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Editorial

Glazy and Gory-Neuroendocrine Tumour Lung

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Received: November 02, 2023; **Published:** November 06, 2023

Pulmonary carcinoid tumour emerges as a well differentiated neoplasm exhibiting neuroendocrine differentiation. Tumefaction is subdivided into typical carcinoid tumour or neuroendocrine tumour grade I and atypical carcinoid tumour or neuroendocrine tumour grade II.

Neoplastic classification is contingent to mitotic count assessed within 2 mm^2 area along with or absence of tumour necrosis.

Typical carcinoid tumour categorically demonstrates tumour magnitude > 0.5 centimetres, mitotic count < 2 per 2 mm^2 area and absence of tumour necrosis. Neoplasm exhibits cogent morphological features as neuroendocrine configuration articulating monomorphic tumour cell population inundated with moderate to abundant eosinophilic cytoplasm, 'salt and pepper' nuclear chromatin and inconspicuous nucleoli.

Additional terminology of well differentiated neuroendocrine tumour or grade 1 (G1) to grade 3 (G3) neuroendocrine neoplasm is contemplated as non applicable to pulmonary carcinoid tumour.

As per current classification of World Health Organization (WHO), neoplasm may be scripted as a neuroendocrine tumour (NET) incriminating pulmonary parenchyma.

Cogent surgical eradication of the neoplasms manifests as a recommended therapeutic strategy. Prognostic outcomes are superior.

Pulmonary neuroendocrine tumour represents < 1% of pulmonary carcinomas and ~ 2% of pulmonary neoplasms subjected to surgical extermination.

Commonly, adult subjects < 60 years are incriminated. However, pulmonary carcinoid tumour is frequently exemplified within paediatric population. A female predilection is observed. Pulmonary carcinoid exhibits a predisposition for Caucasian population [1,2].

Factors contributing to disease emergence are represented as cogent family history of pulmonary carcinoids or genetic mutations within MEN1 gene.

Pulmonary carcinoids express minimal proportionate somatic genetic mutations. Genomic mutations within chromatin remodelling genes as MEN1 may be encountered [1,2].

Of obscure aetiology, pulmonary carcinoid tumour may arise in concurrence with diffuse idiopathic pulmonary neuroendocrine cell hyperplasia or carcinoid tumorlets.

Tumefaction appears non concordant to high grade pulmonary neuroendocrine carcinoma or cigarette smoking.

Pulmonary carcinoid tumour may emerge within proximal airways as trachea and incriminate up to distal bronchioles. Neoplasm preponderantly arises within centric airways (~ 85%) wherein main and lobar bronchi are commonly involved, in contrast to peripheral airways (~ 15%) [1,2].

The commonly enunciated central pulmonary carcinoid appears as a gradually progressive lesion and exemplifies cogent clinical symptoms as airway obstruction, infection or haemorrhage. An estimated 5% neoplasms are associated with metastasis, which is commonly confined to regional lymph nodes. Exceptionally, distant metastasis may appear and configure as osteoblastic metastases into bone [1,2].

Cogent clinical symptoms are contingent to localization of the neoplasm. Peripheral carcinoid tumour is commonly asymptomatic. Central carcinoid may represent with clinical features as dyspnoea, cough, wheezing, haemoptysis, repetitive infection of respiratory tract or pneumonia occurring secondary to airway obstruction. Paraneoplastic syndromes are infrequently associated and appear concurrent with distant metastases into hepatic parenchyma.

Carcinoid syndrome is observed in < 2% subjects and is constituted of flushing, diarrhoea or cardiac valvular disease. Cushing's syndrome is enunciated in ~ 4% subjects. Additionally, various infrequently exemplified endocrine syndromes may ensue.

Cytological smears obtained from broncho-alveolar lavage (BAL) or bronchial brushings may appear non representative as the neoplasm is superimposed by mucosal epithelium. Central pulmonary carcinoid manifests with a 10 year survival of ~70% [1,2].

Peripheral carcinoid incriminates peripheral pulmonary parenchyma and is commonly confined subjacent to the pleura. The asymptomatic lesion is discovered incidentally. Prognostic outcomes are favourable. Regional lymph node metastases are exceptionally observed. Tumefaction may be appropriately alleviated with comprehensive surgical excision [1,2].

Cytological examination exhibits loosely cohesive cell groups and isolated, singular cells which may circumscribe branching capillaries. Distinct rosettes may be configured.

Neoplastic cells appear uniform, miniature, spherical, elongated or plasmacytoid and are pervaded with scanty, granular cytoplasm. Tumour cell nuclei appear regular, are imbued with 'salt and pepper' nuclear chromatin, miniature nucleoli and display smooth nuclear outline. Nuclei depict absence of nuclear moulding or nuclear 'crush' artefact. Mitotic activity is exceptional to absent. Tumour necrosis is absent [2,3].

Grossly, pulmonary carcinoid tumour appears as well circumscribed, spherical to elliptical neoplasm with a tan hue and magnitude varying from 0.5 centimetres to 9.5 centimetres. Frequently, tumefaction is confined to bronchial lumen and may configure a sessile or pedunculated lesion engendering partial or complete obstruction of incriminated bronchial lumen. Peripheral neoplasms appear at a distance from the airway or bronchial lumen [2,3].

Upon frozen section, neoplasm is comprised of homogenous cellular population demonstrating mild cellular and nuclear atypia. Tumour configures a predominantly organoid pattern, thereby segregating the neoplasm from encompassing inflammatory cells. Nuclear chromatin is fine. Mitotic activity may be challenging to discern. Stromal hyalinization and vascularity is significant, thereby demarcating the lesion from carcinoma [3,4].

Upon microscopy, pulmonary carcinoid tumour displays distinctive diagnostic criterion as tumour magnitude ≥ 5 millimetres. Mitotic figures appear < 2 mitoses/2 mm^2 area. Tumour necrosis is absent. Neuroendocrine tumour exhibits specific tumour configurations as organoid, trabecular, nested, pseudo-glandular, follicular, papillary or articulated rosettes [3,4].

Tumour cells appear as uniform, polygonal cells pervaded with moderate to abundant eosinophilic cytoplasm, spherical to elliptical nuclei with 'salt and pepper' nuclear chromatin and inconspicuous nucleoli. Besides, spindle shaped cells or clear cells may be encountered. Intervening stroma is fine and significantly vascular. Nevertheless, foci of stromal hyalinization or configuration of cartilage or bone may ensue [3,4].

Gene	Molecular alteration
EGFR	Mutation (~35%)
KRAS	Mutation (25%)
HER2	Mutation (~6.7%), amplification (~22%), overexpression (~23%)
ALK	Chromosomal rearrangement (~8%)
MET	Amplification (~4%), mutation (~4%)
BRAF	Mutation (~5%)
RET	Chromosomal rearrangement (~2%)
ROS1	Chromosomal rearrangement (~1.7%)
NTRK	Gene fusions (~1%)

Table: *Driver mutations within non small cell carcinoma lung [4].*

Pulmonary neuroendocrine tumour appears intensely and diffusely immune reactive to chromogranin, synaptophysin, CD56 and INSM1. Besides, tumour cells appear immune reactive to pan-cytokeratin and thyroid transcription factor-1 (TTF-1). An estimated < 50% of atypical carcinoids appear immune reactive to TTF-1. Rb gene is preponderantly expressed within pulmonary carcinoid tumour.

Ki67 proliferative index appears < 20%, in contrast to high grade neuroendocrine tumours as small cell carcinoma or large cell neuroendocrine carcinoma.

Neoplastic cells appear immune non reactive to CDX2, calcitonin or prostate specific antigen (PSA) [5,6].

Pulmonary neuroendocrine tumour requires segregation from neoplasms such as atypical carcinoid tumour, carcinoid tumourlet, small cell carcinoma lung, large cell neuroendocrine tumour, paraganglioma, medullary carcinoma thyroid, well differentiated neuroendocrine tumour of gastrointestinal tract, salivary gland-type neoplasms, thymoma type A, prostatic adenocarcinoma, carcinoma breast, metastatic carcinoid tumour and metastases from lobular carcinoma breast, paraganglioma or glomangioma [5,6].

Pulmonary carcinoid tumour may be adequately categorized upon cytological assessment or histological examination of surgical tissue samples. Besides, distinction between typical carcinoid tumour and atypical carcinoid tumour is optimally obtained upon cogent evaluation of surgical specimens wherein assessment of tumour necrosis or mitotic activity is beneficial and diagnostic.

Pulmonary carcinoid tumour exhibits elevated levels of plasma chromogranin A. Bronchoscopy exhibits a polypoid, endobronchial lesion commonly confined within central airways [5,6].

Computerized tomography (CT) of thoracic cavity demonstrates a lobulated, well circumscribed tumour nodule confined to major bronchi. Symptoms of airway obstruction as atelectasis or bronchiectasis may be encountered.

Positron emission tomography (PET) exemplifies minimal to moderate contrast uptake with mean standardized uptake value (SUV) at 3.4. Pulmonary carcinoid tumour may be optimally subjected to surgical extermination which is contemplated as a recommended mode of primary therapy for eradicating localized neoplasms and loco-regional tumours amenable to surgical resection [5,6].

Metastatic tumours or neoplasms unamenable to surgical intervention techniques may be managed with somatostatin analogues as octreotide, targeted chemotherapy with agents such as everolimus, interferon therapy, peptide receptor radionuclide therapy or adoption of various chemotherapeutic agents [5,6].

Pulmonary carcinoid tumour is associated with superior prognostic outcomes and displays 5 year survival of ~ 90%. Regional lymph node metastasis occurs in ~ 9% tumours whereas upon initial tumour detection distant metastasis is observed in up to 5% neoplasms. Distant metastasis occurs predominantly within hepatic parenchyma and bone.

Factors contributing to prognostic outcomes emerge as

- Tumour, node metastasis (TNM) staging of pulmonary carcinoid tumour.
- Neoplastic dissemination through air spaces, a feature associated with inferior prognostic outcomes.

Immune reactive Ki67 appears as a debatable diagnostic feature [5,6].

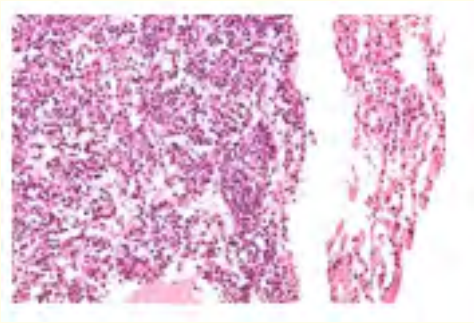

Figure 1: *Pulmonary carcinoid tumour demonstrating an organoid pattern with tumour cells imbued with abundant eosinophilic cytoplasm, vesicular nuclei with prominent nucleoli. Surrounding stroma is hyalinised and vascular [7].*

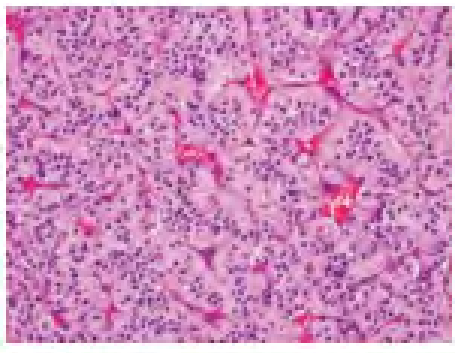

Figure 2: *Pulmonary carcinoid delineating an organoid pattern with tumour cells incorporated with abundant eosinophilic cytoplasm, vesicular nuclei and prominent nucleoli. Circumscribing stroma is hyalinised and vascular [8].*

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7. Image 1 Courtesy: Wikipedia.

8. Image 2 Courtesy: Science direct.

Volume 22 Issue 11 November 2023