Review Article

Precursor lesions of lung tumors

Indranil Chakrabarti [1,*], **Sujaya Mazumder**[1]

[1]*Dept. of Pathology and Laboratory Medicine, All India Institute of Medical Sciences, Kalyani, West Bengal, India*

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ABSTRACT

Lung cancer is the leading cause of cancer deaths globally with many new cases diagnosed each year. Recent studies have shown that an accumulation of various genetic abnormalities results in progressive morphologic changes in bronchial epithelium. Such changes are part of the continuum from precursor lesions to invasive lung cancers. Improvement in diagnostic modalities has made the detection of such preneoplastic lesions possible and resection at this stage confer excellent prognosis. The World Health Organization (WHO) has recognized atypical adenomatous hyperplasia/ adenocarcinoma in situ, squamous dysplasia/ squamous cell carcinoma in situ, and diffuse idiopathic pulmonary neuroendocrine cell hyperplasia as the precursor lesions of adenocarcinoma, squamous cell carcinoma, and carcinoid tumors respectively. This review summarizes the key features of these preneoplastic lesions based on the current understanding and knowledge.

1. Introduction

Lung cancer is a major cause of cancer mortality and morbidity in India with 5.3% of new cancer cases irrespective of gender and 8% of new cancer cases in males as per Globocan 2020 statistics.[1] It is also the most common cause of cancer death worldwide, with 1.8 million deaths estimated globally in 2018.[2] Some of the causal risk factors for lung cancer include smoking combustible tobacco products, radon exposure, other occupational agents like asbestos, and outdoor air pollution.[3] The predominant histological types of lung cancer are small-cell lung carcinoma (SCLC) and three major types of non-small cell carcinoma (NSCLC) namely adenocarcinoma, squamous cell carcinoma (SCC), and large-cell carcinoma (LCC). Smoking remains the most important risk factor for adenocarcinomas, SCLC, and SCC.[3]

In the lung, the central and peripheral airways are structurally and functionally different and they give rise to different cancer types. The central compartment consists of the major bronchi and their branches while the peripheral compartment consists of the respiratory bronchioles and alveoli. The epithelium of the lung develops from a single primordial stem cell which gives rise to specialized stem cells of the central and peripheral compartments.[4] Histologically, the central airways are lined by pseudostratified epithelium having basally located basal cells and neuroendocrine cells, tall ciliated luminal cells, as well as mucous-secreting cells. The basal cells and the neuroendocrine cells act as the specialized stem cells in these central airways[5] and give rise to SCC and neuroendocrine tumors respectively. On the other hand, the terminal bronchioles are lined by short ciliated cells and non-ciliated, non-mucous secretory cells or bronchiolar cells which are better known as club cells (previously known as Clara cells). The alveoli are lined by simple flattened squamous cells (type

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* *Corresponding author.*
  E-mail address: drinch@rediffmail.com (I. Chakrabarti).

I alveolar pneumocytes) and surfactant-producing larger granular cuboidal cells (type II pneumocytes).[4] Here, in these peripheral airways, the club cells and the type II pneumocytes function as stem cells.[5] These cells are linked to the development of peripherally located adenocarcinomas.

Just like most of the epithelial tumors, lung cancers gradually evolve through a series of premalignant changes.[6] The sequence of events leading to squamous cell carcinoma may be basal cell (reserve cell) hyperplasia -> metaplasia -> dysplasia -> Carcinoma in situ, as has been recognized for long.[7–9] Similarly, the continuum of events leading to the development of adenocarcinoma passes through the stages of atypical hyperplasia of type II pneumocytes and/or club cells and subsequent adenocarcinoma in situ which in turn give rise to minimally invasive adenocarcinoma (MIA) and subsequently invasive adenocarcinoma.[10]

In the 2021 WHO classification of lung tumors, these precursor lesions have been discussed in detail and specific (essential and desirable) criteria have been laid down.

The precursor lesions for adenocarcinomas are atypical adenomatous hyperplasia (AAH) and adenocarcinoma in situ (AIS) while those for squamous cell carcinomas are squamous dysplasia (SD) and squamous carcinoma in situ (SCIS). Again, diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) has been identified as a precursor lesion for carcinoid tumors. However, high-grade neuroendocrine carcinomas (NECs) are not associated with DIPNECH. Although no precursor lesion has been identified with certainty for small cell carcinomas, they are believed to arise from bronchial epithelium which shows evidence of molecular damage.[4]

2. Atypical Adenomatous Hyperplasia (AAH)

The WHO 5th edition of lung tumors defines atypical adenomatous hyperplasia as a small (usually ≤ 5 mm), localized proliferation of atypical (mild to moderate atypia) type II pneumocytes and/or club cells that line the alveolar walls and sometimes respiratory bronchioles.[11]

AAH occurs in the centriacinar region near the respiratory bronchioles often close to the pleura.[11] It is mostly undetectable on imaging but occasionally larger lesions of AAH and most cases of AIS appear as pure ground-glass nodules (pGGNs) on thin-section computed tomography (TSCT).[12] The lesions are typically incidentally detected during the examination of surgical specimens of lung adenocarcinoma or on autopsy studies.[11] It is a diagnosis that can only be given on resection specimen and not on cytology, small core needle or transbronchial biopsy since the lesion needs to be examined in entirety for diagnosis.

AAH has been shown to harbor driver mutations such as in KRAS, EGFR, and BRAF as well as loss of heterozygosity on 3p, 9p, 16p, 17q, and 17p.[11]

Grossly, the focus of AAH is an ill-defined, 5mm or less sized, greyish or tan-yellow nodule, more likely found in resection specimens of lung carcinoma, particularly adenocarcinoma.[11] It can also be multifocal. Microscopically, the lesion maintains an alveolar structure lined by a discontinuous monolayer of proliferating, mild to moderately atypical type II pneumocytes and/or club cells. Club cells are columnar cells with eosinophilic and cytoplasmic snouts while Type II pneumocytes are cuboidal with finely vacuolated to clear cytoplasm.[11] The atypia is limited to a mild increase in N:C ratio, nuclear hyperchromasia, and occasional intranuclear inclusions but mitosis is extremely rare.

AAH expresses TTF1 and is considered to be the precursor of AIS and adenocarcinoma.[11]

3. Adenocarcinoma in Situ of the Lung

Adenocarcinoma in situ (AIS) is a preinvasive, localized lung adenocarcinoma that is small in size (≤ 30 mm), with neoplastic cells growing along the pre-existing alveolar structures (pure lepidic growth with no stromal, vascular or pleural invasion). AIS is an intermediate step between AAH and the minimally invasive adenocarcinoma (MIA).[10]

Just like AAH, it occurs in the periphery of the lung, close to the pleura and the diagnosis cannot be made based on a small biopsy or cytology as it requires complete sampling of the lesion which is only possible on resection specimen.

AIS is usually incidentally detected on CT scans. They usually appear non-solid but may be partly solid or even solid, especially in mucinous AIS. They may have a so-called bubble-like appearance on CT.[10,12,13]

These lesions are part of the 'adenocarcinoma spectrum' lesions and also harbor driver mutations such as KRAS, and EGFR similar to AAH, MIA, and invasive adenocarcinoma, thus indicating a progression over time from AAH to adenocarcinoma.[10,14] However, the rate of mutation may vary between these lesions.

Grossly, AIS appears as a poorly defined nodule with a maximum measurement of 30 mm and a tan or pale cut surface. Tiny airspaces can often be seen on the cut surface and usually lack a solid appearance.[10] However, they may be solid if they are mucinous or contain a scar.[15,16] The tumor should be sampled in its entirety to rule out any invasive component as in the presence of an invasive component it will be labelled as minimally invasive adenocarcinoma (MIA) or invasive carcinoma depending on the depth of invasion.[10]

Microscopically, AIS can be either non-mucinous, mucinous, or mixed mucinous and non-mucinous histology.[15] However, most cases of AIS are of non-mucinous type (with neoplastic type II pneumocyte and/or club cell differentiation) and they may need to be differentiated from AAH, MIA, and lepidic-predominant

adenocarcinoma.[10]

Non-mucinous AIS consists of a lepidic growth pattern with a continuous monolayer of back-to-back neoplastic cells growing along pre-existing alveolar structures, sometimes with evidence of cell overlap, mild stratification, or minor cellular tufting.[10] However, papillary or micropapillary patterns as seen in invasive adenocarcinomas, are absent. The cells may show mild to moderate atypia comprising various combinations of nuclear membrane irregularity, anisocytosis, hyperchromasia, increased N:C ratio, hobnailing etc.[16,17] Alveolar septal widening with sclerosis/elastosis may be present in the so-called sclerosing variant of AIS.[10,17] Spread through air spaces (STAS), which is a spreading phenomenon of lung cancers indicates a worse prognosis and is defined as the presence of tumor cells within air spaces in the lung parenchyma beyond the edge of the main tumor.[15] STAS as well as intra-alveolar tumor cells within the tumor should be absent in AIS.[10,15] By definition, AIS should also be devoid of evidence of lymphatic, vascular, stromal, or pleural invasion. Mucinous AIS is extremely rare and histologically is comprised of tall columnar cells (sometimes resembling goblet cells) with abundant cytoplasmic mucin, basal nuclei, and minimal or no atypia.[10] Nonmucinous AIS stains positive with immunohistochemical stains like Napsin A and TTF1 while mucinous AIS rarely express TTF1 protein.[10,17] Mucinous AIS just like mucinous adenocarcinoma of the lung is CK 7 and CK 20 positive but nonmucinous AIS is only positive for CK 7 and not CK 20.[17]

AIS is coded as Tis (AIS) in the TNM staging of lung carcinoma to distinguish it from squamous cell carcinoma in situ (SCIS) which is denoted by Tis (SCIS) and TisN0M0 is defined as stage 0.[10,15]

Incidentally detected AIS appearing as pure ground-glass opacities < 10 mm on chest CT are carefully followed up and complete resection is undertaken only if size or opacity increases.[10,18] If this noninvasive lesion is completely resected, the patients should have 100% disease-free survival and recurrence-free survival rates.[10,19]

4. Squamous Cell Dysplasia and Squamous Cell Carcinoma in Situ (SCIS)

These 2 morphologically identifiable alterations of airway epithelium harbor genetic mutations as well as epigenetic changes and serve as the harbinger of squamous cell carcinoma of the lung.

The essential criteria include squamous differentiation of bronchial epithelium associated with mild, moderate, or severe degrees of dysplasia and carcinoma in situ. The dysplasia and SCIS are evidenced by progressive abnormalities in nuclear features, and epithelial thickness along with cell size, maturation, and orientation.[20]

When the bronchial epithelium is exposed to carcinogens and irritants like tobacco smoke for long, it may show basal cell hyperplasia or squamous metaplasia with loss of goblet cells and ciliated cells. However, they are not considered preneoplastic lesions. Further exposure leads to the accumulation of additional somatic genetic alterations and the cells pass through the various degrees of dysplasia (mild, moderate, and severe) ultimately culminating in SCIS.

Examination of sputum, bronchioloalveolar lavage (BAL) fluid, bronchial brushings, and biopsies are the various non-invasive or minimally invasive procedures that make sampling of the large airways relatively easy compared to the peripheral airways and better understanding of the various preinvasive lesions of the central airways like squamous precursor lesions.[4]

SCIS is less common in the larger airways like the trachea. They usually arise near the bifurcations in the segmental bronchi, subsequently extending into lobar and subsegmental branches as nodular/polypoid lesions (25% of cases) or flat lesions (75% of cases) and can be multifocal.[20]

These preinvasive squamous lesions are particularly common in males, users of combustible tobacco, patients of underlying chronic lung diseases like chronic obstructive airway disease, and those exposed to asbestos and other occupational carcinogens.[20]

They are not detected on chest CT or PET scans and are often incidentally detected on bronchoscopy. Advanced and sophisticated techniques like white-light reflectance bronchoscopy (WLB) in combination with autofluorescence bronchoscopy (AFB), narrow-band imaging (image-enhanced endoscopy), optical coherence tomography, radial probe endobronchial ultrasound, etc. are used for highlighting the lesions.[20]

The pathogenesis of these precursor lesions is related to the genetic and epigenetic changes caused by field cancerization of the tracheobronchial tree on exposure to the various carcinogens present in cigarette smoke.[20] The sequential changes start with the loss of heterozygosity at chromosomes 3p and 9p21 and later affect the tumor suppressor genes like RB1 (Chromosome 13q14), TP53 (Chromosome 17p13), APC (Chromosome 5q21) and genes located in the 8p21-p23 locus.[21–24] Recent evidence suggests frequent somatic and copy-number alterations in the TP53, CDKN2A, SOX2, and AKT2 genes and chromosomal instability signature in SCIS.[25]

As mentioned before, the distinction between different subtypes of dysplasia and SCIS is based on nuclear features, and epithelial thickness along with cell size, maturation, and orientation. Cases of SCIS are positive for CK5/6 and p63/p40 just like their invasive counterparts.[20]

SCIS is classified as Tis (SCIS) but dysplasia does not find a place in the 8th edition of TNM classification of malignant tumors. Studies show up to 37% of severe

dysplasia and 88% of SCIS will persist or progress. Early detection and resection at this stage results in 100% curability however multifocality is a problem.[20]

5. Diffuse Idiopathic Pulmonary Neuroendocrine Cell Hyperplasia (DIPNECH)

DIPNECH is a preinvasive condition that may develop into carcinoid tumors, mostly typical carcinoids (TC), and is characterized by multifocal hyperplasia of pulmonary neuroendocrine cells associated with tumorlets.[26]

Neuroendocrine neoplasms (NENs) of the lung represent a spectrum of diseases. They are broadly classified as neuroendocrine tumors (NETs) and neuroendocrine carcinomas (NECs) The NETs include the low-grade typical carcinoid (TC) and intermediate-grade atypical carcinoid (AC) while neuroendocrine carcinomas (NECs) comprise small cell (lung) carcinoma (SCLC) and large cell neuroendocrine carcinoma. However, unlike the pulmonary carcinoids (PC), no precursor lesion has been identified for NECs.

Neuroendocrine cells are present in the normal lungs with an incidence of 1 per 2500 epithelial cells and they usually proliferate secondary to inflammation and interstitial fibrosis of the lung parenchyma but such hyperplasia of neuroendocrine cells may be idiopathic as in DIPNECH.[27] However, DIPNECH has also been reported in the setting of multiple endocrine neoplasia type 1 (MEN 1).[26]

Such proliferation of neuroendocrine cells can cross the basement membrane to form tumorlets and carcinoid tumors. Tumorlets are nodular proliferations of neuroendocrine cells with a size < 5 mm in diameter, that invade beyond the bronchiolar wall while typical carcinoids are usually ≥ 5 mm in diameter with mitotic rate < 2 mitoses/2 mm^2 and have no necrosis.[26]

DIPNECH is mostly seen in the setting of nonsmoker, middle-aged (in their fifth or sixth decade) females, and usually arises from the terminal bronchioles. High-resolution CT scan with expiratory phase may pick up the characteristic mosaic pattern with air trapping seen in DIPNECH and additionally identify multiple bilateral small nodules corresponding to tumourlets (< 5 mm) or carcinoids (≥ 5 mm in diameter).[26,27]

Patients having DIPNECH may be asymptomatic or may present with clinical symptoms (DIPNECH syndrome).

Those without symptoms are incidentally detected on high-resolution CT scans done for a different reason with the help of the characteristic findings mentioned above. On the other hand, symptomatic patients usually suffer from constrictive bronchiolitis and present with a chronic history of cough, dyspnoea, and wheezing like asthma.[26]

Although the tumourlets appear as multiple grey-white nodules < 5 mm, the lesion of DIPNECH cannot be identified. However, microscopy shows the neuroendocrine cell hyperplasia and/or tumourlets involving small airways. As per Marchevsky et al,[28] neuroendocrine cell hyperplasia may be defined as the presence of ≥ 5 neuroendocrine cells (singly or in clusters) not crossing the basement membrane of the bronchiolar epithelium (unlike the tumorlets or carcinoid tumors) while multifocality is defined as involvement of ≥ 3 bronchioles. However, such criteria need further validation.[26] The neuroendocrine cells have a moderate amount of amphophilic or eosinophilic cytoplasm and round, oval, or spindle-shaped nuclei with salt-and-pepper type chromatin with the positivity of Pancytokeratin, neuroendocrine markers (chromogranin, synaptophysin, CD56), and TTF1 along with negative staining for p40/p63 and high-molecular-weight cytokeratins.[26]

The prognosis of these lesions is usually good and steroids and/or beta agonists are used to treat DIPNECH syndrome associated with constrictive bronchiolitis.[26,29] Rare cases may progress and may require lung transplantation.[26,28–30]

6. Conclusion

To conclude, the present review highlights the various preinvasive or precursor lesions of lung tumors that slowly evolve over time passing through a continuum of often recognizable changes due to the gradual accumulation of somatic mutations and epigenetic changes. With the increasing sensitivity of various diagnostic modalities, these lesions are often detected incidentally and have contributed to the understanding of the multistage pathogenesis of lung cancers.

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8. Conflict of Interest

None.

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Author biography

Indranil Chakrabarti, Additional Professor https://orcid.org/0000-0002-3651-2986

Sujaya Mazumder, Assistant Professor