23

Neoplastic Disorders of the Lung

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DEFINITION

Lung cancer is the leading cause of cancer death for men and women in the United States. An estimated 1.3 million people die worldwide of lung cancer each year. Lung cancer causes 28% of all cancer deaths in the United States, more than the next three most common cancers (i.e., colon, breast and prostate) combined.

Most lung cancers are classified as two major types: *small cell lung carcinoma* (SCLC) (E-Fig. 23-1) and *non–small cell lung carcinoma* (NSCLC). NSCLCs are more common and include squamous cell carcinoma (E-Fig. 23-2), adenocarcinoma (E-Fig. 23-3), and large cell carcinoma (E-Fig. 23-4). SCLCs account for less than 20% of all lung cancers.

EPIDEMIOLOGY

Smoking is the leading cause of lung cancer, a cause-effect relationship that was recognized as early as the 1940s. The risk of lung cancer is proportionate to cigarette pack-years smoked (i.e., packs per day multiplied by years smoked), with a peak incidence in the sixth and seventh decades. Compared with never-smokers, men who smoke are 23 times more likely and women 13 times more likely to develop lung cancer. Ex-smokers show a persistent risk of lung cancer throughout life.

Passive smoking is thought to be the cause of lung cancer for a significant percentage of nonsmokers who develop the disease. Nonsmokers who live with smokers have a more than 20% to 30% increased risk of developing lung cancer. However, nonsmokers do develop lung cancer that is thought to be unrelated to environmental tobacco exposure; the cause of this phenomenon is poorly understood.

Other risk factors for lung cancer include environmental hazards such as asbestos exposure. Tobacco smoking in the setting of asbestos exposure is thought to have a multiplicative effect on risk. Radon exposure, such as that seen in miners, also increases the risk of lung cancer by approximately 10%. Radon exposure in the home is less significant, but home radon testing is recommended and legally mandated in some states.

PATHOLOGY

The exact mechanisms by which risk factors promote lung cancer remain unclear, but if unopposed, they are likely to cause genetic abnormalities that promote oncogenic transformation of lung epithelial cells. Because of the inherent redundant repair mechanisms available to the lung, however, many genetic insults appear necessary to irreversibly mutate and activate genes such as the *RAS* gene family, *ERBB* gene family, *RB1, MYC, SRC,* suppressor genes such as *CDKN1A* and *TP53,* and genes encoding growth factors such as gastrin-releasing peptide, insulin-like growth factor, and epidermal growth factor. Epidermal growth factor receptor mutations are prominent in nonsmokers who develop lung cancer and may indicate a unique molecular basis for lung cancer in those patients.

Non–Small Cell Lung Carcinomas

Squamous cell carcinomas arise from the epithelial layer of the bronchial wall as normal columnar epithelial cells undergo metaplasia, eventually being replaced by increasingly atypical squamous epithelial cells. A localized carcinoma, called *carcinoma in situ*, forms and later extends beyond the bronchial mucosa as it becomes invasive. Histologically, squamous cell carcinomas can be distinguished from other NSCLCs by the presence of keratinization, pearl formation, and intercellular bridging.

Adenocarcinomas can form glandlike structures and produce mucus. The tumor cells stain positive for carcinoembryonic antigen (CEA), mucin, and surfactant apoprotein. Slower-growing forms appear to grow and spread along preexisting alveolar walls.

Large cell carcinomas lack the glandular and squamous features typical of other NSCLCs and cytologic features typical of SCLCs. In this respect, it is considered a diagnosis of exclusion.

Small Cell Lung Carcinoma

Small cell carcinoma is strongly associated with cigarette smoking. Tumor cells are of pulmonary neuroendocrine cell origin. Released factors are often associated with paraneoplastic syndromes.

CLINICAL PRESENTATION

Patients may complain of mild cough, dyspnea, increased sputum production, chest pain, and weight loss. Hemoptysis may indicate local airway inflammation or erosion of the neoplasm into surrounding vascular structures. Localized pleuritic chest pain suggests pleural involvement or chest wall invasion (E-Fig. 23-5). Hoarseness is caused by involvement or compression of the left recurrent laryngeal nerve and suggests a mediastinal or hilar mass or significant lymphadenopathy. Dysphagia suggests esophageal involvement or compression by lymph nodes.

A pleural effusion is observed in 9% of patients, is often unilateral, and can be related to direct tumor involvement of the pleura or obstruction of lymph flow from the mediastinal nodes (E-Fig. 23-6). The superior vena cava is involved in less than 5% of patients, but obstruction may result in superior vena cava syndrome, which is characterized by edema of the face and upper