 5 year survival of stage IV disease is ~73%. Radiation therapy is an optimal, recommended treatment strategy for alleviating diverse histologic subtypes of nasopharyngeal carcinoma. Surgical intervention is applicable to subjects unresponsive to radiation therapy [3,4].

Tumour	Node	Metastasis
TX: Tumour cannot be assessed	NX: Lymph nodes cannot be assessed	
Tis: Tumour *in situ*		
T0: Tumour absent from nasopharynx	N0: Lymph node metastasis absent	M0: Distant metastasis absent
T1: Tumour confined to nasopharynx, extends to oropharynx or nasal cavity	N1: Tumour spreads to ≥ 1 cervical or retropharyngeal lymph nodes, is ≤ 6 cm and immune reactive to EB virus	M1: Distant metastasis into various organs as lungs
T2: Tumour depicts para-pharyngeal extension, into oropharynx and absent bony metastasis	N2: Tumour extension into bilateral cervical or retro-pharyngeal nodes ≤ 6 cm	
T3: Tumour extends into nasal sinuses or adjacent bones	N3: Tumour extends to supraclavicular nodes or ≥ 1 bilateral cervical nodes > 6 cm	
T4: Tumour extends into skull, cranial nerves, hypopharynx, parotid gland, ocular, retro-bulbar or adjacent soft tissue		

Table: *TNM classification of nasopharyngeal carcinoma [1,2].*

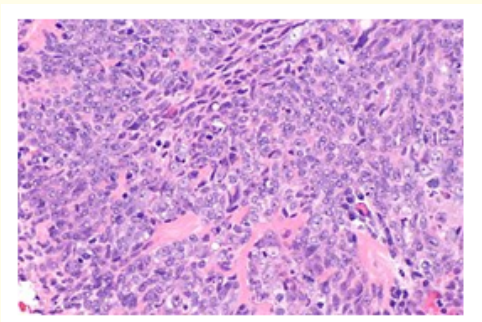

Figure 1: *Nasopharyngeal carcinoma depicting nests of squamous cells with indistinct margin, eosinophilic cytoplasm, vesicular nuclei and mitotic figures [5].*

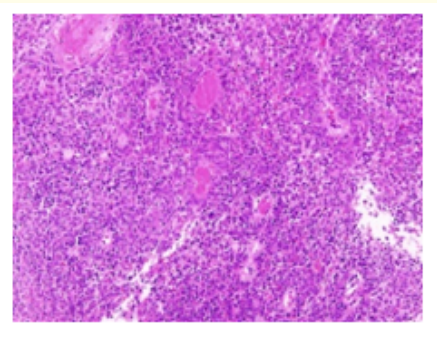

Figure 2: *Nasopharyngeal carcinoma exhibiting clusters of squamous epithelial cells with ill-defined boundaries, eosinophilic cytoplasm and absent intercellular bridges surrounded by lymphoid and plasma-cellular stromal inflammatory infiltrate [6].*

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5. Image 1 Courtesy: Libre Pathology.

6. Image 2 Courtesy: Science direct.

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