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Sidling and Swerve-NUT Carcinoma-Lung

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Editorial

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Abbreviations: FISH: Fluorescent in Situ Hybridization; NGS: Next Generation Sequencing; TTF: Thyroid Transcription Factor; EGFR: Epidermal Growth Factor Receptor.

Editorial

NUT carcinoma incriminating pulmonary parenchyma emerges as an aggressive, malignant, poorly differentiated neoplasm characteristically demonstrating genomic rearrangements within NUT gene. The aggressive NUT carcinoma frequently implicates thoracic cavity or aero-digestive tract. However, terminology of NUT midline carcinoma appears obsolete.

Neoplasm delineates a nonspecific morphological countenance and demonstrates diffuse architecture composed of monotonous tumour cells permeated with enlarged nuclei, prominent nucleoli and frequently discerned cytoplasmic clearing, intermingled with foci of abrupt keratinization.

Upon immunohistochemistry, a pathognomonic speckled nuclear expression of NUT protein appears within ≥ 50% of tumour cells. Cogent NUT genetic rearrangements may be detected by fluorescent in situ hybridization (FISH). An equivalent gender predisposition is encountered. Although tumefaction may arise within young individuals, no age of disease emergence is exempt [1,2].

NUT carcinoma commonly arises within mediastinum or upper aero-digestive tract. Infrequently, sites such as salivary glands, retroperitoneum, pancreas or urinary bladder may be implicated [1,2]. NUT carcinoma is posited to arise due to somatic reciprocal genetic translocation within the NUT gene with consequent expression of an oncogenic NUT fusion gene. However, categorical contribution of environmental or infectious aetiological agents appears absent. Neoplastic cells preponderantly (~70%) delineate reciprocal chromosomal translocation t with consequent emergence of BRD4::NUT genetic fusion. Around 30% lesions display BRD3::NUT genomic fusion. Notwithstanding, NUT fusion counterpart genes as NSD3, ZNF532 or ZNF592 are exceptionally encountered.

Fluorescent in situ hybridization (FISH) and NUT immunohistochemistry can be optimally adopted to detect NUT genetic rearrangements, a manoeuver which demonstrates 100% sensitivity and specificity. Next generation sequencing (NGS) or reverse transcription polymerase chain reaction (RT-PCR) may be employed to detect exceptionally observed NUT genetic fusions which may be challenging to discern by fluorescent in situ hybridization (FISH) [2,3]. Frequently, TP53 and PIK3CA genetic mutations are enunciated. NUT carcinoma exemplifies cogent clinical symptoms pertaining to incriminated anatomic site and extent of tumour. Tumours implicating thoracic cavity may represent with clinical symptoms as cough, dyspnoea, haemoptysis, pericardial effusion or pleural effusion. Neoplasm exhibits an extremely aggressive clinical course with tumour associated mortality occurring within few months [2,3].

NUT carcinoma may be challenging to discern upon cytological examination as neoplasm is devoid of significant, discernible foci of squamous epithelial differentiation. However, disseminated dyskeratotic cells may be observed, indicative of the neoplasm [2,3]. Grossly, evaluation of comprehensive surgical resection specimens is exceptional as tumour frequently appears advanced upon initial discernment. Neoplasm may appear deceptively well demarcated from adjacent anatomic structures [3,4]. Upon microscopy, tumefaction displays a primitive countenance

and is constituted of monotonous cells of intermediate magnitude with frequently enunciated cytoplasmic clearing, enlarged nuclei and prominent nucleoli. A diffuse tumour architecture along with dis-cohesive and inconsistently spaced tumour cells is enunciated. Neoplastic cells are entangled within foci of tumour necrosis with prominent inflammatory infiltrate comprised preponderantly of neutrophils [3,4]. Disseminated foci of abrupt keratinization are observed. Occasionally, pseudo-glandular configurations may appear. Foci of intermingled mucoid stroma and crushing artefact may ensue [3,4]. Upon ultrastructural examination, tumour cells depict short micro-villous apex, intracellular desmosomes and junctional complexes. Additionally, cytoplasmic tonofilaments, polyparticulate glycogen, lipid droplets and electron dense granules may be exemplified [3,4].

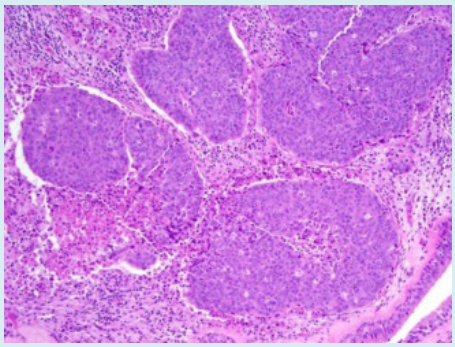

Figure 1: NUT pulmonary carcinoma demonstrating lobules of primitive, monotonous, small round cells permeated with minimal cytoplasm with cytoplasmic clearing, enlarged nuclei and prominent nucleoli. Foci of abrupt keratinization are seen. Surrounding stroma is preponderantly infiltrated by neutrophils [5].

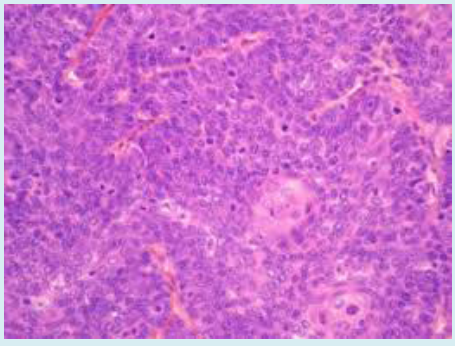

Figure 2: NUT pulmonary carcinoma delineating aggregates of primitive, monotonous, small round cells pervaded with minimal cytoplasm with cytoplasmic clearing, enlarged nuclei and prominent nucleoli. Foci of abrupt keratinization are seen. Circumscribing stroma is infiltrated by prominent neutrophilic infiltrate [6].

TNM staging of non-small cell carcinoma lung as per American Joint Committee on Cancer 8th Edition [3,4].

Primary Tumour

- **TX:** Primary tumour cannot be assessed or tumour discerned by malignant cells encountered within sputum or bronchial washings although non visualized upon imaging or bronchoscopy
- **T0:** No evidence of primary tumour
- **Tis:** Carcinoma in situ, squamous cell carcinoma in situ, adenocarcinoma in situ or a 'pure' lepidic pattern with tumour magnitude ≤ 3 centimetres
- **T1mi:** Minimally invasive adenocarcinoma ≤ 3 centimetre diameter with a predominantly lepidic pattern and ≤ 5 millimetres depth of invasion
- **T1a:** Tumour ≤ 1 centimetre magnitude OR exceptionally, a superficial, spreading tumour of variable magnitude with tumour invasion confined to bronchial wall which extends proximal to main bronchus T1b: Tumour magnitude > 1 centimetres and ≤ 2 centimetres
- **T1c:** Tumour magnitude > 2 centimetres and ≤ 3 centimetres
- **T2:** Tumour magnitude > 3 centimetres and ≤ 5 centimetres or tumour incriminates main bronchus irrespective of distance to carina in the absence of involvement of carina. Tumour invades visceral pleura OR is associated with atelectasis or obstructive pneumonitis which extends to hilar region and confined to partial or comprehensive (100%) pulmonary parenchyma
- **T2a:** Tumour magnitude > 3 centimetres and ≤ 4 centimetres along with minimally a singular aforesaid features
- **T2b:** Tumour magnitude > 4 centimetres and ≤ 5 centimetres
- **T3:** Tumour magnitude > 5 centimetres and ≤ 7 centimetres OR tumour directly invades parietal pleura, chest wall OR tumour confined to superior sulcus, phrenic nerve or parietal pericardium or presence of disparate tumour nodule within singular pulmonary lobe
- **T4:** Tumour magnitude > 7 centimetres or tumour of variable magnitude with invasion into diaphragm, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, oesophagus, vertebral body or carina or presence of disparate tumour nodule within an ipsilateral, different pulmonary lobe.

Regional lymph Nodes

- **NX:** Regional lymph nodes cannot be assessed
- **N0:** Regional lymph nodes metastasis absent
- **N1:** Tumour metastasis into ipsilateral peribronchial, ipsilateral hilar or intrapulmonary lymph nodes along

with direct tumour extension into lymph nodes

- **N2:** Tumour metastasis into ipsilateral mediastinal or subcarinal lymph nodes
- **N3:** Tumour metastasis into contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene or supraclavicular lymph nodes

Distant Metastasis

- **M0:** Distant metastasis absent
- **M1a:** Distant metastasis with disparate tumour nodules within contralateral pulmonary lobe, pleural nodules, pericardial nodules, malignant pleural effusion or malignant pericardial effusion
- **M1b:** Distant metastasis into singular extra-thoracic metastasis confined to singular organ or singular non regional lymph node
- **M1c:** Distant metastasis into multiple extra-thoracic sites confined to singular organ or multiple organs.

Prognostic staging of non-small cell carcinoma lung as per American Joint Committee on Cancer 8th Edition

- **occult carcinoma:** TX, N0, M0
- **stage 0: Tis, N0, M0**
- **stage IA1:** T1mi, N0, M0 OR T1a, N0, M0
- **stageIA2:** T1b,N0,M0
- **stageIA3:**T1c, N0,M0
- **stage IB:** T2a, N0, M0
- **stage IIA:** T2b, N0, M0
- **stage IIB:** T1a, T1b, T1c, N1, M0 OR T2a, T2b, N1, M0 OR T3, N0, M0
- **stage IIIA:** T1a, T1b, T1c, N2, M0 OR T2a, T2b, N2, M0 OR T3, N1,M0 OR T4, N0, N1, M0
- **stage IIIB:** T1a, T1b, T1c,N3, M0 OR T2a, T2b, N3, M0 OR T3,T4, N2, M0
- **stage IIIC:** T3, T4, N3, M0 •stage IVA: Any T, any N, M1a OR any T, any N, M1b
- **stage IVB:** Any T, any N, M1c

NUT pulmonary carcinoma appears immune reactive to NUT, keratin or high molecular weight keratin, p63, p40, p16 and intensely immune reactive to MYC within primitive cell component. Tumour cells appear immune non-reactive to CD99, synaptophysin, FL1, epidermal growth factor receptor (EGFR), HER2 or focally non-reactive thyroid transcription factor 1(TTF1) [7,8]. NUT pulmonary carcinoma requires segregation from neoplasms such as focally keratinizing or basaloid squamous cell carcinoma, thymic carcinoma, small cell carcinoma lung, Ewing's sarcoma, adamantinoma of bone, mediastinal germ cell tumour, desmoplastic round cell tumour, diffuse large B cell lymphoma or porocarcinoma [7,8]. NUT carcinoma is associated with nonspecific morphological features. Thus, cogent disease discernment may be challenging. Miniature tissue samples may not consistently delineate specific morphological features. However, an amalgamation of subtle morphological alterations concurrent with precise NUT immunohistochemistry may appropriately categorize the neoplasm. Occasionally, mediastinal tumefaction may be associated with elevation of serum alpha fetoprotein [7,8]. NUT carcinoma can be optimally treated with manoeuvers such as surgical eradication, chemotherapy and radiation therapy. However, options for surgical approaches may be minimalistic on account of surgically inaccessible tumour sites, especially with neoplasms confined to thoracic anatomic zones [7,8].

Adoption of radiotherapy is associated with superior prognostic outcomes, in contrast to conventional chemotherapy. NUT carcinoma exemplifies adverse prognostic outcomes. Median duration of survival from initial tumour discernment appears one month to 6.7 months [7,8].

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