**Respiratory sys pathology / Lec. 5 Dr. Methaq Mueen**

**Human coronaviruses:**

* **Coronaviruses**: are **enveloped, RNA viruses** that infect humans and animals
* **Weakly pathogenic coronaviruses** cause **mild cold-like upper respiratory tract infections**, while **highly pathogenic** ones may cause **severe, often fatal pneumonia**.
* An example of a highly pathogenic type is (**COVID-19),** a strain that emerged in late 2019 in China that is producing a still evolving pandemic. It binds the **ACE2 protein** on the surface of pulmonary **alveolar epithelial cells**, explaining the tropism of these viruses for the lung.
* With highly pathogenic forms in susceptible hosts, typically older individuals with comorbid conditions (DM, COPD, and heart failure), the host immune response and locally released cytokines often produce **acute lung injury (ALI) and ARDS.**

**The pathological changes in respiratory system that produced in COVID19 infection:**

* All viral infections produce similar morphologic changes. Upper respiratory infections are marked by **mucosal hyperemia** and **edema**, infiltration of the **submucosa** by mononuclear cells (mainly **lymphocytes and macrophages**), and **overproduction of mucus secretions(catarrhal inflammation).**
* **Suppurative secondary bacterial infection** may superimposed.
* Virus may induced **tonsillitis , sinusitis , otitis media, laryngitis, laryngotracheobronchitis and bronchiolitis.**
* There is Impairment **of bronchociliary function** induce bacterial superinfection with more marked suppuration.
* Plugging of small airways may give rise to **focal lung atelectasis.**
* With more severe bronchiolar involvement, widespread plugging of terminal airways by **cell debris**, **fibrin**, and **inflammatory exudate** may, if prolonged, lead to fibrosis, resulting in permanent lung damage.

**Lung involvement** :

* **Predominant** is an **interstitial inflammatory reaction** involving the walls of the alveoli.
* Other forms like patchy (bronchopnemonea) or if involve whole lobes (lobar) bilaterally or unilaterally may occur especially if **secondary bacterial infection** superimposed.
* **Pleuritis** or **pleural effusions** are **infrequent**.
* **The histologic pattern depends on the severity of the disease.**
* The alveolar septa are widened and **edematous** and usually contain a mononuclear inflammatory infiltrate of **lymphocytes, macrophages**, In **severe cases, neutrophils** may also be present.
* The **alveoli may be free of exudate**, but in many patients there is intra-alveolar proteinaceous material and a cellular exudate.
* When complicated by **ARDS, pink hyaline membranes line the alveolar walls** .Eradication of the infection is followed by reconstitution of the normal lung architecture.

Superimposed bacterial infection modifies this picture by causing **ulcerative bronchitis**, **bronchiolitis**, and **bacterial pneumonia**

**Clinical Features**

* The clinical course is **extremely variable**.
* Many cases appear as **severe upper respiratory tract infections** .
* the major manifestations may consist only of **fever, headache, and myalgia** and Cough
* **Viral pneumonias** are usually mild and resolve spontaneously without any lasting sequelae.
* **interstitial viral pneumonias**
* The edema and exudation often cause ventilation-perfusion mismatch
* leading to **hypoxemia**

**LUNG TUMORS**

* **Bronchogenic carcinomas** constitute **95%** of primary lung tumors;
* the remaining **5%** includes **bronchial carcinoids, sarcomas, lymphomas, and a few benign lesions.**
* Most common **benign** lung tumor is **hamartoma**

**Bronchogenic Carcinomas:**

* Carcinoma of the lungis the commonest cause of cancer-related deaths in industrialized countries.
* The rate of increase among males is slowing down, but it continues to accelerate among females; this is undoubtedly related to the strong relationship of cigarette smoking and lung cancer.
* Most patients are in the age group of 50-60 years.
* **The prognosis of lung cancer is very poor**
* **The 5-year survival rate for all stages combined is about 15%.**

**WHO classification for histologic types of lung carcinomas :**

* **Adenocarcinoma 50%. -Squamous cell carcinoma 20%. - Small cell carcinoma 15%.**
* **Large cell carcinoma 2% -Other 13%**

 **For therapeutic purposes, carcinomas of the lung are divided into two groups:**

1. **Small-cell lung cancer (SCLC).**
2. **non-small-cell lung cancer (NSCLC), includes:**
3. squamous cell
4. adenocarcinomas
5. large-cell carcinomas
* The reason for this division is that virtually all SCLCs have metastasized by the time of diagnosis and therefore are not curable by surgery. The best treatment by chemotherapy, with or without radiation.
* In contrast, NSCLCs usually respond poorly to chemotherapy and are better treated by surgery.
* In addition, these two groups show molecular genetic differences.

**Etiology and Pathogenesis**

1. **The role of Cigarette smoking:**
* There is a great relation between lung carcinoma and the amount of daily smoking, tendency to inhale &duration of smoking habit.
* **Statistical evidences:** The increased risk is 60 times greater in habitual heavy smokers (two packs a day for 20 years) than in nonsmokers
* For unclear reasons, it appears that women are more susceptible to carcinogens in tobacco than men.
* **the carcinogenic effects of tobacco smoke extend to those who live and work with smokers Passive smoking increases the risk to twice that of nonsmokers**

 **Squamous and small-cell carcinomas show the strongest association with smoking.**

1. **The role of occupation-related environmental agents:**
* These may act alone or synergistically with smoking to be related to some lung cancers, for e.g. **radon, dusts containing arsenic, chromium, uranium, nickel, vinyl chloride, and mustard gas.**
* Exposure to **asbestos** increases the risk of lung cancer **5 times in nonsmokers**. Whereas those **who smoke have a 55-fold greater risk.**
1. **Role of hereditary (genetic) factors:**
* Not all persons exposed to tobacco smoke develop cancer.
* It seems that the effect of carcinogens is modulated by hereditary (genetic) factors.
* **Squamous cell carcinoma: TP53 (tumor suppressor gene )**in 60% to 90% of squamous cell carcinoma in situ
* **Small cell carcinoma:** inactivation of both **TP53 and RB,** amplification of genes of the **MYC family**
* **Adenocarcinoma:**
* **KRAS gene (roughly 30% of tumors),**
* **EGFR, in 10% to 15% of tumors;**
* **ALK, in 3% to 5% of tumors**

**these are important to recognize because they often can be targeted with specific inhibitors**

**4- *Air Pollution :*** increases the risk of lung cancer, especially in smokers, through several different mechanisms. Chronic exposure to air particulates may cause Lung irritation, inflammation, and repair, (any chronic inflammation and repair increases the risk of a variety of cancers).

**Squamous cell carcinoma:**

* Common in **male.**
* Related to **smoking**
* arise **centrally** (hilar origin).
* **Areas of squamous metaplasia , dysplasia are seen in the adjacent mucosa.**

**MIC**. squamous cell carcinoma is either well differentiated s characterized by the presence of **keratinization** (squamous pearls or markedly eosinophilic cytoplasm) and/or **intercellular bridges.**

This features are prominent in well-differentiated tumors, are easily seen but not extensive in moderately differentiated tumors, and are focally seen in poorly differentiated tumors.

**Adenocarcinoma:**

 **It is characterized by:**

* Seen commonly in **female.**
* It is the common type seen in **nonsmokers.**
* It arises in more **peripheral locations**.
* It grows more **slowly.**
* Sometimes it is **seen near areas of scarring**
* **Mic**. invasive malignant epithelial tumor with **glandular differentiation** or **mucin production** by the tumor cells. It grows in various patterns, including acinar, papillary, micropapillary, and solid.

**Small cell carcinoma:**

* Highly malignant, **most aggressive**.
* **Metastasize widely.**
* **Not cured by surgery**.
* Has **strong relation to smoking**.
* Arise **centrally (hilar).**
* **Mic.** The cells appear small ( 2x the size of lymphocyte), dark nucleus, scant cytoplasme ill-defined cell borders, finely granular nuclear chromatin (salt and pepper pattern), and absent or inconspicuous nucleoli . The cells are round, oval, or spindle shaped, and nuclear molding is prominent.
* . The mitotic count is high. The cells grow in clusters that exhibit neither glandular nor squamous organization. Necrosis is common and often extensive**.**
* Small cell ca. are **derived from neuroendocrine cells of the lung,** and hence they express a variety of **neuroendocrine markers in** addition to many **polypeptide hormones** that may result in **paraneoplastic syndromes.**

**Large cell carcinoma**

* Highly anaplastic tumor.
* It may represent poorly differentiated squamous or adenocarcinoma.
* The cells appear so large, bizarre, and even giant cells could be seen.
* Is an undifferentiated malignant epithelial tumor that lacks the cytological features of other forms of lung cancer. The cells typically have large nuclei, prominent nucleoli, and a moderate amount of cytoplasm.
* **Combined Carcinoma.** Approximately 4% to 5% of all lung carcinomas have a combined histology, including two or more of the aforementioned types

**Clinical presentation of bronchogenic carcinoma:**

* The age is around 50 -60 yrs.
* It is considered as the most aggressive neoplasm.
* Presenting symptoms: **cough, weight loss, chest pain, dyspnea, increase sputum production and hemoptysis.**
* Most commonly it is discovered by its secondary spread.

**Course & prognosis**

* Carcinomas of the lung are silent lesions that more often than not have spread beyond curable resection at the time of diagnosis. Too often, the tumor presents with symptoms related to metastatic spread to the brain (mental or neurologic changes), liver (hepatomegaly), or bones (pain).
* Overall, NSCLCs have a better prognosis than SCLCs.
* When NSCLCs (squamous cell carcinomas or adenocarcinomas) are detected before metastasis or local spread, surgery is possible by lobectomy or pneumonectomy.
* **SCLCs, on the other hand, is almost always have spread by the time of the diagnosis, even if the primary tumor appears small and localized**. Thus, surgical resection is not a practical treatment. They are very sensitive to chemotherapy but invariably recur. Median survival even with treatment is 1 year.

**Paraneoplastic syndromes**

Up to10% of all patients with lung cancer develop clinically overt paraneoplastic syndromes. These include:

1. Hypercalcemia caused by secretion of a parathyroid hormone-related peptide.

2. Cushing syndrome (from increased production of ACTH);

3. Inappropriate secretion of ADH

4. Neuromuscular syndromes, including a myasthenic syndrome, peripheral neuropathy, and polymyositis

5. Clubbing of the fingers and hypertrophic pulmonary osteoarthropathy

6. Hematologic manifestations, including migratory thrombophlebitis, nonbacterial endocarditis, and disseminated intravascular coagulation.

**Hypercalcemia is most often encountered with squamous cell carcinomas, the hematologic syndromes with adenocarcinomas.**

**The remaining syndromes are much more common with small-cell neoplasms, but exceptions occur.**

**Metastatic tumors:**

The lung is a frequent site of metastatic tumors from all over the body; it is **more common than the primary.** It reaches the lung by lymphatic, blood, or direct continuity as in esophageal carcinoma.

**Carcinoid Tumors**

* It represent 1% to 5% of all lung tumors.
* Most patients with these tumors are younger than 60 years of age.
* The incidence is equal for both sexes.
* Approximately 20% to 40% of patients are nonsmokers.
* It is **a neuroendocrine tumor with low-grade malignant potential.**

subclassified into ***typical***and ***atypical carcinoids*.**

**Morphology:** Carcinoids may arise centrally or may be peripheral.

 **Grossly :** the central tumors grow as spherical polypoid masses that commonly project into the lumen of the bronchus and are usually covered by an intact mucosa .They rarely exceed 3 to 4 cm in diameter.

**Histologically,** the tumor is composed of organoid, trabecular, palisading, ribbon, or rosette-like arrangements of cells separated by a delicate fibrovascular stroma. The individual cells are regular and have uniform round nuclei and a moderate amount of eosinophilic cytoplasm.

**Typical carcinoids** have few mitoses and lack necrosis, while **Atypical carcinoids** have more mitoses and/or foci of necrosis, increased pleomorphism, have more prominent nucleoli, and are more likely to grow in a disorganized fashion and invade lymphatics.

**Behavior: Most** carcinoid tumors **DO NOT metastasize** , **DO NOT secrete hormones**

Some might show metastasis to the local L.N and **some** may secrete hormones. It follow a relatively benign course for long periods

**Treatment:** Surgical resection.

**THE PLEURA**

* May be involved by **primary or secondary tumors**.
* **The secondary involvement is more common**.
* The most common secondary comes **from the lung and breast carcinoma**.

**Malignant mesothelioma:** is a rare cancer of mesothelial cells, usually arising in the parietal or visceral pleura , In the USA **approximately 50% of individuals with this cancer have a history of exposure to asbestos.** The latent period for developing malignant mesotheliomas is long (25 to 40 years) after initial asbestos exposure.

**Grossly:** The lung is enclosed by a thick, soft, gelatinous, gray-white tumor**.**

* **Mic.:** one of three patterns:

1. **Epithelial:** in which cuboidal cells line tubular and microcystic spaces, into which small papillary buds project.

2. **Sarcomatoid,** in which spindled cells grow in sheets

3. **Biphasic**, having both sarcomatoid and epithelial areas

**Clinical feature**: chest pain, dyspnea, recurrent pleural effusions

The lung is invaded directly, and there is often metastatic spread to the hilar lymph nodes and, then to the liver and other distant organs.

50% of patients die within 12 months of diagnosis, and few survive longer than 2 years.

Aggressive therapy (surgery, chemotherapy and radiotherapy) seems to improve this poor prognosis in some patients.