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Commentary

Tack and Permute-NUT Sinonasal Carcinoma

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NUT carcinoma of sinonasal tract is a carcinoma demonstrating characteristic genomic translocations confined to NUT gene. Neoplasm is engendered by genetic translocations within the NUT gene situated upon chromosome 15q14 and a commonly enunciated BRD4 gene confined to chromosome 19p13. Tumefaction frequently delineates foci of squamous differentiation.

Morphologically, neoplasm is configured of primitive round cells admixed with zones of abrupt keratinization. Upon immunohistochemistry, speckled nuclear immune reactivity of NUT1 is exemplified, a feature which may be employed as a sensitive and specific indicator of neoplastic emergence. The malignant neoplasm enunciates an aggressive clinical course and median survival of < 1 year.

Demonstrating nuclear protein in testis (NUT), sinonasal carcinoma with NUT genetic translocation was previously denominated as NUT midline carcinoma. Tumefaction exhibits a predilection for sites confined to midline areas.

Originally described within paediatric population, no age of disease emergence is exempt. Besides, a specific gender or geographic predisposition is absent. Factors contributing to neoplastic emergence remain obscure [1,2].

NUT sinonasal carcinoma categorically depicts genetic translocations within NUT gene situated upon chromosome 15q14. Besides, BRD4-NUT genetic fusion situated upon chromosome 19p13 is observed in nearly two thirds (~67%) instances. Also, neoplasm may depict BRD3-NUT or NSD3-NUT genetic fusions.

Aforesaid genomic fusions may obstruct epithelial differentiation and sustain proliferation of tumour cells.

In situ hybridization may be employed for discerning high risk variants of human papilloma virus (HPV) and Epstein Barr virus (EBV) which appear consistently non reactive [2,3].

An estimated one third (~35%) neoplasms incriminate head and neck, commonly the sinonasal tract. Although no site of disease emergence is exempt, tumefaction may be confined to diverse midline sites as the mediastinum.

The malignant NUT sinonasal carcinoma with an aggressive biological behaviour delineates a median survival of < 1 year [2,3].

Grossly, neoplasm is confined to multiple anatomic subsites and exhibits extensive tumour infiltration into surrounding tissues. Cut surface is non specific, grey/white to tan and frequently exemplifies prominent foci of tumour necrosis [3,4].

Upon microscopy, neoplasm is constituted of primitive, miniature to intermediate spherical cells permeated with minimal, indistinct to clear cytoplasm, monotonous spherical to elliptical nuclei with variably prominent nucleoli [3,4].

Abrupt foci of squamous differentiation constituted of squamous epithelial cells incorporated with clear to eosinophilic cytoplasm are observed. Besides, keratin pearls may be configured. Foci of spindle shaped cells are frequently enunciated.

Mitotic activity is significant and tumour necrosis is preponderant. A subset of neoplasms delineate an intense infiltration of neutrophils [3,4].

Upon ultrastructural examination, tumour cells display abundant cytoplasm, prominent tonofilament bundles, scattered pleomorphic granules and numerous desmosomal junctions. Besides, enlarged, irregular nuclei permeated with prominent, compact nucleoli are observed [3,4].

TNM staging of carcinomas of nasal cavity and paranasal sinuses as per American Joint Committee on Cancer 2018 [3,4].

Primary tumour (maxillary sinus)

- TX: Primary tumour cannot be assessed.
- Tis: Carcinoma *in situ*.
- T1: Tumour limited to maxillary sinus mucosa with absent erosion or destruction of bone.
- T2: Tumour inducing bone erosion or bone destruction with extension into hard palate or middle nasal meatus, except extension to posterior wall of maxillary sinus and pterygoid plates.
- T3: Tumour invades bone of posterior wall of maxillary sinus OR subcutaneous tissues OR floor or medial wall of orbit, pterygoid fossa, ethmoid sinus.
- T4: Moderately advanced disease or significantly advanced, localized disease:
- T4a: Moderately advanced, localized disease, tumour invades anterior orbital contents OR cutaneous surface of nose or cheek with minimal extension into anterior cranial fossa OR pterygoid plates or sphenoid sinus OR frontal sinus.
- T4b: Significantly advanced, localized disease, tumour invades orbital apex OR dura OR brain OR middle cranial fossa OR cranial nerves other than maxillary division of trigeminal nerve (V2) OR nasopharynx OR clivus.

Primary tumour (nasal cavity and ethmoid sinus)

- TX: Primary tumour cannot be assessed.
- Tis: Carcinoma *in situ*.
- T1: Tumour restricted to singular subsite along with or devoid of bone invasion.
- T2: Tumour invading two subsites within a singular region or extending to incriminate adjacent region within naso-ethmoidal complex along with or devoid of bone invasion.
- T3: Tumour extends to invade medial wall or floor of orbit, maxillary sinus, palate or cribriform plate.
- T4: Moderately advanced disease or significantly advanced, localized disease:
- T4a: Moderately advanced, localized disease, tumour invades anterior orbital contents OR cutaneous surface of nose or cheek OR pterygoid plates OR sphenoid sinus OR frontal sinus OR demonstrates minimal extension into anterior cranial fossa.
- T4b: Significantly advanced, localized disease, tumour invades orbital apex OR dura OR brain OR middle cranial fossa.

Regional lymph nodes

- NX: Regional lymph nodes cannot be assessed.
- N0: No regional lymph node metastasis.
- N1: Tumour metastasis into a singular, ipsilateral lymph node ≤ 3 centimetre in greatest dimension with absent extra-nodal extension (ENE-).
- N2a: Tumour metastasis into singular ipsilateral lymph node ≤ 3 centimetre magnitude with extra-nodal extension (ENE+) OR singular ipsilateral lymph node > 3 centimetre diameter and ≤ 6 centimetre in greatest dimension with absent extra-nodal extension (ENE-).
- N2b: Tumour metastasis into multiple ipsilateral lymph nodes <6 centimetre in greatest dimension along with absent extra-nodal extension (ENE-).
- N2c: Tumour metastasis within bilateral or contralateral lymph node(s) <6 centimetre in greatest dimension with absent extra-nodal extension (ENE-).
- N3a: Tumour metastasis into a lymph node > 6 centimetre in greatest dimension with absent extra-nodal extension (ENE-).
- N3b: Tumour metastasis into singular ipsilateral lymph node > 3 centimetre in greatest dimension along with extra-nodal extension (ENE+) OR within multiple ipsilateral, contralateral or bilateral lymph nodes any of which may depict extra-nodal extension (ENE+) OR within singular contralateral lymph node of variable magnitude with extra-nodal extension (ENE+).

'U' designation is adopted to indicate regional lymph node metastasis above lower border of cricoid (U). 'L' designation may be adopted for regional lymph node metastasis below lower border of cricoid (L). Examination of few regional lymph nodes devoid of tumour metastasis categorizes the tumefaction as pN0 stage. Midline regional lymph nodes are contemplated as ipsilateral lymph nodes.

Selective neck dissection encompasses examination of > 10 regional lymph nodes. Comprehensive neck dissection or radical or modified radical neck dissection encompasses examination of > 15 regional lymph nodes.

Distant metastasis

- M0: Distant metastasis absent.
- M1: Distant metastasis present.

Prognostic staging of carcinomas of nasal cavity and paranasal sinuses as per American Joint Committee of Cancer 2018:

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

Neoplastic cells appear immune reactive to NUT1, pancytokeratin, epithelial membrane antigen (EMA), p63, p40, CD34 or INI1.

Tumour cells appear immune non reactive to CD99, NKX2.2, S100 protein, synaptophysin or chromogranin [4,5].

NUT sinonasal carcinoma requires segregation from neoplasms such as basaloid squamous cell carcinoma, sinonasal undifferentiated carcinoma, high grade neuroendocrine carcinoma, adamantinoma-like Ewing sarcoma or SMARCB1 deficient sinonasal carcinoma. NUT sinonasal carcinoma appears minimally responsive to radiation therapy and conventional chemotherapy [4,5].

Cogent clinical trials document rapid response to administration of extra-terminal bromodomain inhibitors, as observed within few incriminated subjects. However, prognostic outcomes remain inferior [4,5].

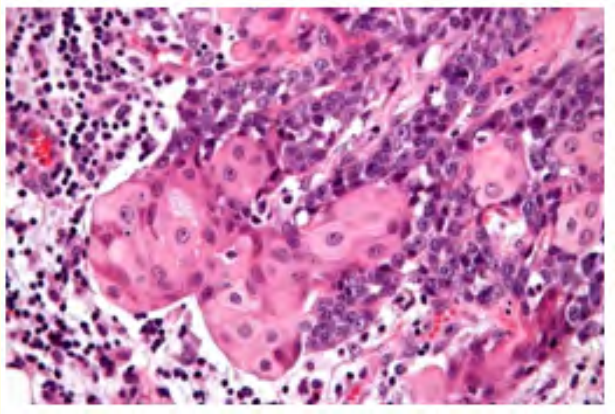

Figure 1: *NUT carcinoma demonstrating an infiltrate of small round cells imbued with minimal cytoplasm and monomorphic nuclei with high nucleocytoplasmic ratio and prominent nucleoli. Foci of squamous differentiation and keratin deposition are encountered [6].*

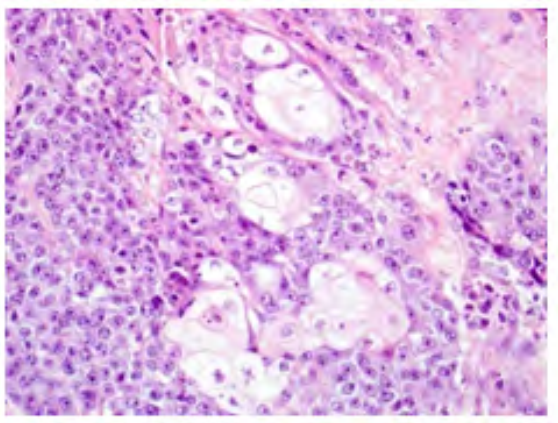

Figure 2: *NUT carcinoma delineating a population of small round cells incorporated with minimal cytoplasm and monomorphic nuclei with high nucleocytoplasmic ratio and prominent nucleoli. Foci of squamous cellular differentiation are observed [7].*

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6. Image 1 Courtesy: Wikipedia.

7. Image 2 Courtesy: Pathology outlines.

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