Pathology Lecture #31
Pulmonary Lecture #3
Obstructive Lung Disease
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These descriptions to the slides are adjuncts to the lectures. These descriptions are not meant to replace either the lectures or the reading assignments, but to aid in your review of the images and text slides.

1. The major functions of the lung are to replenish oxygen and excrete carbon dioxide.

2. Diffuse pulmonary disease can be classified as either: (1) obstructive (airway) or (2) restrictive (decreased parenchymal compliance).

3. In restrictive lung disease there is decreased lung expansion accompanied by decreased total lung capacity and forced vital capacity (FVC). The expiatory flow rate, as measured by the forced expiatory volume at one second (FEV_1), is normal or proportionately reduced in restrictive lung disease. Hence, the ratio of FEV_1 to FVC ratio is near normal in restrictive disease. In obstructive lung disease, TLC and FVC are normal but the FEV_1 is decreased, thus the FEV_1 to FVC ratio is decreased. The various disorders of the pulmonary system are first classified as either obstructive or restrictive lung disease since this is often the clinical presentation of such diseases.

4. In the normal lung, the parenchyma is pale white throughout and homogeneous in both upper and lower lobes. As seen here, normal lung lacks the black and blackish-tan mottling which results from inhalation of soot and other pollutants. The major structures at the hilus are the bronchi and great vessels. At the periphery are the small bronchioles and alveolar ducts.

5. In this closer view of the cut surface of the lung, the interlobular septa (black arrow) outline the parenchyma into secondary lobules, which are about 2 cm in greatest dimension. The vascular lumina within the interlobular septa represent veins and the smaller lumina are lymphatics. Note again, the parenchyma is homogeneous (gross).

6. In these lungs, the right lung is normal, being pale white and homogeneous, and lacks any sooty black staining. The lung on the left is atelectatic. Atelectasis, also known as collapse, is loss of lung volume due to inadequate expansion of air spaces. The lung is deep red and would feel solid on palpation (gross).

7. The tracheobronchial tree is a series of dichotomously branching tubes. The conducting zone, made up of the first 16 generations of airways to the level of the terminal bronchioles (TB), does not participate in oxygen and carbon dioxide exchange. The transitional and respiratory zone in which gas exchange occurs includes the respiratory bronchioles (RB), alveolar ducts (AD), and alveolar sacs (AS), all of which give rise to alveoli. Although the cross-sectional area

of the individual airway decreases with each generation (bifurcation), the total cross-sectional area increases markedly because of an increase in the number of airways.

8. The three-dimensional figure shows the upper conducting airways with a microscopic cross-section though the trachea. Throughout the upper airways there is a significant component of smooth muscle and elastic tissue. These muscle and tissue components allow the trachea, bronchi, and bronchioles to maintain their lumen size during inspiration and expiration, and to constrict with the appropriate neural or pharmacologic stimulus. The intertwining bundles of smooth muscle are wrapped around in a bandlike fashion around the bronchial wall, much as one would wrap a rubber band around a pencil. The mucosa of the conducting system is lined with psuedostratified, tall, ciliated, columnar cells admixed with mucus-secreting goblet cells. Submucosal mucus glands are dispersed throughout the trachea and bronchi, but not the bronchioles.

9. This schematic diagram of the secondary lobule demonstrates its pyramidal shape, with the base abutting against, or directed toward, the visceral pleural and the apex pointing toward the hilus. The fibrous interlobular septa contain both lymphatics and veins. The secondary lobules are the structural subunits of the lung.

10. Here, the pulmonary artery bed has been injected with contrast media and a roentgenogram shows the architecture of the functional subunit of the lung, the acinus. The acini branch peripherally, within the secondary lobules, radiating outward from the center of the lobule. Within each secondary lobule are three to five acini.

11. Review. The secondary lobule is the structural subunit of the lung, which begins with the terminal or nonrespiratory bronchiole. The secondary lobule consists of 3 to 5 acini, which, again, are the functional subunit of the lung.

12. All the structures within the acinus, which consist of respiratory bronchioles (RB), alveolar ducts (AD), and alveolar sacs (AS), have alveoli as outpouchings in their walls.

13. This is a normal lung showing bifurcation of a terminal bronchiole in the center. You cannot appreciate the three-dimensional interrelationships in this histologic section. The honeycombed alveolar sacs and alveoli are the thin-walled structures lined by epithelium and contain capillaries within their walls.

14. In this three-dimensional diagram of the acinus arising from the terminal bronchiole, you can appreciate the smooth muscle wrapped around the airways. This wrapping is important in understanding the severe narrowing and constriction that can occur after stimulation of these smooth muscle bundles. Elastic fibers wrap around the respiratory structures, which keep them open during expiration. Starting at the level of the respiratory bronchiole, alveoli begin to arise. The alveolus is the gas exchange structure of the lung.

15. The pulmonary artery, which carries blood away from the heart (right ventricle) to the lung, contains venous blood. The pulmonary vein, which carries blood from the lungs back to the heart (right ventricle), contains arterial blood. Not shown in this diagram is the bronchial artery that carries oxygenated blood from the aorta to the lung.

16. The most important function of the lung is gas exchange. Here, in this three-dimensional figure of the acinus, the relationship of the pulmonary vein, pulmonary artery, and bronchial artery are depicted. We can see the intimate relationship between the pulmonary vasculature and the alveoli. It is important to remember that when one thinks alveolar wall, one should automatically think capillary bed. The exchange of air and blood gases takes place within these alveolar walls.

17. This is a normal chest x-ray (CXRAY). CXRAYs will be used in the lecture to correlate pathophysiologic process. The more dense a material, the whiter it appears, whereas air appears black. In this CXRAY, the heart is normal in size, the pulmonary vasculature appears normal, no lesions or hyperlucencies of the parenchyma are present, and the angles of the diaphragm are sharp.

18. This diagram very simplistically points out the essential features of gas exchange. Oxygen during inspiration from air (pO_2 = 100 mm) enters the alveolus, crosses the alveolar epithelium and capillary endothelium, and enters the venous blood (PO_2 = 40 mm). Carbon dioxide (CO_2) from the venous circulation (PCO_2 = ~45 mm) diffuses from the alveolar capillary, across the capillary endothelium, across the alveolar epithelium, and is expired. We will not be discussing arterial blood gas interpretation per se, however, arterial blood gas findings will be correlated with pathophysiologic processes.

Room Air		Arterial Blood Gas	Venous Blood Gas
PO_2	100	~100	~45
PCO_2	~0	40	45-50

19. Microscopic structure of the alveolar wall (Robbins, Figure 13-1). Shown in the figure are the capillary lumen surrounded by alveoli. In the alveolus on the left, the alveolar epithelial cell and the capillary endothelial cell are fused upon the thin basement membrane, forming an ultra-thin membrane for gas exchange. Separating the alveolar air space on the right from the capillary lumen are four cell types. The first, the Type I alveolar lining cell, is quite thin and attenuated, containing few organelles. About 95% of the alveolar air space is lined by Type I cells (membranous pneumocyte). The second cell type, the Type II alveolar lining cell, is cuboidal, has microvilli along its surface membrane and contains numerous cytoplasmic organelles (granular pneumocytes). The Type II cell secretes surfactant from lamellar bodies, which is necessary to keep the alveolus from collapsing during expiration. The Type II cell is the main cell necessary for repair after destruction of the Type I cell. The third cell type is the capillary endothelial cell, which lines the intertwining network of anastomosing capillaries and lies on a basement membrane. The fourth type of cell is the interstitial cell, the cell of origin of collagen, elastin, and the supporting connective tissue elements within the alveolar walls. In parts of the alveolus, the membranes of the Type I cell and endothelial cell are fused, forming an ultra-thin membrane for gas exchange.

20. The chest wall, intercostal muscles, and diaphragm act as bellows to move air in and out of the lungs. Extrapulmonary disorders that affect the ability of the chest wall to function as a bellows (e.g. severe obesity, kyphoscoliosis), and neuromuscular disorders, such as Guillain-Barre Syndrome, which affects respiratory muscles and the diaphragm, are known as restrictive pulmonary disorders.

21. A brief and simplistic review of spirometry. Spirometry is the single most important test of pulmonary function. During spirometry, the patient inhales and exhales with full effort. Measurements are made of airflow rate and change in volume of the respiratory system. Most clinical information is provided form analysis of the expiratory maneuver. The fundamental measurement of spirometry is the vital capacity (VC) or forced vital capacity (FVC), which is the sum of the maximal volume of air that can be inhaled (inspiratory VC) and exhaled (expiratory VC). To measure the expiratory VC, the patient inhales to his or her greatest lung volume and forcibly exhales until air can no longer be expelled. The amount of air expired in one second is the forced expiratory volume (FEV_1).

22. Normal vs. obstructive spirometry. The forced expiratory volume (FEV_1) is the amount of air expired in the first second. Commonly, The FEV_1 is expressed as a ratio or percentage of the forced vital capacity (FVC). In a healthy person, at least 70% of the FVC is exhaled within the first second. In patients with severe obstructive airway disease, as little as 20-30% of the FVC may be exhaled in the first second. This ratio of FEV_1/FVC is an extremely useful and reproducible measurement. In the spirometric tracing of a healthy patient, shown on the left, the FEV_1/FVC ratio or percentage is greater than 90%. In the tracing of a patient with obstructive pulmonary disease, shown on the right, the ratio is less than 25%.

23. Lung disease can deceptively be classified as either obstructive or restrictive, as discussed earlier. Distinction between the two terms is useful in correlating the results of pulmonary function tests with the radiologic and histologic findings of an individual patient. This slide summarizes the spirometric basis for the distinctions.

24. The various lung diseases are classified as either obstructive or restrictive. We will not be discussing extrapulmonary disorders further.

25. The obstructive lung diseases to be discussed are summarized. The obstructive lung diseases share a major symptom, dyspnea, and are accompanied by chronic or recurrent obstruction with the lung.

26. The basis of bronchial hyperreactivity is not entirely clear.

27. The clinical symptoms of asthma are episodic and reflect acute airway obstruction.

28. It is customary to classify asthma based on the presence or absence of underlying immune disorder. The clinical symptoms of asthma are episodic.

29. A triggering agent or stimulus causes bronchial constriction because of bronchial hyperresponsiveness. Bronchial hyperresponsiveness is thought to be due to chronic bronchial inflammation. With atopic asthma (type I hypersensitivity), the bronchial inflammation is easily explained, but this is not so with intrinsic asthma.

30. Irrespective of the type of asthma (extrinsic or intrinsic), the common denominator underlying all forms of asthma is reversible bronchoconstriction due to chronic bronchial inflammation.

31. The essential features of atopic (extrinsic) asthma are summarized.

32. Inhaled allergens (antigens) stimulate induction of T-helper cells, which release cytokines such as IL-4 and IL-5. These cytokines, in turn, promote IgE production by B cells, growth of mast cells (IL-4), and growth and activation of eosinophils (IL-5).

33. On re-exposure to antigen, the immediate reaction is triggered by antigen-induced cross-linking of IgE bound to IgE receptors on mast cells in the airways. These cells release pre-formed mediators which open tight junctions between epithelial cells. Antigen can then enter the mucosa to activate mucosal mast cells and eosinophils, which in turn release additional mediators. The mediators considered important in the pathogenesis of asthma include leukotrienes, prostaglandins, and platelet-activating factor (PAF). Collectively, either directly or via neuronal reflexes (vagal (parasympathetic), the mediators induce bronchospasm, vascular permeability (edema), or mucus production. This immediate phase occurs about 30-60 minutes after antigen exposure. The subsequent late phase of asthma lasts for hours and brings a fresh round of mediator release and additional bronchoconstriction, mucus production, and edema. Factors, particularly from eosinophils (e.g. myelin basic protein, eosinophilic cationic protein), cause epithelial damage and further exacerbate the situation. Eosinophils thus can amplify and sustain the inflammatory response without additional exposure to antigen.

34. The agents that cause intrinsic or nonatopic asthma are listed in this slide.

35. The mechanism of bronchial inflammation and hyperresponsiveness is not clear in intrinsic asthma. The agents responsible for initiating intrinsic asthma will cause bronchoconstriction in both normal and asthmatic subjects.

36. The morphologic findings in asthma are summarized.

37. The lungs in a patient dying of asthma are hyperinflated, covering the pericardial sac. Otherwise, the lungs in this case are pristine.

38. The bronchioles are filled with thick tenacious mucus.

39. Curshmann's spirals are whorls of epithelial cells within mucus plugs.

40. The microscopic features of asthma are summarized.

41. Comparison of a normal bronchiole with a bronchiole of a patient with asthma (Robbins, Figure 13-3). In the patient with asthma, there is basement membrane thickening, actually due to collagen increase from cytokine-mediated activation of myoblasts to secrete collagen, along with smooth muscle hyperplasia. An increased number of submucosal mucus glands with mucus accumulation are found within the bronchiole lumen, along with increased numbers of eosinophils, mast cells, basophils, and macrophages.

42. Asthma: Clinical course.

43. We will now turn our discussion to the diseases collectively referred to as chronic obstructive pulmonary disease (COPD). We will begin with the major disorders of COPD, which are emphysema and chronic bronchitis. These two conditions often coexist.

44. Smoking is the major pathogenic mechanism for both emphysema and chronic bronchitis. Emphysema is characterized by permanent enlargement of the air spaces distal to the terminal bronchioles and is accompanied by destruction of their walls. Chronic bronchitis is defined as a persistent cough for at least three consecutive months in at least two consecutive years.

45. Patients with predominant emphysema and those with predominant bronchitis will have distinct anatomic and clinical characteristics. Many patients, however, have overlapping features of damage at both the acinar (emphysema) and the bronchial (bronchitis) level.

46. Although chronic bronchitis and emphysema may begin as separate entities, quite often there is eventual progression such that both diseases are present in the same patient to some degree. In this schematic representation of the evolution of chronic bronchitis (left) and emphysema (right), bronchial injury and destruction of the alveolar wall are most often initiated by damage from cigarette smoking. Although both can culminate in chronic bronchitis and emphysema, the pathways are different and either one may predominate.

47. Both emphysema and chronic bronchitis ultimately lead to obstructive airway disease. Loss of airway elastic recoil during expiration leads to airway collapse and obstruction.

48. The essential feature of either emphysema or chronic bronchitis complicated by emphysema is a markedly decreased FEV_1 to FVC ratio, as seen in the spirogram on the right.

49. Robbins, Figure 13-4. There are various forms of emphysema. A: Diagram of the normal acinus distal to the terminal bronchiole. B: Centrilobular emphysema with dilation that affects the respiratory bronchioles initially but affects the entire acinus with progression. C: Panacinar emphysema initially affects the alveolar ducts and alveoli, but later extends to include the respiratory bronchioles.

50. This table summarizes the various forms of emphysema. Centriacinar (centrilobular) emphysema is the most common (95%) and is the form most associated with cigarette smoking. The lesions are most severe in the upper lobes and in particular the apices. Both emphysematous and normal airspaces exist in the acinus and lobule. Panacinar (panlobular) emphysema tends to occur mostly in the lower lung zone and is associated with alpha-1-antitrypsin deficiency (to be discussed later). In distal acinar emphysema, the proximal acinus is normal whereas the distal acinus is affected. The emphysema is most striking adjacent to the pleura and septa and is most severe in the upper lobes. This form is responsible for spontaneous pneuomothorax in young adults.

51. The essential features of the incidence of emphysema are summarized.

52. Robbins, Figure 13-5. Comparison of centriacinar (centrilobular) and panacinar (panlobular) emphysema. A: The pulmonary arteries have been injected with barium (white). The emphysematous foci (E) abut the arteries, but normal alveolar spaces are adjacent to the

septa (S). B: In panacinar emphysema there is generalized distribution of the emphysematous foci.

53. The alveolar wall destruction and airspace enlargement of emphysema is due to excessive protease or elastase activity unopposed by the appropriate anitprotease activity.

54. Smoking decreases antielastase activity and promotes the release of elastases. Smoke impacts at the bifurcation of the respiratory bronchioles, which is the site most often seen in centriacinar (centrilobular) emphysema.

55. The effects of cigarette smoking and the protease-antiprotease hypothesis.

56. The bifurcations of the respiratory bronchioles, the site of centriacinar (centrilobular) emphysema.

57. Centrilobular (centriacinar) emphysema (left), with central areas showing emphysematous damage (E). The airspaces surrounding the damaged areas are relatively spared. Panacinar emphysema (right) involves the entire pulmonary architecture.

58. Macroscopic appearance of the lungs in emphysema.

59. Emphysema with large subpleural bullae. Bullae are large airspaces (>1 cm) and tend to be subpleural in the apices, and can be seen in any of the forms of emphysema.

60. Lung with emphysema. The apical pleura are markedly thickened and loss of lung parenchyma due to emphysema can be readily appreciated.

61. A thin section of lung showing marked loss of pulmonary parenchyma.

62. The pleura are thickened in this lung and the emphysematous changes are subpleural.

63. The histologic development of emphysema is summarized.

64. Microscopic section of normal lung.

65. Microscopic features of emphysema. There is thinning and destruction of alveolar walls and enlargement of the airspaces.

66. In this microscopic image of emphysema, there is enlargement of the airspaces, some alveolar walls are thinned, and some are thickened. The bronchiole shows squamous metaplasia with chronic inflammation.

67. The patient with emphysema presents with steadily progressive dyspnea. Hyperventilation is common and expiration is slow. Blood gas abnormalities do not occur until very late.

68. The classic patient with emphysema is known as the "pink puffer" and the patient with just chronic bronchitis is known as a "blue bloater". In reality the diseases confound one another, yet it is convenient to at least separate them as to clinical findings.

69. A "pink puffer" with emphysema.

70. The "blue bloater" of chronic bronchitis with a barrel chest from secondary emphysema.

71. Clubbing of the fingers due to chronic hypoxemia.

72. Clinical consequence of COPD.

73. Death from emphysema.

74. CXRAY of emphysema. The lung fields appear hyperlucent and the heart "narrow" due to expansion of the chest.